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   – **Professor Dr. Ștefana Petrescu** is the Director of the Biochemistry Institute in Bucharest. She has been granted the Emil Racoviță Award of the Romanian Academy for her work on tyrosinase folding in 2002. She has been the President of the Romanian Society of Biochemistry and Molecular Biology since 2010. She is also the Deputy-Editor of Molecular Life.

   – **Professor Diana Ionescu** is a Clinical Professor of Pathology at the University of British Columbia, Medical Lead of Anatomic Pathology at BC Cancer in Vancouver, BC, and served as the residency program director for the Anatomic Pathology Residency Program. She is also the Canadian Anatomic and Molecular Pathology (CAMP) and Pathology-Oncology Digital Series (CAMP-PODS) course director. She is recognized as one of the two main leading lung cancer pathologists in Canada.

   – **Dr. Gabriela Gheorghe** is an **Associate Professor** of Pathology at St. Jude, the leading hospital for pediatric hematological malignancies in the US. She has been in practice for more than twenty years and has a particular interest in Molecular Pathology and Cytology.

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Doru Paul, MD, PhD

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Should We Expand the Use of Granulocyte-Colony Stimulating Factors (G-CSF) during the COVID-19 Pandemic?

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Abstract

Cancer patients are considered more susceptible to the SARS-CoV-2 infection. Higher rates of respiratory failure and death were reported in cancer patients and COVID-19, compared with the general population. Among other measures deemed to protect this vulnerable subcategory, both ASCO and ESMO recommended the extension of G-CSF use, to include prophylactic administration in all patients receiving regimens with 10%-20% risk of febrile neutropenia (FN) and also in regimens with risk of FN <10%, if patients were considered with poor bone marrow reserve due to comorbidities or advanced age. However, accumulating data reported in several recent publications suggested a direct involvement of the high neutrophil count, due to G-CSF stimulation, in the development of the adult respiratory distress syndrome (ARDS), the hallmark of the severe COVID-19 disease. In addition, some recent evidences suggest that G-CSF may hamper the efficacy of the mRNA vaccine. This paper reviews the most important data reporting higher rates of respiratory failures and death associated with G-CSF treatment in cancer patients and SARS-CoV-2 infection. Therefore, we consider that the current recommendation of expanding the G-CSF use in cancer patients during the COVID-19 pandemic should be reconsidered. The most important protective measures for cancer patients remain specific vaccination and a rigorous compliance with the general protective measures, whereas the G-CSF should be administrated as traditionally recommended by the current guidelines.

Keywords: *COVID-19, G-CSF, cancer, neutropenia*

Review Articles

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1. Background

The COVID-19 pandemic has profoundly affected the global population and the health care systems across the world. As of November 2021, more than 250 million infected cases and more than 5 million deaths associated with COVID-19 have been reported globally (1). Initially, patients with cancer were considered more vulnerable to SARS-COV-2 infection due to the coexisting chronic diseases, overall poor health status, and systemic immunosuppressive condition caused by both cancer and anticancer treatments (2). Recent reports confirmed this assumption, with the largest meta-analysis showing an overall case fatality rate due to COVID-19 in cancer patients of 22.4% (3), compared with 7.2 % in patients without cancer (4).

As such, the main oncology societies in United States (ASCO) and Europe (ESMO) had published guidelines on how to mitigate the impact of SARS-CoV-2 pandemic on patients with cancer, stipulating some specific recommendations, including prioritization of cancer treatment according to the goal of therapy, using telemedicine to avoid frequent hospital visits, switch to oral drugs when available, and postponing the medical interventions which, were believed to be non-essential (5-7). In the same context, recommendation was made that patients with active cancer and those on treatment should be prioritized for vaccination and should be immunized when any authorized vaccine is available to them. Individuals with cancer have an appropriate, protective immune response to vaccination without experiencing any more side effects than the general population (8).

2. Rationale for expanding the G-CSF use during the COVID-19 pandemic and the current recommendations.

A special attention was paid on the use prophylactic G-CSF during COVID-19 pandemic. Neutropenia induced by anti-cancer therapies is one of the most common side effects seen in cancer patients, commonly accompanied by a decrease in other hematopoietic lineages, like anemia and/or thrombocytopenia. Soon after the onset of the pandemic, both ASCO and ESMO recommended the extension of G-CSF use, to include prophylactic administration in *all* patients receiving regimens with 10%-20% risk of febrile neutropenia (FN) and also with regimens with *risk of FN <10%,* if patients were considered with poor bone marrow reserve due to comorbidities or advanced age (6, 9). Therefore, the majority of patients receiving chemotherapy would have received G-CSF support whatever the FN risk might be. By acting this way, it was expected to reduce the risk of hematologic complications associated with cancer chemotherapy and thereby to minimize the patient exposure in the clinic for supplementary analysis and treatment, the referral to the emergency department and hospital occupancy in times when these places may be in short supply and/or pose an exposure risk for this vulnerable population. Moreover, for patients presenting with FN after chemotherapy who have not previously received prophylactic treatment with pegylated G-CSFs, the recommendation was that *all patients* be started on G-CSFs to shorten the time to neutrophil recovery (6).

3. The potential detrimental effect of G-CSF on COVID-19 course

Despite this enthusiastic initiative for expanding the G-CSF indications, some indirect alarming data emerged from published series correlating the high leukocyte level with the odds of in-hospital death due to SARS- COV 2 infection (OR = 6.60 (3.02–14.41), $p<0.0001$, for the white blood cell count level > 10×10^9/L)(10). In addition, it has been suggested that the G-CSF may increase pulmonary inflammation and enhance production of inflammatory

cytokines such as interleukin-6 associated with severe COVID-19 (11). Autopsies of COVID-19 patients have shown neutrophil extravasation in the alveolar spaces of lungs, raising concerns that G-CSF administration and the resulting neutrophil expansion could lead to exaggerated neutrophil responses, worsening respiratory function (12).

Former knowledge about the non-COVID-19 “Acute Respiratory Distress Syndrome” (ARDS) recognized the neutrophil influx into the extravascular compartments of the lungs as a primordial characteristic. In ARDS, neutrophils and their toxic mediators can cause tissue injury, including an increase in lung epithelial and endothelial permeability, which, leads to the influx of protein-rich alveolar edema and arterial hypoxemia. Neutrophilia is common in the broncho-alveolar lavage fluid of patients with ARDS and the extent of this correlates with clinical outcome. ARDS is associated with elevated levels of primed neutrophils within the systemic circulation, suggesting that ARDS may be associated with a failure of neutrophil depression, thus providing a potential ‘crosstalk’ mechanism for the remote organ damage that is the predominant cause of mortality and long-term morbidity in patients with ARDS. In fact, mortality from ARDS correlates with the extent of neutrophilia in the lung (13). Very important, the G-CSF is the dominant colony-stimulating factor released from lung cells in response to pro-inflammatory cytokines (14). In addition, neutrophils are important contributors to both venous and arterial thrombus formation and progression. Neutrophil extracellular traps promote vessel occlusion by providing a scaffold for platelets, red blood cells, and procoagulant molecules, enhance coagulation through both the intrinsic and extrinsic pathways. Vascular neutrophilic inflammation and immune thrombosis are characteristics of COVID-19 infection and have been described as being associated with G-CSF treatment (15).

Addressing the impact of G-CSF treatment during the SARS-CoV-1 infection, the paper by Lazarus et al. raises the hypothesis that Granulocyte Macrophages-Colony Stimulating Factor (GM-CSF) may be a better choice for neutrophil count support due to a broader range of biologic activities. The G-CSF receptors are expressed primarily on neutrophils and bone marrow precursor cells whereas the GM-CSF- receptors are, more widely expressed being present on neutrophils, monocytes, eosinophils, dendritic cells, basophils, and, possibly, B cells. Therefore GM-CSF may be responsible for a broader range of biologic activities than G-CSF as well as anti-bacterial, anti-fungal, and anti-viral properties (16). Moreover, some data suggest that GM-CSF may be effective in treating some pulmonary conditions like the acute respiratory distress syndrome (ARDS) (17). The suggestion was that in persons with lung infection and/or ARDS, GM-CSF may be a safer drug than G-CSF (16). On the other hand, an open-label multicenter, randomized clinical performed in China suggests a higher lymphocyte count recovery with G-CSF administration in patients with COVID-19 pneumonia and lymphocyte count < 800 per μL. Moreover, the number of patients developing critical illness (2% vs 15%) or dying (HR, 0.19; 95% CI0.04-0.88) was reduced in the G-CSF treated group. However, some important limitation of the study, including the exclusion of patients with comorbidities and an imbalance in the use of antivirals and dexamethasone, may have precluded a reliable conclusion based on the recorded data (18).

Anecdotal case reports were among the first to rise the hypothesis of correlating the COVID-19 related ARDS with G-CSF treatment in cancer patients. Nawar and colleagues reported 3 persons with ARDS in the setting of COVID-19 with rapid deterioration of lung function after receiving G-CSF (19). Taha and colleagues report similar rapid deterioration in someone with COVID-19-related ARDS receiving G-CSF,

concluding: "*This rapid neutropenia recovery and the robust inflammatory response in COVID-19 raise concerns about G-CSF safety in patients with COVID-19"* (20). Moreover, a retrospective study of 83 neutropenic oncological patients who simultaneously had neutropenia and an infection with COVID-19 showed that the respiratory failure and death was associated with the number of days of G-CSF treatment (OR = 1.4, 95% CI [1.1-03.92], p= 0.01). The authors concluded that a prolonged G-CSF treatment could be disadvantageous for cancer patients with infections by COVID-19, due to a higher probability of worse outcome (21).

The last updated data related to this issue were recently published in a "*Major Article*" of the *Clinical Infectious Disease* (official publication of the Infectious Diseases Society of America) (22). The authors performed a retrospective analysis of 379 cancer patients at Memorial Sloan Kettering Cancer Center who tested positive for COVID-19 and received cancer directed therapy within 30 days of their COVID-19 diagnosis between March 11 and November 16, 2020. The majority of cancer types were breast cancer (24%), colorectal cancer (11%), lung cancer (10%), lymphoma (7%) and prostate cancer (7%). Two hundred twenty-seven (60%) patients received cytotoxic chemotherapy within 30 days of their COVID-19 diagnosis. Meanwhile, 28 (7.4%) patients received either filgrastim or pegylated filgrastim. Among the 379 patients, 130 (34.3%) were hospitalized for the management of COVID-19 symptoms. The primary composite endpoint was the occurrence of respiratory failure (defined as the requirement for high-flow nasal oxygen, non-rebreather, bi-level positive airway pressure [BIPAP], and mechanical ventilation) or death following COVID-19 diagnosis. Using an extended Cox model with G-CSF encoded as a time-dependent covariate, the researchers found that G-CSF administration was significantly associated with increased risk of hospitalization in patients with COVID-19 (HR3.54, 95% CI1.25-10.0, p=0.017). The association remained significant when considering patients who had asymptomatic COVID-19 (HR 18.31, 95% CI 2.51-96.8, p=0.008). Similarly, among the 130 patients who were hospitalized, G-CSF administration was associated with increased need for high levels of oxygen supplementation and death (HR 3.56, 95% CI 1.19-10.2*,* p=0.024), while neutropenia was not (HR 0.95, 95% CI 0.39-2.1, p=0.907). Based on the neutrophil count, the patients were stratified into "high" (defined as a >50th percentile increase in ANC, equivalently, a fold change of >=4) or "low" responders to G-CSF. The poorer outcome was predominantly seen in the "high responders" group (HR 7.78, 95% CI 2.05-27.9, p=0.004), whereas a non-significant trend was noted for the "low responders" (HR 4.04, 95% CI 0.80-16.7, p=0.086). Interestingly, in the multivariate model, neutropenia by itself did not portend a worse outcome (HR: 0.95, 95% CI0.39–2.1, p=0.907). Moreover, the severity of neutropenia (ANC nadir) was not correlated with G-CSF use (Wilcoxon *P* value 0.55), which, ruled out the possibility of G-CSF being reserved for cases with more severe neutropenia (22).

Besides a possible detrimental impact on the COVID 19 course, the G-CSF treatment may hamper the efficacy of the mRNA vaccine, as suggested by a recently published paper. The authors prospectively analyzed a cohort of 366 cancer patients who completed the two mRNA-BNT162b2 vaccine doses. Some 285 patients were on active treatment within the previous 28 days before the first vaccine dose whereas some 81 patients discontinued such treatment. A multivariate analysis showed no interaction between cytotoxic chemotherapy and antibody response, but ECOG PS2 and G-CSF use were significantly associated with lower IgG titer and lack of seroconversion after either dose of vaccine (for G-CSF

usage HR0.20, p=0.003 after first dose and HR0.26, p=0.01 after the second dose). In addition, the G-CSF usage was associated with an increased risk of vaccine associated side effects (for fever OR= 3.37, p=0.022) (23).

Conclusions

In conclusion, it is reasonable to consider that the recommendation for expanding the use of G-CSF during the COVID-19 pandemic should be reevaluated, as several high quality reports and meta-analysis do not show cancer patients to be at higher risk of developing more severe COVID-19 disease even when receiving anti-cancer therapy (24, 25). Strong evidences suggest that the high neutrophil count related to G-CSF treatment may worsen the COVID-19 course, including higher risk of respiratory failure and death. In addition, a detrimental impact on mRNA vaccine efficacy and safety was recently suggested. Recommendation for G-CSF administration should remain as traditionally specified by the guidelines: regularly for FN risk > 20%, for FN risk of 10-20% in the presence of other patient related risk factors and refrained in case of FN risk <10%. In case of established FN, G-CSF should be administered only in high-risk cases (26). When it comes to COVID-19 pandemic and cancer patients, we strongly advice in favor of anti SARS-CoV-2 vaccination, including the third booster dose, along with rigorous compliance with the general protective measures (hand washing, mask wearing, social distancing).

Abbreviations:

ARDS – Acute Respiratory Distress Syndrome
COVID-19 – Corona-Virus Disease of 2019
FN – Febrile Neutropenia
G-CSF – Granulocyte-Colony Stimulating Factor
GM-CSF – Granulocyte Macrophages-Colony Stimulating Factor
ASCO – American Society of Clinical Oncology
ESMO – European Society of Medical Oncology
ANC – Absolute Neutrophil Count

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Gastric Cancer: Applicability and Feasibility of Molecular and Histological Classification in Clinical Practice

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Abstract

Gastric cancer (GC) is the fifth most common type of cancer and the third leading cause of cancer-related deaths in the world. GC is a heterogeneous disease with diverse molecular and histological subtypes, which, may have different therapeutic implications. Using sophisticated molecular technologies and analyses, 3 separate groups recently provided genetic and epigenetic molecular classifications of GC: Singapore-Duke, The Cancer Genome Atlas project (TCGA) and the Asian Cancer Research Group (ACRG). These molecular classifications are time-consuming, complex, and costly and require sophisticated molecular technologies, which, prevent their widespread availability and use in clinical practice. Therefore, several practical pathological classifications were developed using immunohistochemical stains, fluorescent in situ hybridization and/or polymerase chain reaction (PCR), which, approximate, albeit not perfectly, the molecular classifications of GC. These are simple algorithms, less expensive and easy to reproduce in any pathology laboratory. Both molecular and histological classifications should be used for choosing adequate therapy and stratification purposes in clinical trials. This is a review of current molecular and pathological classification of GC.

Keywords: *gastric cancer, pathology classification, molecular classification*

Review Articles

Introduction

Gastric cancer (GC) is a major global health problem and the third leading cause of cancer related deaths worldwide. The incidence is highest in Asia (with over half of all GC cases globally diagnosed in East Asia), Eastern Europe, and South America with comparatively lower rates in Africa, North America, and Europe. The overall survival for resected gastric cancer patients is poor; for US population, 5-year survival is

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64% (local), 28.2% (regional) and 5.3% (distant metastases), with overall 5-year survival of 32.4% (1).

The disappointing survival rates are due to the limited treatment options and tumor heterogeneity, especially at the molecular level, with limited targetable biomarkers. Surgery is the 1st line treatment for GC, producing an overall survival rate of 60 - 70% for early-stage disease. High GC incidence nations such as Japan and Korea now implement routine screening for early detection when the disease is highly curable. In many less developed countries, however, GC is mostly detected only in its advanced stages, precluding curative surgical resection, and necessitating systemic treatment. The low efficacy of current therapies results in advanced or metastatic GC having a low survival rate of 5–20%, and a particularly poor prognosis for peritoneal GC recurrence (2).

Pathological Classification of Gastric Cancer

Historically, GC was classified morphologically by Lauren in 1965 in 2 main categories: intestinal type and diffuse type (Fig.1) (3). This classification is still widely accepted by pathologists and clinicians in contemporary practice. Intestinal and diffuse GC exhibits numerous differences in pathology, epidemiology and etiology. *Intestinal type* is more common in older males, frequently associated with Helicobacter pylori infection, which, leads to gastric atrophy, intestinal metaplasia, low-grade dysplasia, high-grade dysplasia, and intestinal type adenocarcinoma, in a stepwise progression, known as Correa cascade (4). *Diffuse type* tends to occur in younger patients, mostly females and may occur in familial clusters. Histologically, these tumors lack expression of adhesion molecules and typically show an infiltrative, poorly differentiated, poorly cohesive appearance. Somatic and germline mutations in a number of genes contribute to diffuse type of GC: E-cadherin (CDH1), TP53, RHOA, CTNN1A, and CMTM2. Approximately 1–3% of all GC are due to hereditary diffuse gastric cancer (HDGC), with 30-40% of those associated with germline mutations in CDH1 (5).

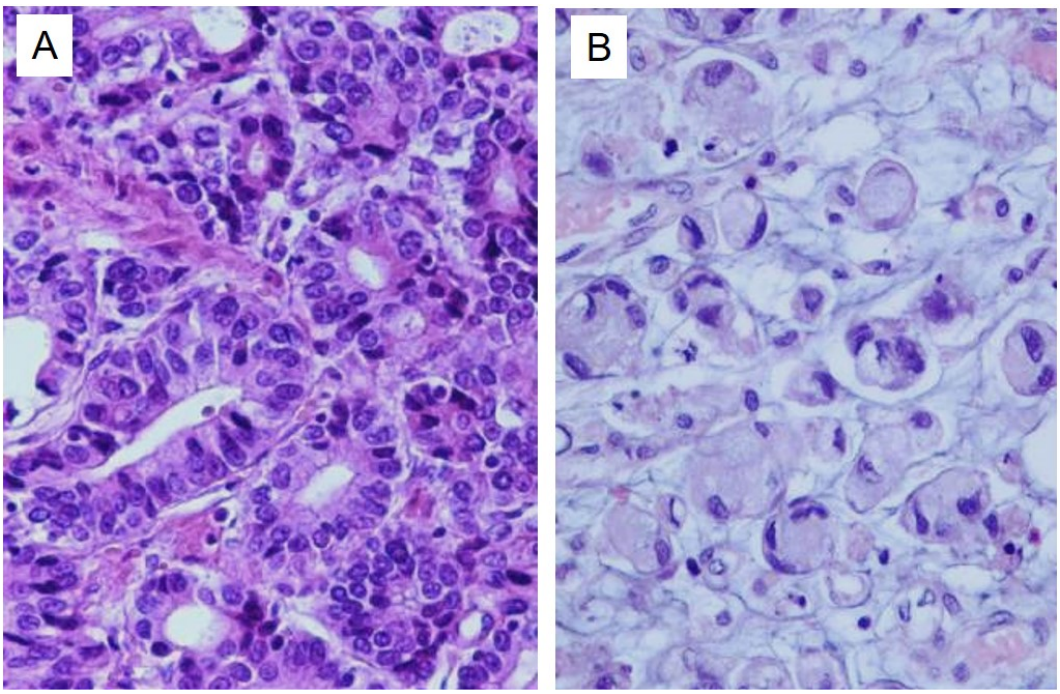


Fig. 1. Lauren Classification of Gastric Cancer (1965)

Table 1. Evolution of Histological Classification of Gastric Malignant Epithelial Tumors

Lauren 1965	WHO 2000	WHO 2010	WHO 2019
Intestinal	Papillary Tubular (grade 1-3)	Papillary Tubular, well and moderately differentiated	Papillary Tubular, well and moderately differentiated
Indeterminate Indeterminate/ intestinal/diffuse	 Mucinous	Tubular, poorly differentiated (solid) Mucinous	Tubular, poorly differentiated (solid) Mucinous
Diffuse	Diffuse (signet ring carcinoma)	Poorly cohesive carcinoma (including signet ring carcinoma and other variants)	Poorly cohesive carcinoma NOS Signet ring carcinoma
Mixed adenocarcinoma	Mixed adenocarcinoma	Mixed adenocarcinoma	Mixed adenocarcinoma
Not defined	**Histological variants of carcinoma:** Adenosquamous carcinoma Squamous cell carcinoma Undifferentiated carcinoma Small cell carcinoma Others **Carcinoid**	**Histological variants of carcinoma:** Adenosquamous carcinoma Squamous cell carcinoma Undifferentiated carcinoma Carcinoma with lymphoid stroma (medullary) Hepatoid carcinoma Others **Neuroendocrine neoplasms:** *Neuroendocrine tumors* (*NET)* NET G1 (carcinoid) NET G2 *Neuroendocrine carcinoma (NEC)* Large cell Small cell Mixed adeno-neuroendocrine carcinoma (MANEC) ECL and serotonin producing NET Gastrin producing NET (gastrinoma)	**Adenocarcinoma:** Carcinoma with lymphoid stroma Hepatoid carcinoma Paneth cell carcinoma Adenocarcinoma with enteroblastic differentiation Parietal cell adenocarcinoma Mucoepidermoid carcinoma Micropapillary adenocarcinoma Adenosquamous carcinoma Squamous cell carcinoma Undifferentiated carcinoma NOS: Large cell carcinoma with rhabdoid phenotype Pleomorphic carcinoma Sarcomatoid carcinoma Carcinoma with osteoclast like giant cells Gastroblastoma *Neuroendocrine tumor NOS* NET grade 1 NET grade 2 NET grade 3 Gastrinoma NOS Somatostatinoma NOS Enterochromaffin-cell carcinoid ECL-cell malignant carcinoid *Neuroendocrine carcinoma NOS* Large cell Small cell Mixed neuroendocrine–non neuroendocrine neoplasm (MiNEN)

The World Health Organization (WHO) Classification of Tumors of the Digestive System, published in 2000 based on the views of the Working Group meeting in 1999, classified gastric carcinoma into adenocarcinoma, intestinal and diffuse type, and several subtypes: papillary, tubular and mucinous adenocarcinoma, signet ring cell, adenosquamous, squamous, small cell and undifferentiated carcinoma. This classification had several shortcomings: it was purely descriptive, with little clinical utility; it did not address several subtypes, like mixed diffuse and intestinal type carcinomas, poorly differentiated carcinomas without signet ring cells; and finally, it included small cell carcinomas in the same category with adenocarcinomas, only carcinoid tumors being considered a separate category (Table 1). All these histologic types were recognized by American Joint Committee on Cancer (AJCC) staging manual 5th edition (1997) and staged using the same staging system, except for carcinoid tumors.

Some of the shortcomings were addressed by the subsequent edition of WHO book, published 10 years later. To the previously described categories of papillary, tubular and mucinous adenocarcinoma, a new category was added: poorly cohesive carcinoma, which, included signet ring carcinoma and other variants, as well as mixed adenocarcinoma. Maybe the most important change was separation of neuroendocrine neoplasms as a separate category, which, includes neuroendocrine tumors (NET) grade 1 and grade 2, neuroendocrine carcinoma (NEC), large cell and small cell type, mixed adeno–neuroendocrine carcinoma (MANEC), and NET producing gastrin and serotonin (Table 1). A list of the most common genetic alterations found in intestinal and diffuse types of gastric cancer were included in this edition.

In the meantime, the AJCC staging manual went through two new editions: 6th edition (2002) and 7th edition (2010). Both editions still included and staged small cell carcinoma together with the other epithelial carcinomas, while carcinoid tumors were a separate category. Finally, the 7th edition created a single separate staging category for well differentiated NET and well differentiated NEC of stomach, small intestine, colorectal and duodenal ampulla.

The latest edition of the WHO book (5th edition), published in 2019, based on the debates of the WHO Classification of Tumors Editorial Board meeting in 2018, significantly expanded the classification of malignant epithelial tumors. Adenocarcinoma was classified in several subtypes: tubular, parietal cell, mixed, papillary NOS, micropapillary NOS, mucoepidermoid, mucinous, signet ring cell, poorly cohesive, medullary carcinoma with lymphoid stroma and hepatoid adenocarcinoma. Undifferentiated carcinoma has several subtypes: large cell carcinoma with rhabdoid phenotype, pleomorphic carcinoma, sarcomatoid carcinoma, carcinoma with osteoclast-like giant cells. Neuroendocrine neoplasms were classified in NET NOS, with the following subtypes: NET grade 1, grade 2, grade 3, gastrinoma, somatostatinoma, enterochromaffin cell carcinoid (ECL) and ECL carcinoid, malignant. Neuroendocrine carcinoma NOS continues to remain a separate category, with large cell and small cell subtypes. MANEC has been renamed as mixed neuroendocrine–non neuroendocrine neoplasm (MiNEN). Gastroblastoma was added as a separate category. Probably the most significant addition was the inclusion of the new genetic and epigenetic molecular classifications proposed by The Cancer Genome Atlas Research Network (TCGA) and the Asian Cancer Research Group (ACRG). The latest edition of the AJCC staging manual (8th edition) published in 2017 and the College of American Pathologists (CAP) Cancer Protocol Templates, which, are frequently updated, created separate pathologic staging systems for well differentiated neuroendocrine tumors, separate for each

gastrointestinal site, while NEC and MiNEN are staged using the same template as carcinomas.

Molecular Classification of Gastric Cancer

Gastric cancer is a highly heterogeneous disease from molecular point of view, in dire need of specific biomarker-driven cancer therapies. There have been several efforts to perform large-scale molecular profiling and classification of GC, summarized in Table 2.

Familial gastric cancer

About 10% of GC show familial clustering, but only approximately 1-3% of GC are associated with inherited gastric cancer predisposition syndromes, such as hereditary diffuse gastric carcinoma (HDGC), familial adenomatosis polyposis syndrome (FAP), hereditary nonpolyposis colorectal carcinoma (HNP CC/Lynch syndrome), juvenile polyposis syndrome, Peutz-Jeghers syndrome, Li-Fraumeni syndrome and gastric hyperplastic polyposis syndrome (6).

HDGC is an autosomal dominant disorder with high penetrance. Approximately 30-40% of patients have a germline mutation in the tumor suppressor E-cadherin gene (CDH1). The inactivation of the second allele through mutation, methylation and/or loss of heterozygosity eventually triggers the development of gastric cancer (7-9). Underexpression or complete loss of E-cadherin is associated with epithelial–mesenchymal transition (EMT), a poor prognostic indicator. The presence of this mutation confers over 80% lifetime risk of gastric carcinoma, and prophylactic total gastrectomy after confirmation of CDH1 mutation is the only procedure that increases survival (10). Additionally, annual mammography and breast MRI starting at age of 35 are recommended for women with HDGC, due to their increased risk of lobular breast cancer (11). The histologic phenotype of HDGC corresponds to diffuse type in Lauren classification, or poorly cohesive type with signet ring cells in WHO fifth edition. Relatively characteristic to HDCG in early stage is a pagetoid-like spread of signet ring carcinoma cells (signet ring carcinoma *in situ*), which, has not been reported in the sporadic form of signet ring carcinoma (12). CDH1 genetic testing of blood for germline mutation should be performed in Clinical Laboratory Improvement Amendments (CLIA)-certified molecular diagnostic laboratories in USA, or laboratories with expertise in CDH1 gene analysis.

Beyond hereditary GC, the more common sporadic form of diffuse type GC has also been associated with E-cadherin loss, either through somatic mutation or promoter hypermethylation. Recently, a pair of studies published in *Nature Genetics* expands our understanding of diffuse type GC by describing novel recurrent mutations of *RHOA*, encoding the small GTPase RhoA, in 14.3%–25.3% of patients (13,14). These findings implicate RHOA as a novel candidate driver for diffuse gastric cancer.

Human epidermal growth factor receptor 2 (HER2)

HER2 is a member of the epidermal growth factor receptor (EGFR) family, which, includes ErbB2/HER2, ErbB3/HER3, and ErbB4/HER4. All of them are oncogenic drivers and were described initially in lung cancer, breast cancer and glioblastoma, and later in colon cancer, bladder, ovary, cervix, stomach and gastroesophageal junction (GEJ) cancers (15). Inhibitors of these receptors have been associated with the most successful results of targeted cancer therapies to date, including antibody therapeutics (trastuzumab and cetuximab), small molecule tyrosine kinase inhibitors (osimertinib, erlotinib, afatinib, gefitinib, lapatinib, mobocertinib and tucatinib) and the newly developed drug conjugates (trastuzumab emtansine and trastuzumab deruxtecan) (16,17).

Table 2. Current Molecular Classifications of GC

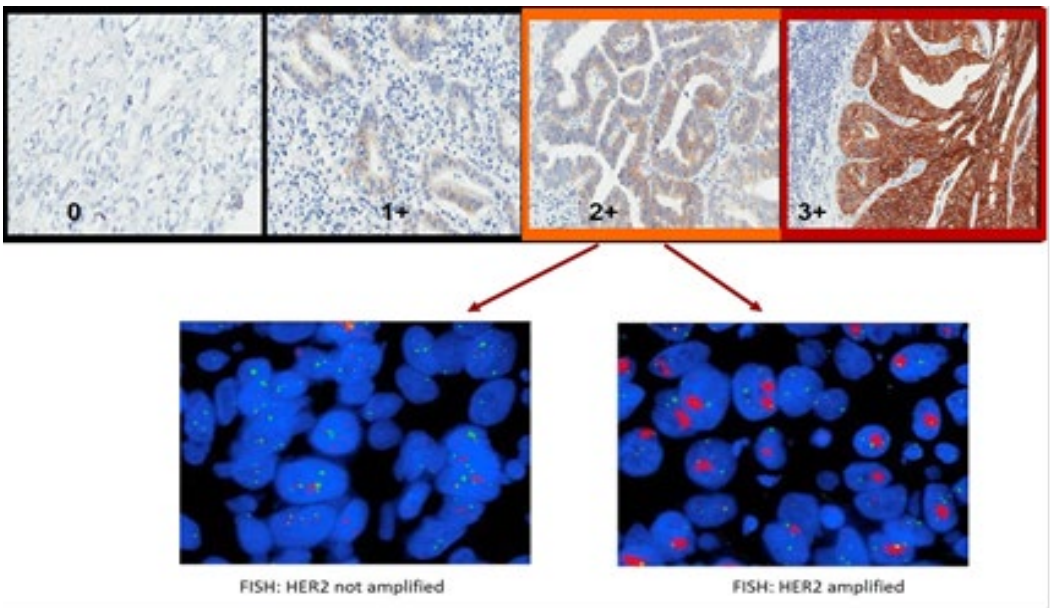
Current molecular classifications of GC					
The Cancer Genome Atlas (TCGA) 2014	**EBV** EBV-CIMP PIK3CA mutations PD-L1/PD-L2 expression	**MSI** MLH1 promoter hypermethylation Hypermutated Gastric CIMP	**GS** CDH1, RHOA mutations Diffuse histology Younger females	**CIN** TP53 mutations Intestinal histology	
Singapore-Duke 2013			**Mesenchymal** Low level of CDH1 Low TP53 Diffuse histology PIK3CA-mTOR inhibitors	**Proliferative** High TP53 Intestinal histology	**Metabolic** Low TP53 No histologic correlation 5-FU+surgery
Asian Cancer Research Group (ACRG) 2015		**MSI** ARID1A, KRAS, PIK3CA	**MSS/EMT** Loss CDH1	**MSS/TP53-** TP53 mutations, ERB2, EGFR, MDM2, GATA6	**MSS/TP53+** EBV, APC, ARID1A, KRAS, PIK3CA, SMAD4
		Intestinal histology Antrum Early stage Best prognosis	Diffuse histology Younger age Worst prognosis	Intestinal histology	Intestinal histology
				Male	Male
				Intermediate prognosis	Intermediate prognosis

HER2 gene amplification and overexpression of the HER2 protein by immunohistochemistry was discovered in gastric carcinoma in 1986 (18). The rate of HER2 overexpression in gastric adenocarcinoma ranges from as low as 4% to as high as 53% (19-23), with an average of 20% in a large meta-analysis (23). HER2 overexpression is more often noted in intestinal type carcinoma adenocarcinomas located at proximal stomach, cardia and gastroesophageal junction. A large phase 3 international clinical trial (ToGA trial) showed that the humanized monoclonal antibody against HER2, trastuzumab (Herceptin), when combined with chemotherapy (capecitabine or 5-FU and cisplatin) prolongs overall survival and progression free survival in patients with HER2 positive advanced gastric carcinoma (24). Based on this study, in 2010, trastuzumab was approved by FDA in USA, Health Canada and by the European Commission for the treatment of HER2 positive metastatic gastric or GEJ adenocarcinoma in combination with standard chemotherapy, for patients who have not received prior treatment for metastatic disease.

In the ToGA trial, HER2 was assessed by immunohistochemistry and scored as 0, 1+ (negative), 2+ (equivocal) and 3+ (positive). The tumors showing equivocal (2+) staining were confirmed by fluorescent in situ hybridization (FISH), which, if showed amplification of HER2 were considered

positive and patients were eligible for therapy with trastuzumab (Fig.2A). HER2 scoring criteria in GC are slightly different from breast cancer, requiring either complete, basal lateral or lateral membranous staining, unlike breast HER2 interpretation which, requires completely circumferential staining. Another difference between breast and gastric cancer HER2 interpretations is the amount of tumor cells required: small clusters composed of minimum 5 tumor cells in biopsies of gastric or GEJ cancer, and 10% of tumor cells in resection specimens respectively, are adequate for evaluation (Fig. 2B).

A.



B.

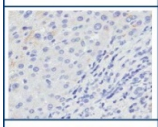
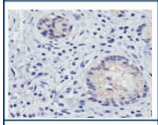
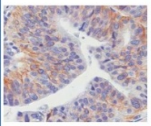
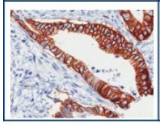
	Score	Surgical specimen – staining pattern	Biopsy specimen – staining pattern	HER2 overexpression assessment
	0	No reactivity or membranous reactivity in any tumor cells	No reactivity or no membranous reactivity in any tumor cell	Negative
	1+	Faint / barely perceptible membranous reactivity in **≥10% of tumor cells**	Tumour cell cluster with a faint / barely perceptible membranous reactivity **irrespective of percentage** of tumour cells stained	Negative
	2+	Weak to moderate complete, basolateral or lateral membranous reactivity in **≥10% of tumour cells**	Tumor cell cluster with weak to moderate complete, basolateral or lateral membranous reactivity **irrespective of percentage** of tumor cells stained	Equivocal
	3+	Strong complete, basolateral or lateral membranous reactivity in **≥10% of tumor cells**	Tumor cell cluster with a strong complete, basolateral or lateral membranous reactivity **irrespective of percentage** of tumor cells stained	Positive

Fig. 2. HER2 testing in gastric cancer: A. Immunohistochemical staining is interpreted as negative (score 0 and 1+), equivocal (score 2+) and positive (score 3+). Tumors with equivocal (2+) staining should be confirmed by fluorescent in situ hybridization (FISH), which, analyzes the ratio between HER2 gene copy number and chromosome 17 centromere. HER2/CEP17 ratio > 2 in over 20 tumor cells is considered HER2 amplified. B. HER2 scoring guidelines in gastric cancer in biopsy and resection specimens, according to the ToGA trial.

Current recommendations are to use immunohistochemistry as the initial testing methodology, with FISH or silver in situ hybridization (SISH) used only to retest equivocal (2+) cases (25). There is a strong demonstrated concordance in HER2 expression between biopsy and resection specimens (26), therefore, most of the time there is no need to re-test HER2 on the resection.

Therefore, HER2 has been established as the first, and, so far, the only approved molecular biomarker available for gastric cancer patients in clinical practice and recommended by CAP (27), and trastuzumab is the first FDA approved molecular targeted agent for the treatment of gastric cancer.

Singapore-Duke Classification of Gastric Cancer

The gastric cancer project 2008 Singapore cohort (28) was one of the first major projects that tried to identify the key oncogenic pathways deranged in gastric cancer, associated with a significant impact on survival. Using gene expression signatures, an *in-silico* strategy to map patterns of oncogenic pathway activation in 301 primary gastric cancers was developed. Also, 3 oncogenic pathways, subsequently validated in gastric cancer cell lines, were described: proliferation/stem cell, NF-kappaB, and Wnt/beta catenin.

A follow-up study of the Singapore cohort conducted by Lei et al. (29) compared gene expression patterns among 248 GC from Singaporean patients and identified 3 major subtypes:

1. proliferative – characterized by high genomic instability, TP53 mutations and DNA hypomethylation

2. metabolic – more sensitive to 5-fluorouracil (5-FU) than other subtypes

3. mesenchymal – with features of cancer stem cells; cell lines of this subtype are particularly sensitive to inhibitors of phosphatidylinositol-3-kinase/mammalian target of rapamycin (PI3K/mTOR) pathway.

The Cancer Genome Atlas (TCGA) Gastric Cancer Molecular Classification

In 2014, as part of TCGA project, the genome and proteome of gastric cancer were extensively characterized in order to uncover molecular subtypes and identify dysregulated pathways and potential therapeutic targets (30). Fresh frozen tissue and matched germline DNA samples of 295 primary gastric adenocarcinoma not previously treated with chemotherapy or radiation therapy were studied by using 6 different molecular platforms (array-based somatic copy number analysis, whole exon sequencing, array-based DNA methylation profiling, mRNA sequencing, micro-RNA sequencing and reverse-phase protein array), with 77% of tumors tested with all 6 platforms.

Analysis of data created a decision tree which, separated the gastric cancer in 4 distinct subtypes, with the following characteristics:

1. Epstein-Barr virus (EBV; 9% of patients)-characterized by EBV positivity, these tumors had higher prevalence of DNA promoter hypermethylation, frequent PIK3CA, ARID1A and BCOR mutations, with rare TP53 mutations. All EBV positive tumors exhibited extreme CpG island methylator phenotype (CIMP), distinct from that in the MSI subtype. They displayed CDKN2A (p16) promoter hypermethylation but lacked the MLH1 hypermethylation characteristic of MSI associated CIMP. Mutations in PIK3CA, ERBB3, ERBB2 and EGFR were noted. EBV gastric cancers were mostly in males and located in the fundus or body and had prolonged survival (31).

2. Microsatellite high instability (MSI; 22% of patients)-included tumors with elevated mutation rates and hypermethylation (including hypermethylation MLH1 promoter). Absent from this group were BRAF mutations, commonly seen in MSI colorectal cancer. These patients tended to be older

females and morphologically, the gastric cancer was intestinal type.

3. Genomically stable (GS; 50% of patients) - the tumor has had a low mutational burden and low somatic copy number aberration. Clinically, these group demonstrated more aggressive disease, with 73% of tumors occurring in younger patients, showing diffuse histology, with CDH1 mutations and RHOA mutations.

4. Chromosomal instability (CIN; 20% of patients) - the tumors show high somatic copy number aberrations, aneuploidy and focal amplification of receptor tyrosine kinases (RTKs) (i.e., EGFR, ERBB2 and ERBB3), and, VEGFA, MET, TP53, APC mutations.

In theory, amplifications of RTKs are amenable to blockade by therapeutics (RTK inhibitors); VEGFA can be targeted by the VEGFR2-targeting antibody (ramucirumab), and amplifications of cell cycle mediators (CCN E1, CCN D1 and CDK 6), are amenable to therapy by inhibition of cyclin-dependent kinases (32). These tumors are more frequent at the gastroesophageal junction/cardia and show intestinal morphology.

Asian Cancer Research Group (ACRG) Gastric Cancer Molecular Classification

The ACRG expanded upon the TCGA analysis by performing additional expression analyses and correlated the results to their institutions high-quality clinical outcomes, which, included recurrence and survival. In its initial study, whole genome sequencing was performed in 49 patients, and recurrent somatic mutations were identified (33). A year later, ACRG published the results of gene expression profiling, genome-wide copy number microarrays and targeted gene sequencing on an additional 251 patients, for a total of 300 primary GC tumor specimens. Tissue was obtained at the time of total or subtotal gastrectomy from Samsung Medical Center in Korea. All patients were chemotherapy naïve. Long follow-up was available (median 86.4 months). Based on a decision tree, similar with TCGA group, they identified four molecular subtypes that were associated with survival and recurrence patterns after surgery (34):

1. Microsatellite high instability (MSI; 23% of patients) - This subtype had the best prognosis, and more than half of patients were diagnosed with early-stage cancer (stage I–II), similar with TCGA MSI subset. MSI subtype was associated with the presence of hypermutation, with mutations in several genes: K-ras (23.3%), the PI3K-PTEN-mTOR pathway (42%), ALK (16.3%) and ARID1A (44.2%).

2. Microsatellite stable/ epithelial mesenchymal type (MSS/EMT; 15% of patients) - The EMT subtype had a lower number of mutation events compared to the other MSS groups. These tumors were mostly present in young patients (median age 53 years), showed diffuse type histology, presented at advanced stages (stage III–IV) and were more commonly located in the antrum and body. This subtype had the worst overall prognosis and recurrence free survival. Although 80% of MSS/EMT tumors showed diffuse morphology, overall, only 27% of all diffuse gastric cancers in this study were part of this subgroup, which, suggests that more than 70% of diffuse gastric cancer had a better prognosis. This group is similar with the GS group of TCGA. EMT and MSI exhibited a mutually exclusive pattern.

3. MSS/TP53+ (26.3% of patients) - these tumors showed intact TP53, frequent EBV infections and mutations in APC, ARID1A, KRAS, PIK3CA, SMAD4 genes.

4. MSS/TP53- (35.7% of patients) - these tumors showed functional loss of TP53, with the highest prevalence of TP53 mutations (60%) and a low frequency of other mutations: ERBB2, EGFR, MDM2, GATA6. TP53 is the most mutated gene in gastric cancer. TP53 signature was measured in this study based on 2-genes: CDKN1A (p21) and MDM2. Intact TP53 in

group 3 means high signature score (TP53+) whereas functional loss of TP53 means low signature score in group 4 (TP53-). TP53 activity signature correlated with the TP53 mutation status.

As opposed to the TCGA analysis, ACRG group run a survival analysis on their cohort of patients, and they validated on three separate independent cohorts: Samsung Medical Center 2 (n=277); Singapore cohort (n=200); TCGA cohort (n=205). They noticed that the gastric cancer subtypes were statistically correlated to the overall survival in all four cohorts, either individual or combined datasets. The best overall survival was present in the MSI group both in each individual cohort, and in the combined cohorts, while the MSS/EMT subtype had the worst overall survival. The pattern of recurrence for each GC subtype was also investigated as an exploratory analysis using clinical data from the ACRG and Samsung Medical Center cohort. The MSS/EMT group had a higher risk of recurrence compared to the MSI group (63% versus 23%). Additionally, they observed that the first site of recurrence was related to subtypes as follows: MSS/EMT subtype had a higher percentage of peritoneal seeding versus all other subtypes (64% versus 23%); also, the MSI and MSS/TP53 subgroups showed a high percentage of metastases limited to the liver 23% and 21% respectively) versus the MSS/EMT and MSS/TP53+ subtypes (4.6% and 8% respectively). When compared with the other reported molecular subtypes (TCGA and Singapore cohorts), they noticed similarities, such as tumors with MSI in both ACRG and TCGA subtypes, and between the GS, EBV and CIN TCGA subtypes and the ACRG subtypes MSS/EMT, MSS/TP53+ and MSS/TP53 - respectively (Table 2). However, they noticed several differences in terms of cohort, molecular mechanism, driver gene and prognoses association. For example, tumors classified as TCGA CIN subtype were present across all ACRG subtypes. Also, the diffuse type histology was lower in the TCGA cohort (24% in TCGA versus 45% in ACRG), with most diffuse type cases present in the TCGA GS group, but only 27% cases present in the ACRG MSS/EMT subtype. This is suggestive of less heterogeneity present in the diffuse subtype in the TCGA cohort. Also, CDH1 mutations, frequent in the TCGA GS subtype (37%), were infrequent in the ACRG MSS/EMT subtype (2.8%). Additionally, RHOA mutations were more prevalent in the MSS/TP53-and MSS/TP53+ then in the TCGA GS group. All of these differences suggest that the TCGA GS type is not equivalent to the ACRG MSS/EMT subtype. In general, the Singapore and TCGA subtypes are similar with the notable exception that there is no equivalent subtype that corresponds to the ACRG MSS/TP53+ or MSS/TP53-, making the ACRG classification rather unique. These molecular signatures of gastric cancer have important clinical implications for molecular screening and targeted therapy agents development. However, a significant hurdle for the use of molecular signatures in clinical practice is the cost and availability of these tests.

Several intrepid pathologists have tried to come up with clinically feasible and cost-effective strategies and developed varied subtyping algorithms using immunohistochemical stains and/or FISH, tying to approximate the molecular subtypes of GC. Some of these algorithms are described in the section below.

Development of a practical immunohistochemical algorithm for the identification of molecular subtypes of gastric cancer

In 2016, Kim et al. had described a ten-stain panel, using EBER, mismatch repair (MMR) proteins (MLH1, PMS2, MSH2, and MSH6), receptor tyrosine kinases (HER2, EGFR, and MET), PTEN, and p53 protein. This panel is extensive, with several immunostains (i.e., EGFR, MET, PTEN) that are not routinely utilized in surgical pathology labs (35).

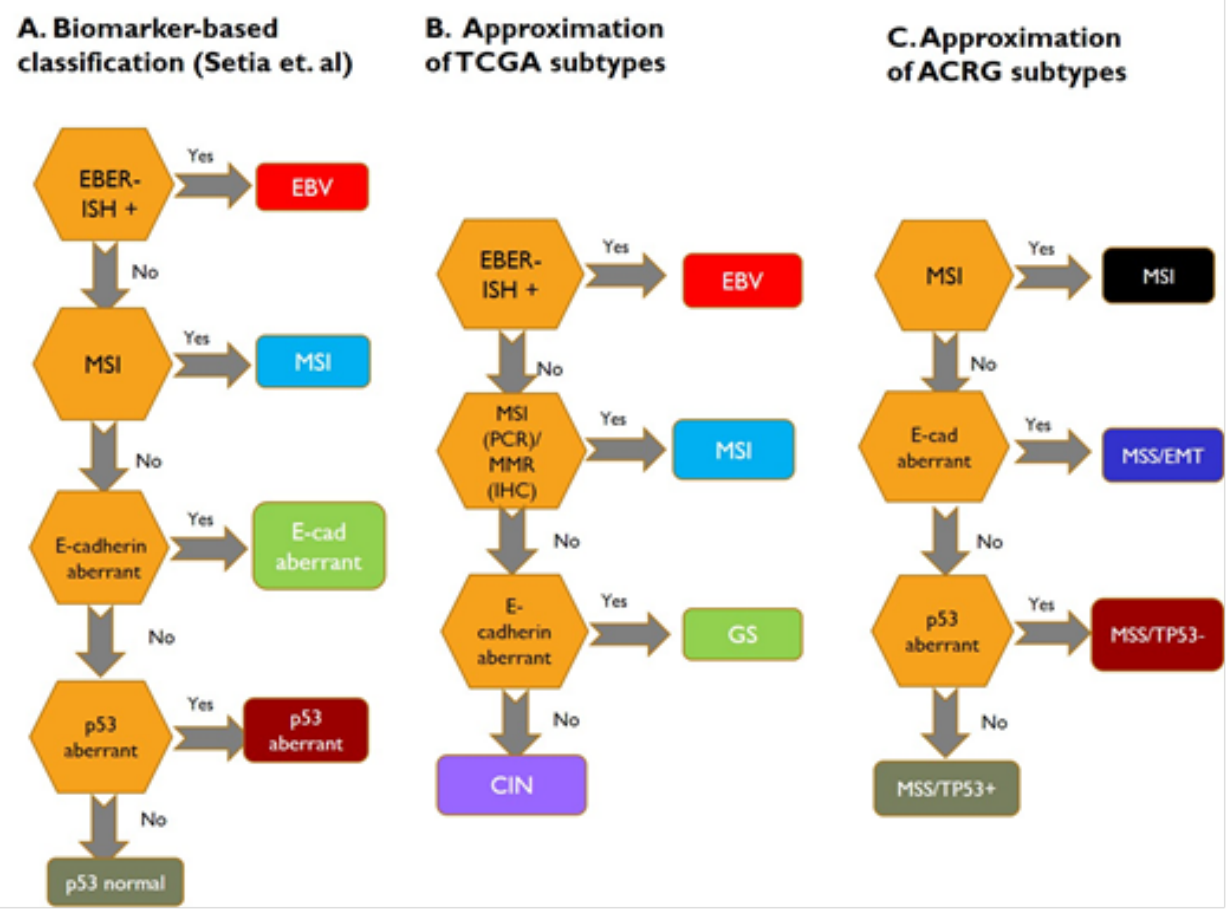


Fig. 3. Practical pathological algorithms that approximate molecular classification of gastric cancer. A. Integrated classification. B. TCGA classification. EBER in situ hybridization separates EBV group; immunohistochemical stains for MMR or PCR separate MSI group; E-cadherin immunohistochemical stain separate genomically stable (GS) group and the remainder are chromosomal instability (CIN) group. C. ACRG classification. Immunohistochemical stains for MMR or PCR separate MSI group; aberrant E-cadherin stain (complete loss or faint cytoplasmic staining) separate MSS/EMT group; aberrant p53 immunostain (strong staining in >70% of tumor cells) separates the MSS/TP53- group; the remainder group with wild-type (normal) p53 staining pattern is MSS/TP53+ group.

This was a large study conducted on 438 consecutive patients with advanced gastric adenocarcinoma from South Korea. The biomarkers were performed on whole sections slides - a clear advantage over the subsequent studies, the majority performed on tissue microarrays (TMA) blocks, which, include a very small tumor sample (cores of 1 or 2 mm).

The same year, Setia et. al group proposed a 5-tier classification algorithm, based on 14 biomarkers, which, included EBER in situ hybridization and immunohistochemical stains for mismatch repair proteins (MLH1, PMS2, MSH2 and MSH6), E-cadherin, PD-L1, MUC 2, CDX2, CD10, MUC 5AC, MUC6 and HER2 (36). These biomarkers were performed on TMA blocks constructed from 146 primary gastric cancers. This team described 5 different groups of GC (Fig. 3A):

1. EBER positive (5%) - these tumors showed a prominent lymphoid infiltrate, and they were associated with PD-L1, which, suggests a potential role for immunotherapy with anti-PD1/PD-L1 monoclonal antibodies. EBV cluster showed a trend towards better survival, however not statistically significant.

2. MMR deficient (16%) – which, correlates with the MSI group from both TCGA and ACRG classifications

3. E-cadherin aberrant (21%) - most of the tumors in this group were diffuse type (90%). This group correlates with the genomically stable group of the TCGA, the MSS/ EMT subgroup of the ACRG and the mesenchymal group of the Singapore classification.

4. Aberrant TP53 expression (51%) - further subclassified into intestinal type (33%, based on MUC2 and/or CD10 expression), gastric type (32%, MUC5AC and/or MUC6 positive) and normal type (20%, CD10, MUC2, MUC5AC and MUC6 negative). The subclassification based on MUC and CD10 immunostains has no clinical impact and is purely morphological.

This group was similar to the CIN group of TCGA, the proliferative subtype of Singapore classification and MSS/TP53- of ACRG. The majority (81%) were intestinal type, and a trend of HER2 expression was noted. Gastric cancer with aberrant TP53 expression may benefit from targeted therapy with receptor tyrosine kinase blockers (HER2, EGFR, VEGFR, c-MET), cell cycle (CCNE1, CCND1, CDK6) inhibitors and fibroblast growth factor receptor 2 inhibitors.

5. Normal TP53 expression (wild-type)- corresponding to the metabolic subtype in Singapore classification, is highly sensitive to 5-FU therapy.

These groups are not mutually exclusive; however, they approximate well the recently described genetic classifications of gastric cancer. More importantly, they are easy to perform in most pathology laboratories and they use common immunohistochemical stains and FISH.

Several other authors have attempted to develop a practical algorithm to approximate the molecular classification. In 2019, a Canadian group used 5 commonly used immunohistochemical stains (p53 and MMR proteins MLH1, MSH 2, MSH 6 and PMS 2) and EBV in situ hybridization on TMA blocks constructed from 107 gastric cancers (37). They created a subtyping algorithm based on TCGA classification, using a series of dichotomizing steps:

1. EBV–CIMP tumors, identified by EBER positivity
2. MSI tumors, based on MMR immunostains
3. CIN
4. GS

The latter 2 groups were based simply on histology (diffuse versus intestinal/mixed types), using the rationale that GS tumors were enriched for diffuse histology in the TCGA classification; HER2 and diffuse histology were mutually exclusive in their cohort. The logic behind this approach was that addition of any other markers would make the subtyping cumbersome and difficult to implement in clinical practice.

The Canadian team also approximated ACRG molecular subtypes based on MMR, which, identifies the MSI subtype; and the microsatellite stable (MSS) tumors were subclassified further using p53, which, identifies the MSS/TP53- and MSS/TP53+ groups. My personal opinion is that this method is elegant and easy to implement in clinical practice; also, it is cost effective and can be performed in any pathology lab.

A large Korean research consortium developed and validated another simplified algorithm as a surrogate for molecular subtypes of gastric cancer, using EBV in situ hybridization, MSI PCR testing and immunohistochemical stains for E-cadherin and p53 on 894 gastric cancers (38). Five successive groups were described: EBV, MSI, E-Cadherin loss (EBV negative/ microsatellite stable/ EMT- like) group, aberrant p53 (EBV negative/ microsatellite stable/ EMT- like/ TP53-) group and normal p53 (EBV negative/ microsatellite stable/ EMT- like/ TP53+) group.

Studies on immunophenotypic classification of GC are currently ongoing. At present, the immunohistochemical definition of GC subtypes, especially related to the TP53 and E-cadherin genes expression, is still unsettled. In general, according to the criteria

of Ando et. al (39), aberrant TP53 expression in tumor cells is demonstrated by strong and diffuse staining of more than 70% of the tumor cells nuclei. A completely negative staining or patchy and weak staining is an indication of a wild type TP53 gene. A complete loss of membranous staining or a faint cytoplasmic reactivity of E-cadherin is indicative of an aberrant expression of this gene. A complete membranous or a heterogeneous cytoplasmic/ membranous staining pattern are considered normal E-cadherin staining patterns (36).

Therapeutic considerations

A better understanding of the various molecular characteristics of gastric cancer is critical for diagnostic assessment, prognostic evaluation, and the development of new therapeutic strategies for this aggressive disease. In GC, heterogeneity is present not only between different patients but, also, significantly, within the same patient where it can be both intra- and inter-temporal and spatial and temporal.

At present, there are several targeted agents FDA-approved for the treatment of gastric cancer: trastuzumab, ramucirumab, pembrolizumab, bemarituzumab, larotrectinib and entrectinib.

Based on the ToGA trial (24), **trastuzumab** was FDA approved in 2010 for patients with HER2 positive tumors for first line treatment in combination with chemotherapy. Based on the REGARD trial (40), **ramucirumab** (a VEFGR2 inhibitor) was FDA approved in 2014 as a second line treatment in patients with unresectable or metastatic disease following treatment with a fluoropyrimidine- or platinum-containing therapy. Ramucirumab is the first biological treatment given that has demonstrated a survival benefit as a single drug in patients with advanced gastric or GEJ adenocarcinoma progressing after first-line chemotherapy. Based on the seminal study by Le at. al (41), **pembrolizumab** (an anti-PD-1) was approved in 2017 for the treatment of cancer patients with microsatellite instability-high (MSI-H) markers or mismatch repair deficient (dMMR) markers. For gastric cancers expressing PD-L1 and negative for HER2, **pembrolizumab** was approved in 2017 as a third line of treatment in patients with disease progression after two or more systemic therapies, including fluoropyrimidine- and platinum-containing chemotherapy and, if appropriate, HER2/neu-targeted therapy (42, 43). PD-L1 testing as a companion diagnostic test (PD-L1 IHC 22C3 pharmDx) for pembrolizumab, is an immunohistochemical stain performed on formalin-fixed embedded tissue and is scored assessing immunoreactivity of tumor cells and immune cells, using the CPS scoring method (44, 45). The CPS was defined as the total number of tumor cells and immune cells (including lymphocytes and macrophages) stained with PD-L1 divided by the number of all viable tumor cells, then multiplied by 100 (https://www.captodayonline.com/scoring-gastric-gej-cancers-pd-l1-expression/). According to the KEYNOTE 059 study, CPS score $\geq$1 predicts response to the PD-1 inhibitors (46, 47).

Additionally, **pembrolizumab** was also approved for solid tumors showing high tumor burden (TMB) who had progressed following prior treatment and lacked alternative treatment options. Based on data from the KEYNOTE-158 study, high TMB was defined as ≥10 mutations/Mb by next generation sequencing (NGS), regardless of MSI status (48). TMB is broadly defined as the number of somatic mutations per megabase of analyzed genomic sequences. TMB predicts response to immunotherapy both in MSI-H and MSS populations, and is independent of the level of PD-L1 expression, suggesting a potential role of TMB to identify additional subgroups of patients who may benefit from immunotherapy (49). In GC, the TMB cutoff may vary, from 14 mutations/Mb (50) to 10 mutations/Mb (51) or 8.8 in another study

(52), but it is always associated with better response to immunotherapy.

Based on 3 separate studies (53) in 2018, FDA granted accelerated approval to **larotrectinib** for adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, that are either metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory alternative treatments or whose cancer has progressed following treatment. This was the second tissue-agnostic FDA approval for the treatment of cancer after the **pembrolizumab** approval described above. Identification of positive NTRK gene fusion status may be determined in local laboratories using NGS or fluorescence in situ hybridization (FISH). Current ESMO recommendations include pan-TRK immunohistochemistry as an approved method to screen for NTRK gene fusions (54). However, NTRK fusions are extremely rare in GC in Asian patients (55), and one German study found none in 438 Caucasian patients with GC (56), therefore testing for NTRK in GC may not be that useful.

Entrectinib was the third FDA-approved tissue-agnostic drug based on the presence of a biomarker (NRTK) across different types of tumours. Like **larotrectinib**, **entrectinib** is an oral NTRK, ROS1, and ALK inhibitor and appears to be effective against a range of NTRK fusion–positive tumor types. The drug has shown clinically meaningful and durable responses in NTRK-positive tumors. However, similar to **larotrectinib**, it is so rare in GC that its testing is not cost effective.

More recently, based on the FIGHT study (57), in April 2021, FDA granted breakthrough therapy designation to **bemarituzumab** for use in combination with modified FOLFOX6 chemotherapy as first-line treatment in metastatic or locally advanced GC or GEJ adenocarcinoma fibroblast growth factor receptor 2b (FGFR2b) positive and HER2-negative.

Summary

Pathologists play a crucial role in evaluating the histology and the biomarker results and establishing the appropriate biomarker detection methods. Delineating MSI-H/dMMR tumors and determining HER2 positivity, are straightforward and can be performed in any pathology lab using routine immunohistochemical stains and/or in situ hybridization methods and polymerase chain reaction (PCR) tools. Currently, CAP recommends testing only for HER2 in patients with inoperable, locally advanced, recurrent or metastatic gastric and GEJ adenocarcinomas for whom trastuzumab therapy is being considered, while NCCN guidelines recommend additional universal testing for MSI/MMR by PCR/IHC in all newly diagnosed patients. PD-L1 testing, using an approved FDA companion diagnostic test, may be required for locally advanced, recurrent or metastatic gastric and GEJ adenocarcinomas for whom therapy with PD-1 inhibitors is considered.

The latest advances in molecular methods have increased our understanding of GC biology and led to the development of new comprehensive molecular classifications. The TCGA project was a landmark effort that provided a molecular classification of GC, which, may serve as a valuable adjunct to histopathology. As a result of the TCGA database presence, 4 subtypes with distinct clinical and molecular features of GC were described: EBV, MSI, GS and CIN. However, the TCGA subtypes did not show significant correlations with overall and disease-free survivals (OS and DFS), and this may be due to several factors: the duration of follow-up, the heterogeneity of patients; ethnicities, the geographical distribution and the treatment received. The ACRG group expanded upon the TCGA database analysis by performing additional expre-

ssion analyses and correlated the results to their institutions outcomes, which, included both data on survival and recurrence. They also described four subtypes of gastric cancer (MSI, MSS/EMT, MSS/TP53+ and MSS/TP53-), which, unlike the TCGA group classification, were associated with survival and specific recurrence patterns after surgery.

These molecular classifications are time-consuming, extremely complex, costly and require sophisticated molecular technologies, which, prevent their widespread availability and use in clinical practice. Therefore, development of practical, easy to use and cost-effective classification systems for predicting prognosis or treatment response is needed. Immunohistochemical, in situ hybridization and/or PCR ancillary tests are excellent surrogates that approximate the molecular classification.

Currently, several algorithms for phenotyping gastric cancer using immunohistochemical markers and in situ hybridization have been published. Most of the studies done for this purpose employed TMAs, which, sample only a small portion of tumors. A simple and practical algorithm uses EBV in situ hybridization in order to identify EBER, MMR protein expression (using MLH1, MSH2, MSH6 and PMS2), E-cadherin and p53 immunohistochemical stains (Fig. 3B, C) as surrogate markers for the TCGA and ACRG subgroups. Although they do not match perfectly with the molecular subgroups, all these biomarkers are easily available in any pathology laboratory and represent a cost effective, practical and easy to use algorithm which, approximates genomic profiling and could be an alternative in guiding targeted therapies. They can be used in addition to the already established and approved tests for HER2, PD-L1 and MSI/MMR.

A good communication between the medical oncologists and the pathologists is a must as it facilitates effective tissue collection, proper tissue triage and appropriate histopathological and biomarker testing. Providing a detailed clinical history to the pathologists including information about the clinical stage, the resectability, and the therapy envisioned, may guide the nature of biomarkers that should be tested for. This is especially useful when the amount of tissue is limited, for example, in a mucosal biopsy, where sequential testing for single biomarkers may exhaust the tissue. In these situations, a comprehensive genomic profiling via an NGS validated platform is recommended to identify HER2, MSI/MMR, PD-L1, TMB and NTRK mutations.

Abbreviations:

GC – gastric cancer
TCGA – the Cancer Genome Atlas project
ACRG – Asian Cancer Research Group
PCR – polymerase chain reaction
US – United States
HDGC – hereditary diffuse gastric cancer
WHO – World Health Organization
AJCC – American Joint Committee on Cancer
NET – neuroendocrine tumors
NEC – neuroendocrine carcinoma
MANEC – mixed adeno–neuroendocrine carcinoma
NOS – not otherwise specified
ECL – enterochromaffin cell carcinoid
MiNEN – mixed neuroendocrine–non neuroendocrine neoplasm
CAP – College of American Pathologists
FAP – familial adenomatous polyposis syndrome

HNP CC – hereditary nonpolyposis colorectal carcinoma
EMT – epithelial–mesenchymal transition
CLIA – Clinical Laboratory Improvement Amendments
GEJ – gastroesophageal junction
FDA – The United States Food and Drug Administration
SISH – silver in situ hybridization
5-FU – 5-fluorouracil
PI3K/mTOR – phosphatidylinositol-3-kinase/mammalian target of rapamycin
MSI – microsatellite high instability
GS – genomically stable
CIN – chromosomal instability
RTK – receptor tyrosine kinases
EBV – Epstein-Barr virus
MSS – Microsatellite stable
EMT – Epithelial mesenchymal transition
MMR – mismatch repair
EBER – Epstein-Barr virus-encoded small RNAs
FISH – fluorescence in situ hybridization
TMA – tissue microarray
MSI-H microsatellite instability-high
dMMR – mismatch repair deficient
CPS scoring – combined positive score
PD-1/PDL-1 – programmed cell death protein 1/ programmed cell death-ligand 1
TMB – high tumor burden
NTRK – neurotrophic receptor tyrosine kinase
VEGFA – vascular endothelial growth factor A
VEGFR – vascular endothelial growth factor receptor
NGS – next generation sequencing
ESMO – European Society of Medical Oncology
FGFR2b – fibroblast growth factor receptor 2b
OS – overall survival
DFS – disease free survival

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Practice-changing Clinical Studies in Prostate Cancer: an Update for the Medical Oncologist

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Abstract

With new updates every year on cancer diagnosis, treatment, and follow-up, the face of oncology is changing rapidly. With the new guidelines issued this year and, also, with the recently published phase III trials' results, we aim to summarize key changes and updates for prostate cancer patients. We searched PubMed and international societies' databases for recent articles and chose those with relevant information for everyday clinical practice. Our review includes assessments for specific diagnostic methods and the most recent treatment options available for prostate cancer.

Keywords: review, prostate cancer, guidelines, clinical practice

Review Articles

1. Introduction

Prostate cancer (PC) is the fourth most common cancer and the second most frequent cancer in men, and is one of the leading causes of cancer-related deaths worldwide and the fourth cause of cancer-related death in the USA in 2020 (1). Recently, the European Society of Medical Oncology (ESMO) and the European Association of Urology (EAU), as well as the National Comprehensive Cancer Network (NCCN) updated their guidelines on screening, diagnosis, treatment and follow-up of prostate cancer patients.

2. Methods

Besides the European and American guidelines, we conducted a search in the PubMed database based on the keywords "prostate cancer", "metastatic", "hormonal therapy", "castration", and "immunotherapy". We selected papers published in the last two years and included phase III trials and studies with a significant number of participants, based on the relevance of the information and the applicability in real-life situations.

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3. Discussion

3.1. Workup

It is commonly stated that PSA screening of men decreases cancer mortality but also leads to unacceptable overdiagnosis and significant overtreatment. Thus, current recommendations suggest using this method of screening in men over 50 years or over 45 years in case of positive family history (2,3).

The main change regarding workup is the recommendation (class IB) of performing multiparametric magnetic resonance imaging (mpMRI) before prostate biopsy. A positive mpMRI is defined by a PIRADS score of at least 3. However, there is growing concern that the increased use of mpMRI would lead to more unnecessary biopsies and overdiagnosis of PC. Risk calculator models such as the recently validated Rotterdam Prostate Cancer Risk Calculator and the globally recognized STAR-CAP, are increasingly used to better predict the outcomes of and adapt treatment (4). When indicated, targeted transperineal MRI fusion biopsies proved to have an increased detection rate of clinically significant PC and fewer adverse effects compared to transrectal biopsies.

Tumor extension assessed by MRI, Gleason score and initial PSA values are used to classify prostate cancers as low risk, intermediate-risk or high-risk disease (5). In the most recent guidelines published by ESMO, the low-risk category refers to men with a T1/2 stage, a Gleason score ≤ 6 and PSA less than 10. In this case, no further imaging method is required. For the intermediate or high-risk categories, further evaluation of nodal or distant metastatic disease using at least a bone scan, a whole-body MRI, a CT/PET

CT or, if available, prostate-specific membrane antigen (PSMA)-PET-CT is recommended (6). Currently, the emergent method of liquid biopsies is of great interest in the process of cancer diagnosis, therapy, prognosis and follow-up. It is dramatically changing modern oncology by analyzing circulating tumor cells and circulating cell-free DNA (cfDNA), with the latter containing circulating tumor DNA (ctDNA) in cancer patients. cfDNA refers to extracellular DNA which originates from tumor-associated necrosis or physiological apoptosis. ctDNA may have similar genetic alterations with both the primary tumor and its distal metastases, and represents an important source of information. A study by Barata et al. has given a novel perspective on the direct clinical implications of integrating liquid biopsies into general practice. (7).

Recent studies have proved that cfDNA is a promising biomarker for screening and early detection of PC (8). Also, a study conducted by Lau et al. concluded that detecting ctDNA in patients with clinically localized PC can be used as a prognostic marker as it is associated with rapid disease progression (9). However, Hennigan et al. have demonstrated that the blood of patients with localized disease has a lower quantity of ctDNA, making it more difficult to assess (10). As shown by an editorial published by EMSO in 2021, a multitude of unknown variables that need further research remain (11).

3.2. Hormonal and Chemotherapy

Surgery and/or radiotherapy (RT) are the main therapeutic options for localized PC. For patients with low-risk disease, active surveillance is a Class IA recommendation. The ProtecT trial compared active therapy versus monitoring and there was no statistically significant difference after a 10-year follow-up (12). In patients with high-risk disease, the best approach based on two trials would be RT in association with androgen deprivation therapy (ADT) or radical prostatectomy (RP) (13). In case of bio chemical relapse of the disease after RP, the current recommendations are salvage radiotherapy with at least 66 Gy alongside ADT, which is known for its radio-sensitizing effect (14). A phase III trial, GETUG-AFU 17, has shown that adjuvant radiotherapy has no benefit for event-free survival in patients compared to early salvage radiotherapy

(SRT) (15). Early SRT should be given immediately after the first sign of PSA rise (16).

A high number of studies have been conducted in order to investigate the useful ness of neoadjuvant or adjuvant hormone treatment. Several trials have shown the benefit of adding neoadjuvant ADT to high-risk PC and, also, to unfavorable intermediate-risk localized PC. Docetaxel-based chemotherapy in high-risk localized disease has been proven in a meta analysis based on CHAARTED, GETUG-15 and STAMPEDE trials to improve the relapse-free survival rate by 8% (17,18). Regarding metastatic hormone-naïve PC, two phase III trials, CHAARTED and STAMPEDE, established the benefit of docetaxel in combination with ADT for these patients, as it significantly improved overall survival (OS) from 47.2 months to 57.6 months (19,20).

Another study conducted by Roy et al. evaluated the impact of concomitant medications on biochemical outcome in localized PC patients. Metformin intake doubled the risk of biochemical relapse, while sulfonamide-based concomitant alpha blockers nearly tripled risk (21).

For over half a century, androgen deprivation therapy was the first line of treatment for metastatic PC, after LHRH agonists replaced surgical castration as the gold standard. Recently, the androgen axis was effectively targeted with new therapies such as androgen receptor-targeted agents (apalutamide, enzalutamide) and a CYP17 inhibitor (abiraterone) (22). Patients with a low volume disease should be offered the combination of ADT with prostate RT as suggested by CHAARTED trial's criteria (20).

LATITUDE and STAMPEDE have demonstrated that the addition of abiraterone to ADT also improves overall survival by 7%, while another phase III trial, TITAN, has demonstrated that apalutamide has a significant improvement in 2-year-OS. Enzalutamide has been shown by two trials (ENZAMET and ARCHES) to have an 8% improvement in 3-year-OS data (23). Taking into consideration that docetaxel and abiraterone can produce adverse effects with greater impact on quality of life, they should be offered to compliant patients with fewer comorbidities and good performance status.

Castration-resistant prostate cancer (CRPC) refers to disease progression (biochemical or radiological) under ADT and having serum testosterone at castrate levels, meaning <50ng/dl. Three trials (SPARTAN, PROSPER and ARAMIS), tested a modern antiandrogen combined with ADT, and have shown that apalutamide, enzalutamide or darolutamide bring improvements to overall survival in both metastatic-free and non-metastatic castration resistant prostate cancer (M0- CRPC) patients (Table 1) (24).

Unfortunately, there are also many patients that are diagnosed with metastatic CRPC de novo. Recent studies have emphasized the importance of genetic counseling and testing for germline mutations, at least for patients with strong family history, with hereditary breast and ovarian cancer syndrome and Lynch syndrome and with high risk PC or intraductal histology (25).

For these patients, first-line treatment options include abiraterone, enzalutamide and docetaxel-based chemotherapy. The first two can be starting options for asymptomatic or mildly symptomatic patients with chemotherapy-naïve metastatic castration resistant prostate cancer (mCRPC), while docetaxel should be the first option for those with rapidly progressing disease or predominantly visceral metastases (2). In case of disease progression under chemotherapy, the treatment options are the second AR targeted drugs or cabazitaxel, which appears to be superior and, moreover, has recently been approved in Romania (24). In the CARD study, the median PFS for cabazitaxel was 8 months compared to 3.7 months for abiraterone or enzalutamide and the median OS was 13.6 months vs 11.0 months (26).

Table 1. Combined androgen blockade for M0-CRPC

	SPARTAN **Apalutamide vs placebo**	**PROSPER** **Enzalutamide vs placebo**	**ARAMIS** **Darolutamide vs placebo**
n	806 vs 401	933 vs 468	955 vs 554
Metastasis free survival (mo)	40.5 vs 16.2 (p<0.001)	36.6 vs 14.7 (p<0.001)	40.4 vs 18.4 (p<0.001)
Overall survival (mo)	73.9 vs 59.9 (p<0.001)	67.0 vs 56.3 (p<0.001)	NR vs NR

n - number of patients; mo - months; NR - not reached

Regarding a second-line treatment for mCRPC, it is important to mention that there is evidence of cross resistance between enzalutamide and abiraterone and current guidelines do not recommend the use of a second AR inhibitor (27).

An important trial, ALSYMPCA, has emphasized that for a progressive bone-pre dominant symptomatic mCRPC, radium-223, a bone-targeted alpha-emitter, significantly increased OS. However, its use is restricted to patients who are ineligible for first-line therapies or still have progressive disease after two lines of systemic treatment (28).

This year, Mao et al. published a study regarding the synergistic antitumor effect of the ZD55-IL-24 oncolytic adenovirus combined with radiotherapy in PC in vitro and in vivo trials. They found that this combination can induce apoptosis in tumoral cells by increasing their radiosensitivity and inhibit angiogenesis (29).

3.3. Immunotherapy

In recent years, immune checkpoint inhibitor therapy has been correlated with a significant improvement in the survival of patients with solid tumors. Unfortunately, data on mCRPC remains unclear and needs further investigation as prostate cancer appears to be an immunologically “cold” tumor (30). Recent results indicate that mCRPC has a low response to immunotherapy. This may be related to several factors: low tumor mutational bur den, loss of tumor suppressor gene, low prevalence of genetic defects and silencing of major histocompatibility complex-1 (31).

Although the development of immune checkpoint monoclonal antibodies represents a breakthrough in cancer therapy, the detection of specific biomarkers that predict treatment response remains a dynamic area of research in oncology. The most commonly used biomarker nowadays is the quantitative expression of PD-L1, which has been reported to have a significant expression for both mCRPC and primary PC (30). Vicier et al. published a study that assessed the PD-L1 expression in men with PC after undergoing prostatectomy and concluded that a lower expression is associated with a lower risk of biochemical relapse and presence of metastasis (32).

Recent data have shown that there are special populations of PC patients who can benefit from immunotherapy and these are represented by the patients with MSI-H tumors (33).

According to Willi et al., enzyme deficiency can lead to microsatellite instability (MSI) in cancer, and is associated with high levels of mutation neoantigens, but only 2-3% of PC cases have been shown to have high microsatellite instability (MSI-H) tumors (34). Barataet al. reported the first case series of clinical activity of pembroli zumab for MSI-H mCRPC. In this study, durable and profound responses were observed in nearly half of the MSI-H tumors (7).

Another study published by Graff et al. has shown evidence that ipilimumab, a fully

human monoclonal antibody promoting antitumor activity, can increase antitumoral activity and progression-free survival in patients with mCRPC, although without an improvement in overall survival (35).

3.4. Other genetic-alteration driven therapy

An increased number of DNA errors leading to high tumor neoantigen expression has been observed in patients with mutations in the DNA damage repair genes (BRCA1, BRCA2, CDK12, ATM) (36,37).

For patients with genetic mutations, a new class of drugs has been introduced, known as poly-adenosine diphosphate-ribose polymerase (PARP) inhibitors (31,38).

There are several ongoing trials for PARP inhibitors alone or in various combi nations for mCRPC. Currently, two drugs, olaparib and rucaparib are approved as a new line of treatment for patients who have a progressive disease after first and second generation of androgen receptor axis-targeting agents, taxane-based chemotherapy, radium-223 and immunotherapy with Sipuleucel-T or pembrolizumab (38). The recent PROfound trial, a prospective randomized phase III trial, screened 4425 patients with mCRPC and found that 778 had qualifying alterations (39).

3.5. Future directions

Considering the recent technological advancements in artificial intelligence, technology is becoming more and more involved in solving medical dilemmas.

There is a great interest shown in developing and validating a deep learning algorithm for Gleason grading of PC. In a recent study published in JAMA Oncology, Nagpal et al. presented a deep learning system (DLS) for reading digital prostate biopsy specimen sections. The results show a similar rate of identifying tumor specimens between DLS and pathologists, as well as significantly better agreement rates on Gleason pattern vs. pathologists. Considering the high interobserver variability in Gleason grading, DLS could function as a decision tool, with significant therapeutic implications streamlining the diagnostic flow (40).

Recently, a machine learning based analysis has been developed in order to predict metastatic disease or high-risk pathological tumor features in primary PC with the use of ^{18}[F]DCFPyL PET metrics. Lymph node involvement for these patients is an important diagnostic finding. Currently their involvement in cancer is investigated with an extended pelvic lymph node dissection. Prostate-specific membrane antigen is a type-II transmembrane protein highly over expressed on PC cells. Therefore, quantitative measures of its expression are widely used as a biomarker for risk stratification. The machine learning algorithm developed by Cysouw et al. was able to predict disease risk in primary PC patients and they stated that PSMA PET radiomics may capture tumor aggressiveness by carrying genomic as well as histopathological information (41).

4. Conclusion

Prostate cancer treatment is rapidly evolving. The latest guidelines are intended to offer patients the best diagnostic and treatment options. Our brief review offers clinicians several tips on the 2020-2021 updates for the management of prostate cancer.

Abbrevations:

PC – Prostate cancer
ESMO – European Society of Medical Oncology
EAU – European Association of Urology
NCCN – National Cancer Comprehensive Network

mpMRI – multiparametric magnetic resonance imaging
cfDNA – circulating cell-free DNA
ctDNA – circulating tumor DNA
RT – radiotherapy
ADT – androgen deprivation therapy
RP – radical prostatectomy
SRT – salvage radiotherapy
OS – overall survival
CRPC – castration-resistant prostate cancer
mCRPC – metastatic castration resistant prostate cancer
MSI – microsatellite instability
MSI-H – high microsatellite instability
PARP – poly-adenosine diphosphate-ribose polymerase
DLS – deep learning system
CT– computed tomography
PET – CT-positron emission tomography-computed tomography
MRI – magnetic resonance imaging
PFS – progression free survival
AR – androgen receptor
PD-L1 – program-death ligand 1

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EGFR Point of Care Clinical Testing using Idylla Platform Decreases Laboratory Turnaround Time in Advanced Stage Non-Small Cell Lung Cancer, as Compared to New Generation Sequencing

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Abstract

Background: Patients with advanced-stage non-small cell lung cancer (NSCLC) benefit from a short time-to-treatment (TTT) due to disease severity. Patients at BC Cancer with NSCLC undergo OncoPanel testing, a next-generation sequencing assay, for potential oncogenic drivers prior to treatment as outlined by CAP-AMP-IASLC guidelines. Genetic testing via OncoPanel takes more than two weeks and commonly contributes to an increased TTT. The novel ultra-rapid Idylla EGFR testing platform may decrease TTT in patients who are EGFR mutation positive (M+) due to the mutual exclusivity of actionable mutations. This study evaluates the lab turnaround time (TAT) of the Idylla EGFR testing platform and compares it to that of the OncoPanel.

Methods: A group of patients (N = 235) with stage IIIB or stage IV lung adenocarcinoma diagnosed between November 1, 2020 and May 1, 2021 had both OncoPanel and Idylla EGFR testing. The time at which the sample was received in the lab, the time of Idylla EGFR test reporting, and the time of OncoPanel reporting were recorded for each patient. Differences in the lab TAT between the OncoPanel and Idylla EGFR test were compared using a paired t-test within the cohort.

Results: The mean lab TAT for the Idylla and OncoPanel tests were 3.4 days (Range: 0-8 days) and 15.8 days (Range: 12-31 days), respectively. It was observed that the lab

Original Research

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TAT of the Idylla EGFR test was faster by an average of 12.4 days (Range: 6-29 days, p<0.01, 95% CI: [11.9, 12.8] days) than the OncoPanel TAT (N=235).

Conclusions: The lab TAT of the Idylla EGFR test is significantly shorter than of OncoPanel testing. In patients who are EGFR M+, molecular testing could be completed considerably faster using the Idylla EGFR testing platform since further genetic testing is unlikely to yield additional actionable information. Using the Idylla EGFR test as part of a reflexive molecular testing repertoire in advanced-stage NSCLC patients could thus reduce patient TTT.

Keywords: NGS, Idylla, EGFR, lung cancer, NSCLC

Background

Patients with advanced-stage non-small cell lung cancer (NSCLC) benefit from a short time-to-treatment (TTT) due to disease severity and often advanced stage at presentation. In more recent years, treatments for NSCLC have been advanced with the introduction of molecular testing in the treatment algorithm. For patients with advanced-stage NSCLC, genetic testing should be performed before delivering treatment as outlined in the guidelines set by the College of American Pathologists (CAP), Association for Molecular Pathology (AMP), and the International Association for the Study of Lung Cancer (IASLC) (1).

EGFR mutations are particularly common in patients with advanced NSCLC, especially in those with adenocarcinoma histology (2, 3). The incidence of *EGFR* mutations in lung cancer differs between Caucasian (range: 7%–36%) and Asian patients (range: 20%–76%) (2). As EGFR remains the most prevalent targetable oncogenic mutation in NSCLC, its rapid identification in advanced-staged NSCLC would significantly shorten time to treatment for these patients. Since most targetable molecular drivers are mutually exclusive, a positive EGFR result will inform the clinician of the best course of action at an earlier time point, and avoid further, more comprehensive and expensive testing.

The Idylla (Biocartis, Mechelen, Belgium)™ platform is a fully-automated, real-time PCR-based molecular testing system with applications to a wide range of clinical settings, where all the reagents required for sample preparation and PCR detection are provided in a single cartridge that can then be easily and rapidly loaded into the system. The system requires as little as 25 nanograms of tumor DNA, which is evaluated for single gene molecular changes, such as EGFR mutations, in less than three hours. This assay is validated in the BC Cancer Genetics and Genomics Laboratory (CGL) for clinical reporting. This study's objective is to evaluate the TAT of the Idylla EGFR testing platform and compare it to that of the OncoPanel.

Methods

This prospective study was performed on patients diagnosed with NSCLC and referred to BC Cancer to undergo OncoPanel clinical testing, a next-generation sequencing (NGS) assay, which screens 41 of the most common potential oncogenic genes, including EGFR. Genetic testing via OncoPanel takes more than two weeks to complete from the time the tumor sample is received in the laboratory to the time at which the genetic report is released to the ordering physician (lab TAT). OncoPanel testing commonly contributes to an increased TTT due to its lengthy TAT. The aim of the study is to compare TAT for patients with lung adenocarcinomas having EGFR testing performed by Idylla and compared to OncoPanel, the existing clinical mutational testing at BC Cancer, at the time of this study.

Case Selection

The samples were obtained from a group of patients (N = 235) with stage IIIB or stage IV lung adenocarcinoma diagnosed between November 1, 2020 and May 1, 2021 that had both OncoPanel and Idylla EGFR testing. Among these samples, specimens submitted for the identification of EGFR T790M resistant mutations, and samples with less than 500 nanograms of total extracted DNA were excluded, in order to ensure sufficient DNA for both Idylla and OncoPanel testing, and to focus this study on identification of *de novo* EGFR mutations. Prospective, real life clinical testing was performed on 235 advanced stage NSCLC patients, identified using the above criteria, and were concomitantly tested using the Idylla platform, and the clinically requested next generation sequencing (NGS) OncoPanel. The time at which the sample was received in the lab, the time of Idylla EGFR test reporting, and the time of OncoPanel reporting were recorded for each patient.

Statistical Analysis

Differences in the TAT between the OncoPanel and Idylla EGFR test were compared using a paired t-test over each patient. The analysis was performed using base R (version 4.0.2).

Results

The mean lab TAT for the Idylla and OncoPanel tests were 3.4 days (Range: 0-8 days) and 15.8 days (range: 12-31 days), respectively. It was observed that the lab TAT of the Idylla EGFR test was faster by an average of 12.4 days (range: 6-29 days, $p<0.01$, 95% CI: [11.9, 12.8] days) than OncoPanel TAT (Figure 1).

This TAT included specimen accessioning at referral laboratory, microtome cutting and H&E slide preparation, tumor content assessment and DNA extraction and preparation, qPCR, and automated analysis.

For a select few cases, in view of clinical urgency, tumor tissue was loaded directly to the Idylla cartridge without extraction. This allowed for same day resulting and explains the Idylla TAT range of 0-8 days. However, for the vast majority of cases, in order to accurately compare results between Idylla and OncoPanel, extracted DNA was used for both tests.

After the tests were performed, results were released on the patient's medical record on the same day or the subsequent day to allow for appropriate treatment planning.

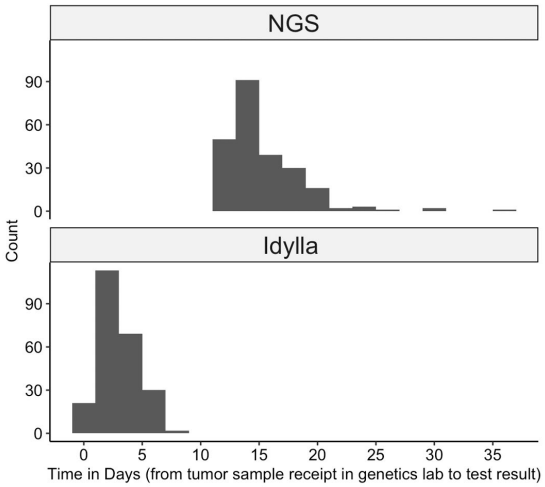

Fig. 1: Comparison of Idylla and NGS TATs (N=235). Distributions do not overlap, demonstrating a unanimously lower TAT in favor of the Idylla EGFR test.

Discussion

This study demonstrates that the Idylla EGFR test TAT is significantly shorter than NGS testing TAT. As the average Idylla TAT is 3.4 days, compliance with the CAP-IASLC-AMP molecular testing guidelines to have EGFR results within 10 working days from receipt of specimens in the laboratory can be easily achieved. Due to the mutual exclusivity of major oncogenic drivers in NSCLC, a positive Idylla EGFR test would lead to the completion of pretreatment tumor testing and could thereby improve TTT by 12 days on average in this patient population. Additionally, in a reflex but stepwise testing

scenario, cases positive for EGFR by this ultra-rapid panel would not require further, more comprehensive and more expansive testing (due to lack of incremental information), thereby saving NGS testing costs on up to 30.3% of lung adenocarcinoma patients, depending on the EGFR mutation incidence of the tested population (2, 3). The Idylla testing platform can be easier implemented and validated than other sequencing platforms in a variety of clinical settings, as it only requires limited infrastructure and training. Further research into the cost of implementing Idylla EGFR testing is required as patients who are EGFR mutation negative will undergo both Idylla and NGS testing. While the Idylla platform displays improved time and tumor material requirements as compared to NGS, there is a reduction in its comprehensiveness concerning the genes it can test as well as the mutations it can detect (Table 1-EGFR testing by Idylla and OncoPanel).

Other factors contribute to the lengthening of TTT in NSCLC, which are often independent of the testing laboratory, and independent of the technology used for testing. These factors include time for receiving the tumor block from originating hospital to the reference laboratory, interpretation and reporting time, etc. While several steps including evaluation of tissue cellularity and tumor content, DNA extraction and time to releasing the report to the ordering physician may overlap in length, others show greater variability, and therefore explain the overall decrease in TTT and Idylla TAT; the main contributing factors are shorter sequencing time using Idylla, as compared to any of the commercially available platforms (2.5 hours versus a few days) and shorter reporting time due to the analysis of one gene by Idylla versus multiple genes using NGS.

The number of mutations that can be detected by Idylla is predetermined by specific exonic regions that include hotspot variants (*BRAF*, 7; *EGFR*, 51; *KRAS*, 21) (4). Idylla requires minimal expertise for test performance and its turnaround time and hands-on time are the main advantages various other characteristics of these technologies, including required upfront extraction, minimal FFPE (formalin fixed paraffin embedded) tissue input, and type of output of results are summarized in Table 1.

Table 1. Practical characteristics of EGFR Mutation Assay and OncoPanel Assay

	Idylla EGFR	**OncoPanel**
Sequencing Time	150 min	Few Days
Hands-on Time	10 min	Hours
EGFR Mutations	51 SNV/del/ins	Full exon coverage
Upfront DNA Extraction	Yes	Yes
Minimal Input: FFPE	1×5 µm FFPE section and ≥10% tumor cells	6×5 µm FFPE section and ≥20% tumor cells
Data Processing	Proprietary algorithm	Lab Developed Algorithm
Expertise	Low	High
Output	Somatic hotspot mutations in EGFR	Any EGFR alterations requiring curation
Bioinformatics Assessment Needed	No	Yes

The analysis of the mutation detected is automatically performed by the Idylla platform and a report including the presence and type of EGFR mutation is generated. The NGS platform requires extensive bioinformatics analysis, highly trained personnel performing data analysis and interpretation of the results generated by the machine. Such characteristics suggest that the Idylla platform could be implemented in non-expert centers where no sequencing machines or expert technicians are currently available (5). Therefore, even pathology laboratories without molecular expertise could successfully use this method as long as a pathologist confirms the presence of a tumor on the slide, prior to testing (6-8). This high success rate depends on appropriate triaging and tissue handling, as tissue input is a pivotal determinant of the assay sensitivity and performance (9).

If reflex-testing using this technology may not be feasible, Idylla's shorter TAT over NGS testing could be beneficial in various clinical scenarios. For example, in patients with poor performance status, identification of EGFR mutation 12 days earlier may represent a lifesaving clinical step and should be considered on a case-by-case basis. Due to the difference in response to immunotherapy reported in NSCLC adenocarcinomas harboring driver mutations, timely identification of EGFR negative patients, in the right clinical scenario, may contribute to decreased immunotherapy TTT.

Conclusions

Molecular EGFR testing is completed considerably faster using the Idylla EGFR testing platform and this allows faster time to treatment for EGFR positive patients allowing rapid access to targeted therapy, and for EGFR negative patients allowing rapid access to immunotherapy.

Abbreviations:

EGFR – epidermal growth factor receptor
NSCLC – non-small cell lung cancer
TTT – time-to-treatment
CAP – College of American Pathologists
AMP – Association for Molecular Pathology
IASLC – International Association for the Study of Lung Cancer
CGL – Cancer Genetics and Genomics Laboratory
NGS – next-generation sequencing
TAT – turnaround time

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Long Term Survival in Patients with Metastatic Adenocarcinoma of the Lung in the Era of Targeted Agents

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Abstract

Background: Several studies have shown that tyrosine kinase inhibitors (TKI) and chemotherapy improve the short term and median survival of patients with metastatic adenocarcinoma of the lung (MAL), but there is less data on the long-term survival (LTS) of these patients.

Methods: A univariate retrospective analysis was performed on 174 patients with MAL diagnosed at our institution between 2009 and 2011, and with up to a 5-year follow-up. Overall survival was estimated using the product-limit method and drawing the Kaplan-Meier curves and compared using the log-rank test.

Results: Factors associated with a statistically significant survival benefit in our patients were having undergone lung surgery, female gender, never smokers, bronchioalveolar histology, and lower TNM nodal stage. Particularly, prior lung surgery was shown to improve survival in patients treated with erlotinib. This was also true when comparing patients from a historical cohort as well. Among patients with Epidermal Growth Factor Receptor (EGFR) mutation, there was no statistically significant difference in survival amongst patients treated with either surgery or erlotinib.

Conclusion: In our patients with MAL the only treatment modality that improved LTS in a statistically significant way was lung surgery. This is an important finding as National Cancer Comprehensive Network (NCCN) guidelines consider surgery as a treatment option only in MAL with isolated lesions.

Keywords: lung cancer, targeted therapy, EGFR mutation, long term survival

Original Research

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Background

According to the Surveillance, Epidemiology and End Results (SEER) database, lung cancer remains the leading cause of cancer related deaths in the United States. The number of projected new lung cancer cases for 2021 is 235,760, which compromised 12.4% of all new cancer cases (1). Given the significant healthcare burden that this group of malignancies poses, improving long-term outcomes for these patients is extremely important.

Over the past years, the treatment landscape for lung cancer has changed dramatically, with the approval of several checkpoint inhibitors for use in various histologic subtypes and lines of therapy. Despite this advance, patients with non-small cell carcinoma (NSCLC) harboring driver mutations were excluded from immunotherapy studies, and their treatment options have been focused on the use of targeted therapies.

The use of next generation sequencing (NGS) methods allowed for the discovery and description of mutations that are considered fundamental for cancer transformation and progression. Targetable driver mutations are present in all histological types of NSCLC (including adenocarcinoma, squamous cell carcinoma (SCC), and large cell carcinoma), but they are most commonly found in adenocarcinoma. In-depth characterization of these mutations fully benefited the treatment of cancer, and FDA clinically approved several small molecules targeting key protein products of these aberrant genes. In lung adenocarcinoma, the most common “driver” mutation occurs within epidermal growth factor receptor (EGFR) gene. EGFR is a transmembrane tyrosine kinase receptor that has been shown to be overexpressed, leading to worse overall survival in many malignancies, particularly NSCLC (2). Several mutations in the EGFR gene have been found to lead to this overexpression or constitutive activity of the receptor and promote oncogenesis (3). Erlotinib (Tarceva, OSI Oncology/ Genentech/ Roche), a tyrosine kinase inhibitor was approved for metastatic lung adenocarcinoma in the recurrent setting in 2004 (4). In 2010, in advanced NSCLC, it was approved as maintenance therapy after platinum chemotherapy, and in 2013 it was approved as first-line single agent in patients with advanced NSCLC with an EGFR mutation (5,6).

Several studies showed a benefit in progression free survival (PFS) in patients with advanced EGFR mutated lung adenocarcinoma (Stage IIIB/IV) who received either treatment with erlotinib, or chemotherapy (7). None of these studies showed a benefit in the overall survival of patients that received erlotinib, thus the long-term survival of such patients has remained ill defined. In 2016, Lin et al. published data for 5 year survival of 137 patients with EGFR mutated MAL treated with erlotinib with a 14.6% 5 year survival rate. Factors that were found to be associated with longer overall survival were exon 19 deletion, absence of extrathoracic (in general), or, specifically, brain metastases, and non-smoking status (8). Initially we analyzed data for patients treated during 2003-2008.

The aim of this study is to address the issue of overall survival in patients treated with erlotinib and to identify factors that may influence it.

Materials and methods

Patients

We reviewed the North Shore Hospital tumor registry and Monter Cancer Center medical records between 2009 and 2011 and identified 174 patients diagnosed with metastatic adenocarcinoma of the lung (MAL).

We chose the 2009-2011 interval for several reasons: in 2009 the IPASS randomized trial proved the benefit of TKIs in the treatment of patients with EGFR-mu-

tated MAL (9); also in 2009 erlotinib started to be used in the frontline setting of EGFR mutated metastatic adenocarcinoma of the lung in USA, with only two other TKIs, afatinib and gefitinib, approved in the same setting. We analyzed only patients treated with erlotinib.

A cohort of patients diagnosed with MAL during 2003-2008 was also used for comparison. 298 patients were initially identified, 79 patients were removed because of incomplete data and 219 patients were considered for analysis.

We collected the following information: age, sex, date of diagnosis, vital status, survival and treatment i.e. erlotinib, chemotherapy, surgery including type of surgery, radiotherapy including duration and organ targeted by radiotherapy, EGFR mutational status and type of mutations (when known), site of metastases: lung only, bone only, brain metastases (mets), nodal status, presence or not of bronchioalveolar histology.

Exclusions

Patients were excluded from the analysis if they did not receive any treatments i.e. chemotherapy, surgery, radiotherapy or erlotinib, or if their chemotherapy or radiotherapy treatment status was unknown. There were no patients with unknown status for surgery. 59 patients were excluded based on these criteria.

Statistical analysis

We collected descriptive statistics data for demographic factors including age at diagnosis, gender, smoking status (never, former, current), location of metastases (lung/brain/bone), EGFR mutation status, treatment regimen (chemotherapy, erlotinib, radiotherapy, surgery), radiotherapy target (brain, lung, palliative), type of surgery (lobectomy, wedge resection), bronchioalveolar histology, nodal status, survival in months, survival status (dead/alive). We used descriptive statistical methods for analysis (mean and standard deviation for continuous factors, proportion for continuous factors).

All the computations were done using a statistical analysis software (SAS). For each demographic factor given above, overall survival was estimated using the product-limit method and compared using the log-rank test. Those factors that were significantly associated with overall survival in this univariable screen ($p<0.05$) were described.

A univariate retrospective analysis was performed on 174 patients with MAL diagnosed at our institution between 2009 and 2011, and with up to a 5-year follow-up. Most patients received multiple treatment modalities. Overall survival was estimated using the product-limit method and drawing the Kaplan-Meier curves and compared using the log-rank test. Patients alive at last follow-up were censored.

Due to a limited number of patients, a multivariable Cox regression to examine the joint effects of different factors on overall survival was not performed. Backward selection was used to remove those variables that did not contribute information to the model.

Results

Demographics

Out of 174 patients analyzed, 33 patients received erlotinib, of which 13 had proven EGFR-mutated tumors. There were four statistically significant differences between the erlotinib group (N=33) and the non-erlotinib group (N=141). First, the patients in the erlotinib group were older, with a mean age of 72.4 years vs 65.5 years in the non-erlotinib group ($p=0.0327$). The second statistically significant difference between the two groups was the smoking status. The erlotinib group contained more never smokers than the non-erlotinib group 75% vs

13.5% (p<0.0001). The third statistically significant difference between the two groups was the administration of chemotherapy. 100% (33/33) of the patients in the erlotinib group received chemotherapy besides erlotinib. Only 80.9% (114/141) patients in the non-erlotinib group received chemotherapy (p=0.0062). The fourth statistically significant difference was lung surgery. Only 3% (1/33) of the patients in the erlotinib group had surgery vs 22.6% (26/141) of the patients in the non-erlotinib group.

Other factors like gender, bronchioalveolar component, nodal stage, the administration of radiotherapy, presence of lung, brain or bone only metastases were not statistically different between the two groups. The demographic data of the patients are included in Table 1.

Table 1. Demographic and Patients Clinical Characteristics

	Erlotinib n=33	Non-Erlotinib n=141	
Continuous Factors	**Mean (SD)** **Median (Q1, Q3)**	**Mean (SD)** **Median (Q1, Q3)**	**p-value***
Age	72.4 (13.9) 74.0 (61.0, 82.0)	66.5 (11.4) 67.0 (57.0, 77.0)	**0.0327**
Categorical Factors	**n (percent)**	**n (percent)**	**p-value****
Gender			
Female	21 (63.6%)	78 (55.3%)	0.3851
Male	12 (36.4%)	63 (44.7%)	
Smoking Status***			
Never	24 (75.0%)	19 (13.5%)	**<0.0001**
Former	7 (21.9%)	76 (53.9%)	
Current	1 (3.1%)	46 (32.6%)	
Bronchioalveolar Component***			
Yes	1 (3.0%)	8 (6.1%)	0.6890
No	32 (97.0%)	124 (93.9%)	
Nodal Stage***			
0	10 (32.3%)	36 (27.5%)	0.5958
1-3	21 (67.7%)	95 (72.5%)	
Lung Surgery			
Yes	1 (3.0%)	26 (18.4%)	**0.0277**
No	32 (97.0%)	115 (81.6%)	
Chemotherapy			
Yes	33 (100.0%)	114 (80.9%)	**0.0062**
No	0 (0.0%)	27 (19.1%)	
RT			
Brain	8 (24.2%)	38 (27.0%)	0.2512
Lung	1 (3.0%)	17 (12.1%)	
Other or None	24 (72.7%)	86 (61.0%)	
Lung Metastases Only***			
Yes	5(15.2%)	26 (19.0%)	0.6093
No	28 (84.8%)	111 (81.0%)	
Presence of Brain Metastases***			
Yes	11 (33.3%)	49 (35.8%)	0.7929

No	22 (66.7%)	88 (64.2%)	
Bone Metastases Only***			
Yes	5 (15.2%)	22 (16.1%)	0.8982
No	28 (84.8%)	115 (83.9%)	

* Mann-Whitney test
** Chi-square test or Fisher's exact test, as appropriate
*** sample sizes vary due to missing data

Table 2. Factors Associated with Survival in Patients with Metastatic Adenocarcinoma of the Lung

	Survival (% alive) and Associated 95% Confidence Interval at:			
Factor	**24 months**	**60 months**	**Median Survival in Months (95% CI)**	**p-value**
Treatment				
Erlotinib	42.4% (25.6%, 58.3%)	0.0%	18.8 (12.9, 37.0)	**0.0160**
Non Erlotinib	18.8% (12.7%, 25.8%)	9.4% (4.5%, 16.5%)	8.8 (7.6, 10.1)	
Gender				
Male	15.2% (8.1%, 24.3%)	0.0%	7.6 (5.9, 9.7)	**0.0019**
Female	29.4% (20.7%, 38.7%)	11.5% (4.8%, 21.4%)	14.0 (9.3, 18.8)	
Smoking Status				
Never Smoker	40.1% (25.2%, 54.5%)	5.8% (0.6%, 20.8%)	20.5 (12.9, 25.0)	**0.0463**
Current Smoker	17.5% (8.2%, 29.6%)	0.0%	8.7 (4.8, 14.9)	
Former Smoker	17.1% (10.0%, 26.0%)	12.5% (6.2%, 21.1%)	9.0 (7.0, 10.8)	
Lung Surgery				
Yes	51.9% (31.9%, 68.5%)	32.6% (14.0%, 52.8%)	28.5 (8.7, *)	**<0.0001**
No	17.9% (12.1%, 24.7%)	0.0%	9.3 (8.1, 11.9)	
Radiotherapy				
Brain	22.6% (11.7%, 35.6%)	0.0%	9.5 (6.6, 14.9)	**0.0320**
Lung	5.6% (0.4%, 22.4%)	0.0%	5.1 (4.2, 9.8)	
Other or None	26.6% (18.7%, 35.3%)	11.0% (4.9%, 19.9%)	12.5 (8.7, 15.3)	
Chemotherapy				
Yes	22.0% (15.6%, 29.0%)	0.0%	10.1 (8.7, 14.0)	0.7395
No	31.3% (14.9%, 49.1%)	19.6% 7.1%, 36.4%)	5.6 (2.7, 20.4)	
Lung Mets Only				

Yes	44.6% (26.7%, 61.0%)	29.1% (13.7%, 46.4%)	20.4 (8.3, 43.2)	**0.0054**
No	19.1% (13.0%, 26.1%)	4.0% (0.9%, 10.7%)	9.5 (8.1, 12.7)	
Brain Metastases Present				
Yes	27.4% (16.8%, 39.1%)	0.0%	12.5 (8.7, 19.0)	0.5649
No	21.8% (14.5%, 29.9%)	11.9% (6.3%, 19.2%)	9.0 (8.0, 12.9)	
Bone Mets Only				
Yes	11.1% (2.8%, 25.9%)	3.7% (0.3%, 15.9%)	9.0 (5.9, 9.8)	**0.0681**
No	26.2% (19.2%, 33.7%)	8.3% (3.0%, 17.1%)	11.9 (8.7, 14.9)	
Bronchioalveolar Component				
Yes	55.6% (20.4%, 80.5%)	37.0% (6.8%, 69.3%)	50.0 (0.43, *)	**0.0106**
No	20.8% (14.8%, 27.6%)	4.5% (1.2%, 11.5%)	9.7 (8.3, 12.7)	
Nodal Stage				
0	40.1% (25.9%, 53.9%)	17.0% (6.2%, 32.4%)	15.3 (9.7, 28.5)	**0.0083**
1-3	14.6% (8.8%, 21.8%)	7.6% (2.9%, 15.4%)	8.8 (7.8, 11.1)	

* could not be estimated, based on the pattern of the data

Factors Associated with Improved Survival

Univariate analysis of several demographic factors including; gender, treatment, smoking history, lung surgery, radiation therapy, chemotherapy, location of metastatic disease, nodal stage and bronchioalveolar histology was performed. Of these, the factors that were associated with a statistically significant survival benefit in our patients were: having undergone lung surgery, female gender, never smokers, bronchialveolar histology, and N0TNM nodal stage. There was no statistically significant association with lung metastases only, brain mets, bone mets only, chemotherapy administration. Interestingly, radiation therapy administration did not seem to improve survival. This data is summarized in Table 2.

Lung Surgery Contributes to Improved Survival in Patients Receiving Erlotinib

Interestingly, the survival analysis of the 174 patients cohort revealed that MAL patients receiving erlotinib had a statistically significant (P=0.0160) inferior LTS compared with the non-erlotinib MAL patients (Figure 1). The results were even more impressive because both the short term 24 months survival and the median survival was better in the erlotinib group: 42.4% (25.6%,58.3%) vs 18.8% (12.7%, 25.8%) and, respectively, 18.6 months (12.9-37) vs 8.6 months (7.6,10.1) (Figure 1).

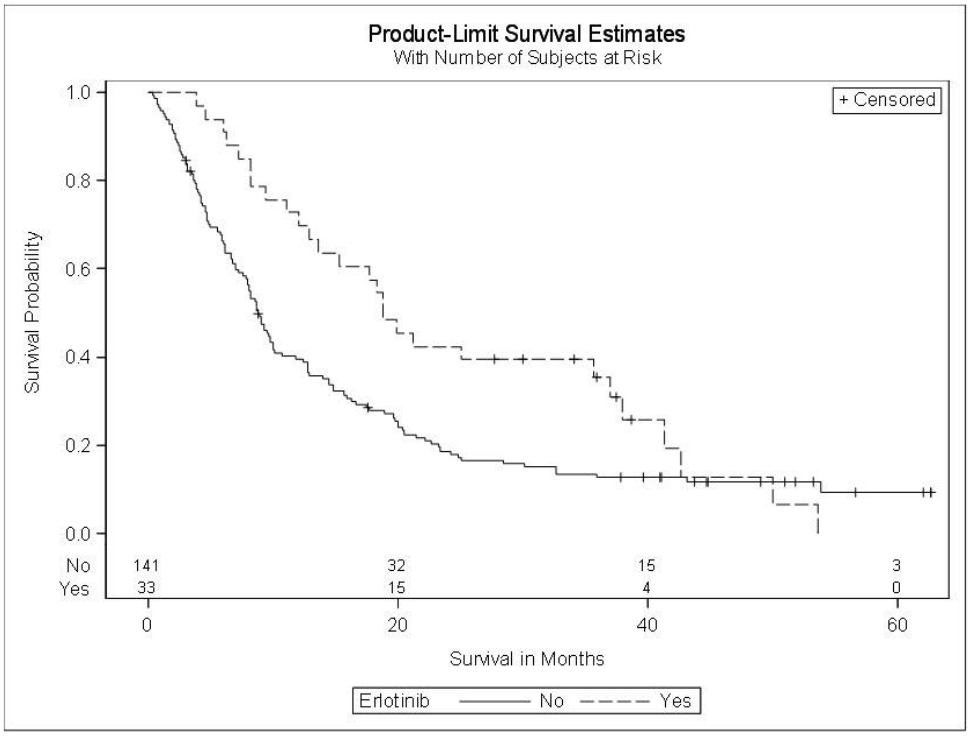

Figure 1: Summarizes the survival of patients on erlotinib therapy versus non-erlotinib therapy. At the 40-month time point, there were 4 patients observed to be alive in the erlotinib group versus 15 in the non-erlotinib group.

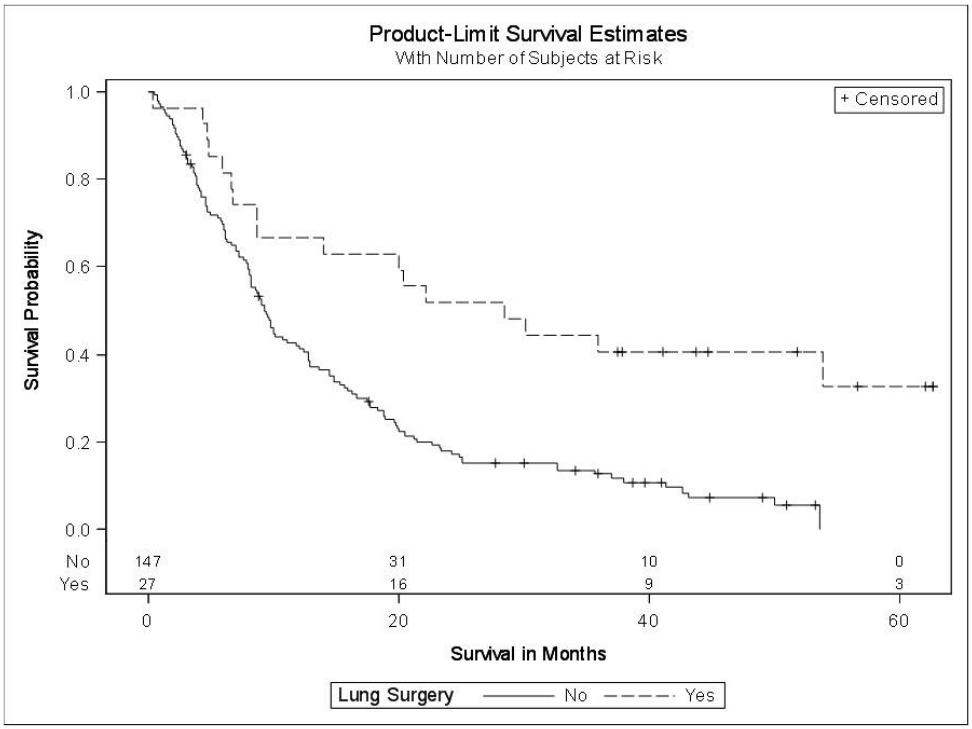

Figure 2: Summarizes the survival of patients with lung surgery versus non-lung surgery

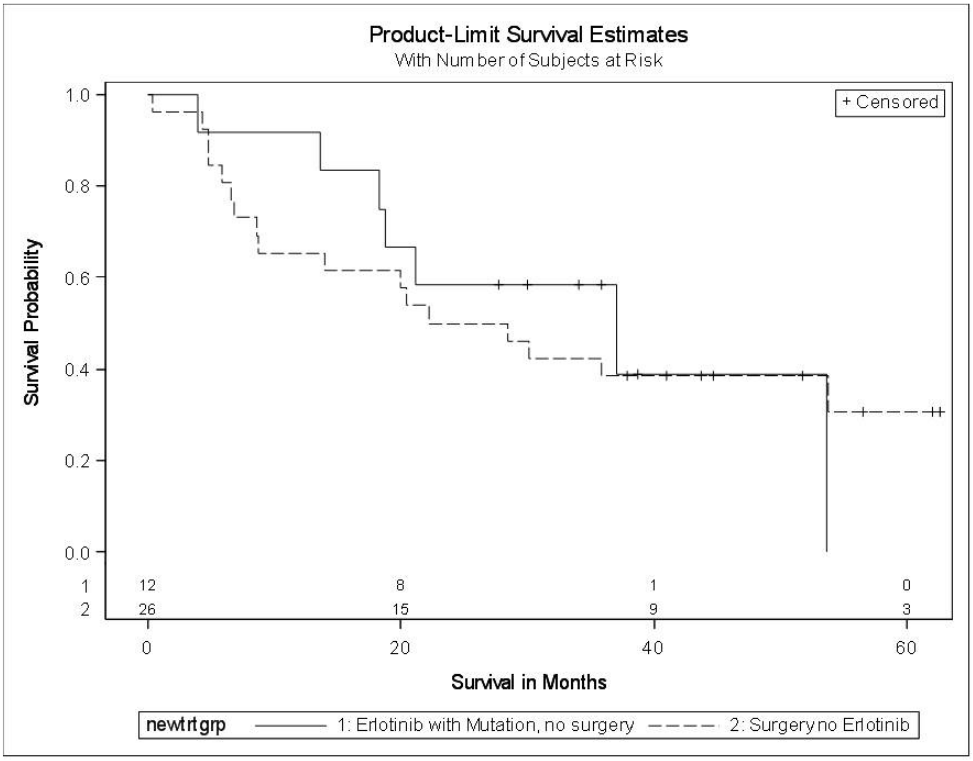

Figure 3: Summarizes the benefit of surgery versus erlotinib in patients with EGFR mutations. Given the improvement in survival with surgery, this figure compares survival benefit of surgery in the non-erlotinib group vs the benefit of erlotinib in the group of patients with tumors harboring EGFR mutations.

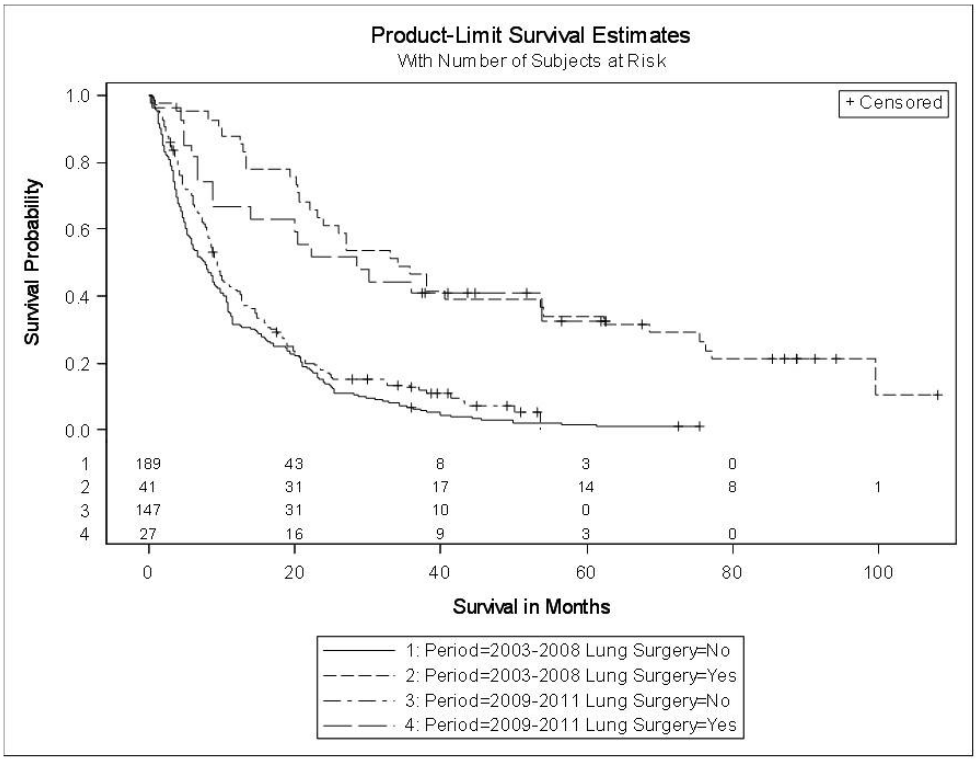

Figure 4: Kaplan Meier survival curves of lung surgery vs non-lung surgery at different time periods (2003-2008) and (2009-2011), respectively.

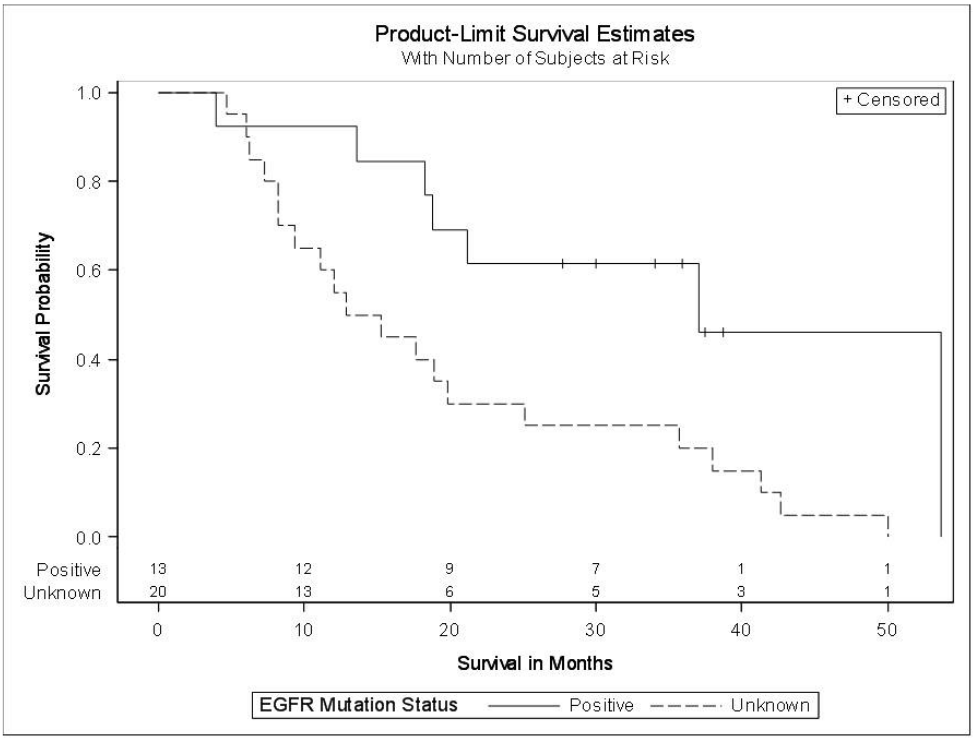

Figure 5: Kaplan Meier survival curves of EGFR mutation status positive (13 patients) vs EGFR mutation status unknown (20 patients)

Given that having had lung surgery was found to have a statistically significant effect on survival, we performed Kaplan Meier analysis of this particular group of patients as well. Patients that had lung surgery had significantly better 24 months, 60 months, and median survival than patients that did not have lung surgery. 24 months benefit was 51.9% (31.9% to 68.5%) vs 17.9% (12.1% to 24.7%). 60 months benefit was 32.6% (14.0% to 52.8%) vs 0.0% and median survival benefit was 28.5 months (8.7*) vs 9.3 months (8.1 to 11.9). This was strongly statistically significant (<0.0001). (Figure 2.)

Treatment with erlotinib was compared to the treatment with surgery particularly for the patients with EGFR mutations. The 24 months and the median survival favored the erlotinib EGFR mutated tumors group, 58.3% (27.0%, 80.1%) vs 50.0% (29.9%, 67.2%) and 37.0 months (13.6, 53.7) vs 25.3 (8.7, * could not be estimated), respectively, but the 60 months survival was favoring the non-erlotinib surgery group, 30.8% (12.8%, 50.8%) vs 0.0%. These results were not statistically significant. (p=0.8335). (Figure 3).

In order to further investigate the survival advantage brought by surgery, we also investigated a cohort of patients diagnosed with MAL between 2003-2008. The results were the same with the 2009-2011 patient cohort, with a net advantage in terms of survival at 24 months, 60 months for the patients that had lung surgery vs the patients that did not have lung surgery. The 24 months benefit was 61.0% (44.4%, 74.0%) vs 14.3% (9.8%, 19.7%), the 60 months benefit was 34.1% (20.3%, 48.5%) vs 1.7% (0.5%, 4.5%) and the median survival benefit was 34 months (22.0, 54.0) vs 7.6 months (5.7, 9.1) and again this was strongly statistically significant (<0.0001). (Figure 4).

Erlotinib Improves Survival for Patients with EGFR mutations

It is important to note that the cohort of patients receiving erlotinib included a combination of patients with (N=13) or without

documented EGFR mutation (N=20). Thus, a comparison of the survival between the patients in the erlotinib group with EGFR-mutated tumors vs the patients in the erlotinib group with unknown mutational status of their tumors was performed as well. There was a statistically significant advantage in terms of the 24 months survival for the patients taking erlotinib with EGFR-mutated tumors vs the patients taking erlotinib with an unknown mutational status of their tumors (Figure 5).

Discussion

In our retrospective cohort study the only treatment modality that significantly improved LTS was lung surgery. This is a striking finding as NCCN guidelines only considers surgery as a treatment option in MAL with isolated lesions (15). Our observations are also supported by the results of a retrospective Chinese study that reported a 5-year disease free survival (DFS) rate and an overall survival (OS) rate of 59.6% and 82.4%, respectively, in patients with multiple adenocarcinomas of the lung located either in the ipsilateral or contralateral lung that were treated with surgery (16). Also, more recently, another Chinese study (24) reported an estimated 3-year OS of 42.2% in 88 patients with metastatic lung cancer (77.3% adenocarcinomas) treated with surgery as part of a multimodality treatment plan. Univariate analysis showed age, sex, smoking history, clinical T stage, tumor histology, and site of metastases, treatment for metastases and adjuvant treatment as the major factors that were significantly associated with OS of patients ($P<0.05$). No prognostic significance was observed with respect to Charlson Comorbidity Index score, clinical N stage and extent of pulmonary resection. It is important to note that for our cohort we compared N0 with N1-3 disease as opposed to the Zhang et al. that compared N0-1 with N2-3 disease. After adjusting in multivariate analysis, only age, clinical T stage, site of metastases and adjuvant treatment remained statistically significant for prognostic prediction.

It is important to note that in our 2009-2011 cohort the majority, 67%, (18/27), of patients had a lobectomy or a pneumonectomy compared to the 2003-2008 cohort when only 43% (18/42) of patients had advanced surgery; in 2009-2011 period the majority of patients had a wedge resection with similar survival benefit. In large randomized series, lobectomy showed to have survival benefit over wedge resection, and is considered standard of care now in USA. A note of caution is needed though. Some patients in these retrospective cohorts were staged according to the TNM 6th edition. In TNM 6th edition, patients with lesions of identical histology located in a different lobe of the ipsilateral lung were considered M1, and therefore stage IV, as opposed to the TNM 7thand TNM 8theditions in which these lesions are considered T4 disease, and therefore stage IIIA/IIIB (17). Another limitation of our study is that a retrospective review of pathology and/ or molecular analysis of the resected tumors was not performed, and it is not known whether some of the lung lesions represented multiple primaries versus metastases.

It has been well established that there is a higher incidence of brain metastases in EGFR mutated MAL patients (70%) compared to EGFT WT (38%) (10). The high incidence of brain metastases in MAL patients with EGFR mutated tumors was also confirmed in the 13 EGFR mutated patients in our series. 8/13(62%) patients with EGFR-mutated tumors in the erlotinib group had brain metastases vs 48/141 (34%) patients in the non-erlotinib group. Other studies have suggested that the biology of the EGFR mutated tumors intrinsically predisposes the patients to wide spread metastases and does not allow them to have potentially curable surgery. In a report from Japan comparing patients with MAL with or without somatic EGFR-mutations, the EGFR mu-

tated group (98 patients analyzed) had a significantly greater number of metastatic lesions in the brain and bone, as compared to the wild-type group [(148 patients analyzed), brain: median (range) 3(1-93) vs 2 (1-32), p=0.023; bone: 3 (1-12) VS. 2 (1-270; P=0.035, respectively)]. In addition, EGFR mutations were significantly more frequent in patients that had multiple lung lesions compared to those that did not. The authors concluded that EGFR signaling may contribute to multiple metastases within the lung, as well as to the brain and bone (11). Thus, one confounding factor in our cohort is that the patients who ultimately underwent surgery, may have had an overall lower burden of disease, rendering them surgical candidates in the first place and having an impact on their outcomes.

Currently, surgery is not listed among the treatment choices in the metastatic lung cancer treatment guides (NCCN Guidelines, for example, reference 15). However, there have been reports of patients undergoing lung surgery in certain circumstances with improved outcomes. For example, at the opening ceremony of 16th IASCL World Conference on lung cancer that took place in September 2015 in Denver, Colorado, Emily Bennet Taylor, a metastatic lung cancer survivor, brought to the attention of the participants that surgery is an important treatment modality for some patients with metastatic lung cancer that can lead to cure in some of them, like herself. When she was 28 years old, Emily was diagnosed with metastatic lung cancer confined to the lungs and, after having an excellent response to 6 cycles of neo-adjuvant chemotherapy, she had pneumonectomy of her right lung followed by radiotherapy. Four years and a half later, she was still in complete remission and through her commitment and courage, she became an inspiration to the lung cancer patients community all over the world. There have been several retrospective studies that showed improved outcomes using an aggressive surgical management in selected patients with oligometastatic disease defined as patients who present with single organ site of synchronous or metachronous disease with no evidence of lymphatic spread (12).

Another consideration is that when lung cancer is multifocal, it is often difficult to distinguish separate lung primaries from intrapulmonary metastases. An argument favoring lung surgery in these cases is a report describing multiple different genetic mutations in multiple synchronous lung adenocarcinoma- some sensitive other resistant- to EGFR targeted TKIs (13).

A large retrospective analysis of 2094 Chinese patients treated with surgery defined as either “radical” or “palliative”, examined the difference in outcomes for 363 patients treated post-operatively with TKI and also analyzed based on the type of EGFR mutation. Overall survival in patients with EGFR exon 19 deletion was superior to that of exon 21 L858R mutations. This suggests that in patients treated with both adjuvant TKIs, there may be a difference in survival based not only on the presence of an EGFR mutation, but also on the exact type of mutation (14).

The results of our retrospective study did not provide a definitive answer to the question whether erlotinib increases LTS in patients with EGFR-mutated MAL. Recently the results of a large retrospective Chinese study suggested that an age younger than 60, absence of extrathoracic spread and EGFR TKI treatment duration of more than one year may play an important role in survival beyond five years (18).

The study of five-year survival in patients with EGFR treated with TKI by Lin et al. unfortunately did not comment on how many patients underwent surgical treatment. However, they did find that patients with no extrathoracic metastases had improved outcomes. It is unclear if this group did also have surgical interventions as part of their treatment, which may have contributed to the prolonged survival. In addition, their co-

hort was treated between 2002-2009, when TKI use and surgical approaches were somewhat different compared to after 2009, as previously mentioned.

It is conceivable that their results are more similar to what was shown by us in our 2003-2008 historical cohort (7). The main difference between our study and the study of Lin et al is the fact that we looked beyond the EGFR positivity and erlotinib use to other factors (i.e. surgery) that may impact long term metastatic lung cancer survival.

Lastly, an important limitation of our study was that the erlotinib group included both patients with and without EGFR mutation. Due to the limited number of proven EGFR mutated patients in our retrospective cohort, we are unable to determine whether or not the combination of surgery plus TKI vs. surgery alone had an impact in this group.

Conclusions

The factors associated with long-term survival in our retrospective cohort of 174 patients diagnosed with MAL between 2009-2011 were: female gender (p=0.0019), lung surgery (p<0.0001), early nodal stage (N0 disease) (p<0.0083) and bronchioalveolar histology(p=0.0106). The presence of metastatic disease localized only to the lungs was of borderline statistical significance (p=0.0054). In our patients with MAL the only treatment modality that improved LTS in a statistically significant way was lung surgery.

In 2021 the drug of choice for the front line treatment of EGFR mutated MAL became osimertinib and erlotinib is no longer used in this setting. As reported recently by Ramalingam et al. in NEJM (19) the 3 years survival in patients treated with osimertinib is 54% and it is projected that the 5-year survival of these patients is approximately 30% (20). The benefit of adding TKI post surgery in the adjuvant setting of localized lung cancer has been already established (21, 22). Also, recently as shown by a Chinese group, surgical treatment may improve survival in patients with EGFR mutated MAL treated with EGFR inhibitors that responded to the treatment (23).

As shown by another group recently (24), our retrospective study also demonstrated that it is possible to identify certain subcategories of patients with MAL that can benefit of surgery in the setting of a multimodality cancer treatment. In the future, it will be interesting to investigate in a prospective setting whether the addition of local treatment modalities (i.e. surgery or stereotactic radiotherapy) may further improve the survival of selected patients with EGFR mutated MAL treated with osimertinib.

Statements:

Author's contribution: DP contributed to the design of the study, the data analysis and the writing of the article. MR contributed to the writing of the article.

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The Impact of Oncology Rotation on Medical Students' Perception of Cancer

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Abstract

Background: Cancer is a major health concern globally, with accelerated advancements in terms of understanding its physiopathology and treatment protocols. These rapid advancements make the determination of the ideal method of educating students in Medical Oncology increasingly difficult. The purpose of this research paper is to evaluate how students from the University of Medicine and Pharmacy of Craiova, Romania perceive certain topics related to cancer and the specialty of Medical Oncology, in order to improve their education in this field.

Material & Methods: We compared questionnaires consisting of 28 scaled-response questions and one free-response question filled in by 40 students at the beginning and end of their oncology clinical rotation. The questions were assigned numerical values so that statistical analysis could be performed.

Results: After their clinical oncology rotation, students in the Faculty of Medicine had more confidence in diagnosing cancer (p=0.012), and had a better understanding of the implication of the side effects of treatment in patients who can no longer be cured (p=0.04). Students in the Faculty of Nursing were better able to understand the risks and benefits of treatment after their clinical oncology rotation (p=0.007) and had increased confidence in recognizing cancer symptoms (p=0.001).

Conclusion: The results of our study show that after clinical placement, students experienced an increase in empathy for cancer patients; correspondingly, there was an increased likelihood that students would consider oncology as a specialty in the future. Students began to recognize cancer as a chronic condition and were better able to consider the psychosocial issues after their clinical placement.

Keywords: oncology, medical students, survey, undergraduate education, career

Original Research

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Introduction

Cancer is a major health concern globally, with more than 50% of people born after 1960 developing a form of cancer in their lifetime (1).

Because modern treatments are able to prolong survival in many patients, cancer requires medical care comparable to chronic diseases. The disease is therefore managed by various health care professionals, not only those working in oncology (2). Students who will pursue careers as family practitioners, general physicians, radiologists, pathologists and surgeons will participate, to a various extent, in procedures complementary to the field of oncology, such as prevention, screening, diagnosis, and follow-up (3).

A survey conducted in the UK revealed that only 10% of newly qualified doctors felt confident managing oncological emergencies, and only 15% felt they possessed sufficient knowledge regarding chemotherapy and radiotherapy (4). Another study involving interns in Australia and New Zealand showed that two-thirds of the surveyed participants were unaware of the prognosis of certain malignancies, and that one-third felt they were unable to identify a melanoma reliably (5).

As our understanding of oncological diseases evolves and treatment protocols change, determining the ideal method of educating students in Medical Oncology becomes increasingly difficult, requiring longer periods of study for students to effectively incorporate all knowledge. By consulting with students, valuable improvements in the educational process can be made.

The discipline of 'Oncology' is taught in the Faculty of Medicine during the fifth year of study for an entire semester, which is 14 weeks long. The theoretical concepts are taught during a weekly two-hour course. This is followed by clinical rotations in the oncology departments of university hospitals. The clinical rotation is scheduled for 2 hours a week, and allows students to participate in the diagnosis and treatment of patients with malignant diseases, under the strict guidance of medical oncologists. The discipline 'Nursing Oncology' is intended for students of the Faculty of Nursing during the fourth year of study. Similarly, the subject is taught over 14 weeks, with students attending classes and participating in weekly clinical rotations.

The purpose of this research was to evaluate how students of the Faculty of Medicine and the Faculty of Nursing at the University of Medicine and Pharmacy of Craiova, Romania, perceived the treatment experience of cancer patient prior to and following their mandatory rotation in Oncology.

Material & Methods

Participants

This study included two groups of students: one group composed of 5th year medical students enrolled in the Faculty of Medicine, and a second group composed of 4th year students enrolled in the of the Faculty of Nursing, who performed their Oncology training at the University of Medicine and Pharmacy Craiova, with a clinical rotation in the Department of Oncology at 'Filantropia' Clinical Hospital in Craiova, Romania.

Study design

At the beginning and the end of their Oncology training, students were invited to fill out a questionnaire that was initially designed, piloted and conducted on third-year medical students attending a two-week rotation in oncology and palliative care in Freeman Hospital, Newcastle upon Tyne, UK (6). The questionnaire consisted of 28 scaled-response questions. Twenty-seven questions were designed using a six-point Likert scale ranging from 'strongly agree' to 'strongly disagree', while the 28th question "Would you consider a career in oncology?"

had the following answers: “Yes”, “No”, or “Maybe” (Table 1). The questionnaire also included one question inviting a free text response: “Why would you/would you not consider a career in oncology?”.

We distributed identical questionnaires to students from both faculties on the first and last day of their clinical oncology rotation, and we anonymized them by assigning a study number to each of the students who completed the questionnaire. Student participation was voluntary.

Table 1. Statements used in the questionnaire (6).

Statement number	Statement
1	I believe cancer should be approached as a chronic condition.
2	I feel death and dying are too strongly emphasized in patients with cancer, compared to other illnesses.
3	In my opinion, cancer is likely to leave the patient with significant long-term morbidity.
4	I always associate cancer with a shortened duration of life.
5	I tend to feel optimistic about the outcome of current cancer treatments.
6	I feel oncology is a depressing specialty.
7	I believe a physician should disregard side effects if the treatment will prolong life in a patient who can no longer be cured.
8	I believe when exploring what a diagnosis may mean, the physician should lead the discussion not the patient.
9	I believe physicians should place more importance on cancer management than a person’s social and psychological factors.
10	I believe patients have adequate opportunity to participate in choosing their treatment.
11	I believe clinicians are attentive to the symptoms and problems of cancer patients.
12	I believe cancer patients should be well informed about their prognosis and diagnosis.
13	I believe psychosocial aspects are adequately considered and addressed in patients with cancer.
14	I believe that information about diagnosis and prognosis can be detrimental to the patient.
15	I feel uncomfortable using the word “cancer” with patients.
16	I believe patients who can no longer be cured should be encouraged to enter clinical trials.
17	I believe clinicians deliberately avoid using the word “cancer” when dealing with patients.
18	I believe patients receive unacceptable toxicity in relation to benefit they gain when receiving systemic chemotherapy.
19	I believe all anti-cancer treatment should improve quality of life.
20	I believe discussion and implementation of end-of-life care has a positive impact.
21	I believe multidisciplinary team involvement is advantageous to individual patient care.
22	I believe all anti-cancer treatment should prolong life.
23	I feel confident in my ability to break bad news to patients.
24	I am aware of complications of management of cancer.
25	I feel confident in recognizing red flag symptoms.
26	In my opinion palliative care and cancer should be taught separately in the curriculum.
27	I feel confident in making a diagnosis of cancer.
28	Would you consider a career in oncology?

Data Analysis

The questionnaires were paired using candidate numbers. Numerical values from 1 to 6 were assigned to the first 27 questions, for 'strongly disagree' to 'strongly agree', respectively. The 28th question was assigned numerical values from 1 to 3. We performed data analysis using descriptive statistics and analysis of variance. The responses to the qualitative question were reviewed both individually and together, to identify recurrent themes.

Results

In total, 40 students participated in the study: 15 students from the Faculty of Medicine and 25 from the Faculty of Nursing.

The mean of the responses to the first 27 questions, before and after the clinical placement, are displayed in Figures 1 and 2.

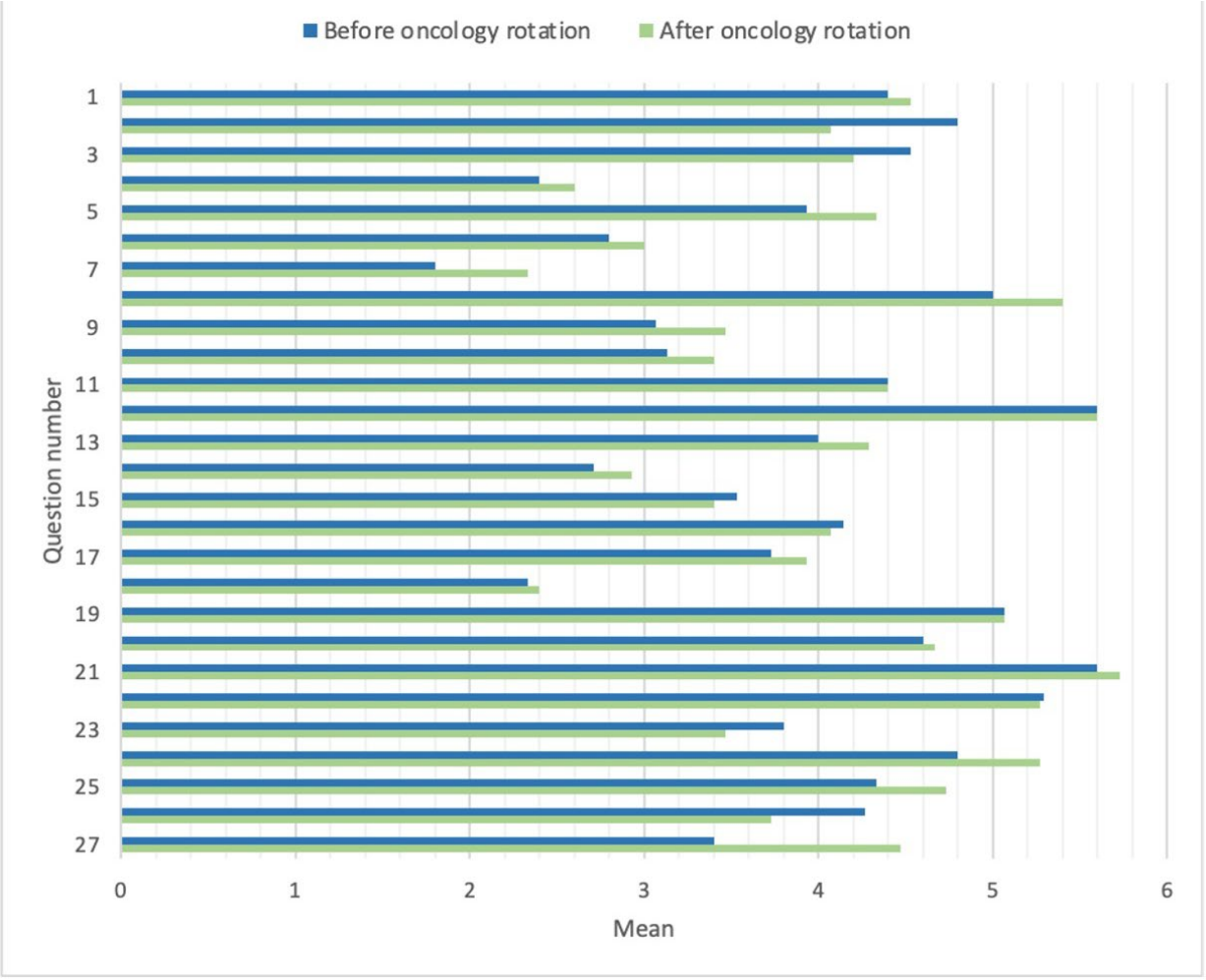

Fig. 1: Responses to the first questions before and after clinical placement – Faculty of Medicine

Faculty of Medicine

15 participants completed the survey: 60% were female (n=9) and 40% were male (n=6). The most striking differences between students were in student confidence in diagnosing cancer (p = 0.023, question 27) and in the manner they perceived side effects of treatment in patients with incurable cancer (p = 0.04, question 7). After the oncology rotation, students strongly agreed (mean = 4.47) with the statement, "I feel confident in making a diagnosis of cancer" when compared to their

responses prior to the rotation (mean = 3.5). Before the rotation, medical students were less likely to believe a physician should disregard side effects in patients who cannot be cured (mean=1.8), than after the rotation (mean = 2.33).

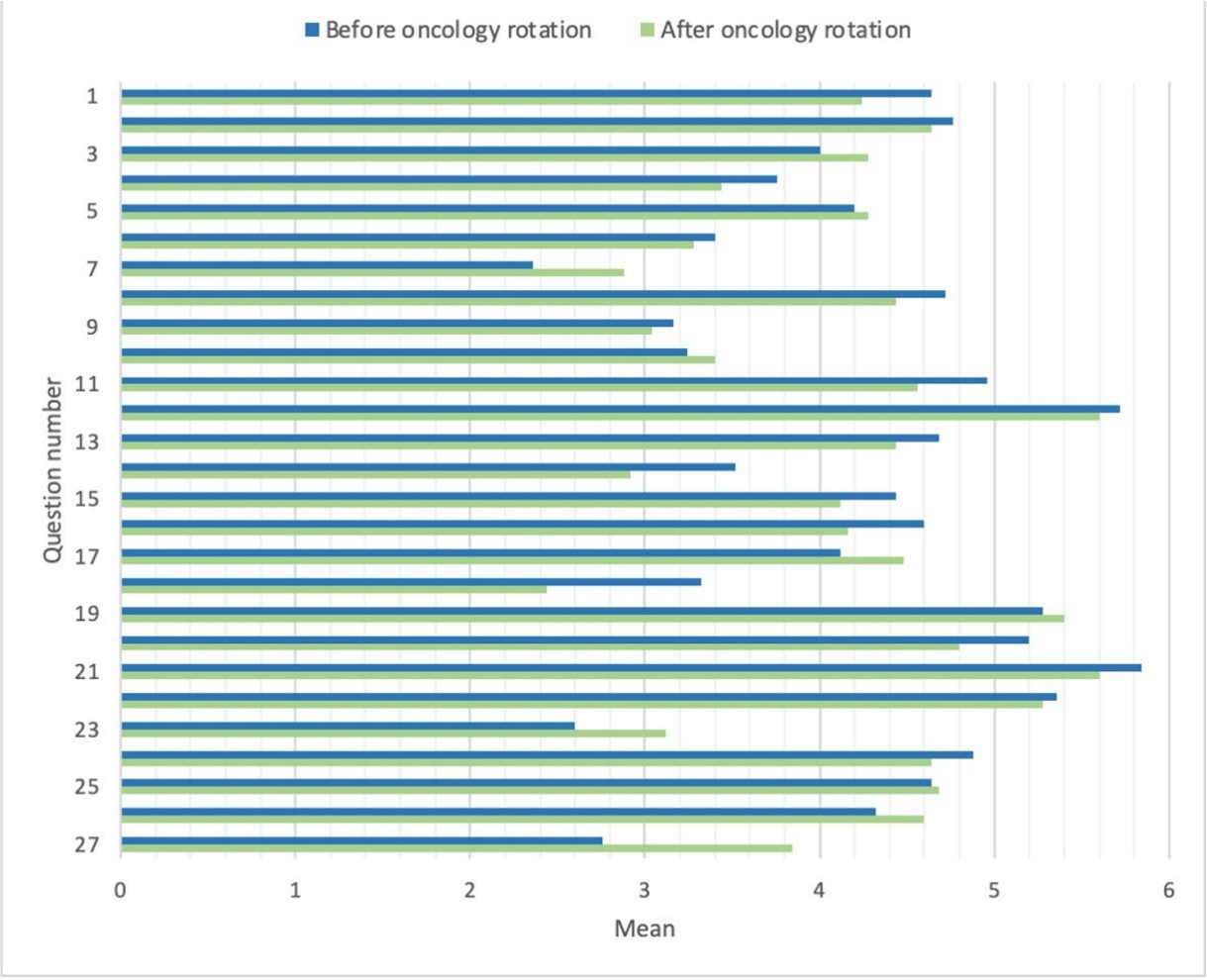

Fig. 2: Responses to the first 27 questions before and after clinical placement – Faculty of Nursing

The strongest areas of agreement among responders were that patients should be well-informed about their prognosis and diagnosis, that the involvement of the multidisciplinary team is beneficial for individual patient care, and that palliative care can have a positive impact on the patient and the family. Similarly, both during and after the rotation, students did not agree on whether they always associated cancer with a short lifespan.

Prior to oncology training, five students at the Faculty of Medicine stated that they would consider a career in oncology, two stated that they would not, and 8 were undecided. After the oncology rotation, eight students said they would consider a career in oncology, one said they would not, and six remained undecided (Figure 3).

Reasons students cited for interest in the specialty of Medical Oncology included the opportunity to work in a multidisciplinary team, and the ability to provide treatments and perform research that can have a major impact on patients' lives. The most common reasons for the lack of interest in the specialty were the difficulty in managing the multitude of symptoms, and the challenge of the psychosocial and spiritual complexity of cancer patients.

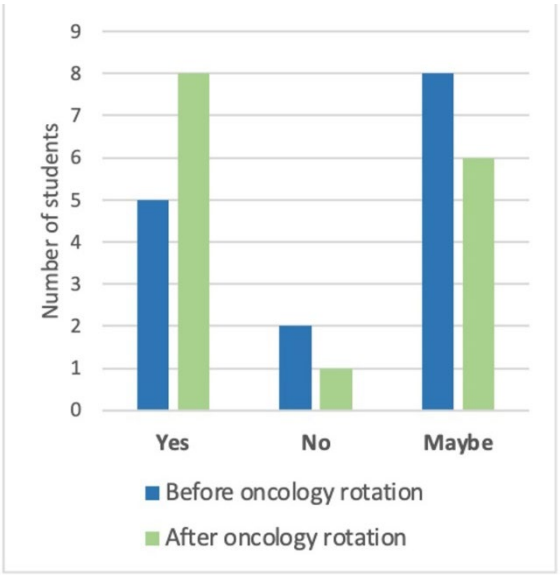

Fig. 3: Responses to question 28 – Faculty of Medicine

Faculty of Nursing

Twenty-five participants completed the survey: 88% were female (n=22) and 12% were male (n=3).

The most significant changes were in students' improved understanding of the benefits of chemotherapy post-clinical rotation (p = 0.007, question 18) found in question 18 (mean before = 2.44, mean after = 3.32; p=0.007) Furthermore, students reported greater confidence in their ability to recognize cancer (question 27, p=0.001) after the clinical rotation (mean=3.84) when compared to before (mean=2.76).

Like the students in the Faculty of Medicine, students in the Faculty of Nursing strongly believed that cancer patients should be informed about their prognosis and diagnosis, that cancer treatment should improve the patients' quality of life, and that the involvement of a multidisciplinary team is advantageous for individual patient care.

Prior to oncology training, one student stated that they would consider a career in oncology, nine students were opposed, and fifteen were undecided. After the training, eight students said they would consider a career in oncology, five said they would not, and twelve remained undecided (Figure 4).

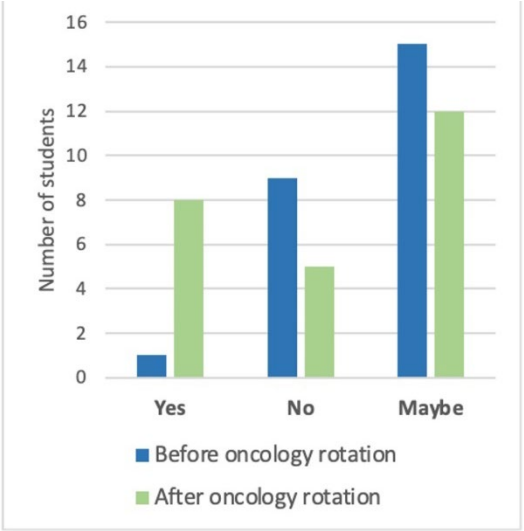

Fig. 4: Responses to question 28 – Faculty of Nursing

The main reasons to select oncology as a career in nursing were the ability to developing-term relationships with patients and their families, and the gratitude expressed by patients. The most common justification for lack of interest in the specialty was that oncology care can be "too depressing" or "an emotional burden".

Discussion

The increase in the aging population in developed countries contributes to the increase in the number of people that will be diagnosed and treated for cancer in the coming decades (7).

Our results show an increase in medical and nursing students' empathy for cancer patients following a clinical rotation in oncology and that specific training in oncology influences students' desires to pursue a career in oncology. Likewise, a study conducted at another institution analyzed the impact of a preclinical oncology course on medical school students and found that clinical training increased empathy towards cancer patients as well as the likelihood of stu-

dents considering oncology as a profession (8). Furthermore, research suggests that students who receive more information about cancer treatment are more likely to have a positive attitude towards treating cancer patients (9). Similarly, we found that, after completing the clinical rotation, students felt more comfortable talking to cancer patients about both physical and psychosocial problems, including death. Students from both faculties gained confidence in recognizing cancer signs and symptoms, as indicated by the significantly different responses to question 27 (Faculty of Medicine, p=0,012; Faculty of Nursing, p=0,001) provided prior to and after clinical placement.

The results of our study show that all students strongly believe that patients should be informed about the diagnosis and prognosis of their disease. An international study has shown that most adults - healthy people, as well as cancer patients from different countries - have expressed a desire to be fully informed about the details of their health condition (10). Prior to 1960, most American physicians did not disclose the truth about their diagnosis to cancer patients (11). In the last two decades, most physicians in the United States and Northern Europe report that they usually fully inform cancer patients about their illness (12). Paradoxically, only a few doctors in these countries tell patients the full truth about the prognosis of their disease. There is also little data on whether physicians respect the wishes of educated patients to be fully informed.

A study contrasted medical and law students' perspectives about informing a cancer patient (who wishes, or alternatively, who does not wish to be told the truth) about diagnosis and prognosis (13). All students equally agreed to fully inform the patient about his diagnosis. However, a smaller percentage of medical students compared to law students agreed to share prognostic information if the patient wanted it ($p = 0.0003$). Notably, more law students than medical students supported disclosing the patient's diagnosis (35% vs. 11%; $p = 0.0004$) and prognosis (26% vs. 7%; $p = 0.0001$) despite the patient's explicit request not to be informed. Disparities in attitudes toward information-giving (between law and medicine students) were a consequence of divergent assessments of whether the information will serve or hurt the patient. Medical students stated that their decisions regarding informing patients were impacted by the belief that physicians should respect the autonomy of their patients. However, law students stated deontological grounds more frequently than medical students, which allude to legal obligations, the avoidance of harm, and veracity. Those findings imply that more future physicians than future lawyers make a distinction between revealing the diagnosis and fully disclosing a dismal prognosis.

It is commonly expected that students will be able to work effectively in a team, withstand the rigors of a medical unit, understand the suffering caused by illness, and increase society's confidence in the healthcare system through their behavior. The results of our questionnaires show that after their clinical oncology rotation, students began to understand not only the chronic nature of cancer, but also the resulting psychosocial issues and the adverse effects of treatment. The strongest areas of agreement were that patients should be adequately apprised of their prognosis and diagnosis, that decision-making and subsequent treatment should involve a multidisciplinary team, and that palliative care can benefit the patient and family. Furthermore, the results of our study demonstrate that after clinical placement, there is an increased likelihood that students will pursue a career in oncology.

Conclusions

Our research shows that a clinical oncology rotation is correlated with a shift in students' knowledge and attitude towards oncology.

Statements:

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SBRT as Salvage Re-irradiation for Isolated in Field Regional Relapse after Bilateral Breast Cancer – a Case Report

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Abstract

Stereotactic body radiation therapy (SBRT) is a type of radiotherapy which, uses a high radiation dose delivered in a single or a few fractions and is employed with local curative intent for early-stage cancer, relapsed cancer or in the oligometastatic setting. The aim of this case report is to illustrate the potential of this technique in the salvage re-irradiation of a late isolated in field regional relapse after bilateral breast cancer.

This is the case of a 65-years-old woman with metachronous bilateral breast cancer (left side-1998, stage IIB, Luminal type; right side-2010, stage IIA, Her2 positive) who received both chemo- and endocrine systemic therapy, underwent surgery and was irradiated on both sides, with a late solitary recurrence in her left internal mammary node chain (2018) treated by SBRT re-irradiation (40 Gy in 5 fractions).Three years after salvage SBRT, under treatment with Palbociclib+Letrozole and thorough follow-up protocol, she is still in clinical complete remission, with a normal CA 15-3 and metabolically inactive residual mass on PET-CT, negative for malignancy on a recent biopsy.

SBRT is becoming a hallmark of oligometastatic disease management and can be invaluable in patients subjected to prior radiotherapy.

Keywords: SBRT, breast cancer, re-irradiation, oligo-recurrent

Clinical Case Reports

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1. Introduction

Stereotactic body radiation therapy (SBRT) is a hypo-fractionated intensity modulated, highly conformal type of external beam radiotherapy which, combines concepts of tight margins, high dose fall-off, motion control and image-guided delivery. As the tumor receives a very high dose per fraction in a limited number of sessions, it has become a preferred approach for the treatment of primary early-stage cancer, especially in the elderly (1,2), oligometastatic disease (3,4) or relapse, as a salvage solution inside or outside a previously irradiated area (5).

2. Case report

2.1 Clinical history

This is the case study of a long-term cancer survivor, now a 68-year woman, with a positive family history of hereditary malignancy (grandparents - gastric and genital cancers), diagnosed with a metachronous bilateral breast cancer and with a recent oligo-recurrence in the left internal mammary nodes chain. She survived stage II B, Luminal type, G2 left breast invasive ductal carcinoma in 1998, for which, she received 6 cycles of Epirubicin - Cyclophosphamide, a left modified radical mastectomy (MRM) and adjuvant 2D radiotherapy (RT) and endocrine therapy (Tamoxifen for only 2 years due to poor tolerance).

Contralateral breast cancer of a different biology was diagnosed 12 years later, as a G3 Her2-positive invasive ductal carcinoma. She underwent upfront surgery (right MRM) in 2010, pT2N0M0L0Pn1, stage IIA, followed by 6 cycles of adjuvant Paclitaxel, 3D conformal RT and Trastuzumab for one year, but no adjuvant endocrine therapy, which, was declined. The patient remained free of disease at the following regular visits.

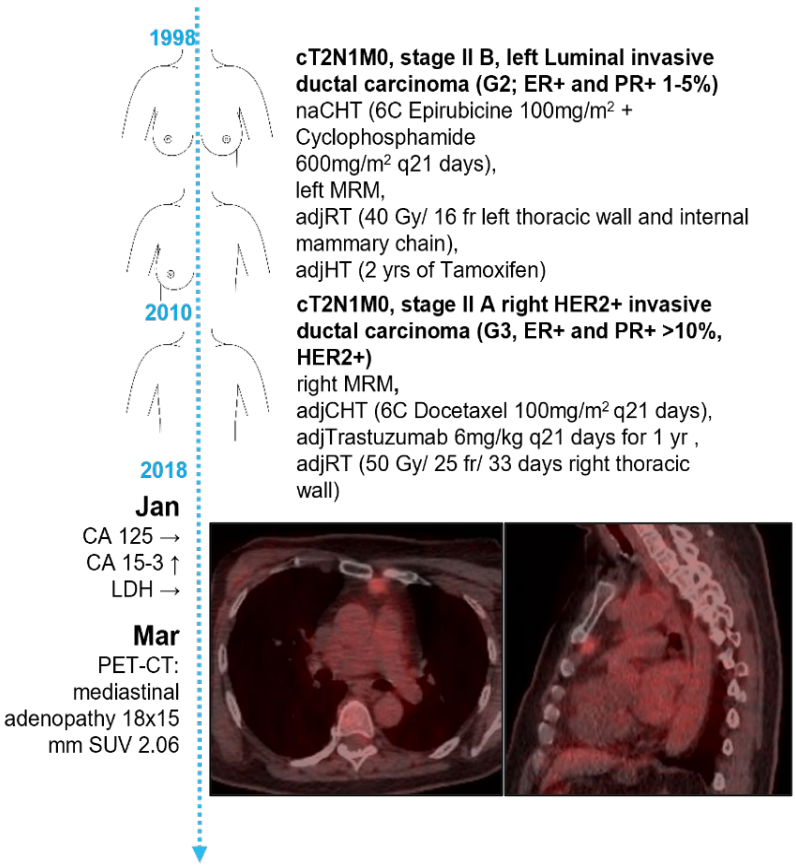

Fig.1: Timeline of disease and therapy

Eight years later, in January 2018, a sudden rise in CA 15-3 level (=51.34 U/mL) prompted a new PET-CT, which, described an upper left internal mammary node (IMN) of 18x15 mm, metabolically highly suspicious of metastasis (timeline in Fig. 1).

A couple of weeks later, a contrast-enhanced, thoracic CT scan showed a growing left parasternal mass in the 2nd left intercostal space measuring 21 mm. An ultrasound-guided biopsy was recommended for the assessment of tumor biology, but it was declined by the patient, as well as any invasive resection procedure, due to potential risks related to the proximity of major blood vessels.

2.2 Treatment description

This left IMN was considered a solitary late recurrence (oligo-recurrence) (6), 20 years after her initial left-sided cancer. The 1998 RT full dosimetry could not be retrieved, the only available information being that she received 40 Gy/16 frwith 2 thoracic tangential fields plus an anterior axillary and supraclavicular field, all delivered by a Theratronics 100 Cobalt machine. Considering the skin late visible toxicity (telangiectasia) and the in-house protocol at that time in the institution where she received RT, we estimated that the left IMN received between 20 and 40% of the prescribed dose. SBRT was proposed in the Multidisciplinary Tumor Board. A 4D-CT simulation was performed in supine position, with acquisition of 3-mm slice sections. The target volume was defined as gross tumor volume (GTV) and its different positions relative to breathing phases (0%, 25%, 75%, 100%) were integrated into an internal target volume (ITV). A 5 mm ITV to planning target volume (PTV) margin was generated. Forty Gy were prescribed to the PTV 80% isodose and delivered every-other-day in 5 fractions by intensity-modulated radiation therapy (IMRT) step and shoot, 6 MV, by an Elekta Infinity linear accelerator (LINAC) with an Agility 5 mm multileaf collimator (MLC). Image-guided radiation therapy (IGRT) with cone beam CT was used for every treatment session. The heart, large vessels, left and right lungs, spinal cord, spinal canal, chest wall and skin were defined as organs at risk and were kept within dosimetry constraints. Excellent coverage of the target volume was obtained (ITV V40=100%, PTV V40= 90.22%), while the heart, left and right lungs were optimally spared, with a mean dose of 2.8, 2.4 and 2.1 Gy, respectively. The spinal cord received a negligible dose. The great vessels and chest wall were kept within constraints (Fig. 2). After completion of SBRT, the patient accepted and started a CDK4/6 inhibitor (Palbociclib 125 mg po qd-for days 1-21/28) and endocrine therapy with Letrozole 2.5 mg po qd.

2.3 Follow up and Results

No acute toxicity whatsoever was recorded during SBRT or in next 3 months (G0 Common Terminology Criteria for Adverse Events - CTCAE 4.0) - the patient was clinically asymptomatic and without any changes at the irradiation site. She was followed at every three months with clinical exam, contrast enhanced CT and CA 15-3 for two and a half years. CTs showed a regressive scar lesion, with no symptoms or signs of radiation fibrosis in the vicinity. Yearly PET-CT showed no pathological uptake. In February 2021 the clinical examination identified a left parasternal mass that elicited a biopsy, which, proved negative for malignancy. As of her last PET-CT in August 2021, the patient has been free from disease and continues the treatment with Palbociclib and Letrozole.

3. Discussion

This case is particular for several reasons. Firstly, because of the timing and topography of an isolated oligo-recurrence after a bilateral metachronous cancer, in a

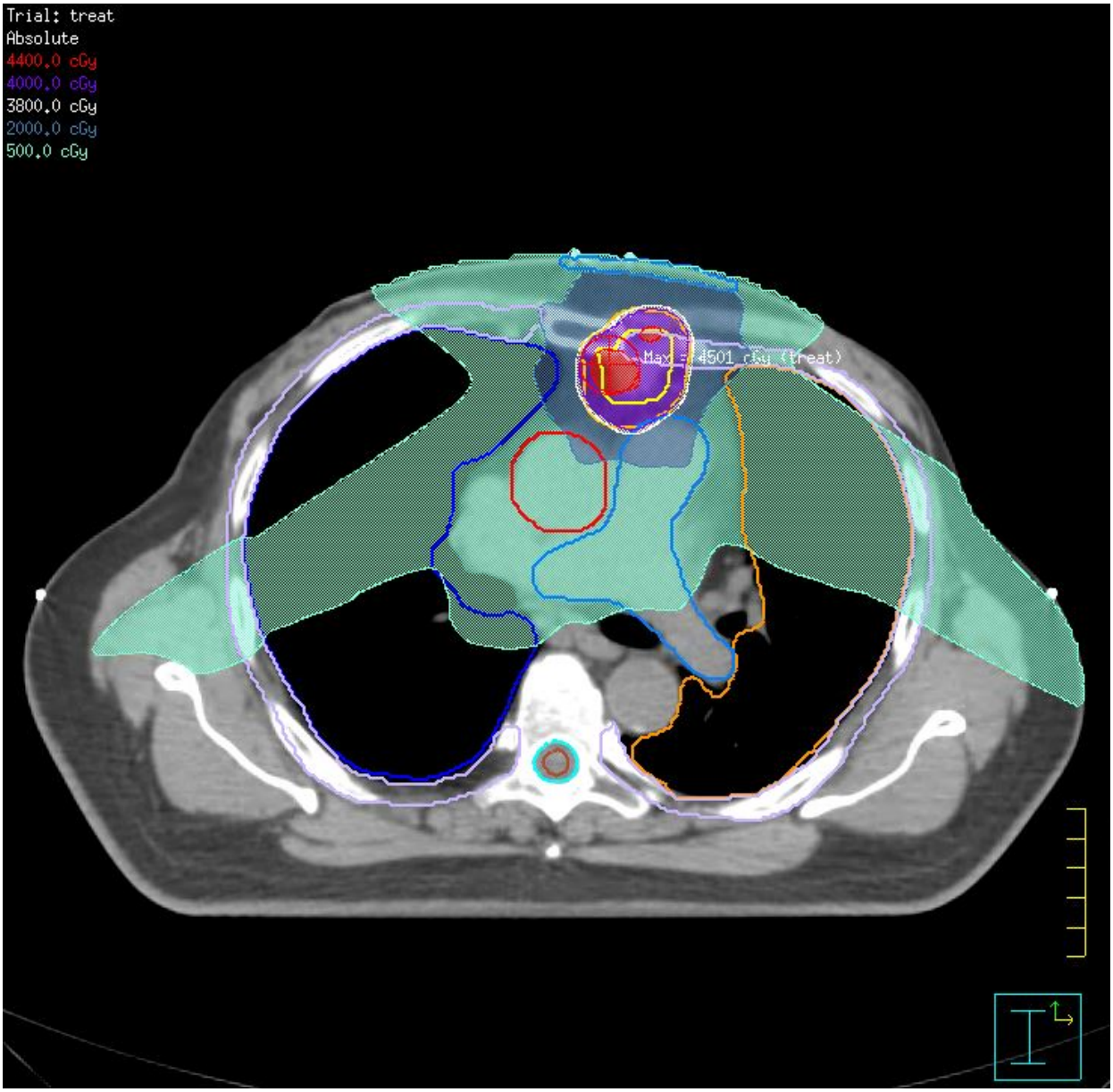

Fig. 2: Isodose lines and maximum dose point (Max), target volumes, and organs at risk

previously irradiated area. Secondly, because of the delicate situation with lack of accurate previous dosimetry available, and finally, from the dire perspective of virtually no available local ablative options (surgery, radio-frequency ablation, or cryotherapy were not suitable due to the endothoracic position and the proximity of major vessels). Since the precise biology of this recurrence was not known, a left breast cancer origin was more probable, although the Her2+ biology did not exclude a contralateral origin as a 'true' metastasis.

In the light of the new consensus on the characterization and classification of oligometastatic disease by Guckenberger et al., this patient can be described as having genuine, de-novo, metachronous oligo-recurrence (6). Since there were no other metastases, a less aggressive biology of the tumor was warranted, which, made the patient an ideal candidate for aggressive local radical treatment.

Recurrence in the IMN is rare at 1.5% but the intrathoracic topography of IMN limits conventional ablative approaches such as surgery, at least among gynecology and

breast surgical oncologists. The literature regarding IMN excision is rather scarce (7). On the other hand, SBRT seems to be a matched pair for oligometastatic disease in modern Oncology. Available studies tend to gather oligometastases of different primary origins and to different sites. SABR-COMET trial, the icon of ablative treatment in oligometastatic disease, showed a 5-year OS rate of 42.3% in the experimental ablative treatment arm versus 17.7% in the standard of care arm (4). Twenty percent of the ablative treatment arm were patients with breast cancer. In Lehrer's et al. meta-analysis on the safety and survival associated with ablative stereotactic radiotherapy for patients with oligometastatic cancers, 13.1% of these were breast cancer patients [8]. Safety can be of real concern in such re-irradiation settings as the above (potential serious skin, lung, chest wall and heart toxicity because of prior irradiation), where dosimetry and patient chart from previous irradiation were difficult to retrieve.

Table 1. Summary of studies employing SBRT for the treatment of oligometastatic disease in breast cancer which, include metastasis to the IMNs

Study	**Patients (lesions no)**	**Type**	**Site of metastases (no of lesions)**	**Therapy (dose)**	**Outcome**	**Toxicity**
Trovo M, et al., 2017 [9]	54 (92)	Prospective phase II multicentric trial	Bone (60) *Lymph nodes (23)* Lung (4) Liver (5)	SBRT*/IMRT (35-40Gy in 3 fr/60 Gy in 25 fr)	1-y PFS 75% 2-y PFS 53% 2-y LC 97% 2-y OS 95%	no ≥ G3 2 pts G2 (pain and fatigue)
Milano MT, et al., 2012[12]	39 (47)	Prospective	Lung (11) *Thoracic lymph nodes (9)* Liver (13) Pelvis/abdomen (2) Brain (1) Bone (11)	SBRT (mostly 50Gy in 5 fr)	2-y OS 74% 2-y FFDM 52 % 2-y LC 87% 6-y OS 47% 6-y FFDM 36% 6-y LC 87%	no ≥ G4-5 1 pts G3 (non-malignant pleural and pericardial effusion)
Milano MT, et al., 2009[13]	40 (85)	Prospective pilot	Liver (33) Lung (19) Bone (17) *Thoracic lymph nodes (14)* Pelvic/abdominal lymph nodes (2)	SBRT (N/A)	4-y OS 59% 4-y PFS 38% 4-y LC 89%	N/A

*Preferred treatment, PFS - progression free survival, OS - overall survival

The addition of radical radiation therapy for breast oligometastases on top of the systemic treatment almost doubled the currently described 2-years PFS of 30% (PFS 53%), with 2-years local control (LC) and overall survival (OS) > 90% [9]. There are extremely few studies of SBRT exclusively for breast cancer, and even less dealing specifically with lymph nodes oligo- recurrence (Table 1) [10]. The phase IIR/III trial NRG BR002 (NCT02364557) was designed to compare standard of care therapy ± SBRT and/or surgical ablation for newly oligometastatic breast cancer. As a side note, by including a Translational Research approach in its design, it could ingeniously set the stage for the future [11].

Lastly, this case also emphasizes the problem of adherence to endocrine treatment. This is generally grim, with up to 1/4 patients enrolled in clinical trials and 3/4 patients in community practice settings who prematurely discontinue adjuvant endocrine therapy, mainly because of poor manage-

ment of side effects [14]. This greatly diminishes the advantages offered in terms of reduced risk of locoregional and distant failure, or death from breast cancer [15].

4. Conclusion

Radiation Oncology underwent dramatic technological and conceptual development, with SBRT as a safe and effective approach of re-irradiation. This case tells the story of radiotherapy in brief, from Cobalt machines, conformal radiotherapy to one of the most sophisticated means of radiation delivery, namely SBRT, as an efficient, safe, and curative in intent option for isolated recurrences, even in previously irradiated areas.

Abbreviations:

SBRT – Stereotactic Body Radiation Therapy
PET-CT – Positron Emission Tomography - Computed Tomography
CA-15-3 – Cancer Antigen 15-3
MRM – modified radical mastectomy
RT – radiotherapy
IMN – internal mammary nodes
GTV – gross tumor volume
ITV – internal target volume
PTV – planning target volume
IMRT – intensity-modulated radiation therapy
LINAC – linear accelerator
MLC – multileaf collimator
IGRT – image-guided radiation therapy
CBCT – cone beam CT
CTCAE – Common Terminology Criteria for Adverse Events
PFS – progression free survival
OS – overall survival

Statements:

Author's contributions:TP wrote the paper, NS provided the technical details, CI detailed the history of the patient, AC and DE reviewed the paper, TP reviewed and approved the final version.

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Statement of Ethics: The accompanying manuscript does not contain any studies carried out by the authors on humans or animals.

Ethical Approval: The treatment strategy/study protocol was approved by a local tumor board/ethics committee.

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A Possible Abscopal Effect of Radioimmunotherapy in a Patient with Advanced Oligometastatic Adenocarcinoma of the Lung

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Abstract

Two randomized phase III studies provided cumulative long-term results, comparing second line treatment with Nivolumab versus Docetaxel in advanced non-small cell lung cancer (NSCLC). With the advances in modern immunotherapy (IO), the potential for even more immune activation by radiation therapy, inducing tumor specific immunity led to a novel role for radiotherapy in systemic disease.

This case study evaluates the benefit of second line immunotherapy with Nivolumab, a PD-1 checkpoint inhibitor, and hypofractionated radiotherapy, in a patient with advanced oligometastatic adenocarcinoma of the lung, with progressive disease after first line chemotherapy, and the analysis of a possible abscopal effect. A50-year-old male, heavy smoker with a 30 years-pack index, presented with a history of left posterior thoracic pain. MRI identified an osteolytic lesion on the 10th rib and a CT scan showed an additional 25 mm nodule in the left upper lobe (LUL) and a 7mm nodule in the left lower lobe (LLL). Resection of the lung nodules and of the osteolytic lesion of the rib were performed. The pathological examination revealed a G2 adenocarcinoma of the lung (ALK and EGFR negative) pT4NxpM1 with metastases in the rib and pleura, with unspecified margins. Chemotherapy was administered, with complete response on imaging after 6 cycles of Gemcitabine/Carboplatin, and hematologic toxicity. After seven and a half months a regional and distant progression of the disease with metastases on the 7^{th} and 10^{th} rib was revealed on PET-CT. Palliative hypofractionated radiotherapy was administered with a dose of 20 Gy/ 5 fr to the painful 7^{th} rib metastasis and the patient started second line treatment with Nivolumab, 240 mg iv q2wks. Three years later, at his last follow-up in November 2021, the patient maintains a PET-CT complete response, with no adverse events.

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Hypofractionated radiotherapy in combination with Nivolumab, an immune check-point inhibitor-(ICI) in second line treatment, in a pretreated patient with stage IV adenocarcinoma of the lung, led to a durable complete response and 36 months progression-free survival. A possible abscopal effect may be suspected in this case.

Keywords: radioimmunotherapy, NSCLC, immune check-point inhibitor, abscopal effect

Introduction

Lung cancer is the most common cancer, with 2,206,771 new cases and 1,796,144 deaths reported in 2020 in both sexes and all ages (1). NSCLC represents 80% of all cases and 40% are at advanced stages (2).

In two phase III studies, CheckMate 017[3] and CheckMate 057 (4,5), Nivolumab, a programmed death-1 (PD-1) inhibitor antibody, improved overall survival (OS) versus (vs) Docetaxel, the standard second line treatment, in pretreated advanced NSCLC. Preclinical and clinical studies demonstrated the potential for even more immune activation by radiation therapy, inducing tumor specific immunity and immunogenic cell death, defining thus a new role for radiotherapy in systemic disease (6, 7, 8).

Case report

The aim of this case study was to evaluate the benefit of second line immunotherapy with Nivolumab, a PD-1 checkpoint inhibitor, and palliative radiotherapy in a patient with stage IV adenocarcinoma of the lung with progressive disease after first line chemotherapy and also to investigatea possible abscopal effect.

The patient in our study is a 50-year-old male, heavy smoker with 30 pack-years index and 13 years of professional exposure to ore dust. The patient underwent gastric ulcer resection in 1994, and had a history of a left posterior thoracic pain from January 2017, with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 1. In June 2017 an MRI identified an osteolytic lesion on the posterior arc of the 10th rib that was confirmed by CT scan (Fig.1). In addition, a 25 mm nodule in the LUL, with spicules towards the mediastinal pleura (Fig. 2) and a 7 mm nodule in the superior segment of the LLL, at the medial extremity of the interlobar cleft (Fig. 3). No pathological lymph nodes or signs of metastatic disease in the upper abdomen were detected. Resections of the nodules and resection of the osteolytic lesion of the rib were performed in August 2017.

The pathological examination revealed a G2 adenocarcinoma of the left lung, with positive immunohistochemistry for thyroid transcription factor (TTF1) and CK7 and negative for CK20 and Napsin A, pT4 (nodules in different lobes), pNx (no lymphadenectomy performed), pM1 (metastases in the rib and pleura), Rx (with unspecified margins). No EGFR mutations or an ALK translocation were found. At that time there was no opportunity for programmed cell death-ligand 1 (PD-L1) testing. Chemotherapy with Gemcitabine and Carboplatin was administered for 6 cycles between June 2017 and January 2018, with hematologic toxicity after the 2nd cycle, but prophylactic administration of growth factors ensured the completion of the next cycles according to the protocol. A complete response was confirmed on PET-CT in February 2018. (Fig. 4,5,6)

There was a debate whether to offer radiotherapy, the status of surgical resection margins was unknown. Further follow-up was decided taking into consideration the advanced stage IV, the surgery that had a rather exploratory and biopsy role and the presentation with no symptoms.

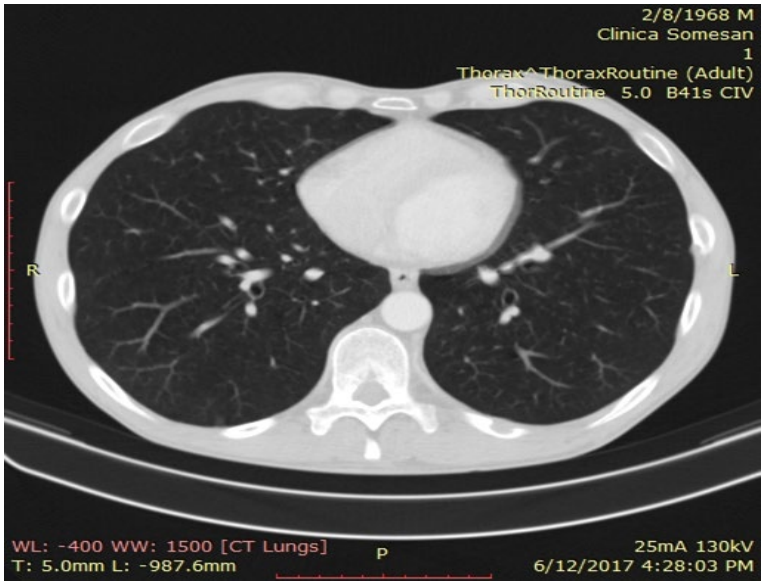

Figure 1: CT scan: Osteolytic lesion on the posterior region of the 10th rib

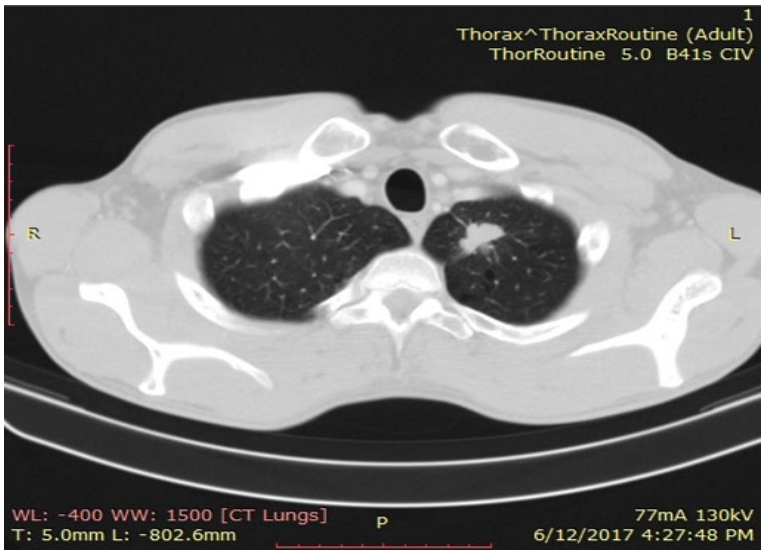

Figure 2: CT scan: a 25 mm nodule in the LUL, with spicules towards the mediastinal pleura

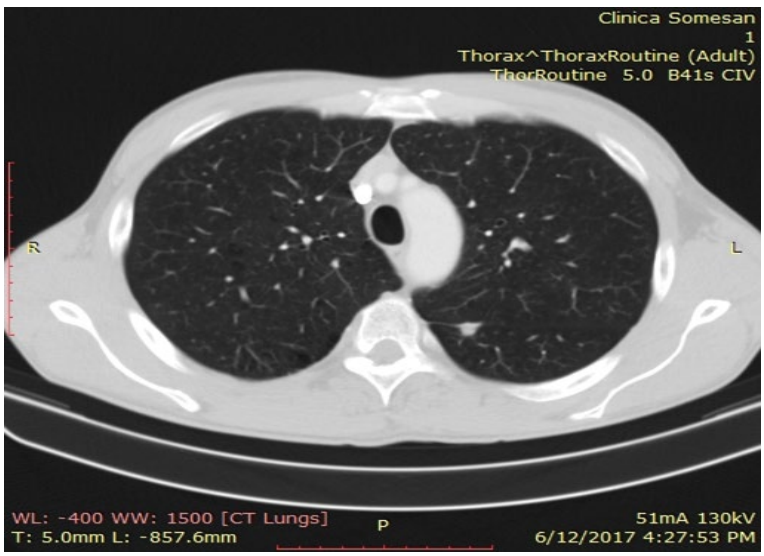

Figure 3: CT scan: a 7 mm nodule in the superior segment of the LLL

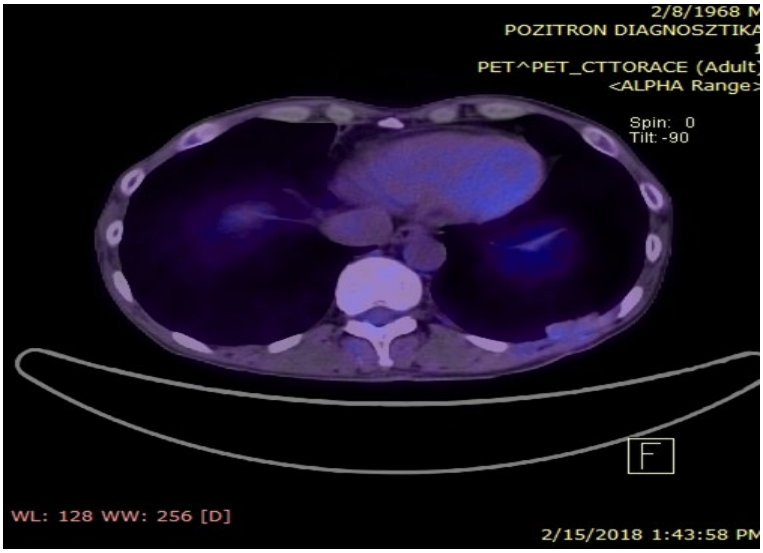

Figure 4: PET-CT (15.02.2018): Complete Response

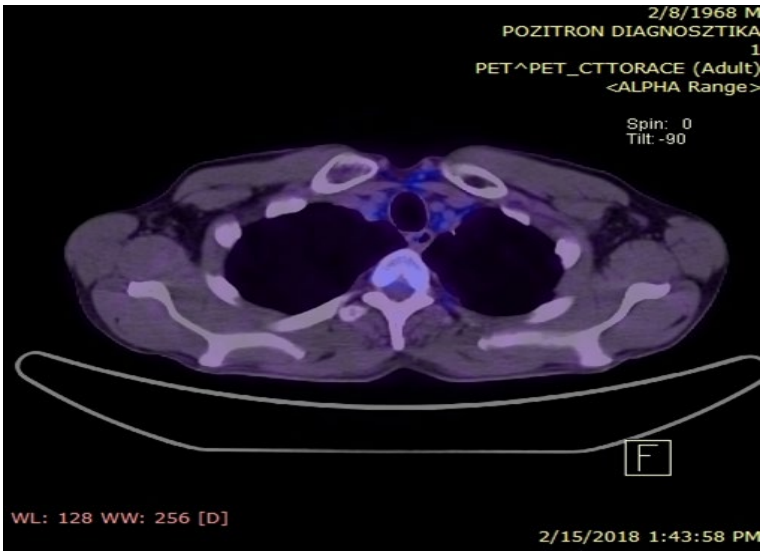

Figure 5: PET-CT (15.02.2018): Complete Response

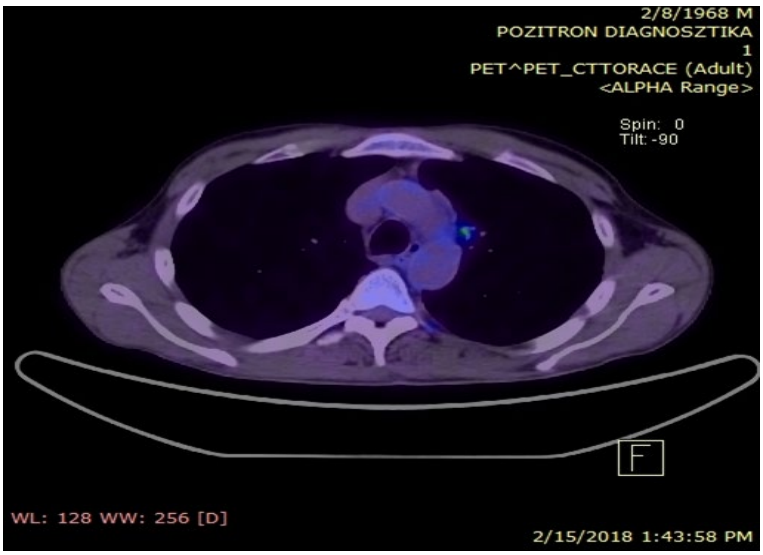

Figure 6: PET-CT (15.02.2018): Complete Response

A bone scan on 14.05.2018 showed no pathologic Technetium fixation. On August 2018 however, the follow-up CT scan raised suspicion and consequent PET-CT (28.09.18) revealed regional (2 new para-aortic nodules) and distant progression of the disease with metastases in the 7th and 10thleft ribs, with a standard uptake value varying between 10.7 – 14 (Figures 7,8).

Palliative hypofractionated radiotherapy was administered between 5-9.11.2018 to the painful metastasis of the 7th rib up to a total dose of 20Gy in 5 fractions, considering the patient's good performance status. Immunotherapy with Nivolumab, 240 mg iv every two weeks was started on November 2018, since PD-L1 testing was not mandatory in the second line treatment. Because the patient became asymptomatic and the treatment was well tolerated, no further radiotherapy was warranted. Until the mid-November 2021 the patient received 77 cycles of Nivolumab with no adverse events, no pain, 4 kilograms weight-gain and a PS=1. A complete response was confirmed by CT scans after 10, 23, 54 and 65 cycles respectively, and by a PET-CT performed in November 2019, after 26 cycles (Figures 9,10). Still on nivolumab and without adverse events, the patient maintains a complete response on control CT, amounting to 36 months progression free survival from the initiation of immunotherapy.

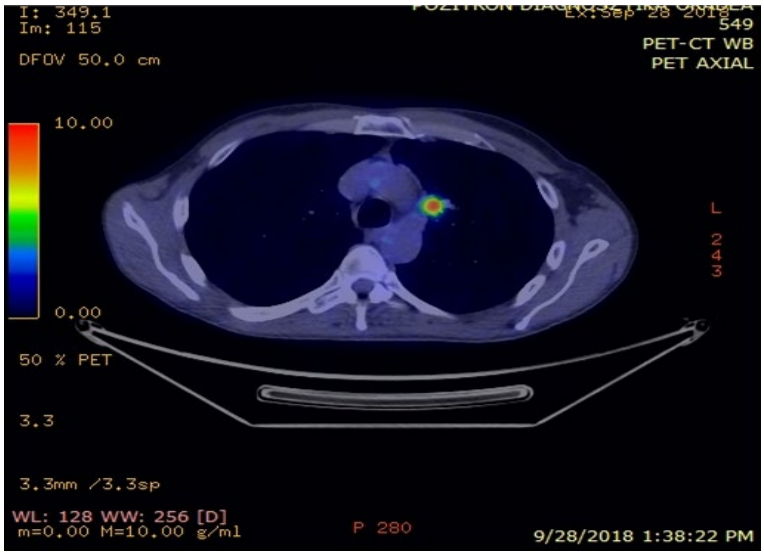

Figure 7: PET-CT: Para-aortic Nodule

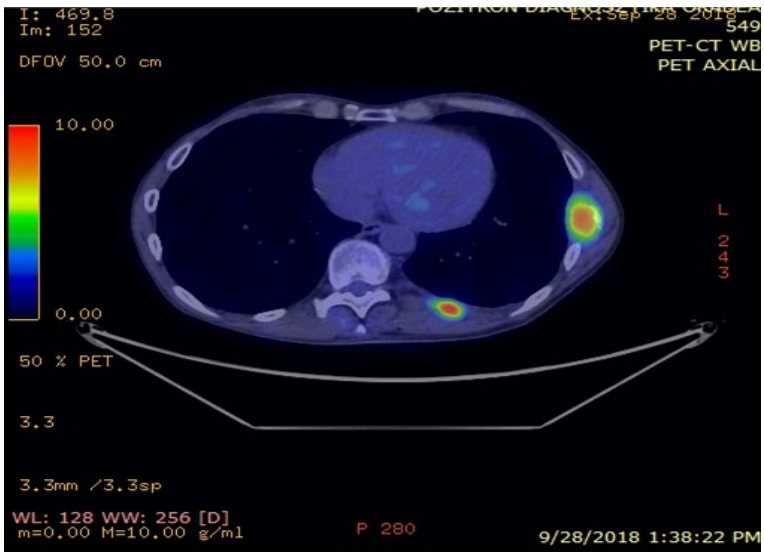

Figure 8: PET-CT: Metastases on the 7th and 10th ribs

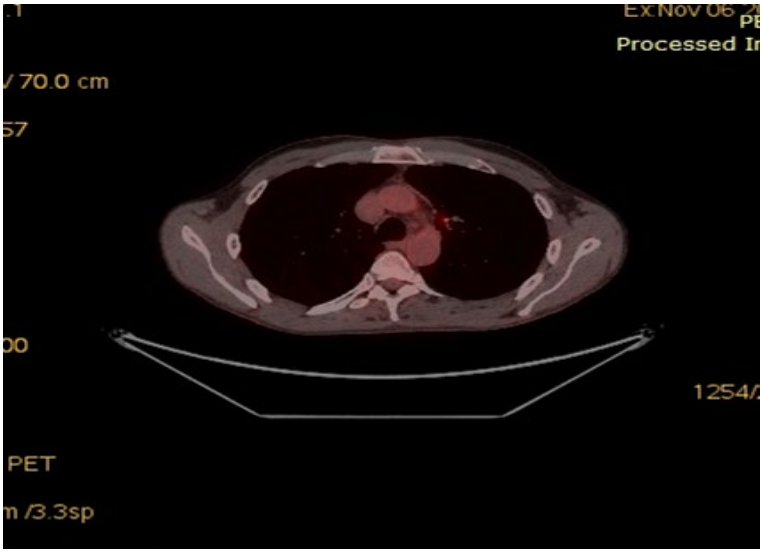

Figure 9: PET-CT: Complete Response

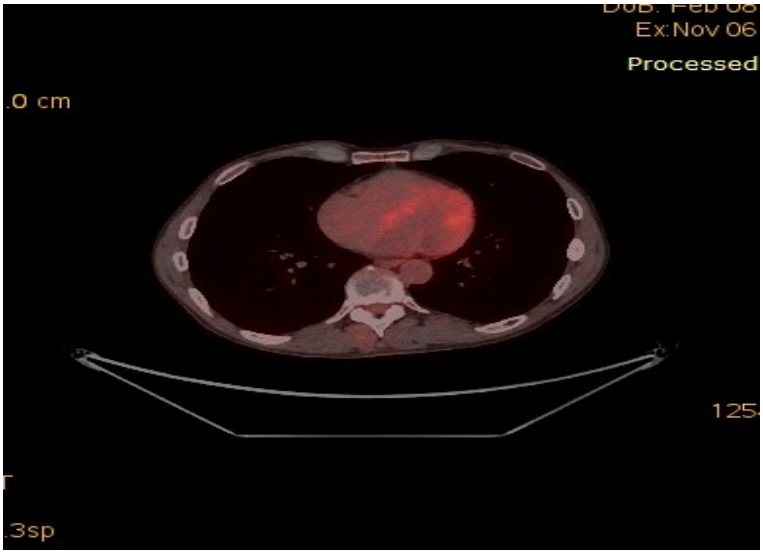

Figure 10: PET-CT: Complete Response

Discussion

The hypofractionated radiotherapy of the symptomatic metastasis on the 7th rib combined after three days with immunotherapy, led to the disappearance of the regional lesions (two para-aortic lymph nodes) and the metastasis on the 10th rib, distant from the irradiated site, outside the 10% isodose, on the radiotherapy plan (Figure 11). This might be considered a possible abscopal effect. This is an interesting phenomenon in radiobiology, which, was first described for radiotherapy by Mole in 1953 and traditionally considered to be the regression as the regression of a non-irradiated metastatic lesions at a distance from the primary site of irradiation (7, 9, 10, 11).

The mechanism can be explained by radiotherapy enhancing immunogenic tumor cell death, by increased expression of immunogenic molecules on the tumor cell surface, including adhesion molecules, death receptors, stress-induced ligands, cryptic antigens, and stimulatory molecules such as MHC-I and CD80, thereby becoming more sensitive to T cell–mediated cytotoxicity. Additionally, in the microenvironment, pro-inflammatory molecules like chemokines, cytokines, danger signals are released, as well as tumor antigens.

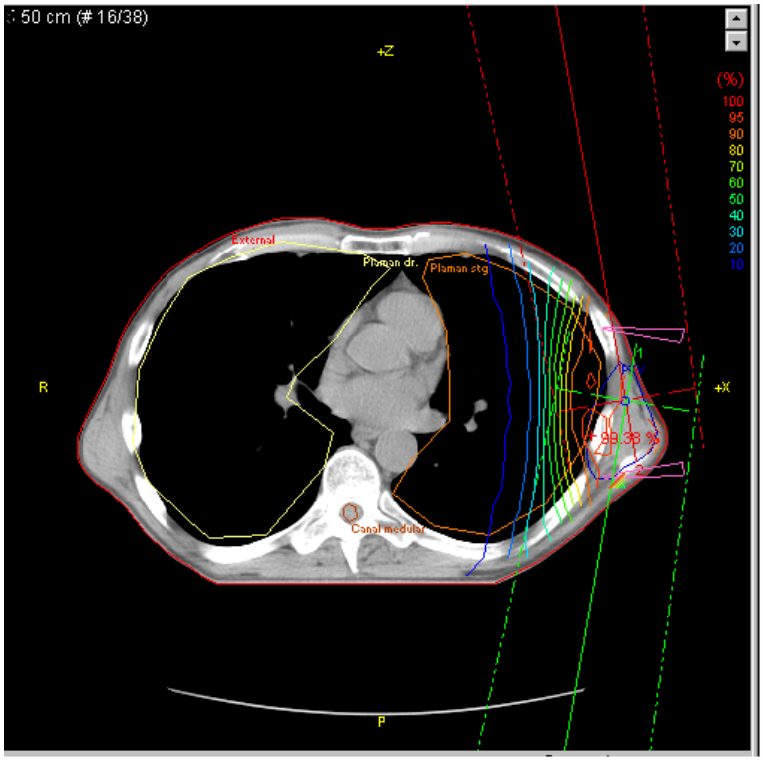

Figure 11: Radiotherapy Plan: 10% isodose dark blue

This causes chemoattraction and infiltration by activated immune cells like dendritic cells, which, encapsulate and process tumor antigens that are presented to the naive CD8 T lymphocytes. These are also recruited, activated and suffer a clonal expansion, becoming able to recognize and destroy tumor cells not only in the irradiated field, but also in the non-irradiated sites too (6,7,8,11). Additionally, it seems that memory T lymphocytes are responsible for the immunological memory and the prolonged effect. It is hypothesized that such effects are due to a systemic antitumor immune response, being thus synergic with immunotherapy. On the other hand, radiotherapy can induce PD-L1expression on the tumor cells, inhibiting the immune cells, which, can be overcome by association of ICI, thus developing the era of radioimmunotherapy. Arguments for abscopal effect are the disappearance of para-aortic lesions and the metastasis on the 10th rib, outside the 10% isodose, while irradiating only the metastasis on the 7th rib. However, considering the sequence and short interval of three days between irradiation and the initiation of nivolumab, the effects are synergic and overlapping. There is evidence of the mutual enhancement present in combination of radiotherapy with immunotherapy, so the concept of abscopal effect has been extended to the activation of the immune system in radioimmunotherapy (12).

Different doses, fractionations of radiotherapy and sequencing with immunotherapy have been tested in preclinical and clinical studies to evaluate the optimal regimen to obtain the best possible results. Higher doses like 5Gy, or 8Gy per fraction, but not too high (20Gy per fraction), are impacting recruitment of immunogenic cells in the tumor, while concurrent administration with immunotherapy seems to be more effective than sequential. Moreover, as the peak of PD-1 upregulation can occur 4-6 days after irradiation, this interval is suggested to be the ideal timing between radiotherapy and immunotherapy (8, 11, 12, 13).Thus, the hypofractionation regimen was chosen as 4 fractions of 5Gy, in a patient with good PS, with good symptom and disease control,

while combining immunotherapy after 3 days. This resulted in a durable complete response without the need for further radiotherapy. It is important to mention that before the era of ICI there was a tendency to recommend the irradiation of all oligometastatic sites in advanced NSCLC (14, 15).

Two phase III studies Check Mate 017 (3) and CheckMate 057 (4,5), obtained improved overall survival (OS) with nivolumab versus (vs) docetaxel obtaining a 5-yearsurvival rate of 12.3% vs 3.6% and 14% vs 2.1% respectively. The pooled analysis of the studies obtained 3-yearsurvival results of 17% vs 8% in the population with squamous and non-squamous NSCLC (16). The 5-year survival rates were 13,4% vs 2.6% and progression free survival of 8% vs 0%. ORR was 19.7% vs 11.2%. Notable was the long duration of response, achieving at 5 years 32.2% vs 0%. Patients without progression after 2, 3 or 4 years, have a probability of 82%, 93% and 100% respectively to be alive at 5 years (17). Thus, the most important question is the duration of treatment with nivolumab, whether to stop treatment after achieving complete response or to continue for two, three, or even four years, considering the higher chance of survival if there is no disease progression. Another option is to continue as maintenance treatment, as long as there is a clinical benefit without adverse events.

The first randomized study to evaluate duration of therapy with a PD-1/PD-L1 inhibitor was the CheckMate 153 trial (18) which, enrolled 1245 patients. Before one year of treatment, 1025 patients discontinued immunotherapy with nivolumab, due to progression, death, study withdrawal, toxicity, or other reasons. At one year, 220 patients remained on treatment and were randomized for continuation versus discontinuation of nivolumab. With minimum post-random assignment follow-up of 13.5 months, median PFS was longer with continuous versus 1-year fixed-duration treatment, obtaining 24.7 months vs 9.4 months, hazard ratio [HR], 0.56 [95% CI, 0.37 to 0.84]. Median overall survival from random assignment was longer with continuous versus 1-year fixed-duration treatment. The frequency of treatment-related adverse events was numerically higher with continuous vs 1-year treatment, but overall, few new-onset events occurred after 1 year. The authors concluded that a survival benefit was observed when nivolumab was continued beyond 1 year compared with a 1-year fixed duration treatment, and a tolerable safety profile was maintained with the longer treatment duration.

Conclusion

We would like to emphasize the synergic effect of hypofractionated radiotherapy, in combination with nivolumab, in the second line treatment of a patient with stage IV ade- nocarcinoma of the lung. We note a long-term complete response on imaging and 36 months of progression free survival, from the initiation of immunotherapy. A possible abscopal effect may be suspected in this case.

Further research should investigate optimal radiotherapy parameters, optimal duration of treatment with PD-1/PD-L1 inhibitors, and the sequencing of the therapies.

Abbreviations:

NSCLC – non-small cell lung cancer
IO – immunotherapy
LUL – left upper lobe
LLL – left lower lobe
ICI – immune check- point inhibitor

OS – overall survival
vs – versus
TTF1 – thyroid transcription factor 1
PD-1/PDL-1 – programmed cell death protein 1/ programmed cell death-ligand 1
ECOG PS – Eastern Cooperative Oncology Group Performance Status
EGFR – epidermal growth factor receptor
ALK – anaplastic lymphoma kinase
PS – performance status

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Magnetic Resonance Guided Radiotherapy for Cardiac Lymphomas: Report of a Case and New Perspectives

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Abstract

Cardiac lymphomas are extremely rare and have poor prognoses. Currently, there are no established guidelines for treatment and the main approaches include surgery, chemotherapy (CHT), possibly combined with radiotherapy (RT), and autologous stem cell transplantation (ASCT). RT's role is controversial and is not considered a standard approach. We describe the case of a patient diagnosed with cardiac lymphoblastic B-cell lymphoma/ acute Lymphoblastic B-cell leukemia and successfully treated with a multimodality approach, including CHT, RT, and ASCT. In particular, the patient was referred to magnetic resonance-guided RT (MRgRT), currently the most advanced available technology in the RT field, which maximizes therapeutic efficacy by exploiting the best soft-tissue resolution of the magnetic resonance images and efficient gating protocols during treatment delivery.

Keywords: cardiac lymphoma, MR guided radiotherapy, gating, MRgRT

Clinical Case Reports

1. Introduction

Primary cardiac tumors are an infrequent clinical entity, with an average incidence of 0.02% in autopsy series. Of these, 75% are benign. Among malignant tumors, the most frequent are sarcomas and lymphomas. Primary cardiac lymphoma (PCL) constitutes about 1.3% of primary cardiac neoplasms, 80% of which are diffuse large

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cell B-cell lymphomas (DLBCL). PCL has a poor prognosis, with an overall median survival of 12 months (1–3). The median age of patients is 63 years and PCL more often involves the right heart (both atrium and ventricle) (4). In most cases, it presents with congestive heart failure due to blood flow obstruction secondary to intracardiac mass growth, but often only with non-specific symptoms, such as dyspnea, chest pain, and general malaise. It may also present as an oncological emergency. The rapid clinical evolution related to advanced organ infiltration in these cases causes cardiac arrythmias and atrioventricular blocks potentially leading to sudden death (1). PCL treatment includes various therapeutic modalities, including CHT, eventually combined with RT, surgery, and even autologous stem cell transplantation (ASCT) (2). The evolution of diagnostic imaging techniques and the introduction of Rituximab in CHT regimens has led to an improved prognosis in PCL patients. Also, modern RT can play an innovative role in association with CHT protocols (5). Recent advancements in RT introduced magnetic MRgRT, as the most advanced RT delivery technology currently available. MRgRT has several clinical applications, as it combines enhanced soft-tissue visualization offered by the onboard MRI, and the direct gating options for motion management purposes. These benefits result in safer irradiation, ensuring that healthy organs are spared efficiently (6). We describe the first case of a patient with intracardiac lymphoblastic B-cell lymphoma/ acute Lymphoblastic B-cell leukemia managed multidisciplinary, and successfully treated with CHT, MRgRT, and ASCT.

2. Case presentation/ History Presentation

A 60-year-old woman with no past medical history was admitted to the emergency department in March 2019 for progressive worsening of dyspnea and asthenia over a three months period. Results from blood tests were within normal ranges, but the ECG showed atrial fibrillation with a high ventricular response. Lower limbs edemas were present, and the patient was diagnosed with heart failure and referred to imaging studies.

A chest CT scan excluded pulmonary embolism and showed a large right atrial lesion. A transthoracic echocardiogram (TTE) and a trans-esophageal echocardiogram (TEE) identified a solid cardiac lesion and a residual ejection fraction (EF) of 42%.

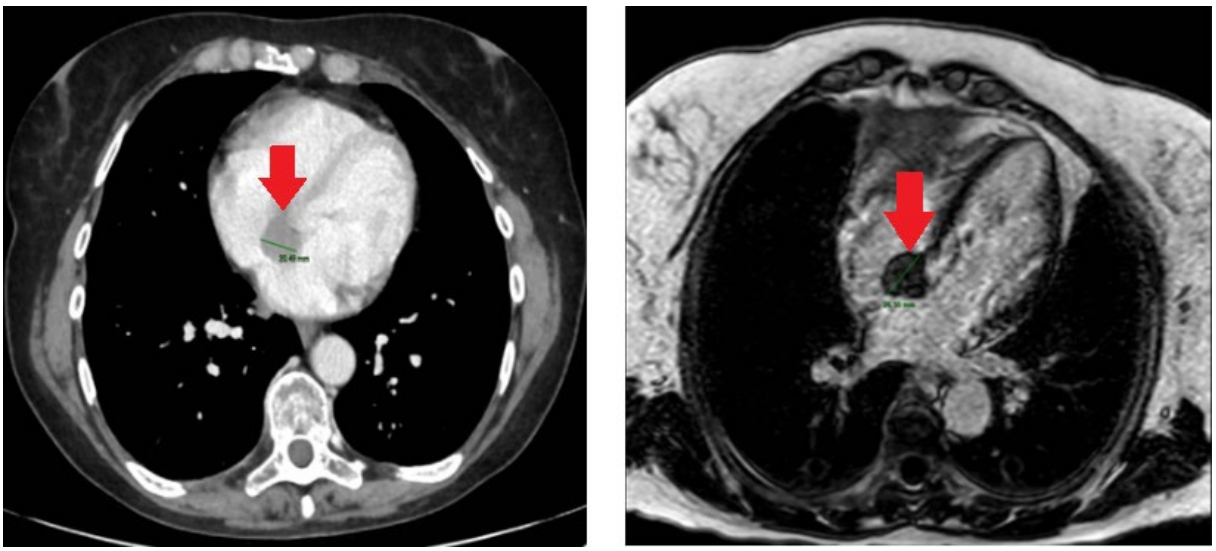

Figure 1. CT (left) and cardiac MRI (right) staging images. The lesion is indicated by red arrows.

The lesion was later confirmed by a cardiac 1.5 T magnetic resonance (MR) (GE Signa Excite, Medical Systems), and measured 48 (dAP) x 63 (dLL) x 53 (dCC) mm. The lesion infiltrated the interatrial septum, the superior venous sinus, and the right atrial roof, surrounding the aortic root almost circumferentially. This finding raised the diagnosis of primary cardiac lymphoma (PCL). Figure 1 shows diagnostic imaging performed for staging.

A biopsy of the lesion was performed in April 2019. Pathologic examination showed fragments of fibro-adipose tissue with a solid structure consisting of small, monomorphic cells, diffusely positive for LCA, TdT, PAX5, and CD10, and negative for CD3, CK AE1/E3, and vimentin on immunohistochemistry. Ki67 proliferative index was 90%. These pathologic findings were compatible with lymphoblastic B-cell lymphoma/ acute Lymphoblastic B-cell leukemia and correlated well with the imaging findings.

The patient underwent disease staging, with bone marrow aspiration and biopsy, and cytogenetic and molecular biology investigations that showed no signs of lymphomatous involvement. She was referred for treatment with chemotherapy.

The patient underwent first-line chemotherapy (CHT) according to the GMALL-ALL/NHL 2002 scheme (including vincristine, methotrexate, cyclophosphamide, and doxorubicin), and she completed A1, B1, A2, B2, and A3 cycles from May 2019 to September 2019. Disease re-evaluation was then performed with TTE and total body CT in September 2019, documenting stable disease according to RECIST criteria. Consequently, the B3 CHT cycle was administered in October 2019.

CHT course has been complicated by G3 thrombocytopenia, G3 anemia, and G3 neutropenia (CTCAE 4.0 scale).

The restaging ^{18}F-FDG PET-CT scan performed in November 2019 showed intense uptake (SUVmax 12) at the level of the interatrial septum known hypodense tissue, with extension to the aortic root, consistent with persistent/recurrent disease. TTE, cardiac MRI, and total body CT were also performed in January 2020, confirming disease persistence/recurrence.

The case was discussed by a multidisciplinary team of hematologists, cardiologists, and radiation oncologists. The decision was to perform inpatient radiotherapy (RT) treatment of the intracardiac lesion, due to increased cardiac risk. Regular TTE and weekly troponin tests were also done.

The patient was then referred to Magnetic Resonance guided Radiotherapy (MRgRT) with a total dose of 30.6 Gy in 17 consecutive fractions on a 0.35 T 6 MV hybrid MR-Linac (MRIdian, ViewRay Inc., USA). This technology was chosen as it takes advantage of MR imaging and direct gating approaches.

A double source of motion had to be managed in this case, with the therapy volumes position being prone to breathing, and heartbeat related spontaneous movements. The treatment was carried out in deep inspiration breath hold (DIBH) based on these evaluations.

The segmentation of both target volumes and organs at risk (OARs) was performed using the 25-second true fast imaging (TRUFI), a type of balanced steady-state free precession (bSSFP) sequence, yielding aT2/T1-weighted contrast, DIBH scans (see figure 2) co-registered with diagnostic imaging available (contrast-enhanced CT and cardiac MR scans), with the assistance of a radiologist specialized in cardiac neoplasms. The cardiac MR sequences used were both T1- and T2-weighted, and contrast-enhanced, to help discriminate between pathological tissue and areas of inflammatory or healthy tissue.

During each RT fraction, the patient could see through a mirror the movement of the target on the online cine MRI acquired on a sagittal plane. Dose delivery was automatically turned off when the target volume moved outside of the boundary region set

prior to delivery. Specifically, a sagittal slice of a volumetric MRI is displayed. It is possible to set the gating structure on this plane (e.g. the target), with the percentage of the target allowed outside the gating structure for the beam to turn off (direct gating).

The patient can actively participate in the treatment by modulating the breathing cycles to put the target in the proper position and thereby to increase gating compliance, thanks to a dedicated visual feedback system through which the cine-MRI is projected on an MR compatible monitor positioned on the vault's wall.

The patient started treatment in February 2020, and RT sessions were well tolerated with no interruptions. After 10 RT fractions, the patient developed two episodes of paroxystic supraventricular tachycardia, which were managed pharmacologically (Verapamil 2.5 mg iv), restoring sinus rhythm.

The subsequent PET-CT scan performed four weeks after the end of RT demonstrated a complete response of the cardiac lesions. However, a new uptake area was observed in the left tibia, and a biopsy later confirmed metastatic disease that was treated with 3D conformal radiotherapy (36 Gy in 18 fractions).

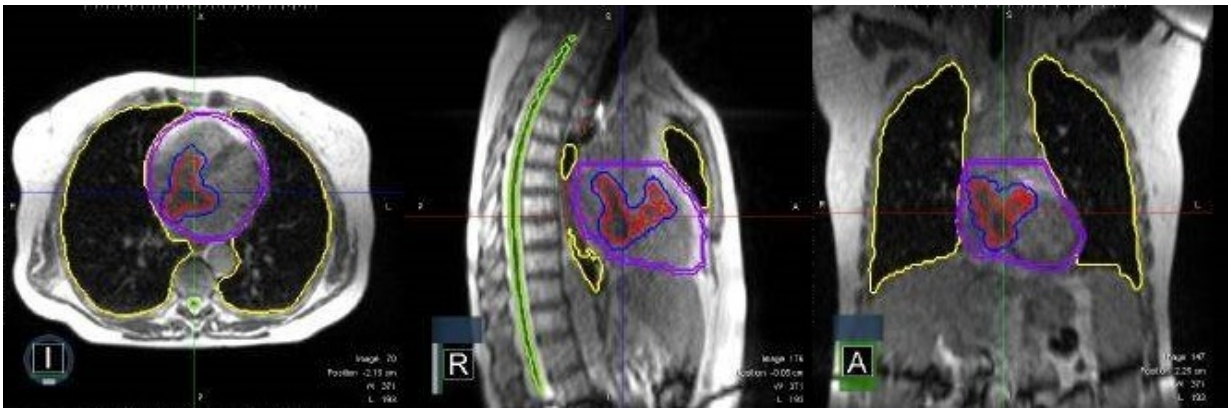

Figure 2. Segmentation of target volume and organs at risk (OARs) on axial, sagittal, and coronal TRUFI simulation scans. The gross tumor volume (GTV) is highlighted in red.

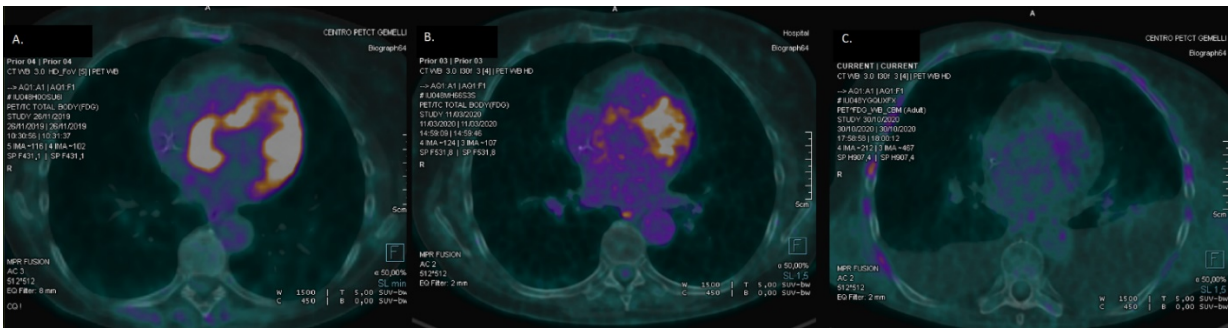

Figure 3. ^{18}F-FDG PET-CT scan: staging (A), one month (B), and eight months (C) after RT re-evaluation

The ^{18}F-FDG PET CT scan carried out subsequently on October 2020 confirmed complete cardiac response (see figure 3).

The patient underwent a successful allogeneic hematopoietic stem cell transplantation from an HLA-identical sister in May 2020. At the last follow-up in January 2021, the patient did not report acute or chronic cardiac toxicity signs, and she was considered free from disease (20 months after diagnosis).

Unfortunately, the patient developed mycotic sepsis shortly after and died of systemic transplantation complications in February 2021.

3. Discussion

At present, there are no specific guidelines for PCL treatment. Being a systemic disease, the therapeutic approach must always include CHT. The R-CHOP regimen (rituximab + cyclophosphamide, doxorubicin, vincristine, prednisone) currently represents the standard of care for cardiac DLBCL. The role of surgery is still unclear and often limited to a palliative setting or to stabilize the clinical condition. Surgery is usually performed as an emergency procedure for debulking purposes, because of blood flow obstruction. In other cases, it helps the efficacy of CHT, especially when hemodynamics is compromised (1).

The use of RT, alone or as consolidation after CHT, is described in the literature, although it is not considered a standard approach. One of the reasons is related to the risk of acute and late cardiac toxicity, increased by the use of therapeutic regimens containing anthracyclines. Cichowska-Cwalińska et al. (2) recently published a review on the role of RT in PCL, concluding that, despite the risk of toxicity and an unclear survival benefit, it can be used as a salvage treatment in patients with cardiac PCL who do not achieve a complete response after CHT.

The goal of using the innovative MRgRT approach was to minimize cardiac toxicity through the use of MR for planning purposes. MR is the preferred imaging modality for cardiac masses due to its best contrast soft-tissue resolution, multiplanar imaging capabilities, and unrestricted field of view (7). This patient's workflow incorporated data from the diagnostic cardiac MR scans to increase contouring accuracy with the 0.35 T TRUFI MR simulation images provided by the hybrid MR Linac. These last images were then used daily for patient positioning and therapy monitoring, according to the usual MRgRT workflow. Furthermore, MR-based gating protocols allow the reduction of uncertainty margins related to therapy volumes, thus avoiding unnecessary irradiation of healthy cardiac surrounding tissue.

4. Conclusion

MRgRT is characterized by excellent patient compliance and a favorable toxicity profile and may be considered an option in the multidisciplinary treatment of primary and secondary cardiac lymphoma.

Abbreviations:

ASCT – autologous stem cell transplantation
18F-FDG PET-CT – 18F-fluorodeoxyglucose positron emission tomography- computed tomography
bSSFP – balanced steady-state free precession.
CHT – chemotherapy
CT – computed tomography
CTCAE – Common Terminology Criteria for Adverse Events;
DIBH – deep inspiration breath hold
DLBCL – diffuse large cell B-cell lymphoma
ECG – electrocardiogram
EF – ejection fraction
GMALL-ALL/NHL – German multicenter ALL – acute lymphoblastic leukemia/ Non-Hodgkin's lymphoma
GTV – gross tumor volume
HLA – Human leukocyte antigen
MR – magnetic resonance
MR-Linac – magnetic resonance – linear accelerator
MRgRT – magnetic Resonance guided radiotherapy

MRI – magnetic resonance imaging
OARs – organs at risk
PCL – primary cardiac lymphoma
R-CHOP – rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
RECIST – Response evaluation criteria in solid tumors
RT – radiotherapy
SUV – standard uptake value
TEE – trans esophageal echocardiogram
TRUFI – true fast imaging
TTE – transthoracic echocardiogram

Statements:

Author's contributions: conceptualization, LB, and AR; methodology, AC and EDM; data curation, MI, FDA and SH; writing— original draft preparation, LB and AR; writing—review and editing, SC and CM; supervision: MB. All authors have read and agreed to the published version of the manuscript.

Consent for publication: The patient recruited in the study signed an informed consent regarding the publication of their data.

Conflict of interest: Dr. Luca Boldrini has active research agreements with ViewRay Inc (Mountain View, CA, USA) and received speaker honoraria for scientific presentations and travel reimbursements.

Statement of ethics: This research study was conducted retrospectively in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Ethical approval: Ethics approval was not required for this study

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About Intelligence (Artificial or Not) – A Discussion with Marcel van Herk

Interview by Monica-Emilia Chirilă[1]

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Professor Marcel van Herk is the chair of radiotherapy physics at the University of Manchester. As a medical physics student, he started developing of a liquid ionization imaging device that later became the Varian PortalVision system for electronic portal imaging. During his Postdoctoral Fellowship at Harvard Medical School, in 1992, Dr. Van Herk started to incorporate 3D image processing in his work, first CT-MR image registration for treatment planning, and later measuring organ motion and other uncertainties in radiotherapy such as delineation variability. Much of this work has been integrated into the Elekta Synergy cone-beam CT image guidance system. For the past 10 years he has held a part-time teaching role as a Professor at the University of Amsterdam working, amongst others, at the integration of microscopic optical imaging into radiotherapy treatment planning. His goal is to conduct research that improves the clinical practice of radiotherapy.

MC: Could you please tell us a few words about your current activity and about your main accomplishments in the field of radiotherapy?

MvH: Well, I work on improving the precision of radiotherapy. I've been very active in image guided radiotherapy, quantifying organ motion, 4D, that kind of stuff, and I like to look for things that are unsolved. One thing that wasn't solved, was delineation. People are delineating tumors but do not agree, so I spent some time observing variation and teaching on that. Now, I think the big questions remaining are regarding tumor biology - what do we need to radiate? Where are the targets? Where's the microscopic disease? Currently, the focus of my work is big data - trying

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Interviews

to learn from the data of thousands of patients that were treated in the past. We try to see for instance, which parts of the patient are the most sensitive to radiation? What happens if you get a little bit more dose here and there? Do you see a difference in outcome? I think it's kind of a natural progression.

MC: Is it difficult to gather this amount of data that you need to analyze?

MvH: I started in Amsterdam, but I work in Manchester now, the biggest Cancer Center in Europe. But treatment data, outcome data is harder to get, so we've linked up with external databases, like the NHS (National Health System). So there is a lot of data. One thing that we can always find out is if the patient is dead or alive. So actually, a lot of the activities aim to predict the outcome. And sometimes you just find really surprising things. For example, we were looking at data from older 3D plans and correlated with the “dead or alive " status, and we found a little spot in the heart which got more dose and was correlated with a worse outcome. That was kind of an eye opener. And that gives us an opportunity, because it is not always possible to spare all the heart, so we can try to avoid the structures which are the most sensitive. It might be the electrical system, but we don't know. So we have to figure it out. We have to run prospective studies, looking at the effects of radiation - we're just finishing one. We looked at cardiac CT, before and after radiotherapy, and so we will hopefully report our findings in the near future.

MC: So you are not only searching for factors to predict the patient outcome, but also to identify toxicity-sensitive structures?

MvH: Yes, both. But it can be very complicated. If you want to compare data from different patients you have to put them together. The organs at risk can be mapped together, but the tumors are in different parts of the body, have different shapes and different sizes.

MC: How do you deal with the variability of the data? There are different devices, different types of scanners, and they produce images that are slightly different.

MvH: Actually, we do a lot of things with the planning data. And that's fairly well standardized. So that's not such a big deal. But obviously, statistics is actually quite complicated, making corrections for confounding factors.

MC: How did you identify these problems that need to be solved, and which later become your research focus? Do you find them by yourself? Or do you collaborate with clinicians and ask their opinions on what may be more difficult in their clinical work?

MvH**:** Of course, I am collaborating with great clinicians and their input is really important. But it's also just… listening. I’ve been around for so long now. I’m just picking up.

MC: How did you get to be involved in this field? Were you interested in that from the beginning of your career or was it something that started to interest you in time?

MvH**:** It's kind of funny story with that, because I studied physics. In school I was good at maths, but also physics. Computer science didn't exist yet. While I was in University I had a one year project. And so I went to the Cancer Institute in Amsterdam and there was a guy building his own computers and doing a lot of technology work. So that is how I got interested in this topic.

MC: What about image guided radiotherapy? Which was the main progress in the last years, in your opinion?

MvH: Well, obviously, we've got all sorts of new scanners, new reconstruction algorithms, MRI guidance, but the fundamental problem is the patient. And I think people often forget that, you know, you can get such beautiful equipments, but if the patient's organs are moving during the imaging, or during treatments, it's never going to be very good. So I think we need to find ways to deal with that. And it's funny, because the medical physicists want to measure stuff. They put a phantom on a scanner and they make measurements, but this does not say anything about the usability, because if you put a patient there, the things are totally different.

MC: Why do you think about image enhancement, in particular the use of the Cone Beam CT(CBCT) as a predictive tool?

MvH: Well, there is something in there, but the CBCT is not very good. And the main reason why it is not very good is because the patient is moving, the organs are moving. So, the best images actually, strangely, you get in the lung where you can do 4D CT. The contrast is very high. We've been looking at how these images change over time, but I don't think it's very predictive. But we're looking at those images to understand what is happening, for instance, to predict whether you need to adapt to treatment. So it's a workflow thing.

What we are now going to do with the cardiac substructures is doing what we call a rapid learning study. So we're treating one way and then at a certain point to kind of change it and we're treating another way and then what we hope to see is a jump in the output. We have to be really careful because if something else changes at the same time, obviously then that's what you measure is not true.

MC: In what fields of radiation oncology do you think artificial intelligence will be most helpful? Is it going to be autocontouring or decision making or something else?

MvH: I think it is contouring, but also this one I mentioned before - the biomarkers - I think that would be quite cool as well. The computer should say: I've measured densities in your body and looked at the picture and you're very weak. I do not like radiomics because it's garbage in and garbage out in a way, and then because the box is so big, you have so many variables. Yes, you can always find something but if you don't correct for the other variables…Actually it might be the same with genetics. Yeah, lots of zillions of people are working on them. But very few studies have found something that actually works.

MC: What's the story of the "van Herk formula"?

We were doing this project with three people (Peter Remeijer, Rasch and Lebesque). We were looking at organ motion and setup errors. And then we couldn't figure it out. Because the doctor says, I want to cover the margin and always treat my patients right. And that was the problem because that margin doesn't exist. So it was literally, I think, over a weekend or so that I thought: Well, shouldn't we do the probability? And then I wrote down most of the equations but Peter actually wrote down the linear equation. That's the margin recipe. The numbers don't mean anything, no doubt. The numbers gave the clinical answer at that time, given the errors basically. And we sold it really well. Because the way that we sold it was to make it really simple.

MC: Did you or do you work for the industry, for the companies which produce radiotherapy devices?

MvH: No, not for, but with the companies. My first project was the portal imaging device, so we created the Varian PortalVision. We worked for decades with Varian, and then we started

working with Elekta for the cone beam CT. I was out with a friend and he invited me to join him to write a grant. The deadline was in just a week. It was on image guided radiotherapy in prostate cancer. I did a little software things. And when Elekta started to build those machines, we were already in the circle, and we wrote the software from scratch and then we provided bug fixes. We were subcontractors. That was big.

I also work with Aquilab on training contouring system. I wrote some software there, but I will probably collaborate with other companies too, in the future. I also have some ideas, but if they are not translated into projects... Even if I give away the software for free, it's not going to be used clinically, it has to be in a company, and it has to be supported, FDA approved and stuff… But companies are difficult in the sense that they often change very quickly. So different people, new head of the group, different vision, priorities… I'm involved with MRI Linac, but only very little.

MC: What you say is very nice, because we need this human part, also.

MvH: And I know you were asking about the companies and that's often difficult because it really depends on a few people. And if they are not there, or they got a new boss, suddenly people don't understand what they have.

MC: About understanding – this raises another question: how do you make people understand what you're thinking about in case there's a gap between your training and their possibility of understanding the concept which you're explaining?

MvH: I just try to explain it very, very simply. But yeah, I think the main problem is people who don't want to listen, they don't understand. If people have a preset idea, then they really don't understand the issue, and you should have started at another level. To explain this, you go back to the basics.

MC: I was thinking that the studies on motion management are becoming even more important, because we are giving a higher dose in less fractions. So, the movement has more impact.

MvH: It is totally true. The amount of technology that you use depends on what you need it for. But if there is a simple solution, that is much better.

MC: Do you think that the MRI Linac will be the best solution for accurately delivering the radiotherapy ?

MvH: There are other tools for image guided radiotherapy, like fiducials and many more. If the MRI Linac could provide imaging in 3D in a fraction of a second, then it could pretty much solve all the problems, but that's not how it is. It's a complicated machine and workflows are really, really difficult. And it's tight, it's claustrophobic. And MRI is slow, and slower than the CT and slower than the CBCT. Because you can take a single slice very quickly, but if you want to take the volume, it takes much longer. Not all the organs move the same, and the longer the workflow is, the more is the chance that the target or the organs at risk would move.

MC: What are your plans for the future? Do you have anything in particular that you're working on that you would like to share with us?

MvH: Yes, no doubt… As I mentioned, one project is focused on measuring the electrical effects of radiotherapy on the heart. Another thing that we're starting up is to use routine imaging for biomarkers. For example – a change in the performance status can influence the change of the treatment, but evaluating the performance status can be subjective. But the images actually

have a lot of information because you can see how the muscles are developed. You can see the liver, you can see the heart (whether it has calcification or not), so there is a lot of information in routine data that we can exploit. It's already there; we just have to find out how to use it. But that's not the most important thing. The most important thing is that this amount of data exists in the past. So we can try out all sorts of algorithms on the old data to see whether that is predictive of what's happening to the patient. So, that is a cool thing. I like that a lot.

MC: Do you work on multiple projects at the same time?

MvH: Yes, lots of, because of the students.

MC: How do you manage to divide your time and energy?

MvH: Well, in normal times I was one of the supervisors, and other supervisors would do the majority of work and I would just walk in and see how it's going and if there is a particular problem and that was fairly efficient. But in lockdown, that doesn't work, so you actually really have to sit for an hour with students - sometimes more, to talk it through because the student is frustrated at home, and it's really difficult. So it's much tougher now, in lockdown, than it is normally. Normally it's only fun. Now it's also fun, but it takes double the amount of time. And double the amount of time to do that means almost no time to do anything.

MC: You mentioned the lockdown times with all the challenges, and I am wondering, how do you find ways to overcome challenges? What drives you? What motivates you to solve your research or work related problems and challenges? How do you manage not to give up?

MvH: Giving up isn't an option, because we can give up on a project, but that does not mean that we can give up on a student. You can give up on an idea, but you can't give up on the students. It is not an option, because you're responsible. And yes, I take that very seriously. One of the postdocs in our university said: I have two supervisors: a good supervisor (my colleague)- he tells me to go to bed early, read, etc; and I have a bad supervisor, who tells me to go to parties. That's me. And I was very, very proud to be the "bad" supervisor.

MC: I recently asked a young researcher in the field of artificial intelligence what he would ask you if he would meet you. His answer surprised me. He said that he would not ask anything, but would only thank you for all that you have done. So, I will do the same, and end by thanking you for your valuable contribution for delivering quality radiation treatments to cancer patients.

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"Learning From Every Patient" – Countdown for the Next Congress of the European SocieTy for Radiotherapy and Oncology (ESTRO)

Interview by Monica-Emilia Chirilă[1]

[1] *Journal of Medical and Radiation Oncology*

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Dr. Anna Kirby is the ESTRO President-Elect and a Consultant Clinical Oncologist working at the Royal Marsden and Institute of Cancer Research, UK. Dr. Kirby graduated from Cambridge University in 1995 with a first-class honors degree in Medicine and Psychology. She completed her oncology training at The Royal Marsden and Guy's and St Thomas' Hospitals followed by a research degree at the Institute of Cancer Research. She specializes in the treatment of patients with breast cancer and leads research into novel breast radiotherapy techniques. She is Chief Investigator of the UK HeartSpare and HeartSpare Plus studies, and breast Lead Investigator on the UK CORE trial evaluating the role of stereotactic radiotherapy in treating metastatic disease.

I would like to thank dr. Kirby for accepting our invitation to share your thoughts on past events, the current situation, and the near future of the European Society for Radiotherapy and Oncology. I would like to take this opportunity to congratulate you on acting as the President-Elect of this prestigious organization that represents our medical specialty, a truly remarkable achievement in your career.

1. What was the reason you chose to become an ESTRO member in the first place, and what prompted you to become more involved in ESTRO activities?

I first became a member of this organization in order to attend the ESTRO 2006 Congress in Leipzig where I presented a poster on outcomes in head and neck cancers. As it happened,

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that meeting changed my career: I met Professor John Yarnold, who persuaded me to start a fruitful partnership in breast radiotherapy research, highlighting the value of networking at the annual congress! A few congresses later, with a research degree in breast radiotherapy under my belt, and appointment to the Royal Marsden as a consultant, I attended the ESTRO Breast Multidisciplinary Course in Athens in 2010 where I met many of the European colleagues with whom I have since collaborated, learning first-hand how ESTRO can facilitate sharing expertise, development of protocols and guidelines, and practice-changing randomized controlled trials. I was invited to join the Scientific Committee for ESTRO 35 in Turin where I learned how a program comes together and, in 2017, I joined the Editorial Board for the Journal of Clinical and Translational Oncology (ctRO, https://www.ctro.science/) through which I've seen how a journal grows. In 2019 I was elected to the ESTRO Board and I was only just starting on the road of discovering more about the inner workings of ESTRO when, in April 2020, I became the Society's President-Elect. It's been a steep but enjoyable learning curve ever since. If I had to sum up what kept attracting me back to ESTRO it is the fact that it's a family of individuals working enthusiastically towards the same goal of improving outcomes in patients being treated with radiation therapy. ESTRO has an irresistible energy and momentum.

2. What is your vision regarding the future of ESTRO policies and the directions the Society should follow?

Well, the focus of my presidential candidacy statement was around facilitating implementation of innovations for immediate benefit to patients throughout Europe and beyond. Of course, there are already many initiatives from HERO, (https://www.estro.org/Science/Activities/HERO) to the Marie-Curie Campaign, (https://mariecurielegacy.org/) to the ESTRO-EORTC E2-RADIatE platform studies (https://www.estro.org/Science/Activities/ E2RADIATE) that move us towards appreciating the ESTRO 2030 vision- *"Optimal radiotherapy for all".* What we could do better is to broaden the pool of volunteers involved in ESTRO activities and discussions on how to effect this are underway.

3. What were the challenges you faced during the COVID-19 pandemic - as a clinician, as part of the ESTRO leadership, and the organizing committee of the annual Congress?

March 2020 is still so vivid in my memory. I remember clearly the day I was asked which of my several dozen breast patients' radiotherapy planning pathways I didn't want to pause? My reaction then was "Until when?" Mercifully, a few of us were already aware of the results of the FAST-Forward fractionation study such that we were able to switch many patients to a five-fraction schedule, and get them through and out before the pandemic really took hold. The peer-review manuscript was prepared rapidly to provide a strong foundation for what has become a durable change in the standard of care. Without this transition, who knows how our radiotherapy departments would have survived the pandemic?

Joining the ESTRO leadership team during a global pandemic has been a little daunting, but the ESTRO Office handled the postponement of ESTRO 2020 brilliantly under the ever-evolving circumstances. Decisions around ESTRO 2021 were, if anything, more challenging, as there was more than one feasible option. As a leadership team, I think we are all delighted that the live meeting went ahead, providing many colleagues with their first opportunity to meet face-to-face in well over a year. The hybrid aspects worked well too, and we will be incorporating the feedback as we move ahead to ESTRO 2022. It seems likely that, whilst prioritizing the networking aspects of face-to-face meetings, the hybrid aspects will stay, allowing many more individuals to access the scientific and educational content of the programs.

4. The ESTRO 2030 Vision is represented by "Radiation Oncology, Optimal Health, For All, Together". How was this new statement adopted, and how do you envision its translation into practice?

The ESTRO 2030 vision was developed during a meeting in Mechelen in February 2018, before I joined the Board and I can't give you any "behind the scenes" details on how the vision statement evolved. That said, I think the statement "Radiation Oncology, Optimal Health, For All, Together" succinctly and clearly summarizes ESTRO's vision. Radiation Oncology is our area of interest and expertise, we want to achieve the best possible outcomes in terms of cancer-free survival with minimum toxicity, we want these outcomes to be available to all patients regardless of where they live, and we want to work together – the RT community, with a multidisciplinary approach, and with all stakeholders involved – to make this possible. ESTRO will continue to prioritize the underpinning science through its congresses, translating research findings into practical recommendations for the clinic through guidelines and educational activities, bringing different disciplines and geographies together through all the aforementioned activities, and working with all stakeholders, including patients, and those involved in healthcare policy, to effect change at healthcare systems levels.

5. What main challenges do you see in achieving ESTRO's strategic priorities, and how will you overcome them?

The obvious current challenge to our day-to-day working practices is the ongoing pandemic, albeit I think human beings, especially those involved in ESTRO, are remarkably adaptable and, in the virtual/ hybrid world ESTRO's reach can potentially be greater with lower resource requirements. Other current challenges include integrating/ implementing innovations into our healthcare systems. These systems are different for each country and region and we need to continue the dialogue with national societies in particular to understand how the ESTRO community can help.

6. How is ESTRO involved in training and supporting the young Radiation Oncologists?

Just as I was attracted to ESTRO by the congresses and educational activities, these remain a great starting point for trainees to observe, learn and network. yESTRO, the young ESTRO committee, has since been formed and does a tremendous job engaging our younger members through the dedicated Congress track, whose program can be tailored to the specific needs and interests of younger members. It is important that we keep the next generation engaged and active in all ESTRO activities from committees to course faculties, as well as facilitating younger members being active in their own institutions and communities. One way to facilitate this is the ESTRO mentoring program, initially planned for 2020 and finally started in 2021, and led by yESTRO along with the Education Council. It is hoped that the CERRO meeting will also restart in 2023 as an annual workshop specifically designed for empowering and connecting future leaders. Membership is also an important channel through which younger members can participate in our community with a dedicated type of membership for professionals in training, alongside agreements with young national societies, to keep membership fees lower for those in training.

7. Which opportunities does ESTRO offer for professionals from countries with a challenging economic background and developing Radiotherapy infrastructure?

ESTRO is an inclusive society and welcomes involvement of any individual working in radiation oncology regardless of location and background. This said, ESTRO appreciates that

different healthcare settings present different challenges for those who wish to either engage with ESTRO activities and/or improve the provision and delivery of radiation oncology in their home nation. In relation to education and training for professionals working in countries with a challenging economic background, special fees are set for both teaching courses and congresses to facilitate access, and there is scope to capitalize on the increasing use of the virtual environment and broaden the reach of ESTRO's scientific and educational outputs.

8. What about the next ESTRO meeting? What plans could you share with us regarding this important educational event?

ESTRO 2022's program is almost complete by the incorporation of the hundreds of abstracts submitted by our community. The theme is "Learning from every patient" and you can expect to see this aspect incorporated throughout the program. The other focus will be on coming together. We very much hope to build on the success of ESTRO 2022 and meet with as many colleagues as possible face-to-face whilst still providing content and value for those who are unable, for whatever reason, to join us in person.

9. How do you manage to keep a life-work balance?

This is a tough question to answer because I don't really know what a perfect work-life balance is. What I do know is that time is a really precious commodity and I try to use it well by throwing myself wholeheartedly into whatever commitment is in front of me, being that a clinic, a talk, or connecting with my family. I know what my priorities are and I try to align my commitments accordingly (not always with complete success).

10. We all face challenges in our day-to-day life. Where do you find sources of inspiration and motivation?

It's really important to me that we all try to live our best lives. Our time on this planet is so short and it's folly to waste it on anything less than being fully alive, connected and present. Music and nature, particularly the sea, inspire me as do stories of human endeavour and impact. I am motivated by desires to make a difference, to get things done and to support those around me to make a positive difference to our world too. That all sounds rather intense now I've written it down. Whilst I can be very focused, those who know me well know that I also like to laugh… a lot. My husband is very, very funny, which is a godsend.

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OPDIVO (nivolumab) - Informaţii esenţiale din rezumatul caracteristicilor produsului

Consultaţi Rezumatul Caracteristicilor Produsului (RCP) înainte de prescriere. Compoziţia calitativă şi cantitativă: Fiecare ml de concentrat pentru soluţie perfuzabilă conţine nivolumab 10 mg. Indicaţii terapeutice: Melanom: OPDIVO este indicat în monoterapie sau în asociere cu ipilimumab pentru tratamentul melanomului în stadiu avansat (nerezecabil sau metastazat) la adulţi. În comparaţie cu monoterapia cu nivolumab, o creştere a supravieţuirii fără progresia bolii (SFP) şi a supravieţuirii generale (SG) pentru asocierea nivolumab cu ipilimumab este stabilită numai la pacienţii cu expresie tumorală redusă a PD-L1 (vezi pct. 4.4 şi 5.1 din RCP). Tratament adjuvant al melanomului: OPDIVO în monoterapie este indicat pentru tratamentul adjuvant al melanomului extins la ganglionii limfatici sau metastazat, la adulţii la care s-a efectuat rezecţie completă (vezi pct. 5.1 din RCP). Cancer bronho-pulmonar altul decât cel cu celule mici (NSCLC): OPDIVO în asociere cu ipilimumab şi 2 cicluri de chimioterapie pe bază de săruri de platină este indicat pentru tratamentul de primă linie al cancerului bronho-pulmonar altul decât cel cu celule mici metastazat, la adulţii ale căror tumori nu prezintă mutaţie sensibilizantă EGFR sau translocaţie ALK. OPDIVO în monoterapie este indicat pentru tratamentul cancerului bronho-pulmonar altul decât cel cu celule mici local avansat sau metastazat, după tratamentul anterior cu chimioterapie, la adulţi. Mezoteliom pleural malign (MPM): OPDIVO în asociere cu ipilimumab este indicat pentru tratamentul de primă linie al mezoteliomului pleural malign nerezecabil, la adulţi. Carcinom renal (RCC): OPDIVO este indicat ca monoterapie pentru tratamentul carcinomului renal avansat după terapie anterioară, la adulţi. OPDIVO în asociere cu ipilimumab este indicat pentru tratamentul de primă linie al carcinomului renal avansat cu prognostic intermediar/nefavorabil, la adulţi (vezi pct. 5.1 din RCP). OPDIVO în asociere cu cabozantinib este indicat pentru tratamentul de primă linie al carcinomului renal avansat, la adulţi (vezi pct. 5.1 din RCP). Limfom Hodgkin clasic (LH clasic): OPDIVO în monoterapie este indicat pentru tratamentul limfomului Hodgkin clasic recidivat sau refractar după transplant autolog de celule stem (TACS) şi tratament cu brentuximab vedotin la adulţi. Cancer scuamos de cap şi gât (SCCHN): OPDIVO în monoterapie este indicat pentru tratamentul cancerului scuamos de cap şi gât recurent sau metastazat, la adulţi la care boala progresează în timpul sau după terapie pe bază de săruri de platină (vezi pct. 5.1 din RCP). Carcinom urotelial: OPDIVO în monoterapie este indicat pentru tratamentul carcinomului urotelial nerezecabil local avansat sau metastazat, la adulţi, după eşecul terapiei anterioare pe bază de săruri de platină. Cancer colorectal (CRC) cu deficienţă de reparare a nepotrivirii ADN-ului (dMMR) sau cu instabilitate microsatelită de grad înalt (MSI-H): OPDIVO în asociere cu ipilimumab este indicat pentru tratamentul cancerului colorectal metastazat cu deficienţă de reparare a nepotrivirii ADN-ului sau cu instabilitate microsatelită de grad înalt, după chimioterapie anterioară pe bază de asocieri de fluoropirimidină, la adulţi (vezi pct. 5.1 din RCP). Carcinom scuamos esofagian (OSCC): OPDIVO în monoterapie este indicat pentru tratamentul carcinomului scuamos esofagian avansat, nerezecabil, recurent sau metastazat, după chimioterapie anterioară pe bază de fluoropirimidine în asociere cu săruri de platină, la adulţi. Tratament adjuvant al cancerului esofagian sau de joncţiune eso-gastrică (OC sau GEJC): OPDIVO în monoterapie este indicat pentru tratamentul adjuvant al cancerului esofagian sau de joncţiune eso-gastrică, la pacienţii adulţi care prezintă boală patologică reziduală după tratament neoadjuvant anterior cu chimioradioterapie (vezi pct. 5.1 din RCP). Adenocarcinom gastric, de joncţiune eso-gastrică (GEJ) sau esofagian: OPDIVO în asociere cu chimioterapie combinată pe bază de fluoropirimidine şi săruri de platină este indicat pentru tratamentul de primă linie al adenocarcinomului gastric, de joncţiune eso-gastrică sau esofagian, avansat sau metastazat, HER2-negativ, la pacienţii adulţi ale căror tumori prezintă expresie PD-L1 cu un scor combinat pozitiv (CPS) ≥ 5. Doze şi mod de administrare: Testare PD-L1: Dacă este specificat în indicaţie, selectarea pacientului pentru tratamentul cu OPDIVO pe baza expresiei tumorale a PD-L1 trebuie confirmată printr-un test validat (vezi pct. 4.1, 4.4 şi 5.1 din RCP). Doze: *OPDIVO în monoterapie:* Doza recomandată de OPDIVO este fie de 240 mg nivolumab la fiecare 2 săptămâni, sau 480 mg la fiecare 4 săptămâni (vezi pct. 5.1 din RCP), în funcţie de indicaţie, după cum urmează: *Melanom (în stadiu avansat sau pentru tratament adjuvant) şi, respectiv, Carcinom renal:* 240 mg la fiecare 2 săptămâni, pe durată a 30 minute sau 480 mg la fiecare 4 săptămâni, pe durata a 60 minute; *Cancer esofagian sau de joncţiune eso-gastrică (tratament adjuvant):* 240 mg la fiecare 2 săptămâni, pe durata a 30 minute sau 480 mg la fiecare 4 săptămâni, pe durata a 30 minute, pentru primele 16 săptămâni, urmat de 480 mg la fiecare 4 săptămâni, pe durata a 30 minute; *Cancer bronho-pulmonar altul decât cel cu celule mici, Limfom Hodgkin clasic, Cancer scuamos de cap şi gât, Carcinom urotelial şi, respectiv, Carcinom scuamos esofagian:* 240 mg la fiecare 2 săptămâni, pe durata a 30 minute. *OPDIVO în asociere cu ipilimumab: Melanom:* Doza recomandată este de nivolumab 1 mg/kg în asociere cu ipilimumab 3 mg/kg, administrată intravenos la fiecare 3 săptămâni pentru primele 4 doze. Această este urmată apoi de o a doua fază în care nivolumab este administrat în monoterapie pe cale intravenoasă fie în doză de 240 mg la fiecare 2 săptămâni sau în doză de 480 mg la fiecare 4 săptămâni. În faza de monoterapie, prima doză de nivolumab trebuie administrată: la interval de 3 săptămâni după ultima doză din terapia asociată nivolumab cu ipilimumab, dacă se utilizează doza de 240 mg la fiecare 2 săptămâni; sau la interval de 6 săptămâni după ultima doză din terapia asociată nivolumab cu ipilimumab, dacă se utilizează doza de 480 mg la fiecare 4 săptămâni (vezi, de asemenea, Tabelul 2 din RCP pentru duratele perfuziei); *Mezoteliom pleural malign:* Doza recomandată este de 360 mg nivolumab administrat intravenos pe durata a 30 minute la fiecare 3 săptămâni în asociere cu 1 mg/kg ipilimumab administrat intravenos pe durata a 30 minute la fiecare 6 săptămâni. Tratamentul se continuă până la 24 luni la pacienţii fără progresia bolii; *Carcinom renal şi cancer colorectal dMMR sau MSI-H:* Doza recomandată este de nivolumab 3 mg/kg în asociere cu ipilimumab 1 mg/kg, administrată intravenos la fiecare 3 săptămâni pentru primele 4 doze. Aceasta este urmată apoi de o a doua fază în care nivolumab este administrat în monoterapie pe cale intravenoasă fie în doză de 240 mg la fiecare 2 săptămâni sau în doză de 480 mg la fiecare 4 săptămâni (numai pentru RCC). În faza de monoterapie, prima doză de nivolumab trebuie administrată: la interval de 3 săptămâni după ultima doză din terapia asociată nivolumab cu ipilimumab, dacă se utilizează doza de 240 mg la fiecare 2 săptămâni; sau la interval de 6 săptămâni după ultima doză din terapia asociată nivolumab cu ipilimumab, dacă se utilizează doza de 480 mg la fiecare 4 săptămâni (numai pentru RCC) (vezi, de asemenea, Tabelul 3 din RCP pentru duratele perfuziei). *OPDIVO în asociere cu cabozantinib: Carcinom renal:* Doza recomandată este fie nivolumab 240 mg la fiecare 2 săptămâni sau nivolumab 480 mg la fiecare 4 săptămâni, administrat pe cale intravenoasă, în asociere cu cabozantinib 40 mg în fiecare zi, administrat pe cale orală (vezi, de asemenea, Tabelul 4 din RCP pentru duratele perfuziei). *OPDIVO în asociere cu ipilimumab şi chimioterapie: Cancer bronho-pulmonar altul decât cel cu celule mici:* Doza recomandată este de 360 mg nivolumab administrat intravenos pe durata a 30 minute la fiecare 3 săptămâni în asociere cu 1 mg/kg ipilimumab administrat intravenos pe durata a 30 minute la fiecare 6 săptămâni şi chimioterapie pe bază de săruri de platină administrată la fiecare 3 săptămâni. După finalizarea a 2 cicluri de chimioterapie, tratamentul se continuă cu 360 mg nivolumab administrat intravenos la fiecare 3 săptămâni în asociere cu 1 mg/kg ipilimumab la fiecare 6 săptămâni. Tratamentul este recomandat până la progresia bolii, toxicitate inacceptabilă sau până la 24 luni la pacienţii fără progresia bolii. *OPDIVO în asociere cu chimioterapie: Adenocarcinom gastric, de joncţiune eso-gastrică sau esofagian*: Doza recomandată este de 360 mg nivolumab, administrată intravenos pe durata a 30 minute în asociere cu chimioterapie pe bază de fluoropirimidine şi săruri de platină administrată la fiecare 3 săptămâni sau de 240 mg nivolumab administrat intravenos pe durata a 30 minute în asociere cu chimioterapie pe bază de fluoropirimidine şi săruri de platină administrată la fiecare 2 săptămâni (vezi pct. 5.1 din RCP). Tratamentul cu nivolumab este recomandat până la progresia bolii, toxicitate inacceptabilă sau până la 24 luni la pacienţii fără progresia bolii. *Durata tratamentului:* Tratamentul cu OPDIVO, fie sub formă de monoterapie sau în asociere cu ipilimumab, trebuie continuat atât timp cât se observă beneficii clinice sau până când nu mai este tolerat de pacient (şi până la durata maximă a terapiei, dacă este specificată pentru o indicaţie). În terapia adjuvantă, durata maximă a tratamentului cu OPDIVO este de 12 luni. În cazul administrării de OPDIVO în asociere cu cabozantinib, tratamentul cu OPDIVO trebuie continuat până la progresia bolii, toxicitate inacceptabilă sau până la 24 luni la pacienţii fără progresia bolii. Tratamentul cu cabozantinib trebuie continuat până la progresia bolii sau toxicitate inacceptabilă. Consultaţi RCP-ul pentru cabozantinib. S-au observat răspunsuri atipice (şi anume, o creştere tranzitorie iniţială a dimensiunii tumorii sau leziuni mici noi apărute în primele câteva luni, urmate de reducerea dimensiunilor tumorilor). La pacienţii cu o stare clinică stabilă, care prezintă semne iniţiale de progresie a bolii, se recomandă continuarea tratamentului cu nivolumab sau cu nivolumab în asociere cu ipilimumab, până la confirmarea progresiei bolii. Nu se recomandă creşterea sau scăderea dozelor pentru OPDIVO administrat în monoterapie sau în asociere cu alţi agenţi terapeutici. Poate fi necesară amânarea sau oprirea administrării tratamentului în funcţie de profilul individual de siguranţă şi tolerabilitate. Recomandările privind oprirea definitivă sau întreruperea temporară a dozelor sunt prezentate în Tabelul 5 din RCP. Recomandările detaliate privind conduita terapeutică în cazul reacţiilor adverse mediate imun sunt prezentate la pct. 4.4 din RCP. Atunci când nivolumab este administrat în asociere cu alţi agenţi terapeutici, se va consulta RCP-ul acestor alţi agenţi terapeutici administraţi în asociere pentru informaţii privind dozele. Tratamentul cu OPDIVO în monoterapie sau în asociere cu alţi agenţi terapeutici trebuie oprit definitiv în caz de: reacţii adverse de grad 4 sau reacţii adverse recurente de grad 3; reacţii adverse de grad 2 sau 3 persistente în pofida abordării terapeutice. Pacienţilor trataţi cu OPDIVO trebuie să li se înmâneze Cardul de atenţionare pentru pacient şi să li se aducă la cunoştinţă riscurile administrării OPDIVO (vezi, de asemenea, prospectul). Atunci când OPDIVO este administrat în asociere cu ipilimumab, dacă se întrerupe temporar administrarea oricăruia dintre aceste medicamente, se va întrerupe temporar şi administrarea celuilalt medicament. Dacă se reia utilizarea după o amânare a administrării dozei, se poate relua administrarea fie a tratamentului asociat sau a OPDIVO în monoterapie, pe baza evaluării individuale a pacientului. Atunci când OPDIVO este administrat în asociere cu chimioterapie, se va consulta RCP-ul pentru celelalte medicamente incluse în terapia asociată pentru informaţii privind dozele. Nu se recomandă creşterea sau scăderea dozelor pentru OPDIVO. Dacă se întrerupe temporar administrarea oricăruia dintre medicamente, se poate continua administrarea celorlalte medicamente. Dacă se reia utilizarea după o amânare a administrării dozei, se poate relua administrarea fie a tratamentului asociat, a OPDIVO în monoterapie sau a tratamentului numai cu chimioterapie, pe baza evaluării individuale a pacientului. Atunci când OPDIVO este utilizat în asociere cu cabozantinib, modificările tratamentului prezentate în Tabelul 5 din RCP se aplică, de asemenea, şi pentru OPDIVO ca parte a tratamentului. În plus, în cazul creşterii valorilor serice ale enzimelor hepatice, la pacienţii cu RCC cărora li se administrează OPDIVO în asociere cu cabozantinib, se impun modificările tratamentului prezentate la pct. 4.2, secţiunea „*OPDIVO în asociere cu cabozantinib pentru tratamentul RCC*", din RCP. *Copii şi adolescenţi:* Siguranţa şi eficacitatea OPDIVO la copii cu vârsta sub 18 ani nu au fost încă stabilite. Datele disponibile în prezent pentru OPDIVO administrat în monoterapie sau în asociere cu ipilimumab sunt prezentate la pct. 4.8 şi 5.1 din RCP, dar nu se poate face nicio recomandare privind dozele. *Vârstnici:* Nu este necesară ajustarea dozei la pacienţii vârstnici (≥ 65 ani). Mod de administrare: OPDIVO este numai pentru administrare intravenoasă. OPDIVO nu trebuie administrat intravenos rapid sau în bolus. Când se administrează în asociere cu ipilimumab şi/sau chimioterapie, OPDIVO trebuie administrat primul urmat de administrarea ipilimumab (dacă este cazul) şi apoi de chimioterapie în aceeaşi zi. Pentru fiecare perfuzie se vor utiliza pungi şi filtre pentru perfuzie diferite. Pentru instrucţiuni privind pregătirea şi manipularea medicamentului înainte de administrare, vezi pct. 6.6 din RCP. Contraindicaţii: Hipersensibilitate la substanţa activă sau la oricare dintre excipienţii enumeraţi la pct. 6.1 din RCP. Atenţionări şi precauţii speciale pentru

utilizare: Trasabilitate: Pentru a avea sub control trasabilitatea medicamentelor biologice, numele și numărul lotului medicamentului administrat trebuie înregistrate cu atenție. Reacții adverse mediate imun: Atunci când nivolumab este administrat în asociere, se va consulta RCP-ul pentru celelalte medicamente incluse în terapia asociată înainte de inițierea tratamentului. Reacțiile adverse mediate imun au survenit cu o frecvență mai mare atunci când nivolumab a fost administrat în asociere cu ipilimumab, comparativ cu utilizarea nivolumab în monoterapie. Reacțiile adverse mediate imun au survenit cu o frecvență similară atunci când OPDIVO a fost administrat în asociere cu cabozantinib, comparativ cu utilizarea nivolumab în monoterapie. Prin urmare, recomandările privind reacțiile adverse mediate imun prezentate la pct. 4.4 din RCP sunt aplicabile pentru OPDIVO ca parte a tratamentului în asociere, cu excepția cazurilor în care se menționează specific. Majoritatea reacțiilor adverse mediate imun s-au ameliorat sau au ajuns la rezoluție prin conduită terapeutică adecvată, inclusiv inițierea corticoterapiei și modificarea tratamentului (vezi pct. 4.2 din RCP). Reacțiile adverse mediate imun care afectează mai mult de un aparat sau sistem pot să apară simultan. În cazul terapiei asociate s-au raportat, de asemenea, reacții adverse cardiace și pulmonare, inclusiv embolie pulmonară. Pacienții trebuie monitorizați continuu pentru depistarea reacțiilor adverse cardiace și pulmonare, dar și a semnelor clinice, simptomelor și rezultatelor anormale ale testelor de laborator sugestive pentru dezechilibre electrolitice și deshidratare înainte de inițierea tratamentului și periodic pe durata acestuia. Pacienții trebuie monitorizați continuu (timp de cel puțin 5 luni după administrarea ultimei doze) deoarece o reacție adversă la tratamentul cu nivolumab sau cu nivolumab în asociere cu ipilimumab poate apărea în orice moment în timpul sau după oprirea terapiei. Pentru mai multe informații privind atenționările și precauțiile speciale pentru utilizare, vezi pct. 4.4 din RCP. Interacțiuni cu alte medicamente și alte forme de interacțiune: Nivolumab este un anticorp monoclonal uman, astfel încât nu s-au efectuat studii privind interacțiunile farmacocinetice. Nu se anticipează ca efectul inhibitor sau inductor asupra enzimelor citocromului P450, al medicamentelor administrate concomitent, să influențeze profilul farmacocinetic al nivolumab. *Terapie imunosupresoare sistemică:* Trebuie evitată utilizarea corticosteroizilor sistemici și a altor terapii imunosupresoare la momentul inițial, înaintea inițierii tratamentului cu nivolumab, din cauza posibilei interferențe cu activitatea farmacodinamică. Cu toate acestea, corticoterapia sistemică și alte terapii imunosupresoare pot fi utilizate după inițierea administrării nivolumab în scopul tratării reacțiilor adverse mediate imun. Fertilitatea, sarcina și alăptarea: Sarcina: Nu există date din utilizarea nivolumab la femeile gravide. Alăptarea: Nu se cunoaște dacă nivolumab se excretă în laptele uman. Fertilitatea: Nu s-au efectuat studii privind efectul nivolumab asupra fertilității. Efecte asupra capacității de a conduce vehicule și de a folosi utilaje: Pacienților trebuie să li se recomande precauție atunci când conduc vehicule sau folosesc utilaje până în momentul în care au certitudinea că tratamentul cu nivolumab nu îi afectează negativ. Reacții adverse: Nivolumab în monoterapie: *Rezumatul profilului de siguranță:* În setul de date cumulat provenit din administrarea nivolumab în monoterapie pentru multiple tipuri de tumori (n = 3771), perioada minimă de monitorizare variind între 2,3 și 28 luni, cele mai frecvente reacții adverse (≥ 10%) au fost fatigabilitatea (46%), durerea musculo-scheletică (31%), diareea (26%), greața (24%), tusea (24%), erupțiile cutanate tranzitorii (24%), dispneea (18%), pruritul (18%), scăderea apetitului alimentar (18%), constipația (17%), durerea abdominală (16%), infecțiile tractului respirator superior (16%), artralgia (15%), febra (14%), vărsăturile (14%), cefaleea (13%) și edemul (11%). Majoritatea reacțiilor adverse au fost ușoare până la moderate (grad 1 sau 2). Pentru o perioadă de monitorizare de minim 63 luni în NSCLC, nu au fost identificate noi semnale de siguranță. Nivolumab în asociere cu ipilimumab: *Rezumatul profilului de siguranță:* Atunci când nivolumab este administrat în asociere cu ipilimumab, se va consulta RCP-ul pentru ipilimumab înainte de inițierea tratamentului. Pentru informații suplimentare privind profilul de siguranță al ipilimumab în monoterapie, vă rugăm consultați RCP-ul pentru ipilimumab. *Melanom:* În setul de date cumulat provenit din administrarea nivolumab 1 mg/kg în asociere cu ipilimumab 3 mg/kg la pacienți cu melanom (n = 448), perioada minimă de monitorizare variind între 6 și 28 luni, cele mai frecvente reacții adverse (≥ 10%) au fost erupțiile cutanate tranzitorii (52%), fatigabilitatea (46%), diareea (43%), pruritul (36%), greața (26%), febra (19%), scăderea apetitului alimentar (16%), hipotiroidismul (16%), colita (15%), vărsăturile (14%), artralgia (13%), durerea abdominală (13%), cefaleea (11%) și dispneea (10%). Majoritatea reacțiilor adverse au fost ușoare până la moderate (grad 1 sau 2). *RCC și CRC dMMR sau MSI-H:* În setul de date cumulat provenit din administrarea nivolumab 3 mg/kg în asociere cu ipilimumab 1 mg/kg pentru multiple tipuri de tumori (n = 666), perioada minimă de monitorizare variind între 17,5 și 27,6 luni, cele mai frecvente reacții adverse (≥ 10%) au fost fatigabilitatea (58%), diareea (41%), durerea musculo-scheletică (39%), erupțiile cutanate tranzitorii (38%), pruritul (35%), greața (30%), tusea (29%), febra (29%), durerea abdominală (22%), artralgia (22%), scăderea apetitului alimentar (22%), infecțiile tractului respirator superior (21%), vărsăturile (21%), cefaleea (19%), dispneea (19%), hipotiroidismul (18%), constipația (18%), edemul (inclusiv edemul periferic) (16%), ametelile (14%), hipertiroidismul (12%), xerodermia (11%), hipertensiunea arterială (10%). Majoritatea reacțiilor adverse au fost ușoare până la moderate (grad 1 sau 2); *MPM:* În setul de date provenit din administrarea nivolumab 3 mg/kg în asociere cu ipilimumab 1 mg/kg la pacienți cu MPM (n = 300), perioada minimă de monitorizare fiind de 22,1 luni, cele mai frecvente reacții adverse (≥ 10%) au fost fatigabilitatea (43%), diareea (31%), erupțiile cutanate tranzitorii (30%), durerea musculo-scheletică (27%), greața (24%), scăderea apetitului alimentar (24%), pruritul (21%), constipația (19%) și hipotiroidismul (13%). Majoritatea reacțiilor adverse au fost ușoare până la moderate (grad 1 sau 2). Nivolumab în asociere cu alți agenți terapeutici: *Rezumatul profilului de siguranță:* Atunci când nivolumab este administrat în asociere, înainte de inițierea tratamentului se va consulta RCP-ul pentru componentele respective ale terapiei asociate. În setul de date provenit din administrarea nivolumab 240 mg la fiecare 2 săptămâni sau 360 mg la fiecare 3 săptămâni în asociere cu chimioterapie la pacienți cu adenocarcinom gastric, de GEJ sau esofagian (n = 782), perioada minimă de monitorizare fiind de 12,1 luni, cele mai frecvente reacții adverse au fost neuropatia periferică (53%), greața (48%), fatigabilitatea (44%), diareea (39%), vărsăturile (31%), scăderea apetitului alimentar (29%), durerea abdominală (27%), constipația (25%), durerea musculo-scheletică (20%), febra (19%), erupțiile cutanate tranzitorii (18%), stomatita (17%), sindromul de eritrodisestezie palmo-plantară (13%), tusea (13%), edemul (inclusiv edemul periferic) (12%), cefaleea (11%) și infecțiile tractului respirator superior (10%). Incidențele reacțiilor adverse de grad 3-5 au fost de 76% pentru nivolumab în asociere cu chimioterapie și de 64% pentru tratamentul numai cu chimioterapie. Durata mediană a terapiei a fost de 6,75 luni (IÎ 95%: 6,11, 7,36) pentru nivolumab în asociere cu chimioterapie și de 4,86 luni (IÎ 95%: 4,47, 5,29) pentru chimioterapie. În setul de date provenit din administrarea nivolumab 360 mg la fiecare 3 săptămâni în asociere cu ipilimumab 1 mg/kg la fiecare 6 săptămâni și 2 cicluri de chimioterapie în NSCLC (n = 358), perioada minimă de monitorizare fiind de 6,5 luni, cele mai frecvente reacții adverse au fost fatigabilitatea (36%), greața (26%), erupțiile cutanate tranzitorii (25%), diareea (20%), pruritul (18%), scăderea apetitului alimentar (16%), hipotiroidismul (15%) și vărsăturile (13%). Majoritatea reacțiilor adverse au fost ușoare până la moderate (grad 1 sau 2). Durata mediană a terapiei a fost de 6,1 luni (IÎ 95% 4,93, 7,06) pentru nivolumab în asociere cu ipilimumab și chimioterapie și de 2,4 luni (IÎ 95% 2,30, 2,83) pentru chimioterapie. Nivolumab în asociere cu cabozantinib: *Rezumatul profilului de siguranță:* Atunci când nivolumab este administrat în asociere cu cabozantinib, se va consulta RCP-ul pentru cabozantinib înainte de inițierea tratamentului. Pentru informații suplimentare privind profilul de siguranță al cabozantinib în monoterapie, vă rugăm consultați RCP-ul pentru cabozantinib. *RCC:* În setul de date provenit din administrarea nivolumab 240 mg la fiecare 2 săptămâni în asociere cu cabozantinib 40 mg o dată pe zi la pacienți cu RCC (n =320), perioada minimă de monitorizare fiind de 16,0 luni, cele mai frecvente reacții adverse (≥ 10%) au fost diareea (64,7%), fatigabilitatea (51,3%), sindromul de eritrodisestezie palmo-plantară (40,0%), stomatita (38,8%), durerea musculo-scheletică (37,5%), hipertensiunea arterială (37,2%), erupțiile cutanate tranzitorii (36,3%), hipotiroidismul (35,6%), scăderea apetitului alimentar (30,3%), greața (28,8%), durerea abdominală (25,0%), disgeuzia (23,8%), infecțiile tractului respirator superior (20,6%), tusea (20,6%), pruritul (20,6%), artralgia (19,4%), vărsăturile (18,4%), disfonia (17,8%), cefaleea (16,3%), dispepsia (15,9%), ametelile (14,1%), constipația (14,1%), febra (14,1%), edemul (13,4%), spasmul muscular (12,2%), dispneea (11,6%), proteinuria (10,9%) și hipertiroidismul (10,0%). Majoritatea reacțiilor adverse au fost ușoare până la moderate (grad 1 sau 2). Pentru informații complete privind reacțiile adverse, vezi pct. 4.8 din RCP. Raportarea reacțiilor adverse suspectate: Profesioniștii din domeniul sănătății sunt rugați să raporteze orice reacție adversă suspectată la: Agenția Națională a Medicamentului și a Dispozitivelor Medicale din România, Str. Aviator Sănătescu nr. 48, sector 1, București 011478- RO, Tel: + 4 0757 117 259, Fax: +4 0213 163 497, e-mail: adr@anm.ro. Supradozaj: În studiile clinice, nu au fost raportate cazuri de supradozaj. Lista excipienților: Vezi pct. 6.1 din RCP. Incompatibilități: OPDIVO nu trebuie perfuzat concomitent în aceeași linie intravenoasă cu alte medicamente. Perioada de valabilitate: Flacon nedeschis: 3 ani. După pregătirea soluției perfuzabile: Stabilitatea fizico-chimică în timpul utilizării este dependentă de modalitatea de pregătire a soluției perfuzabile și de condițiile de păstrare (vezi pct. 6.3 din RCP). Din punct de vedere microbiologic, soluția perfuzabilă pregătită, indiferent de solvent, trebuie administrată imediat. Dacă nu poate fi administrată imediat, intervalele de timp și condițiile de păstrare în timpul utilizării, înainte de administrare, sunt responsabilitatea utilizatorului și, în mod normal, nu sunt mai mari de 7 zile la 2°C până la 8°C sau de 8 ore (din totalul de 7 zile de păstrare) la temperatura camerei (≤ 25°C). Este necesară respectarea tehnicilor de asepsie în timpul pregătirii soluției perfuzabile (vezi pct. 6.6 din RCP). Precauții speciale pentru păstrare: A se păstra la frigider (2ºC–8ºC). A nu se congela. A se păstra în ambalajul original pentru a fi protejat de lumină. Flaconul sigilat poate fi păstrat la o temperatură controlată a camerei de până la 25°C, cu lumină în încăpere, timp de până la 48 de ore. Natura și conținutul ambalajului: 4 ml, 10 ml, 12 ml sau 24 ml de concentrat în flacon a 10 ml sau 25 ml (sticlă de tip I) cu dop (butil-cauciuc) și capac de siguranță detașabil (aluminiu). Cutie cu 1 flacon. Precauții speciale pentru eliminarea reziduurilor și alte instrucțiuni de manipulare: Pregătirea trebuie efectuată de personal instruit în conformitate cu regulile de bună practică, în special în ceea ce privește condițiile aseptice. *Calcularea dozei:* Pentru administrarea dozei totale la un pacient, poate fi necesar mai mult de un flacon de OPDIVO concentrat. *Nivolumab în monoterapie:* Doza prescrisă pentru pacient este de 240 mg sau 480 mg în funcție de indicație, indiferent de greutatea corporală (vezi pct. 4.2 din RCP). *Nivolumab în asociere cu ipilimumab:* Doza prescrisă pentru pacient este exprimată în mg/kg. Pe baza acestei doze prescrise, se calculează doza totală care trebuie administrată. *Nivolumab în asociere cu ipilimumab pentru tratamentul MPM:* Doza prescrisă pentru pacient este de 360 mg, administrată indiferent de greutatea corporală. *Nivolumab în asociere cu chimioterapie:* Doza prescrisă pentru pacient este de 360 mg sau 240 mg, administrată indiferent de greutatea corporală. *Nivolumab în asociere cu ipilimumab și chimioterapie:* Doza prescrisă pentru pacient este de 360 mg, administrată indiferent de greutatea corporală. *Nivolumab în asociere cu cabozantinib:* Doza prescrisă pentru pacient este nivolumab 240 mg sau 480 mg, administrată indiferent de greutatea corporală. Vezi pct. 6.6, secțiunea „Pregătirea și administrarea", din RCP. Deținătorul autorizației de punere pe piață: Bristol-Myers Squibb Pharma EEIG, Plaza 254, Blanchardstown Corporate Park 2, Dublin 15, D15 T867, Irlanda. Numărul(ele) autorizației de punere pe piață: EU/1/15/1014/001-004. Data primei autorizări: 19 Iunie 2015. Data ultimei reînnoiri a autorizației: 23 Aprilie 2020. Data revizuirii textului: Decembrie 2021. Informații detaliate privind acest medicament sunt disponibile pe site-ul Agenției Europene pentru Medicamente http://www.ema.europa.eu.

YERVOY (ipilimumab) - Informaţii esenţiale din rezumatul caracteristicilor produsului

Consultaţi Rezumatul Caracteristicilor Produsului (RCP) înainte de prescriere. **Compoziţia calitativă şi cantitativă:** Fiecare ml de concentrat conţine ipilimumab 5 mg. Ipilimumab este un anticorp monoclonal anti-CTLA-4 complet uman (IgG1κ). **Indicaţii terapeutice:** Melanom: YERVOY în monoterapie este indicat pentru tratamentul melanomului în stadii avansate (nerezecabil sau metastatic) la pacienţii adulţi, și adolescenți cu vârsta de 12 ani sau peste. YERVOY în asociere cu nivolumab este indicat pentru tratamentul melanomului în stadiu avansat (nerezecabil sau metastazat) la adulţi. În comparație cu monoterapia cu nivolumab, o creștere a supraviețuirii fără progresia bolii (SFP) și a supraviețuirii generale (SG) pentru asocierea nivolumab cu ipilimumab este stabilită numai la pacienții cu expresie tumorală redusă a PD-L1 (vezi pct. 4.4 și 5.1 din RCP). Carcinom renal (RCC): YERVOY în asociere cu nivolumab este indicat pentru tratamentul de primă linie al carcinomului renal avansat cu prognostic intermediar/nefavorabil, la adulți (vezi pct. 5.1 din RCP). Cancer bronho-pulmonar altul decât cel cu celule mici (NSCLC): YERVOY în asociere cu nivolumab și 2 cicluri de chimioterapie pe bază de săruri de platină este indicat pentru tratamentul de primă linie al cancerului bronho-pulmonar altul decât cel cu celule mici metastazat, la adulții ale căror tumori nu prezintă mutație sensibilizantă EGFR sau translocație ALK. Mezoteliom pleural malign (MPM): YERVOY în asociere cu nivolumab este indicat pentru tratamentul de primă linie al mezoteliomului pleural malign nerezecabil, la adulți. Cancer colorectal (CRC) cu deficiență de reparare a nepotrivirii ADN-ului (dMMR) sau cu instabilitate microsatelită de grad înalt (MSI-H): YERVOY în asociere cu nivolumab este indicat pentru tratamentul cancerului colorectal metastazat cu deficiență de reparare a nepotrivirii ADN-ului sau cu instabilitate microsatelită de grad înalt, după chimioterapie anterioară pe bază de asocieri de fluoropirimidine, la adulți (vezi pct. 5.1 din RCP). **Doze şi mod de administrare:** Doze: *YERVOY în monoterapie: Melanom:* Regimul de inducţie recomandat pentru YERVOY este de 3 mg/kg, administrat intravenos pe durata a 90 minute la fiecare 3 săptămâni pentru un total de 4 doze. Pacienţilor trebuie să li se administreze regimul complet de inducţie (4 doze) în funcţie de tolerabilitate, indiferent dacă apar leziuni noi sau dacă leziunile existente progresează. Evaluarea răspunsului tumoral trebuie efectuată doar după finalizarea terapiei de inducţie. *YERVOY în asociere cu nivolumab: Melanom:* Doza recomandată este de ipilimumab 3 mg/kg în asociere cu nivolumab 1 mg/kg, administrată intravenos la fiecare 3 săptămâni pentru primele 4 doze. Aceasta este urmată apoi de o a doua fază în care nivolumab este administrat în monoterapie pe cale intravenoasă fie în doză de 240 mg la fiecare 2 săptămâni **sau** în doză de 480 mg la fiecare 4 săptămâni. În faza de monoterapie, prima doză de nivolumab trebuie administrată: la interval de 3 săptămâni după ultima doză din terapia asociată nivolumab cu ipilimumab, dacă se utilizează doza de 240 mg la fiecare 2 săptămâni; sau la interval de 6 săptămâni după ultima doză din terapia asociată nivolumab cu ipilimumab, dacă se utilizează doza de 480 mg la fiecare 4 săptămâni (vezi, de asemenea, Tabelul 1 din RCP pentru duratele perfuziei); *Carcinom renal și cancer colorectal dMMR sau MSI-H:* Doza recomandată este de ipilimumab 1 mg/kg în asociere cu nivolumab 3 mg/kg, administrată intravenos la fiecare 3 săptămâni pentru primele 4 doze. Aceasta este urmată apoi de o a doua fază în care nivolumab este administrat în monoterapie pe cale intravenoasă fie în doză de 240 mg la fiecare 2 săptămâni **sau** în doză de 480 mg la fiecare 4 săptămâni (numai pentru RCC). În faza de monoterapie, prima doză de nivolumab trebuie administrată: la interval de 3 săptămâni după ultima doză din terapia asociată ipilimumab cu nivolumab, dacă se utilizează doza de 240 mg la fiecare 2 săptămâni; sau la interval de 6 săptămâni după ultima doză din terapia asociată ipilimumab cu nivolumab, dacă se utilizează doza de 480 mg la fiecare 4 săptămâni (numai pentru RCC) (vezi, de asemenea, Tabelul 2 din RCP pentru duratele perfuziei); *Mezoteliom pleural malign:* Doza recomandată este de 1 mg/kg ipilimumab administrat intravenos pe durata a 30 minute la fiecare 6 săptămâni în asociere cu 360 mg nivolumab administrat intravenos pe durata a 30 minute la fiecare 3 săptămâni. Tratamentul se continuă până la 24 luni la pacienții fără progresia bolii. *YERVOY în asociere cu nivolumab și chimioterapie: Cancer bronho-pulmonar altul decât cel cu celule mici:* Doza recomandată este de 1 mg/kg ipilimumab administrat intravenos pe durata a 30 minute la fiecare 6 săptămâni în asociere cu 360 mg nivolumab administrat intravenos pe durata a 30 minute la fiecare 3 săptămâni și chimioterapie pe bază de săruri de platină administrată la fiecare 3 săptămâni. După finalizarea a 2 cicluri de chimioterapie, tratamentul se continuă cu 1 mg/kg ipilimumab la fiecare 6 săptămâni în asociere cu 360 mg nivolumab administrat intravenos la fiecare 3 săptămâni. Tratamentul este recomandat până la progresia bolii, toxicitate inacceptabilă sau până la 24 luni la pacienții fără progresia bolii. *Durata tratamentului:* Tratamentul cu YERVOY în asociere cu nivolumab, trebuie continuat atât timp cât se observă beneficii clinice sau până când nu mai este tolerat de pacient (și până la durata maximă a terapiei, dacă este specificată pentru o indicație). S-au observat răspunsuri atipice (și anume, o creștere tranzitorie inițială a dimensiunii tumorii sau leziuni mici nou apărute în primele câteva luni, urmate de reducerea dimensiunilor tumorilor). La pacienții cu o stare clinică stabilă, care prezintă semne inițiale de progresie a bolii, se recomandă continuarea tratamentului cu YERVOY în asociere nivolumab, până la confirmarea progresiei bolii. Testele funcției hepatice (TFH) și testele funcţiei tiroidiene trebuie evaluate la momentul iniţial şi înaintea fiecărei doze de YERVOY. În plus, orice semne sau simptome de reacţii adverse mediate imun, inclusiv diaree şi colită, trebuie evaluate în timpul tratamentului cu YERVOY. Conduita terapeutică în cazul reacţiilor adverse mediate imun poate necesita întreruperea temporară a unei doze sau oprirea definitivă a terapiei cu YERVOY şi iniţierea corticoterapiei sistemice în doze mari. În unele cazuri, poate fi luată în considerare asocierea altei terapii imunosupresoare. Nu se recomandă creșterea sau scăderea dozelor. Poate fi necesară amânarea sau oprirea administrării tratamentului în funcţie de profilul individual de siguranţă şi tolerabilitate. Recomandările detaliate privind conduita terapeutică în cazul reacţiilor adverse mediate imun sunt prezentate la pct. 4.4 din RCP. Tratamentul cu YERVOY în asociere cu nivolumab trebuie oprit definitiv în caz de: reacții adverse de grad 4 sau reacții adverse recurente de grad 3; reacții adverse de grad 2 sau 3 persistente în pofida abordării terapeutice. Atunci când YERVOY este administrat în asociere cu nivolumab, dacă se întrerupe temporar administrarea oricăruia dintre aceste medicamente, se va întrerupe temporar şi administrarea celuilalt medicament. *Grupe speciale de pacienți: Copii şi adolescenţi:* Siguranţa şi eficacitatea YERVOY în monoterapie la copii cu vârsta sub 12 ani nu au fost stabilite. Foarte puține date sunt disponibile. YERVOY nu trebuie utilizat la copii cu vârsta sub 12 ani. Siguranța și eficacitatea YERVOY în asociere cu nivolumab la copii cu vârsta sub 18 ani nu au fost stabilite. Datele disponibile în prezent sunt prezentate la pct. 4.8 și 5.1 din RCP, dar nu se poate face nicio recomandare privind dozele. *Vârstnici:* În general, nu s-au raportat diferenţe în ceea ce priveşte siguranţa sau eficacitatea între pacienţii vârstnici (≥ 65 ani) şi cei mai tineri (< 65 ani). Datele provenite de la pacienții care urmează tratament de primă linie pentru RCC, cu vârsta de 75 ani sau peste, sunt prea limitate pentru a permite formularea unor concluzii referitoare la această grupă de pacienți (vezi pct. 5.1 din RCP). Nu sunt necesare ajustări specifice de doză. *Insuficienţă renală:* Nu sunt necesare ajustări specifice de doză la pacienții cu disfuncție renală ușoară până la moderată. *Insuficienţă hepatică:* Administrarea YERVOY se va efectua cu precauţie la pacienţii cu concentraţii plasmatice ale transaminazelor ≥ 5 x LSVN sau ale bilirubinei > 3 x LSVN înainte de iniţierea tratamentului. Mod de administrare: YERVOY se administrează intravenos. Durata perfuziei recomandată este de 30 sau 90 minute, în funcție de doză. YERVOY poate fi folosit pentru administrare intravenoasă fără diluare sau poate fi diluat cu soluție de clorură de sodiu 9 mg/ml (0,9%) pentru preparate injectabile sau cu soluție de glucoză 50 mg/ml (5%) pentru preparate injectabile până la concentraţii între 1 şi 4 mg/ml. YERVOY nu trebuie administrat intravenos rapid sau în bolus. Când se administrează în asociere cu nivolumab, sau în asociere cu nivolumab și chimioterapie, nivolumab trebuie administrat primul urmat de administrarea YERVOY și apoi de chimioterapie în aceeași zi. Pentru fiecare perfuzie se vor utiliza pungi și filtre pentru perfuzie diferite. Pentru instrucţiuni privind pregătirea și manipularea medicamentului înainte de administrare, vezi pct. 6.6 din RCP. **Contraindicaţii:** Hipersensibilitate la substanţa activă sau la oricare dintre excipienţii enumeraţi la pct. 6.1 din RCP. **Atenţionări şi precauţii speciale pentru utilizare:** Trasabilitate: Pentru a avea sub control trasabilitatea medicamentelor biologice, numele și numărul lotului medicamentului administrat trebuie înregistrate cu atenție. Ipilimumab în asociere cu nivolumab: Atunci când ipilimumab este administrat în asociere, se va consulta Rezumatul caracteristicilor produsului pentru celelalte componente ale terapiei asociate înainte de iniţierea tratamentului. Pentru informaţii suplimentare legate de atenţionări şi precauţii asociate tratamentului cu nivolumab, vă rugăm consultați RCP-ul pentru nivolumab. Majoritatea reacţiilor adverse mediate imun s-au ameliorat sau au ajuns la rezoluţie prin conduită terapeutică adecvată, inclusiv iniţierea corticoterapiei şi modificarea tratamentului. Reacţiile adverse mediate imun au survenit cu o frecvență mai mare atunci când nivolumab a fost administrat în asociere cu ipilimumab, comparativ cu utilizarea nivolumab în monoterapie. Reacții mediate imun: Tratamentul cu ipilimumab este asociat cu reacţii adverse inflamatorii care sunt rezultatul activităţii imune crescute sau excesive (reacţii adverse

mediate imun), corelată cel mai probabil cu mecanismul său de acţiune. Reacţiile adverse mediate imun, care pot fi severe sau care pun viaţa în pericol, pot apărea la nivelul aparatului digestiv, la nivel hepatic, cutanat, al sistemului nervos, endocrin sau la nivelul altor sisteme şi organe. Deşi majoritatea reacţiilor adverse mediate imun au apărut în perioada de inducţie, s-a raportat şi debutul acestora la câteva luni după administrarea ultimei doze de ipilimumab. Cu excepţia cazurilor în care se identifică o altă cauză, diareea, creşterea frecvenţei scaunelor, scaunele sangvinolente, creşterile valorilor TFH, erupţiile cutanate tranzitorii şi endocrinopatia trebuie considerate inflamatorii şi corelate cu terapia cu ipilimumab. Diagnosticul precoce şi conduita terapeutică adecvată sunt esenţiale pentru minimizarea complicaţiilor care pun viaţa în pericol. Recomandările specifice privind conduita terapeutică în cazul reacţiilor adverse mediate imun pentru utilizarea ipilimumab în monoterapie şi în asociere cu nivolumab: vezi RCP. Precauţii specifice afecţiunii: Pacienţi cu melanom ocular, melanom primar la nivelul SNC şi pacienţi cu metastaze cerebrale active nu au fost incluşi în studiul MDX010-20 (vezi pct. 5.1 din RCP). Reacţii legate de administrarea perfuziei: Pacienţii cu reacţii adverse uşoare sau moderate legate de administrarea perfuziei pot fi trataţi cu ipilimumab sau cu ipilimumab în asociere cu nivolumab sub supraveghere atentă. Premedicaţia cu medicamente antipiretice şi antihistaminice poate fi luată în considerare. Pacienţi cu boli autoimune: Ipilimumab poate interfera cu terapia imunosupresoare, ducând la exacerbarea afecţiunii subiacente sau la creşterea riscului de rejet al grefei. Administrarea ipilimumab trebuie evitată la pacienţii cu boli autoimune active severe în care activarea imună suplimentară se asociază cu potenţial iminent de a pune viaţa în pericol. La alţi pacienţi cu antecedente de boli autoimune, ipilimumab trebuie utilizat cu precauţie, după evaluarea atentă a raportului potențial risc-beneficiu pentru fiecare pacient în parte. Pacienţi care urmează o dietă cu restricţie de sodiu: YERVOY conţine sodiu. Acest lucru trebuie avut în vedere la pacienţii care urmează o dietă cu restricţie de sodiu. Administrare concomitentă, respectiv, Administrare secvenţială cu vemurafenib: vezi pct. 4.4 din RCP. **Interacţiuni cu alte medicamente şi alte forme de interacţiune:** Corticosteroizi: Administrarea corticoterapiei sistemice înainte de iniţierea terapiei cu ipilimumab trebuie evitată din cauza potenţialului de interacţiune cu activitatea şi eficacitatea farmacodinamică a acestuia din urmă. Cu toate acestea, corticoterapia sistemică sau terapia cu alte imunosupresoare poate fi utilizată după iniţierea ipilimumab pentru tratamentul reacţiilor adverse mediate imun. Anticoagulante: Deoarece hemoragia digestivă este o reacţie adversă asociată terapiei cu ipilimumab, pacienţii care necesită terapie anticoagulantă concomitentă trebuie monitorizaţi cu stricteţe. **Fertilitatea, sarcina şi alăptarea:** YERVOY nu este recomandat în timpul sarcinii sau la femei aflate la vârsta fertilă care nu utilizează măsuri contraceptive eficace, cu excepţia cazurilor în care beneficiile clinice depăşesc riscul potenţial. Din cauza potenţialului de a determina reacţii adverse la copiii alăptaţi, trebuie luată decizia fie de a întrerupe alăptarea, fie de a opri tratamentul cu YERVOY având în vedere beneficiul alăptării pentru copil şi beneficiul tratamentului pentru femeie. Nu se cunoaşte efectul ipilimumab asupra fertilităţii la femei şi bărbaţi. **Reacţii adverse:** Rezumatul profilului de siguranţă: *Ipilimumab în monoterapie: Foarte frecvente (≥ 1/10):* scăderea apetitului alimentar, diaree, vărsături, greaţă, erupţii cutanate tranzitorii, prurit, fatigabilitate, reacţii la locul administrării perfuziei, febră; *Frecvente (≥ 1/100 şi < 1/10):* durere tumorală, anemie, limfopenie, hipopituitarism (inclusiv hipofizită), hipotiroidism, deshidratare, hipopotasemie, stare de confuzie, neuropatie senzitivă periferică, ameţeli, cefalee, letargie, vedere înceţoşată, durere oculară, hipotensiune arterială, eritem facial tranzitor, bufeuri, dispnee, tuse, hemoragie gastrointestinală, colită, constipaţie, boală de reflux gastroesofagian, durere abdominală, inflamaţie a mucoaselor, anomalii ale funcţiei hepatice, dermatită, eritem, vitiligo, urticarie, eczemă, alopecie, transpiraţii nocturne, xerodermie, artralgie, mialgie, durere musculo-scheletică, spasm muscular, frisoane, astenie, edem, durere, afecţiune asemănătoare gripei, creşterea concentraţiei plasmatice a alanin aminotransferazei, creşterea concentraţiei plasmatice a aspartat aminotransferazei, creşterea concentraţiei plasmatice a fosfatazei alcaline, creşterea concentraţiei bilirubinei sanguine, scădere în greutate. *Ipilimumab în asociere cu nivolumab: Melanom:* În setul de date cumulat provenit din administrarea ipilimumab 3 mg/kg în asociere cu nivolumab 1 mg/kg la pacienţi cu melanom (n = 448), perioada minimă de monitorizare variind între 6 şi 28 luni, cele mai frecvente reacţii adverse (≥ 10%) au fost erupţiile cutanate tranzitorii (52%), fatigabilitatea (46%), diareea (43%), pruritul (36%), greaţa (26%), febra (19%), scăderea apetitului alimentar (16%), hipotiroidismul (16%), colita (15%), vărsăturile (14%), artralgia (13%), durerea abdominală (13%), cefaleea (11%) şi dispneea (10%). Majoritatea reacţiilor adverse au fost uşoare până la moderate (grad 1 sau 2). În rândul pacienţilor trataţi cu ipilimumab 3 mg/kg în asociere cu nivolumab 1 mg/kg în studiul CA209067, la 154/313 (49%) dintre aceştia primul debut al reacţiilor adverse de grad 3 sau 4 a avut loc pe durata fazei iniţiale de administrare asociată. Dintre cei 147 pacienţi din acest grup care au continuat tratamentul în faza de administrare a unui singur medicament, 47 (32%) au prezentat cel puţin o reacţie adversă de grad 3 sau 4 pe durata fazei de administrare a unui singur medicament. Pentru o perioadă de monitorizare de minim 60 luni a pacienţilor din studiul CA209067, nu au fost identificate noi semnale de siguranţă. *RCC și CRC dMMR sau MSI-H:* În setul de date cumulat provenit din administrarea ipilimumab 1 mg/kg în asociere cu nivolumab 3 mg/kg pentru multiple tipuri de tumori (n = 666), perioada minimă de monitorizare variind între 17,5 și 27,6 luni, cele mai frecvente reacții adverse (≥ 10%) au fost fatigabilitatea (58%), diareea (41%), durerea musculo-scheletică (39%), erupțiile cutanate tranzitorii (38%), pruritul (35%), greața (30%), tusea (29%), febra (29%), durerea abdominală (22%), artralgia (22%), scăderea apetitului alimentar (22%), infecțiile tractului respirator superior (21%), vărsăturile (21%), cefaleea (19%), dispneea (19%), hipotiroidismul (18%), constipația (18%), edemul (inclusiv edemul periferic) (16%), amețelile (14%), hipertiroidismul (12%), xerodermia (11%), hipertensiunea arterială (10%). Majoritatea reacţiilor adverse au fost uşoare până la moderate (grad 1 sau 2). În rândul pacienţilor trataţi cu ipilimumab 1 mg/kg în asociere cu nivolumab 3 mg/kg, la 194/666 (29%) dintre aceștia primul debut al reacţiilor adverse de grad 3 sau 4 a avut loc pe durata fazei inițiale de administrare asociată. Dintre cei 474 pacienți din acest grup care au continuat tratamentul în faza de administrare a nivolumab în monoterapie, 168 (35%) au prezentat cel puțin o reacție adversă de grad 3 sau 4 pe durata fazei de administrare a unui singur medicament. *MPM:* În setul de date provenit din administrarea ipilimumab 1 mg/kg în asociere cu nivolumab 3 mg/kg la pacienți cu MPM (n = 300), perioada minimă de monitorizare fiind de 22,1 luni, cele mai frecvente reacții adverse (≥ 10%) au fost fatigabilitatea (43%), diareea (31%), erupțiile cutanate tranzitorii (30%), durerea musculo scheletică (27%), greața (24%), scăderea apetitului alimentar (24%), pruritul (21%), constipația (19%) și hipotiroidismul (13%). Majoritatea reacţiilor adverse au fost uşoare până la moderate (grad 1 sau 2). *Ipilimumab în asociere cu nivolumab și chimioterapie (vezi pct. 4.2)* Atunci când ipilimumab este administrat în asociere, înainte de inițierea tratamentului se va consulta Rezumatul caracteristicilor produsului pentru componentele respective ale terapiei associate. În setul de date provenit din administrarea ipilimumab 1 mg/kg la fiecare 6 săptămâni în asociere cu nivolumab 360 mg la fiecare 3 săptămâni și 2 cicluri de chimioterapie în NSCLC (n = 358), perioada minimă de monitorizare fiind de 6,5 luni, cele mai frecvente reacții adverse au fost fatigabilitatea (36%), greața (26%), erupțiile cutanate tranzitorii (25%), diareea (20%), pruritul (18%), scăderea apetitului alimentar (16%), hipotiroidismul (15%) și vărsăturile (13%). Majoritatea reacțiilor adverse au fost ușoare până la moderate (grad 1 sau 2). Durata mediană a terapiei a fost de 6,1 luni (IÎ 95% 4,93, 7,06) pentru ipilimumab în asociere cu nivolumab și chimioterapie și de 2,4 luni (IÎ 95% 2,30, 2,83) pentru chimioterapie. Pentru informaţii complete privind reacţiile adverse, vezi RCP. Raportarea reacţiilor adverse suspectate: Profesioniştii din domeniul sănătăţii sunt rugaţi să raporteze orice reacţie adversă suspectată la: Agenţia Naţională a Medicamentului şi a Dispozitivelor Medicale, Str. Aviator Sănătescu nr. 48, sector 1, Bucureşti 011478- RO, Tel: + 4 0757 117 259, Fax: +4 0213 163 497, e-mail: adr@anm.ro. **Lista excipienţilor:** Vezi pct. 6.1 din RCP. **Incompatibilităţi:** În absenţa studiilor de compatibilitate, acest medicament nu trebuie amestecat cu alte medicamente. **Perioada de valabilitate:** Vezi pct. 6.3 din RCP. **Precauţii speciale pentru păstrare:** A se păstra la frigider (2°C-8°C). A nu se congela. A se păstra în ambalajul original pentru a fi protejat de lumină. Pentru condiţiile de păstrare a medicamentului după prima deschidere sau diluare, vezi pct. 6.3 din RCP. **Natura şi conţinutul ambalajului:** Cutie cu 1 flacon a 10 ml de concentrat. Cutie cu 1 flacon a 40 ml de concentrat. **Precauţii speciale pentru eliminarea reziduurilor şi alte instrucţiuni de manipulare:** Prepararea trebuie efectuată de personal instruit în conformitate cu reglementările de bună practică, în special în ceea ce priveşte condiţiile aseptice. **Deţinătorul autorizaţiei de punere pe piaţă:** Bristol-Myers Squibb Pharma EEIG, Plaza 254, Blanchardstown Corporate Park 2, Dublin 15, D15 T867, Irlanda. **Data revizuirii textului:** Octombrie 2021. Informaţii detaliate privind acest medicament sunt disponibile pe site-ul Agenţiei Europene pentru Medicamente http://www.ema.europa.eu. Medicament eliberat pe bază de prescripţie medicală restrictivă: PR. Acest material promoţional este destinat profesioniştilor din domeniul sănătăţii.

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