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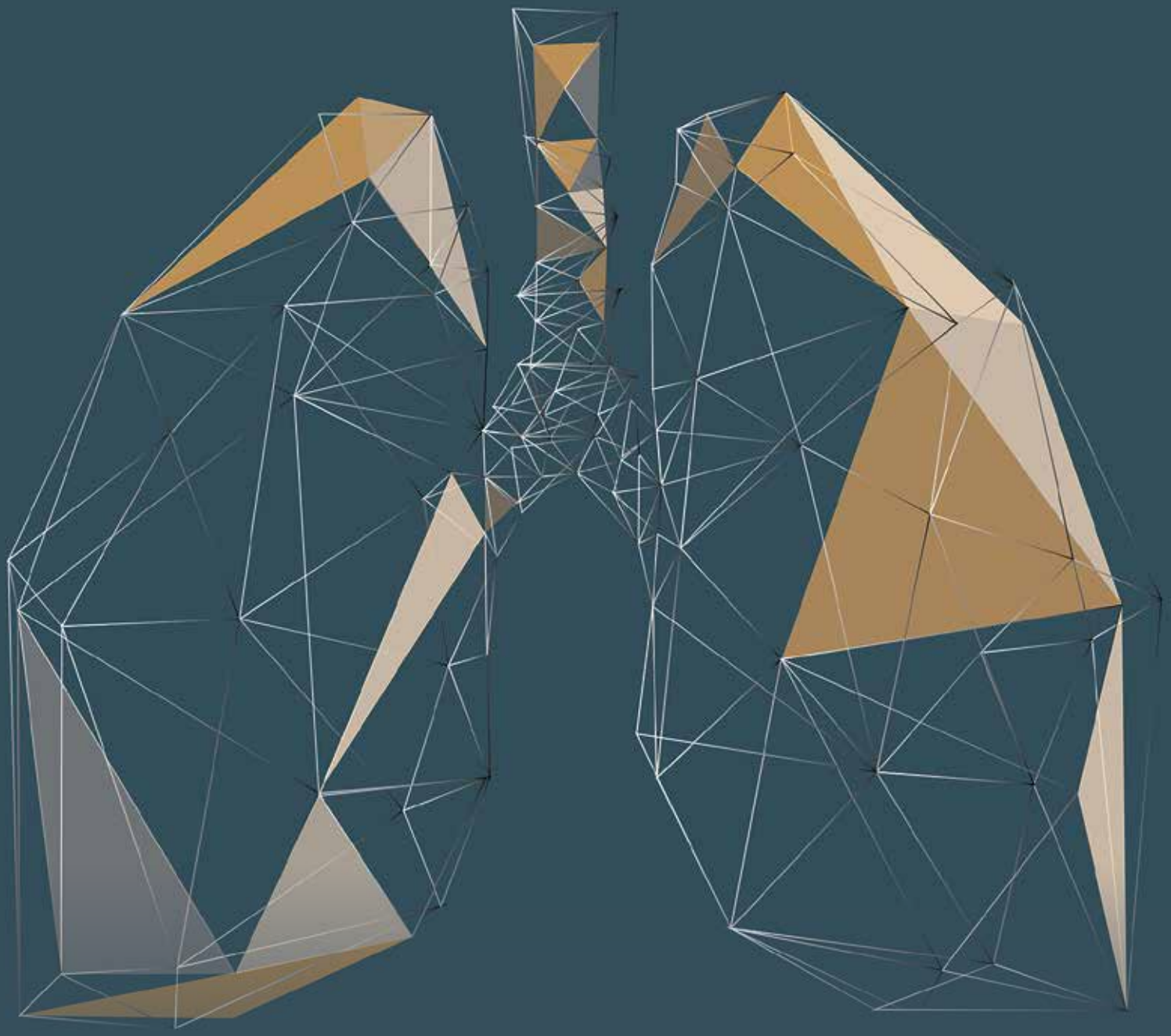

FOCUS ON DIFFICULT TO TREAT PATIENTS WITH ADVANCED NSCLC

LUNG ACADEMY

Future forward in Lung cancer, science and education

FOCUS ON DIFFICULT TO TREAT PATIENTS WITH ADVANCED NSCLC

On September 28th 2022, the Lung Academy hosted a Sanofi supported interactive expert meeting in which *Prof. Dr. Johan Vansteenkiste (University Hospitals Leuven, Belgium)* and *Dr. Ronny Öhman (Skåne University Hospital, Sweden)* discussed the management of difficult to treat advanced non-small cell lung cancer (NSCLC) patients. More specifically, the webinar focussed on the treatment of NSCLC patients with a squamous histology and addressed the optimal treatment strategies for patients with locally advanced disease (stage III).

NSCLC PATIENTS WITH A SQUAMOUS HISTOLOGY

Prof. Dr. Johan Vansteenkiste, University Hospitals Leuven, Leuven, Belgium

SQUAMOUS CELL CARCINOMA AND ADENOCARCINOMA

The previous WHO classification of lung cancer divided NSCLC patients based on morphology of the resection specimen into patients with a squamous cell carcinoma, an adenocarcinoma or so-called large cell undifferentiated carcinomas.[1] For many years, this histological subdivision provided the foundation for an accurate patient diagnosis and optimal medical management, especially for patients with stage IV disease. However, since the diagnosis of NSCLC patients is nowadays primarily based on small biopsies and/or cytology specimens, a new classification for lung cancer in small diagnostic samples was introduced. While the current WHO classification remains to be firmly based on morphology, it is now also supported by immunohistochemistry and molecular analyses. In this classification, patients are morphologically divided into squamous cell carcinoma, adenocarcinoma and non-small cell lung cancer not otherwise specified (NSCLC-NOS). Of note, the latter group still represents about a third of patients, causing significant challenges with respect to treatment decisions. In the absence of a clear morphologic squamous cell or adenocarcinoma pattern, the current classification therefore stipulates that the pathologist should use additional immunohistochemistry assays. By using special stains, the pathologist can differentiate these NSCLC-NOS cases between a 'favour squamous cell carcinoma' (positive staining for P40, P63 or CK5-6 markers) or a 'favour adenocarcinoma' (positive staining for TTF1, CK7 markers) category.[2]

Apart from the histological differences between a squamous cell carcinoma (SCC) and an adenocarcinoma, there are also important clinical differences between the two categories. In fact, patients with adenocarcinoma are usually younger, non- or light-smokers and tend to have a better general condition. These patients can be treated with pemetrexed, anti-angiogenic agents or with targeted therapies for an increasing number of druggable oncogenes (*EGFR, ALK, ROS1, etc.*). In contrast, patients with SCC are usually older, tend to be heavy smokers and often present with major comorbidities. For these patients, a treatment with pemetrexed or bevacizumab is not feasible, and this category of patients lacks druggable oncogenes that can be targeted. As a result, patients with SCC generally have a poorer prognosis than adenocarcinoma patients.

FACTORS THAT CONTRIBUTE TO A POOR PROGNOSIS IN PATIENTS WITH SCC

Smoking

Over the past decades, there has been a changing, global distribution in lung cancer that is strongly associated with the prevalence of smoking. The prevalence of tobacco smoking is now most predominant in Eastern Europe, Asia (except for South-East Asia) and in some regions of South America. Nevertheless, SCC remains to be a major health problem in all regions of the world. Among patients with SCC, smoking is an independent predictor of poorer survival, with a clearly better prognosis for never-smokers. In addition, current smokers also have a slightly worse survival compared with former smokers who quit before their diagnosis.[3,4]

Late detection

While patients with squamous NSCLC often cough and/or have dyspnoea or bronchitis, these symptoms are often not considered to be alarming and as a result a detailed screening for the

Tabel 1. Overall survival of squamous NSCLC with approved first-line IO regimens.

		Median OS IO vs. CT (months)	HR(95%CI) OS in PD-L ≥50%	IO *vs.* CT TRAE discontinuation
IO MONOTHERAPY				
Keynote-024 : pembrolizumab (PD-L1 ≥50%)[18]				
All patients	N= 305	30.0 *vs.* 14.2	0.63 (0.47-0.86)	14 % *vs.* 11%
Squamous	N= 56, 18%		0.73 (0.38-1.39)	
Non-squamous	N= 249, 82%		0.58 (0.41-0.83)	
IMpower110 : atezolizumab (PD-L1 ≥50% TC / (≥10% on IC)[19]				
All patients	N= 205	20.2 *vs.* 14.7	0.76 (0.54-1.09)	7.3% *vs.* 17.1%
Squamous	N= 50, 24%		0.91 (0.45-1.83)	
Non-squamous	N= 155, 76%		0.72 (0.48-1.08)	
EMPOWER-Lung1 : cemiplimab (PD-L1 ≥50%)[20]				
All patients	N= 563	NR *vs.* 14.2	0.57 (0.42-0.77)	6% *vs.* 4%
Squamous	N= 243, 43%		0.48 (0.30-0.77)	
Non-squamous	N= 320, 57%		0.64 (0.43-0.96)	
IO + CHEMOTHERAPY				
Keynote-407 : pembrolizumab + chemotherapy (Any PD-L1)[21,22]				
All patients	N= 559	17.2 *vs.* 11.6	0.71 (0.59- 0.86)	
Squamous	N= 546, 97.7%		0.71 (0.59- 0.86)	
IO-IO + CHEMOTHERAPY				
CheckMate 9LA : nivolumab + ipilimumab + chemotherapy (Any PD-L1)[23]				
All patients	N= 719	15.8 *vs.* 11.0	0.72 (0.61-0.86)	
Squamous	N= 227, 32%		0.63 (0.47-0.85)	
Non-squamous	N= 492, 68%		0.78 (0.63-0.96)	

This table presents data from multiple trials for illustration purposes. Direct cross-trial comparisons should not be made as trial factors differ among trials.

presence of malignant tumours is often delayed in these patients. To no surprise, a truly delayed medical attendance and delayed chest X-ray resulting in a later cancer detection contributes to a negative prognosis. Furthermore, there is a difference in detection rates in low-dose CT screening studies between squamous cell - or adenocarcinoma.[5]

Demography

With regard to demography, patients with SCC are predominantly male patients (69%) of older age. An analysis of the SEER data revealed that 62% of patients with SCC are above 65 years.[6,7] Because of its association with older age, advanced squamous NSCLC might be more challenging to treat.

Location

In general, SCC present as central tumours, meaning more vascular invasion, more bronchial obstruction, and a higher risk for post-obstructive infections. In addition, cavitation may also be an issue in case of SCC tumours. As a result, there is a lower chance for a successful resectability of SCC tumours, and these tumours come with a higher risk for chemotherapy-related complications (especially risks of major infections) and major bleeding.

Comorbidity

Data on simplified comorbidity scores (SCS) and the Charlson comorbidity index (CCI) indicate a big difference in comorbidity between patients with an adenocarcinoma or a SCC. In fact, among SCC patients 57% of patients have a SCS above nine with 52.8% having a CCI of ≥2. These rates are more than twice as high as those for adenocarcinoma patients (20% and 24.5%, respectively). These high comorbidities rates in SCC patients profoundly influence treatment choices as organ dysfunctions such as renal function, heart function, diabetic neuropathy significantly limit the feasible treatment options in these patients. In addition, it is no surprise to see that a higher level of comorbidity is also an independent negative prognostic factor in this setting.[8]

A lack of druggable oncogenes

In 2012, the Cancer Genome Atlas Research Network published the results of a comprehensive molecular profiling effort analysis of 178 resected early stage squamous cell lung carcinoma samples. These findings revealed a relatively high frequency of recurrent somatic alterations, involving several biologic pathways. However, there was a notable absence of canonical alterations in known actionable oncogenes as the ones we know from lung adenocarcinoma.[9] Nevertheless, these initial data did form the basis to assess the drugability of other, recurrently altered pathways and targets in SCC. This effort winnowed the list of potential targets to a handful for initial clinical testing in biomarker-led trials, including *FGFR1* amplification, upstream *phosphatidylinositol 3-kinase (PI3K)* alterations, and G1/S checkpoint aberrations. Unfortunately, however, these trials led to disappointing results with objective response rates (ORR) generally below 10% and a median progression-free survival (PFS) of approximately 2-3 months. Despite a deeper understanding of the genomic alterations that characterise SCC and years of trial work targeting these alterations, personalised therapies thus far remain out of hand.[10]

THE IMMUNE LANDSCAPE IN SCC

On the bright side, SCC has a highly immune-infiltrated micro-environment, making them generally more 'immunotherapy-friendly' tumours than lung adenocarcinoma. In fact, studies show that up to half of the tumour area in SCC harbours CD45+ cells, which play an important role in the activation of T-cells. In addition, elevated frequencies of B- and T-cells are found in SCC tumours and, even more importantly, these tumours are also characterised by increased levels of activated CD8+ T-cells.[11]

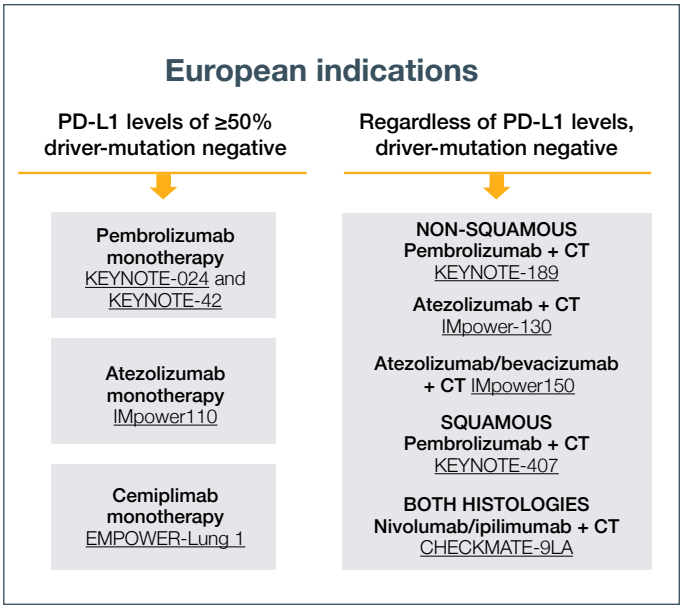

FIGURE 1. European guidelines for the treatment of NSCLC.[17]

Over the past years, several immunotherapeutic agents have been approved in Europe for the treatment of patients with squamous NSCLC: pembrolizumab (January 2017), pembrolizumab plus chemotherapy (March 2019), nivolumab plus ipilimumab plus chemotherapy (November 2020), atezolizumab (May 2021) and cemiplimab (June 2021).[12-16] The current ESMO guidelines for the first-line treatment of NSCLC are based on PD-L1 expression. For patients with PD-L1 levels ≥50% without driver mutations, pembrolizumab, atezolizumab or cemiplimab in monotherapy are recommended. For patients who are driver-mutation negative, regardless of PD-L1 levels, combinations of immunotherapy and chemotherapy are recommended, both for squamous and non-squamous histology (*Figure 1*).[17]

First-line IO monotherapy vs. chemotherapy

Thus far, three clinical trials have led to the approval of IO monotherapy in the first-line treatment of squamous NSCLC.

In **Keynote-024**, pembrolizumab monotherapy was compared to platinum-based chemotherapy in patients with advanced NSCLC and a PD-L1 tumour proportion score (TPS) of ≥50%. Of note, out of the 305 patients enrolled in the trial, only 56 (18%) had a squamous histology. The median overall survival (OS) in the overall population was reported at 30.0 months with pembrolizu-

mab as compared to 14.2 months with chemotherapy (HR[95%CI]: 0.63[0.47-0.86]). For patients with squamous cell histology, the corresponding hazard ratio for OS was 0.73 (95%CI: 0.38-1.39). The discontinuation rate due to treatment-related adverse events (TRAEs) was 14% for immunotherapy and 11% for chemotherapy.[18]

IMpower110 studied atezolizumab versus platinum-based chemotherapy in treatment-naïve, PD-L1 selected NSCLC patients. All patients in this trial had a PD-L1 expression of ≥50% on tumour cells [TCs] or ≥10% on tumour-infiltrating immune cells [ICs], per SP142 immunohistochemistry assay. In this trial, 24% of patients (N= 50) had a squamous histology. The median OS was approximately five months longer for patients treated with atezolizumab, as compared to chemotherapy (20.2 *vs*. 14.7 months, HR[95%CI]: 0.76[0.54-1.09]). For patients with squamous cell histology, the benefit for atezolizumab was also non-significant for a hazard ratio of OS 0.91 (95%CI: 0.45-1.83). The discontinuation rate due to adverse events was 7.3% for atezolizumab *vs*. 17.1% for chemotherapy.[19]

Finally, in **EMPOWER-Lung 1**, patients with histologically or cytologically confirmed advanced NSCLC, were randomly assigned (1:1) to cemiplimab 350 mg (q3w) or platinum-doublet chemotherapy. In the PD-L1 ≥ 50% population, including 563 patients, the median OS was not reached with cemiplimab as compared to 14.2 months with chemotherapy (HR[95%CI]: 0.57[0.42-0.77], p= 0.0002). Interestingly, among patients with a squamous histology (N= 243, 43% of the patients), the benefit of cemiplimab was even more pronounced with a hazard ratio for OS of 0.48 (95%CI: 0.30-0.77). Discontinuation rates due to TRAEs were low at 6% and 4% for cemiplimab and chemotherapy, respectively.[20]

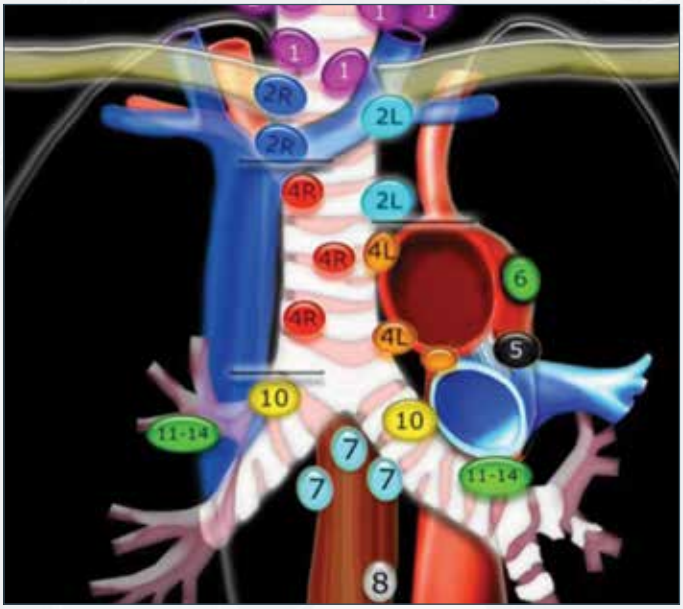

FIGURE 2. Classification of mediastinal lymph noduli (Mountain-Dresler).

First-line immunotherapy plus chemotherapy

Keynote-407 is a randomised, placebo-controlled trial of pembrolizumab in combination with carboplatin and paclitaxel or nab-paclitaxel in patients with metastatic squamous NSCLC. In this trial, adding pembrolizumab to chemotherapy induced a clinically meaningful and statistically significant improvement in OS with a median OS of 17.2 and 11.6 months, respectively (HR[95%CI]: 0.71[0.59-0.86]).[21,22]

First-line double immunotherapy plus chemotherapy

CheckMate 9LA compared first-line nivolumab-ipilimumab plus two cycles of chemotherapy to chemotherapy alone (four cycles) in patients with advanced NSCLC. After a median follow-up of 30.7 months, the median OS was reported at 15.8 and 11.0 months, respectively (HR[95%CI]: 0.72[0.61-0.86]). Of all 719 patients enrolled in this trial, 227 had a squamous histology (32%) and in this subgroup of patients the OS benefit for the immunotherapy-based regimen was even more pronounced with a hazard ratio of 0.63 (95%CI: 0.47-0.85).[23] Importantly, the combination of nivolumab-ipilimumab and chemotherapy as investigated in CheckMate 227, and the combination of pembrolizumab plus ipilimumab (Keynote-598) or durvalumab and tremelimumab (MYSTIC) are not approved in Europe.

CONCLUSION

Because of its association with older age, smoking-related comorbidities and high symptom burden, advanced squamous NSCLC is challenging to treat. As a result, the survival prospect for patients with squamous NSCLC remains to be more dismal than for patients with a non-squamous histology, even in the absence of targetable oncogenic driver mutation. In recent years, however, continued advances in the development of first-line IO-based regimens led to meaningful increases in OS of patients with squamous NSCLC. However, outcomes from phase III clinical trials are heterogeneous, and treatment decisions need to be taken on an individual basis.

LOCALLY ADVANCED (STAGE III) NON-SMALL CELL LUNG CANCER

Dr. Ronny Öhman, Skåne University Hospital, Sweden

Before making treatment decisions in patients with NSCLC it is important to adequately assess the disease stage using the 8th edition of the TNM classification. According to this classification, there are three components that describe the anatomic extent of a tumour: T for the extent of the primary tumour, N for lymph node involvement, and M for metastatic disease. For the disease stage classification, especially the presence and extent of lymph

node involvement is of particular relevance.24 In this respect, the map of the mediastinal and pulmonary lymph nodes proposed by Clifton F. Mountain and Carolyn M. Dresler gained wide acceptance and has become the standard framework for NSCLC staging. Mediastinal lymph nodes are divided into 14 different positions but since it is not possible to sample all of them, 4R, 7 and 4L (*Figure 2*) are considered to be the most important for an appropriate staging. Those are the most central positions and thus the most important ones when it comes to establishing a treatment plan for the patient. Mediastinal lymph nodes can be sampled by the EBUS technique (endobronchial ultrasound) or mediastinoscopy.

PRIMARY INVESTIGATIONS

Apart from a detailed assessment of potential lymph node involvement, almost all NSCLC patients will undergo a CT-scan of the thorax or upper abdomen. For patients that are possible surgical candidates, also a PET-CT scan should be performed and whenever possible, NSCLC patients should also be invited for a brain scan to exclude brain metastases. If metastases are expected, these should be confirmed (or excluded) before making a treatment plan. Before discussing the possibility of surgery with the patient, the patient's lung and cardiac function should be assessed by means of spirometry, CO diffusion test, ergospirometry, regional lung scintigraphy, ECG and/or an exercise test.[25]

Before deciding on the optimal treatment plan for an individual patient, a clear morphological diagnosis is required. If bronchoscopy is not possible, a transthoracal biopsy can be used to provide tissue for the diagnostic work-up. In addition to a histological analysis of this sample, several immunohistochemistry analysis and next-generation sequencing should be performed to look for mutations or fusions involving known oncogenic drivers. For the post-operative management of the patient particularly the level of PD-L1 expression and the EGFR mutation status are of therapeutic relevance. When all information about the patient's disease stage, (brain) metastases, comorbidities, general performance status and treatment preference are collected, the patient's case is often discussed at a multidisciplinary tumour board, involving specialists in pulmonary medicine, radiology, clinical physiology, pathology, oncology and thoracic surgeons.[25]

TREATMENT PLAN WITH CURATIVE INTENT

The treatment plan for patients with stage III NSCLC is usually multimodal, involving surgery, chemotherapy, radiotherapy and/or immunotherapy. While patients with stage IIIA disease are generally considered to be eligible for curative surgery, surgery is not always feasible in patients with stage IIIB or IIIC disease. Of note, apart from the disease stage, also the lung function, the performance status, the age and the presence of certain comorbidities need to be considered when determining the patient's eligibility for surgery. If a patient is considered to be eligible for surgery, the next question is whether or not to use neoadjuvant treatment in an attempt to downstage the tumour. If surgery is not an option, chemo-radiotherapy is the current standard of care.[25]

Chemotherapy

Current chemotherapy regimens for stage III NSCLC patients are usually platinum-based. Since there are much more data on cisplatin compared to carboplatin in this setting, cisplatin remains to be the preferred chemotherapy-backbone in the curative setting. However, cisplatin is not recommended in patients with low kidney function and in patients with a hearing dysfunction. Concurrent chemoradiotherapy for definitive treatment of stage III NSCLC should include a platinum-based doublet, preferably cisplatin in combination with vinorelbin or paclitaxel. Cisplatin plus pemetrexed can only be used for patients with non-squamous histology. Due to toxicity, gemcitabine cannot be used in combination with radiation.[25]

Neoadjuvant radiotherapy

Patients with stage III NSCLC receiving neoadjuvant concurrent chemoradiation should routinely receive a radiation dose of 60 Gy (2 Gy/day for 30 days). However, for selected patients a dose above 60 Gy and up to 70 Gy can be considered. In order not to prolong the neoadjuvant treatment period, radiation should be started no later than cycle 2 of chemotherapy. When there is doubt on the continued eligible for surgery, a new PET-CT scan can be performed after approximately 40 Gy.[25]

Surgery

Nowadays, lung cancer surgery is usually performed using a video assisted technique (VATS), which reduces the hospital stay after surgery with 1 or 2 days. Usually a lobectomy is enough to remove all the tumoral tissue, but for some cases a complete pulmectomy may be required. If the tumour is very close to the central trachea, a sleeve resection could be a way to still facilitate radical surgery. During surgery, a maximum of lymph nodes should be systematically sampled at the site of surgery and in N1 and N2 positions. After surgery, the removed part(s) of the lung should be sent to the pathology lab to assess whether or not there has been a change in the TNM classification. In fact, if a

patient underwent neoadjuvant therapy, there is often a downstaging, especially in the lymph nodes in the mediastinal part.[25]
In case of a narrow surgical resection margin after surgery or when there is pleural engagement, postoperative radiotherapy (20-40 Gy) can be offered to the patient, if not already administered in the neoadjuvant setting.[25]

Adjuvant chemotherapy

Patients with stage II-III disease who did not receive neoadjuvant chemotherapy should routinely be offered postoperative chemotherapy, starting 1-2 months after surgery. The most common chemotherapy regimen in this setting consists of cisplatin/carboplatin plus vinorelbin for 3 or 4 treatment cycles.[25,26]
If the patient has a PD-L1 expression ≥50%, he or she is a good candidate for immunotherapy. Based on results of the IMpower010 study, the patient may receive adjuvant atezolizumab for one year after adjuvant platinum-based chemotherapy.[25,27]
Furthermore, if the patient has an *EGFR* exon 19 deletion or exon 21 L858R mutation, the patient should be offered three years of adjuvant osimertinib after platinum-based chemotherapy, according to the ADAURA study.[25,28]

Chemoradiotherapy

For patients who are not eligible for surgery, chemoradiotherapy represents an alternative treatment with curative intent. In this setting, chemotherapy is usually given for four treatment cycles, combined with 40-60 Gy radiotherapy. For patients who do not have disease progression after two or more cycles of platinum-based chemotherapy and who have a PD-L1 expression >1%, up to one year of consolidation therapy with durvalumab can be of benefit to the patient.[25,29]

Follow up after primary treatment plan

Once the treatment plan has been fulfilled, the patient should enter a follow-up plan to monitor for long term complications or disease recurrence. In the first year after surgery or chemoradiotherapy, a CT-scan of the thorax and upper abdomen should be performed every 2-3 months. In addition, a PET-CT scan is highly recommended, but no sooner than one year after the end of the treatment plan because as inflammation may yield a false positive result. From year one onwards up to year three, the interval of CT-scans of the thorax and upper abdomen can be increased to 4-6 months after which an individual follow-up plan should be installed for years 4 and 5. After five years without any signs of relapse, the patient can officially be declared 'cured'. In some patients, follow-up of potential CNS metastases is also scheduled, although this is not performed routineously.[25]

TREATMENT PLAN FOR STAGE III PATIENTS WHERE A CURABLE TREATMENT PLAN IS NOT POSSIBLE

Unfortunately, the presence of certain comorbidities and/or a very advanced age, may make it impossible to enter a curable treatment plan for a proportion of stage III NSCLC patients. If these patients have a high PD-L1 expression (≥50%), single-agent IO therapy with cemiplimab can result in symptom- and disease control and is generally better tolerated than chemoradiotherapy.[20,25,30]

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▼This medicinal product is subject to additional monitoring.

LIBTAYO® (cemiplimab) – Compulsory information
This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected reactions.

PRESENTATION: concentrate for solution for infusion. Each vial contains 350 mg of cemiplimab in 7 ml. **INDICATIONS:** Cutaneous Squamous Cell Carcinoma: LIBTAYO as monotherapy is indicated for the treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma (mCSCC or laCSCC) who are not candidates for curative surgery or curative radiation. Basal Cell Carcinoma: LIBTAYO as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic basal cell carcinoma (laBCC or mBCC) who have progressed on or are intolerant to a hedgehog pathway inhibitor (HHI). Non-Small Cell Lung Cancer: LIBTAYO as monotherapy is indicated for the firstline treatment of adult patients with non-small cell lung cancer (NSCLC) expressing PD-L1 (in ⩾ 50% tumour cells), with no EGFR, ALK or ROS1 aberrations, who have locally advanced NSCLC who are not candidates for definitive chemoradiation, or metastatic NSCLC. **DOSAGE AND ADMINISTRATION*:** Treatment must be initiated and supervised by physicians experienced in the treatment of cancer. For treatment with LIBTAYO as monotherapy in patients with NSCLC, patients should be selected based on PD-L1 tumour expression using a validated test. **Recommended dose:** 350 mg LIBTAYO, every 3 weeks, administered as an intravenous infusion over 30 minutes. Treatment may be continued until disease progression or unacceptable toxicity. **Administration:** Other medicinal products should not be coadministered through the same infusion line. See the full SmPC for instructions on dilution of the medicinal product before administration. **Dose modifications:** No dose reductions are recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability. Please refer to the full SmPC Table 1 for recommended treatment modifications to manage adverse reactions. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients. **WARNINGS AND PRECAUTIONS*: Traceability:** To improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. **Immune-mediated adverse reactions**: Severe and fatal immune-mediated adverse reactions have been observed with
LIBTAYO. These immune-mediated reactions may involve any organ system. Immune-mediated reactions can manifest at any time during treatment with LIBTAYO; however, immune-mediated adverse reactions can occur after discontinuation of LIBTAYO. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously, such as myositis and myocarditis or myasthenia gravis, in patients treated with LIBTAYO or other PD-1/PD-L1 inhibitors. Monitor patients for signs and symptoms of immune-mediated adverse reactions. Immune-mediated adverse reactions should be managed with LIBTAYO treatment modifications, hormone replacement therapy (if clinically indicated), and corticosteroids. Evaluate patients for suspected immune-mediated adverse reactions to confirm an immune-mediated adverse reaction and to exclude other possible causes, including infection. Depending upon the severity of the adverse reaction, LIBTAYO should be withheld or permanently discontinued. See full SmPC for further information. Immune-mediated pneumonitis, diarrhoea or colitis, hepatitis, nephritis: defined as requiring use of corticosteroids with no clear alternate aetiology, including fatal cases (for pneumonitis, hepatitis and nephritis), have been observed. Patients with suspected pneumonitis should be evaluated with radiographic imaging as indicated based on clinical evaluation. Monitor patients for signs and symptoms of pneumonitis (causes other than immune-mediated pneumonitis should be ruled out), diarrhoea or colitis, or changes in renal function. Also monitor patients for abnormal liver test prior to and periodically during treatment. If indicated, patients should be managed with LIBTAYO treatment modifications, anti-diarrhoeal agents (if appropriate), and corticosteroids. Immune-mediated endocrinopathies: defined as treatment-emergent endocrinopathies with no clear alternate aetiology, have been observed. *Thyroid disorders (Hypothyroidism/ Hyperthyroidism/Thyroiditis):* can occur at any time during the treatment. Thyroiditis can present with or without an alteration in thyroid function tests.
Hypothyroidism can follow hyperthyroidism. Monitor patients for changes in thyroid function at the start of treatment and periodically during the treatment based on clinical evaluation. Manage patients with hormone replacement therapy (if indicated) and LIBTAYO treatment modifications. Manage hyperthyroidism according to standard medical practice. *Hypophysitis, adrenal insufficiency and Type 1 Diabetes mellitus:* Immune-mediated hypophysitis, adrenal insufficiency and immune-mediated type 1 diabetes mellitus, including diabetic ketoacidosis, have been observed. Monitor patients for signs and symptoms of hypophysitis, adrenal insufficiency (during and after treatment) and diabetes (including hyperglycaemia) and manage with LIBTAYO treatment modifications, corticosteroids, hormone replacement and oral anti-hyperglycaemics or insulin (if indicated). Immune-mediated skin adverse reactions: defined as requiring use of systemic corticosteroids with no clear alternate aetiology, including severe cutaneous adverse reactions (SCARs), such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (some cases with fatal outcome), and other skin reactions such as rash, erythema multiforme, pemphigoid, have been reported. Monitor patients for evidence of suspected severe skin reactions and exclude other causes. Manage patients with LIBTAYO treatment modifications and corticosteroids. For symptoms or signs of SJS or TEN, refer the patient for specialised care for assessment and treatment and manage with treatment modifications. Cases of SJS, fatal TEN and stomatitis occurred following 1 dose of LIBTAYO in patients with prior exposure to idelalisib, who were participating in a clinical trial evaluating cemiplimab in Non-Hodgkin Lymphoma (NHL), and who had recent exposure to sulfa containing antibiotics. Patients should be managed with LIBTAYO treatment modifications and corticosteroids. Other immune-mediated adverse reactions: Other fatal and life-threatening immunemediated adverse reactions have been observed including paraneoplastic encephalomyelitis, meningitis, myositis and myocarditis (see full SmPC for the list of other immune-mediated adverse reactions). Noninfective cystitis has been reported with other PD-1/PD-L1 inhibitors. Monitor patients for signs and symptoms of immune-mediated adverse reactions. Manage patients with LIBTAYO treatment modifications and corticosteroids. Solid organ transplant rejection has been reported in the postmarketing
setting in patients treated with PD-1 inhibitors. Treatment with LIBTAYO may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with LIBTAYO versus the risk of possible organ rejection should be considered. Cases of graft-versus-host disease have been reported in the post-marketing setting in patients treated with other PD-1/PD-L1 inhibitors in association with allogeneic hematopoietic stem cell transplant. **Infusion-related reactions**: LIBTAYO can cause severe or life-threatening infusion-related reactions. Monitor patients for signs and symptoms of infusion-related reactions and manage with LIBTAYO treatment modifications and corticosteroids. LIBTAYO should be interrupted or the rate of infusion slowed for mild or moderate infusion-related reactions. Stop infusion and permanently discontinue LIBTAYO for severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. **Patients excluded from clinical studies**: Patients that had active infections, were immunocompromised, had a history of autoimmune diseases, ECOG PS ⩾2 or a history of interstitial lung disease were not included. See SmPC for full list of patients excluded from clinical trials. In the absence of data, LIBTAYO should be used with caution in these populations after careful evaluation of the balance of benefits and risks for the patient. **DRUG INTERACTIONS:** No pharmacokinetic drug-drug interaction studies have been conducted with LIBTAYO. Use of systemic corticosteroids or immunosuppressants before starting LIBTAYO, except for physiological doses of systemic corticosteroid (≤10 mg/day prednisone or equivalent), should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of LIBTAYO. Systemic corticosteroids or other immunosuppressants can be used after starting LIBTAYO to treat immune-mediated adverse reactions. **FERTILITY, PREGNANCY AND LACTATION*:** No data available on the use of LIBTAYO in pregnant women. LIBTAYO is not recommended during pregnancy and in women of child-bearing potential not using effective contraception unless clinical benefit outweighs potential risk. Effective contraception should be used during treatment with LIBTAYO and for at least 4 months after the last dose of LIBTAYO. It is unknown whether LIBTAYO is secreted in human milk. If a woman chooses to be treated with LIBTAYO, she should be instructed not to breast-feed while being treated and for at least 4 months after the last dose. No clinical data are available on the possible effects of LIBTAYO on fertility. **UNDESIRABLE EFFECTS*:** Very common (≥ 1/10): upper respiratory tract infection, anaemia, decreased appetite, cough, diarrhoea, nausea, constipation, abdominal pain, rash, pruritus, musculoskeletal pain, fatigue. Common (≥ 1/100 to < 1/10): urinary tract infection, infusion-related reaction, hypothyroidism, hyperthyroidism, headache, peripheral neuropathy, hypertension, dyspnoea, pneumonitis, vomiting, colitis, stomatitis, hepatitis, nephritis, pyrexia, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatinine increased.

Please refer to the SmPC for the full list of undesirable effects. Health care professionals are asked to report any suspected adverse reactions via their national reporting system. **MARKETING AUTHORISATION HOLDER:** Regeneron Ireland DAC., One Warrington Place, Dublin 2, D02 HH27, Ireland. **LEGAL CLASSIFICATION:** Prescription Only Medicine. **DATE OF LAST REVIEW**: July 2022. Compulsory information based on the EU SmPC as of July 2022 **Before prescribing the product always refer to your full local prescribing information as this information may vary from country to country. Further information from:**

Denmark:
Pakningsstørrelse: 1 x hætteglas 350 mg, 7 ml (50 mg/ml) (Vnr 06 72 73). For dagsaktuel pris se: www.medicinpriser.dk. **Udlevering:** BEGR. **Tilskud:** Ikke tilskudsberettiget**. Indehaver af markedsføringstilladelsen:** Regeneron Ireland Designated Activity Company (DAC), One Warrington Place, Dublin 2, D02 HH27, Irland. **De med * markerede afsnit er omskrevet/ forkortet i forhold til det godkendte produktresumé. Produktresuméet kan vederlagsfrit rekvireres hos Sanofi A/S, Lyngbyvej 2, 2100 København Ø.**

Norway: Fullstendig preparatomtale finnes på hjemmesiden til Statens legemiddelverk, https://www.legemiddelsok.no/ **Reseptgruppe:** C. **Pakninger og priser:** 7 ml (hettegl.) kr 68112,50 **Refusjon CSCC:** Finansieres av sykehus (H-resept) og er besluttet innført av Beslutningsforum. **Refusjon BCC og NSCLC:** Finansieres ikke av sykehus (H-resept). Beslutning fra Beslutningsforum avventes. **Lokal representant for MT-innehaver**; sanofi-aventis Norge AS, Prof. Kohts vei 5-17, 1325 Lysaker

Sweden:
Prescription medication. Not reimbursed. L01FF06. The SmPC is available on www.fass.se. In Sweden Libtayo is provided by Sanofi AB, Box 300 52, 104 25 Stockholm, tel +46 8 634 50 00. For questions on our medicinal products, please contact infoavd@sanofi.com.

Finland:
Marketed package: Libtayo 350mg 7ml, 5756,40€ (1.12.2021). Prescription medication. Not reimbursed. **Local representative:** Sanofi Oy, www.sanofi.fi.

Netherlands:
Aflevering en vergoeding: U.R. Libtayo wordt vergoed via add-on. Voor prijzen zie de Z-index taxe. Deze informatie is het laatst herzien in juli 2022. Voor meer informatie zie de geregistreerde productinformatie. Lokale vertegenwoordiger: Genzyme Europe B.V., Paasheuvelweg 25, 1105 BP Amsterdam, Tel. +31 20 245 4000.

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