BJMO clinic

Belgian Journal of Medical Oncology

Special edition
Immuno-oncology

THE BELGIAN JOURNAL OF MEDICAL ONCOLOGY IS THE OFFICIAL JOURNAL OF THE BELGIAN SOCIETY OF MEDICAL ONCOLOGY (BSMO) AND THE BELGIAN ASSOCIATION FOR CANCER RESEARCH (BACR)

COLOPHON

This publication is a special edition from the publisher of the Belgian Journal of Medical Oncology, Ariez International Publishers BV. The aim of this special is to inform clinicians, active in the field of Oncology, on important Highlights of leading international and national medical symposia & congresses. In addition other new developments, opinions and insights of relevance to daily clinical practice, are discussed with the aim of supporting daily clinical decision making and management of patients with oncologic diseases or adherent symptoms and medical needs.
Special editions are distributed amongst medical specialists in Belgium, such as oncologists, surgeons and radiotherapists.

PUBLISHER AND EDITORIAL OFFICE
Ariez International B.V.
Ms. E. van Zanten, MSc
c/o Oude Houtlei 118-120, 9000 Gent, Belgium
Tel: 0031-75-642 94 20, Fax: 0031-75-642 94 21
E-mail: info@ariez.be

SUBSCRIPTIONS
For paid subscriptions, please refer to the publisher: info@ariez.be.

The content of this special edition of the BJMO was reviewed by the editorial board of the BJMO.

COVER ILLUSTRATION
Getty Images

ISSN-NUMMER
1784-7141

BJMO immuno-oncology special

INTRODUCTION

DEAR COLLEAGUE

Just a couple of weeks ago, the **2018 Nobel Prize in Physiology or Medicine** was awarded to **James P. Allison** and **Tasuku Honjo** "for their discovery of cancer therapy by inhibition of negative immune regulation." They discovered critical receptor-ligands in the interactions between dendritic cells and T-cells and between T-cells and tumor cells more than 25 years ago and subsequently developed the therapeutic approaches that were fundamental to the revolution in clinical cancer therapy that began 15 years ago, initially with anti-CTLA4 antibodies and later with the development of antibodies targeting PD1/PD-L1. These antibodies foster and release anticancer auto-immunity.

The immunotherapeutic revolution in oncology is still ongoing (with varying success), but these agents are already helping patients with a broad range of cancer types. The 2018 immuno-oncology special of the BJMO covers **updates** on various aspects of cancer immunotherapy.

The article on **Head and neck cancer** not only discusses the clinical data with immuno-oncology in this tumor type, but also brings a comprehensive history of cancer immunotherapy efforts throughout the last decades and as such transcends the topic of head and neck cancer.
With the BSMO, we are proud to present the **BSMO Immunomanager program** https://www.bsmo.be/immunomanager/ developed by Sandrine Aspeslagh and colleagues. This on-line tool helps physicians to adequately deal with the typical toxicities seen with immune checkpoint inhibitors.
Merkel cell carcinoma (MCC) has slong been a very difficult to treat and often very aggressive cancer type. Recently, immunotherapy has emerged as a new standard in the treatment of advanced MCC, giving new hope to patients.
Breakthroughs are also coming in the uese of immunotherapy for **triple-negative breast cancer**, a breast cancer subtype without available targeted therapy options.
Together with melanoma, non-small lung cancer has been the tumor type in which the first profound immunotherapy breakthroughts were established. In this issue, the editor has written a review on the current status of immunotherapy for **locally advanced unresectable non-small cell lung cancer.**

The final article of this special BJMO edition is addressing the importance of the **Tumor microenvironment** in modulating the response to the current immune checkpoint inhibitors, a complex target for ongoing additional therapeutic research. As a personal comment I would like to add that some of the apparent differences observed between PD1/PD-L1 inhibitors and the factors that influence their activity might come from inter-trial variability, and as long as we do not have head to head comparisons, they should all be considered equivalent.

We thank all the authors for their effort in assembling this exciting special edition of the BJMO.

Best regards,

Jacques De Grève
Editor-in-Chief


James P. Allison and Tasuku Honjo

Immune-modulating antibodies in head and neck cancer: past, present, and future

P. Szturz MD, PhD[1], J. B. Vermorken MD, PhD[2]

SUMMARY

Squamous cell carcinoma of the head and neck (SCCHN) has recently expanded the growing range of oncologic diseases successfully treated with immune-modulating agents. With the origins dating back to the nineteenth century, the concept of immunotherapy was repeatedly revisited and refined but also rejected and criticized. Currently, its armamentarium comprises tumour-specific antibodies, cancer vaccines, cytokines, adoptive T-cell transfer, and immune-modulating antibodies. Among these approaches it has been the latter one drawing major attention from healthcare professionals. Nivolumab and pembrolizumab are monoclonal immunoglobulins directed against programmed cell death protein-1 (PD-1), an immune-checkpoint negatively regulating T-cells. In second-line recurrent and/or metastatic SCCHN, two phase III studies demonstrated meaningful clinical benefit achieved by these drugs, dubbed checkpoint inhibitors, compared with standard monotherapy (methotrexate, docetaxel, or cetuximab). In the CheckMate-141 trial, nivolumab significantly improved median overall survival (OS) from 5.1 to 7.5 months. A similar benefit achieved by pembrolizumab in KEYNOTE-040 fell short of statistical significance (8.4 *vs*. 6.9 months), probably due to post-study immune-checkpoint therapy leading to a better-than-expected survival in the control arm. However, the classical outcome measures do not fully capture the exceptional activity of these agents. Apart from low frequency of severe adverse events (13% *vs*. 35% with standard therapy), these antibodies can induce durable tumour responses and retain activity even after several previous chemotherapy lines. With their advent in first-line palliative regimens and protocols for locally advanced disease, further progress is expected. Reliable predictive biomarkers are urgently needed, and several candidates are being evaluated. Among them, tumour mutational burden and gut microbiota offer an innovative approach to biomarker-enrichment strategies.

LOOKING BACK AT THE PAST DECADES

Big things have small beginnings. In the case of immunotherapy, the beginnings were scattered across centuries. It took some luck and a lot of effort to accomplish the individual steps and to fit them together as pieces of a jigsaw puzzle. In fact, the revolutionary discovery of vaccination against smallpox (*variola major*) by *Edward Jenner* in 1796 was preceded by a report of *John Fewster* on the protective efficacy of cowpox infection already 30 years earlier. Of note, the long-lasting history of purposeful inoculation with *variola minor* virus should be credited to the Ottoman Empire and probably also to ancient China, which were thus the first to manipulate the human immune system.[1] The implication of immune reactions in cancer biology was pointed out in the second half of the nineteenth century. At

[1]Department of Oncology, Lausanne University Hospital (CHUV), Lausanne, Switzerland

[2]Department of Medical Oncology, Antwerp University Hospital, Edegem, Belgium and Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium

Please send all correspondence to: J.B. Vermorken, Department of Medical Oncology, Antwerp University Hospital Wilrijkstraat 10, 2650 Edegem, Belgium, Tel: +32 3 821 45 48, E-mail: JanB.Vermorken@uza.be

Conflict of interest: P. Szturz received lecturer fee from Merck-Serono.

J.B. Vermorken participated in advisory boards of Amgen, AstraZeneca, Boehringer Ingelheim, Innate Pharma, Merck KGaA, Merck Sharp & Dome Corp, PCI Biotech, Synthon Biopharmaceuticals and received lecturer fee from Merck-Serono, Bristol-Myers Squibb, and Sanofi.

Key Words: Head and neck cancer, targeted therapy, immunotherapy, nivolumab, pembrolizumab, biomarkers, adverse events

What can the tumour microenvironment tell us?

C. Boeckx, PhD[1], E. Smits, PhD[2,3], J. Jacobs, PhD[2,4]

Nowadays, PD-L1/PD-1 immune checkpoint inhibitors have become a key part of the clinical management of cancer. Improving our understanding of anti-cancer immune response, which is influenced by a complex set of tumour, host and environment factors, will further broaden the clinical applicability of these treatments. In this review, we discuss several approaches to evaluate the tumour microenvironment (TME) in clinical practice as well as a view on future predictive biomarkers for cancer immunotherapy.

INTRODUCTION

For several decades, cancer was seen as a mass of tumour cells, whereas nowadays solid tumours are known to be heterogeneous entities in which tumour and host cells interact with each other. This ecosystem, known as the *tumour microenvironment* (TME), is composed of tumour cells, normal epithelial cells, fibroblasts, blood and lymphatic vessels, structural components and infiltrating immune cells. Furthermore, immune evasion has been recognised as a hallmark of cancer, which means that it is a key feature of cancer cells to be able to escape from immune-mediated destruction. These insights are the impetus for the identification of new immunotherapeutic targets and the development of new agents that aim to strengthen the anti-tumour immune response. Cancer immunotherapy encompasses several subtypes of immune treatments, such as therapeutic cancer vaccines, adoptive T-cell transfer, cytokines, monoclonal antibodies and immunomodulatory agents, of which checkpoint inhibitor therapies have been the most broadly successful to date. As the immune infiltrate plays a crucial role in the development and progression of cancer, the evaluation of infiltrating immune cells is of great interest to clinicians, pathologists and researchers.

THE HOST IMMUNE RESPONSE: IMMUNE-EDITING AND THE CANCER IMMUNITY CYCLE

Under normal conditions, any foreign substance or protein can be recognised and destroyed by the immune system. Likewise, the immune system can identify tumour cells and eradicate them before they cause harm.[1] This process is known as *immune surveillance*, where the innate and adaptive immune system work closely together and interact with the tumour cells via direct contact, chemokine or cytokine signalling. Innate immune cells, such as the natural killer cells, can exert direct cytotoxic effects against tumour cells that lack certain major histocompatibility complex (MHC) 1-surface molecules, resulting in the recruitment and activation of other immune cells.[2] Antigen-presenting cells, such as dendritic cells work closely together with the cytotoxic T-cells (CD8+ cells) from the adaptive immune system and both play a crucial role in the *cancer-immunity cycle*. This is a stepwise and cyclic process that must be fulfilled for an immune response to lead to effective killing of tumour cells (*Figure 1*).[3] However, successful completion of this process is only guaranteed when this process is initiated and allowed to proceed and expand iteratively. The generation of this

[1]Roche Diagnostics Belgium, [2]Center for Oncological Research (CORE), University of Antwerp, [3]Laboratory of Experimental Hematology (LEH), Vaccine and Infectious Disease Institute, University of Antwerp, [4]Department of Pathology, Antwerp University Hospital
Please send all correspondence to: Carolien Boeckx, PhD, Roche Diagnostics, Schaarbeeklei 198, Vilvoorde, Belgium
Tel: 0472/787945, E-mail: carolien.boeckx@roche.com

Conflict of interest: Carolien Boeckx is an employee of Roche Diagnostics Belgium. Illustrations were made by www.geert.be
Key words: Tumour microenvironment, immunotherapy, immune phenotypes, PD-L1

Immune checkpoint inhibition in triple negative breast cancer: targeting Achilles' heel?

V. Geldhof[1,2], K. Punie[2,3], H. Wildiers[2,3]

Triple negative breast cancers pose an important challenge both for patients and their clinicians due to their aggressive disease course, poor long-term survival and lack of effective systemic treatment options. Recent scientific advances show that the adaptive immune system harbors the intrinsic capacity to eradicate cancer, generally through mechanisms that involve cytotoxic T-cells. Immune checkpoint inhibition boosts the host-anti-tumor response in many solid tumors, including breast cancer. However, cancer cells acquire ways to evade immunosurveillance and intra-tumoral T-cells are often functionally impaired, resulting in overt clinical cancer. Interestingly, the efficacy of immune checkpoint inhibition appears to correlate with tumor immunogenicity and the tumor mutational burden. Triple negative breast cancer has the highest tumor mutational burden of all breast cancer subtypes and therefore is believed to be the most immunogenic subtype. For this reason, clinical trials to date mainly focus on this specific subtype. Here, we review the accumulating evidence for immune checkpoint blockade in triple negative breast cancer.

INTRODUCTION

Triple negative breast cancers (TNBCs) account for 12-17% of all types of breast cancer and lack (by definition) the expression of estrogen/progesterone receptors and HER2 overexpression and/or amplification. This results in an aggressive disease entity that is resistant to both hormonal and HER2-targeted therapies.[1] In the absence of targeted options and specific treatment guidelines, the current therapy in the advanced TNBC setting consists of standard chemotherapy regimens, associated with poor response rates and short progression-free (PFS) and overall survival (OS).[2]

It is well known that the adaptive immune system has the ability to eradicate malignant cells through mechanisms involving T helper 1-, Natural Killer- and cytotoxic T-cells.[3] In various tumors, including TNBC, a high percentage of tumor infiltrating lymphocytes (TILs) is associated with improved OS.[4,5] Furthermore, compared to paired early TNBC samples, the amount of TILs in advanced TNBC decreases, possibly under the influence of earlier cytostatic treatments but also as tumors evade immunosurveillance.[6] Cancer cells often evade immunosurveillance by various mechanisms resulting in T-cell exclusion and exhaustion e.g. by attracting immunosuppressive cells or hijacking immune checkpoints which prevent excessive T-cell activation in physiological conditions. To date, the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), programmed death-1 (PD-1) and its ligand PD-L1 are the best characterized immune checkpoints and therapeutic administration of antibodies against these proteins (*Table 1*) alleviate the immune system from its cancer-induced restraint.[7]

In a wide array of solid tumors, immune checkpoint blockade (ICB) has emerged as a valuable alternative option to the classical cytotoxic drugs.[7] However, response rates often vary depending on tumor type and (immunosuppressive) characteristics of the tumor micro-environment, and fail-safe predictors for clinical response are currently lacking. Recent evidence hints towards a prediction of response to ICB based on cancer cell mutational burden and the expression of neoantigens,

[1]Laboratory of Angiogenesis and Vascular Metabolism, VIB Center for Cancer Biology, VIB, Leuven, Belgium [2]University Hospitals Leuven, department of general medical oncology, Herestraat 49, 3000 Leuven, Belgium [3]KU Leuven – University of Leuven, department of oncology, Herestraat 49, 3000 Leuven, Belgium. Please send all correspondence to: H. Wildiers, Herestraat 49, 3000 Leuven; Tel: 016/ 346900; E-mail: hans.wildiers@uzleuven.be

Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest

Key words: triple negative breast cancer, pembrolizumab, nivolumab, ateolizumab, nab-paclitaxel, radiotherapy, PARP

BSMO Immunomanager program

S. Aspeslagh[1], V. Kruse[2], E. De Langhe[3], P. Jacques[4], O. Malaise[5], D. Elewaut[4], B. Lauwerys[6], R. Wittoek[4], Y. Piette[4,7], B. Neyns[8]#

Immunotherapy has become a standard of care for patients with many different advanced solid tumors. However, boosting the immune system can induce immune related side effects, referred to as "immune-related adverse events" (irAEs). Because oncologists are not always familiar with these inflammatory autoimmune syndromes, the BSMO immunotaskforce has launched the immunomanager website which summarizes the treatment options for the most frequent irAEs including endocrine (e.g. hypo- and hyperthyroidism), digestive (e.g. colitis), pneumological (e.g. pneumonitis), dermatological and other types of irAEs. In the near future, the BSMO immunotaskforce plans to review these recommendations with Belgian organ specialists and their associations. We believe that through collaborations between organ specialists and oncologists we will be able to establish better recommendations, resulting in a better outcome for cancer patients who develop an irAE during immunotherapy.

INTRODUCTION

In recent years, immunotherapy has revolutionized the way we treat cancer patients. Metastatic patients with several tumor types can now benefit from long lasting clinical responses with checkpoint inhibition. Furthermore, very promising results have been presented with immunotherapy in the adjuvant setting. In Belgium, checkpoint inhibitors are reimbursed for the treatment of different metastatic cancers and since the first of September, nivolumab is also approved for the adjuvant treatment of melanoma (*Figure 1*). The main goal of immunotherapy is to boost the immune system in order for it to eradicate cancer cells. Side effects are mainly related to the fact that the immune system becomes overactive or recognizes 'self' instead of cancer cells. This results in inflammatory autoimmune-like syndromes with symptoms that are often completely different from the classical side effects seen with chemotherapy or targeted therapy. Because of their different pathophysiology these irAEs require a different treatment, mostly requiring temporary immunosuppressive treatment.

In order to better understand the side effects, oncologists need to understand the pathophysiology of these inflammatory autoimmune syndromes and in a sense become immuno-oncologists. Up to now several types of inflammatory autoimmune syndromes ranging from endocrine to gastrointestinal to neurological pathologies have been reported.[1] Thyroid dysfunction occurs rather often (around 10% in patients treated with anti-PD-1 moncolonal antibodies [mAb]), whereas cardiac side effects are very rare (probably <1%). Because oncologists are not always entirely familiar with autoimmune problems, many symptoms may remain unde

[1]Department of Medical Oncology, Institut Jules Bordet – ULB, Brussels, Belgium, [2]Department of Medical Oncology, UZgent -Ghent University, Belgium, [3]Department of Rheumatology, UZ Leuven, Belgium, [4]Department of Rheumatology, UZgent-Ghent University, Belgium, [5]Department of Rheumatology, CHU Liège, Belgium, [6]Department of Rheumatology, UCLouvain, Belgium, [7]Department of Rheumatology, AZ Sint Jan, Brugge, Belgium, [8]Department of Medical Oncology, UZ Brussel, Belgium

Corresponding author contact details

Sandrine Aspeslagh, Institut Jules Bordet, Rue Heger 1, 1000 Brussels, Belgium

E-mail: sandrine.aspeslagh@bordet.be

on behalf of the BSMO immunotaskforce (Other members: Jean-François Baurain, UCLouvain; Oliver Bechter, KUL; Andrée Rorive, CHU Liège); on behalf of the rheumato-onco taskforce (Other members: Valérie Badot CHU Brugmann; Jacques Bentin, CHU Brugmann; Isabelle de Wergifosse, Jessa Ziekenhuis; Silvana Di Romana, CHU St Pierre Caroline Van Durme, CHC Liège; Mark Walschot, UZ Brussel)

Merkel cell carcinoma and immune checkpoint inhibition: where do we stand now?

S. De Keukeleire, MD, drs[1]; V. Kruse, MD, PhD[1]; S. Rottey, MD, PhD[2]

Immune checkpoint inhibition (ICI) has been acknowledged as a breakthrough treatment in multiple advanced cancer types. This is also the case in metastatic Merkel Cell Carcinoma (MCC), a disease that is historically associated with a poor prognosis. Recently, several randomized trials demonstrated superior results of ICI compared to chemotherapeutic agents in patients with metastatic MCC, with less toxicity, an increased overall survival (OS), and more durable responses. Therefore, ICI is now generally considered as a new standard treatment option in this setting.

INTRODUCTION

MCC is a rare, aggressive, neuro-endocrine tumor of the skin. Locoregional recurrence and metastasis of the disease are frequent and the associated mortality rate is high, with a five-year overall survival of 55.6%.[1] The pathophysiology of MCCs is mainly based on UV-exposure, impaired immune function, older age and Merkel cell polyoma virus DNA integration (MCPyV).[2] The current standard treatment for MCC mainly depends on the tumor stage. In patients with localized disease, the standard treatment primarily consists of surgery and/or radiotherapy, while chemotherapeutics are mostly reserved for patients with metastatic disease. In general, MCC is considered to be a chemo-sensitive tumor type. However, due to their rarity, literature data regarding chemotherapy schedules in metastatic MCC are scanty.[1] Currently, patients with metastatic disease are preferably treated with a combination of platinum agents and etoposide. Unfortunately, the responses to these platinum doublets are not durable and patients usually relapse within 8 months. Moreover, patients also suffer from multiple chemotherapy-associated side effects or comorbidities. As such, the need for alternative treatments is acute. Novel therapeutic agents such as anti-angiogenic and anti-apoptotic proteins, PARP (poly-ADP ribose polymerase)-inhibitors, tyrosine kinase inhibitors, mTOR inhibitors and many others are still under investigation in several clinical trials.[3] Recently, many successes have been achieved with ICI in multiple cancer types. MCC remains a rare type of cancer but recent understanding of the disease biology suggested immune susceptibility, making the disease a possible target for ICI. To further decipher its biological mechanisms and analyze the efficiency of these novel therapies, several international, multicenter, novel design and cooperative group trials have been conducted.[4] In this short clinical review, we will discuss the most recent activity and safety data with anti-PD-(L)1 (avelumab, pembrolizumab and nivolumab) and anti-CTLA4 (ipilimumab) agents in MCC.[3]

MERKEL CELL POLYOMA VIRUS DNA INTEGRATION

As previously mentioned, MCPyV DNA integration in the Merkel cell genome is one of the risk factors for tumor development. Overall, 80% of MCCs are MCPyV-positive and this positivity is associated with a better prognosis than MCPyV-negative MCC.[5] Infection with MCPyV is ubiquitous, usually occurs during

[1]Department of Medical Oncology, Ghent University Hospital, Ghent, Belgium, [2]Department of Medical Oncology, Department of Clinical Pharmacology, Ghent University Hospital, Ghent, Belgium

Please send all correspondence to: De Keukeleire Stijn, MD, drs, Department of Medical oncology, UZ Gent, De Pintelaan 151 9000 Ghent, Belgium. E-mail: Stijn.dekeukeleire@uzgent.be, Tel: +32 9 332 12 11

Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest

Key words: Merkel cell carcinoma, immune checkpoint, PD-1, PD-L1, avelumab, pembrolizumab, nivolumab, CTLA4, ipilimumab

Immunotherapy for locally advanced unresectable non-small cell lung cancer

T. Feys, MSc, MBA[1]

The progress that has been made in the last decades in the treatment of stage IV non-small cell lung cancer (NSCLC) has overall not been translated in the curative setting of stage I to III disease. In fact, the list of failed clinical trials aimed at improving the cure rates in this setting is long. The recent successes with immune checkpoint inhibition in stage IV NSCLC formed the basis to also study these agents in the curative setting. The first clinical trials to yield results in this setting evaluate immune checkpoint inhibition as consolidation treatment following chemoradiotherapy in locally advanced, unresectable NSCLC. The PACIFIC trial demonstrated that consolidation therapy with PD-L1 inhibitor durvalumab significantly prolongs both the progression-free (PFS) and overall survival (OS) compared to placebo in patients with disease control after chemoradiotherapy for stage III unresectable NSCLC. These findings have recently led to the EMA indication of durvalumab as a treatment of locally advanced, unresectable NSCLC patients whose tumors express PD-L1 on ≥1% of tumor cells and whose disease has not progressed following platinum-based chemoradiation therapy. In addition to this, recent phase II data show that consolidation pembrolizumab following concurrent chemoradiotherapy substantially prolongs the time to metastasis or death in patients with inoperable stage III NSCLC. Finally, the phase II ETOP NICOLAS trial demonstrated that the addition of nivolumab to concurrent chemoradiotherapy is safe and tolerable in stage III NSCLC with promising efficacy signals. Together all these data support the further exploration of immune checkpoint inhibition in the curative NSCLC setting. Several trials are currently ongoing, including studies on the potential of adjuvant immune checkpoint inhibition in stage II and IIIA disease and trials in the pre-operative setting.

INTRODUCTION

Approximately one third of patients with NSCLC present with unresectable stage III disease. The treatment of these patients remains one of the major challenges of respiratory oncology, despite gradual progress over the past decades. In the 1980s, patients with unresectable stage III NSCLC were treated with radiotherapy as a single modality, resulting in a median OS of about 10 months. However, a meta-analysis reported by *Aupérin et al.* (N= 1,764) demonstrated that adding cisplatin-based chemotherapy to radiotherapy improved the median OS. In fact, in this analysis, concomitant chemoradiotherapy (CRT) was associated with a 4% survival increase at 2 years compared to radiotherapy alone (median OS 12 vs. 14 months; 2-year OS 21.4 vs. 45.4%, 5-year OS 6% vs. 8.2%).[1] A second meta-analysis (N=1,205), also reported by *Aupérin et al.* later demonstrated the superiority of concurrent CRT over sequential CRT. In this analysis, concurrent CRT was associated with a median OS of 18 months, which was significantly longer than the 14 months seen with sequential CRT (HR[95%CI]: 0.84[0.74-0.95]; p= 0.004).[2] This translates into an increase in the 5-year OS rate of 4.5% (15.1% vs. 10.6%).[2] Based on these studies concurrent cisplatin based chemotherapy (cisplatin-etoposide, cisplatin-vinorelbine) delivered concurrently with radiotherapy has been adopted by ESMO as the recommended treatment for locally advanced, unresectable NSCLC.[3]

[1]Ariez International BV, Ghent, Belgium

Please send all correspondence to: T. Feys; Ariez international BV; Oude Houtlei 118, 9000 Gent; E-mail: t.feys@ariez.com; Tel: +32 (0)479 567890

Conflict of interest: The content of this article was not influenced by third parties.

Keywords: non-small cell lung cancer, NSCLC, curative, inoperable, stage III, immune checkpoint inhibition, durvalumab, nivolumab, pembrolizumab