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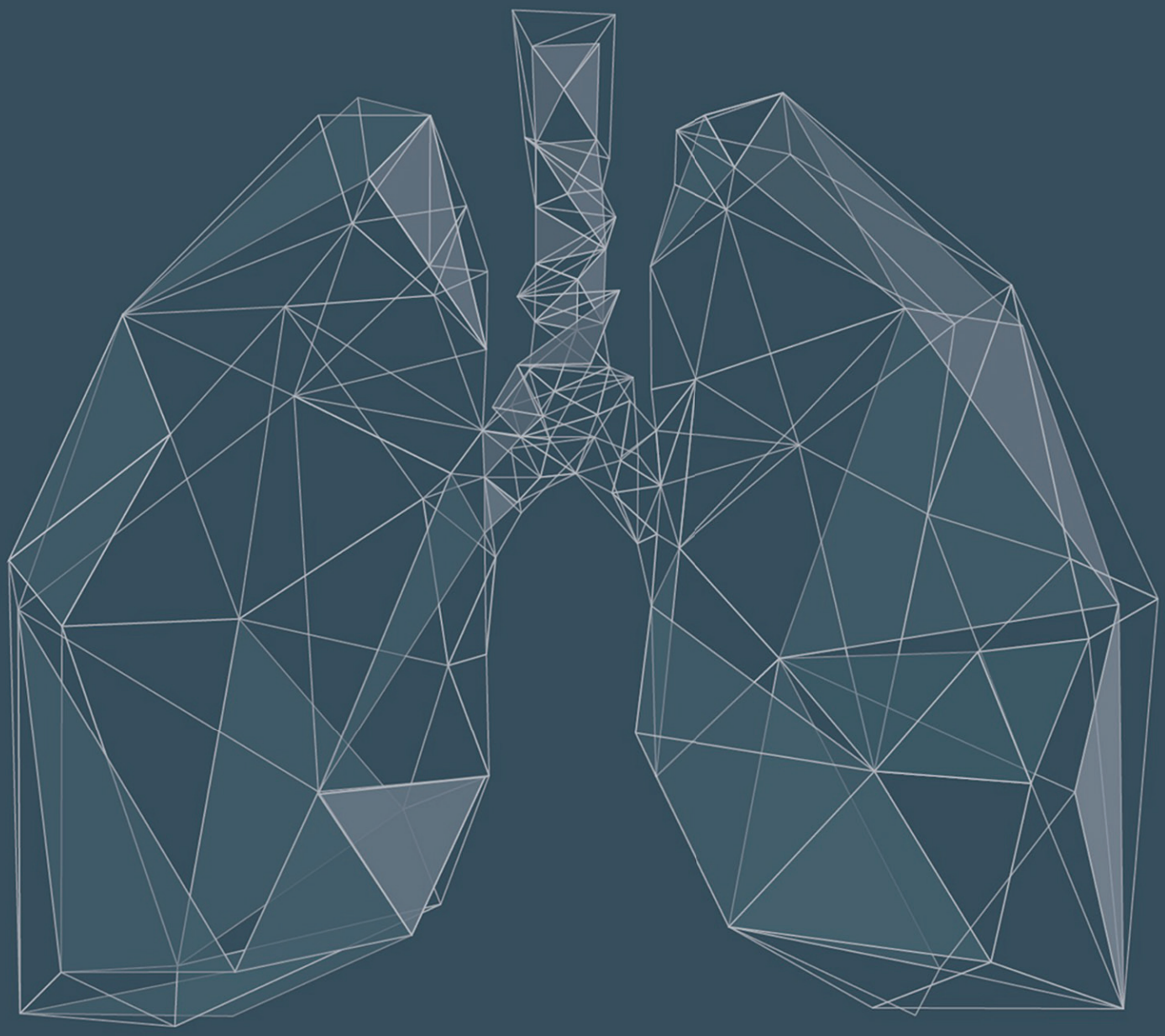

CURRENT STATUS AND FUTURE PERSPECTIVES ON IMMUNOTHERAPY FOR NSCLC

LUNG ACADEMY

Future forward in Lung cancer, science and education

CURRENT STATUS AND FUTURE PERSPECTIVES ON IMMUNOTHERAPY FOR NSCLC

On January 11th, 2022, Sanofi hosted a webinar addressing the current status and future perspectives on immunotherapy for the treatment of non-small cell lung cancer (NSCLC). In a first presentation, *Prof. Martin Reck (Lung Clinic Grosshansdorf, Germany)* discussed the evolving treatment landscape in the first line setting of NSCLC. In a second session, *Prof. Michael Thomas (Thoraxklinik Heidelberg, Germany)* walked us through the optimisation of the management of immune-related side effects. Finally, *Prof. Inge Marie Svane (Centre for Cancer Immune Therapy, Copenhagen University Hospital, Denmark)* shed some light on the future prospects of immune therapeutic strategies and biomarkers. Below, we summarise the key highlights as discussed during the webinar.

THE EVOLVING TREATMENT LANDSCAPE IN FIRST-LINE TREATMENT FOR NSCLC

Over the last decade, major progress has been made in the development of individualised treatment options for patients with NSCLC. First of all, a growing number of treatable oncogenic alterations has been identified leading to a continuously expanding range of targeted therapies. However, most NSCLC patients (roughly 80%) presents with a non-oncogenic driven NSCLC. For these patients, the introduction of immune checkpoint inhibition in the first-line treatment represents a major breakthrough.[1]

Since a cure remains to be elusive in patients with advanced NSCLC, the main treatment goals nowadays consist of long-term control of disease growth, metastases and tumour-related symptoms, together with prolonging the overall survival (OS) with a good quality of life. However, before the advent of immunotherapy in this setting, the 5-year overall survival rates for patients with stage IV NSCLC were suboptimal and did not exceed 10%.[2] The initial proof of principle that anti-PD-(L)1 antibodies could effectively harness the antitumour activity of T-cells was demonstrated in patients with previously treated advanced/metastatic NSCLC. Since then, immune checkpoint inhibitors (ICIs) have quickly moved to the first-line setting and have become a mainstay of first-line treatment of advanced/metastatic NSCLC without targetable genetic alterations, both in monotherapy and in combination regimens. With these new regimens, for the first time a long-term disease stabilisation could be achieved for some patients.[3]

CHECKPOINT INHIBITOR MONOTHERAPY IN PATIENTS WITH HIGH PD-L1 EXPRESSION

Pembrolizumab

In the randomised, open-label, phase III Keynote-024 trial, patients were randomly assigned to pembrolizumab or investigator's choice of platinum-doublet chemotherapy. All patients had previously untreated stage IV NSCLC with a PD-L1 tumour proportion score (TPS) of 50% or greater (by PD-L1 IHC 22C3 pharmDx assay) and no *EGFR/ALK* aberrations.[4] With a median follow-up of five years, pembrolizumab demonstrated clear improvements in OS and progression-free survival (PFS) as compared to chemotherapy. The median PFS was 7.7 months in the immunotherapy arm and 5.5 months with chemotherapy (HR[95%CI]: 0.50[0.39-0.65]). Despite the high rate of patients crossing over from the control arm to pembrolizumab (66.0%), the five-year OS was approximately doubled among patients who received pembrolizumab (31.9% *vs*. 16.3%). The median OS was reported at 26.3 months in the pembrolizumab arm as compared to 13.4 months with chemotherapy (HR[95%CI]: 0.62[0.48-0.81]).[5]

Atezolizumab

IMpower110 is a randomised, open-label, phase III trial involving patients with metastatic non-squamous or squamous NSCLC who did not previously receive chemotherapy and had PD-L1 expression on at least 1% of tumour cells or on at least 1% of tumour-infiltrating immune cells as assessed by the SP142 immunohistochemical assay. Patients were assigned to receive

Tabel 1. Correlation of survival and objective response with baseline PD-L1 proportion scores for cemiplimab versus chemotherapy.[8]

	PD-L1 ≥90%	PD-L1>60 to <90%	PD-L1≥50 to ≤60%	PD-L1<50% or unknown
Number of patients	98 *vs* 94	89 *vs* 90	96 *vs* 96	73 *vs* 74
Overall survival Median, months (95%CI) Hazard ratio (95%CI)	NR (17.3-NE) *vs* 15.1 (11.1-NE) 0.46 (0.25-0.85)	22.1 (17.9-NE) *vs* 12.0 (9.6-19.2) 0.47 (0.27-0.80)	21.9 (13.2-NE) *vs* 14.0 (9.4-19.3) 0.46 (0.25-0.85)	16.5 (11.6-NE) *vs* 15.2 (10.2-NE) 1.082 (0.68-1.72)
Progression-free surviaval Median, months (95%CI) Hazard ratio (95%CI)	15.3 (10.4-18.7) *vs* 5.9 (4.3-6.2) 0.28 (0.17-0.46)	6.2 (4.2-8.4) *vs* 4.2 (4.1-5.7) 0.55 (0.38-0.80)	4.3 (2.8-6.3) *vs* 6.2 (5.0-6.2) 0.79 (0.56-1.12)	4.1 (2.6-6.1) *vs* 5.0 (4.2-6.2) 0.82 (0.56-1.18)
Tumor response Objective response rate, (a95%CI)	46 (36-56) *vs* 18 (11-27)	39 (29-50) *vs* 20 (12-30)	32 (23-43) *vs* 23 (15-33)	26 (17-38) *vs* 22 (13-33)

Date and median (95%CI), hazard ratio (95%CI), and objective response rate % (95%CI). NE=not evaluable. NR=not reached. PD-L1=programmed cell death ligand 1.

intravenous atezolizumab or platinum-doublet chemotherapy. Patient's tumours were wild-type with respect to *EGFR* mutations or *ALK* translocations. In contrast to Keynote-024, crossover was not allowed in this study.[6] After a median follow-up of 31.3 months, the median OS was longer for the high PD-L1 expressing patients treated with atezolizumab as compared to those receiving chemotherapy (20.2 *vs.* 14.7 months, HR[95%CI]: 0.76[0.54-1.09]).

Cemiplimab

EMPOWER-Lung-1 is a multicentre, open-label, global, phase III study of cemiplimab in patients with treatment-naïve stage IIIB, IIIC, or IV squamous or non-squamous NSCLC with PD-L1 expressed in ≥50% of tumour cells (by PD-L1 IHC 22C3 pharmDx assay). In this large trial (N= 710), patients were randomised 1:1 to receive cemiplimab or investigator's choice of platinum-doublet chemotherapy. Crossover from chemotherapy to cemiplimab was allowed following progression. In the intention-to-treat population, a significant improvement in OS (median 22.1 *vs.* 14.3 months, HR[95%CI]: 0.68 [0.53–0.87]; p= 0.0022) was observed with cemiplimab, corresponding to a two-year OS rate of 49% *vs.* 30%. Furthermore, also the PFS was significantly in favour of cemiplimab with 18-month PFS rates of 28% and 4% (median PFS 6.2 *vs.* 5.6 months, HR[95%CI]: 0.59[0.49–0.72]; p< 0.0001), respectively. Interestingly, exploratory analysis of PD-L1 expression proportions (PD-L1 ≥90%; PD-L1 >60% to <90%; PD-L1 ≥50% to ≤60%) showed that PD-L1 proportions correlate with depth of changes in tumour measurement, as well as with incremental improvements in OS, PFS, and objective response rate (*Table 1*). Nowadays, the prognosis for patients with stage III disease who are not suitable for chemo-radiotherapy is poor. In a subgroup analysis focusing on those patients, cemiplimab improved survival benefits with a HR of 0.49 for PFS and 0.48 for OS.[8]

Based on the above described results, a Cochrane review on single ICIs compared to first-line platinum-based chemotherapy for patients with advanced NSCLC concluded that in the PD-L1 expression ≥ 50% group, single-agent ICI improves the OS compared to platinum-based chemotherapy (HR[95%CI]: 0.68[0.60-0.76], p< 0.00001). In addition, a clear signal was seen for an improved tolerability in favour of the checkpoint inhibitors (relative risk 0.43, p< 0.00001).[9]

One of the remaining questions in the management of NSCLC patients is whether patients with high PD-L1 expression (≥50%) should all receive immunotherapy monotherapy or whether some patients would benefit from the addition of chemotherapy. Thus far, there has not been a randomised clinical trial investigating this question. The only available information comes from a retrospective cohort study using the nationwide Flatiron Health Electronic Health Record-derived de-identified US database. This study indicates that withholding chemotherapy in first-line cancer immunotherapy treatment does not appear to impact survival outcomes (OS; p= 0.83 and PFS; p= 0.81).[10] Until more formal data are available, treatment decisions should therefore be made based on the clinical features of the patient and the

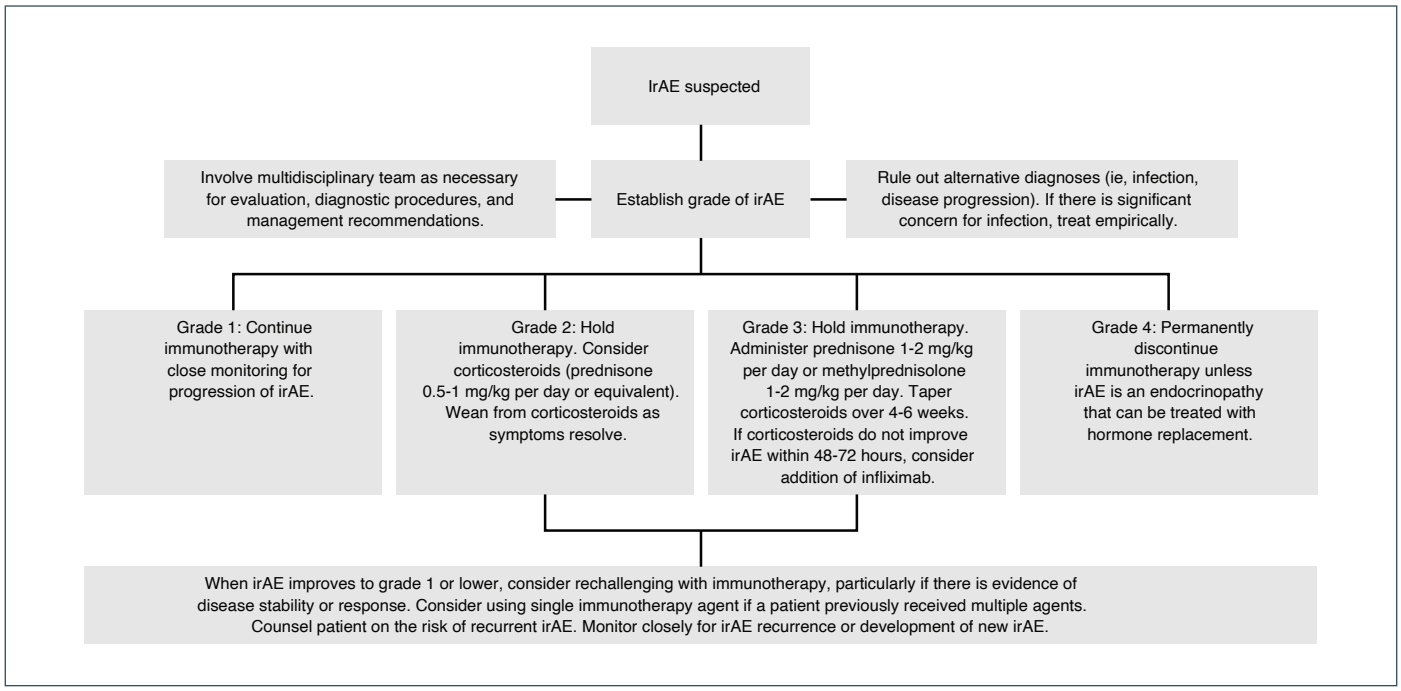

FIGURE 1. Framework for severity-guided management of immune-related adverse events and resumption of immunotherapy.[19]

tumour(s), as well as on the expression of PD-L1. Patients who do not have a high PD-L1 expression are generally treated with combination regimens of chemotherapy with immunotherapy.

CHECKPOINT INHIBITORS IN COMBINATION REGIMENS

Three landmark studies have investigated the efficacy of chemo-immunotherapy in untreated patients with advanced NSCLC: Keynote-189, IMpower150 and Keynote-407. In Keynote-189, patients with untreated stage IV non-squamous NSCLC were randomly assigned (2:1) to receive platinum-pemetrexed plus pembrolizumab or placebo Q3W for 4 cycles, then pemetrexed maintenance plus pembrolizumab or placebo for up to a total of 35 cycles. After a median follow-up of 46.3 months, a persistent improvement in OS was observed in favour of the pembrolizumab plus chemotherapy arm. Interestingly, this OS benefit was evident irrespective of the expression of PD-L1.[11] Also in the Keynote-407 trial, a consistent benefit was seen with the combination of pembrolizumab and chemotherapy in patients with advanced squamous NSCLC. Especially for patients with a high PD-L1 expression (≥1%), there was a clear benefit in OS and PFS.[12] Finally, the randomised, open-label, phase III IMpower150 study evaluated atezolizumab plus carboplatin and paclitaxel (ACP) or atezolizumab, bevacizumab, carboplatin and paclitaxel (ABCP) *vs.* bevacizumab, carboplatin, paclitaxel (BCP) in patients with metastatic non-squamous NSCLC. Patients with any PD-L1 expression status, as assessed by the VENTANA SP142 IHC assay, were included in the study. After a median follow-up of approximately 39 months, the median OS in the intention-to-treat wildtype population improved from 14.7 months in the BCP arm to 19.5 months in the ABCP arm (HR[95%CI]: 0.80[0.67–0.95]). Again, this effect was most pronounced in patients with PD-L1 expressing tumours.[13] With respect to safety, none of the three studies reported new adverse events. However, the chemo-immunotherapy combinations did come with a higher incidence of grade 3-4 TRAEs and TRAEs leading to treatment discontinuation. Therefore, it is evident that patients need to be monitored closely.[11-13]

A final treatment strategy that is being explored uses immunotherapy combinations, alone or in combination with a brief course of chemotherapy. In the CheckMate 227 study, chemotherapy-naïve patients with stage IV or recurrent NSCLC without *EGFR* or known *ALK* alterations, were randomised (1:1:1) to receive nivolumab (NIVO) plus ipilimumab (IPI), nivolumab (plus chemotherapy in patients with PD-L1 <1% expression), or chemotherapy alone. With a minimum follow-up of 49.4 months, patients with PD-L1 ≥1% demonstrated durable benefit with NIVO + IPI *vs.* chemotherapy (HR[95%CI]: 0.76[0.65–0.90]) with 4-year OS rates of 29% and 18%, respectively. Importantly, there was a similar effect on OS in the group of patients with PD-L1 negative tumour (4-year OS rates of 24% and 10%, respectively; HR: 0.64). When looking at the Kaplan-Meier curves, it should be noted that there is some crossing of the curves. As this can be observed in all immunotherapy-combination trials, this has

been the background of adding a brief course of chemotherapy.[14] This was also the case in the CheckMate 9LA trial. In this trial, adult patients with stage IV or recurrent NSCLC were randomised (1:1) to NIVO + IPI + 2 cycles of chemotherapy or 4 cycles of chemotherapy alone. At a minimum follow-up of 24.4 months for OS, patients treated with NIVO + IPI + chemotherapy derived a clear OS benefit as compared to chemotherapy (HR[95%CI]: 0.72 [0.61–0.86]). Similar clinical benefit with NIVO + IPI + chemotherapy *vs*. chemotherapy was observed across all PD-L1 expression levels, including patients with PD-L1 negative tumours.[15] Interestingly, in patients who discontinued all components of nivolumab plus ipilimumab with chemotherapy treatment due to TRAEs (N= 61), efficacy was largely the same as in the intention-to-treat population.[16]

HOW TO OPTIMISE THE MANAGEMENT OF IMMUNE-RELATED SIDE EFFECTS

While being very effective, immune-checkpoint inhibitors also generate specific immune-related adverse events (irAEs). This relatively new family of immune toxicities remains largely unknown to the broad oncology community. Although severe irAEs are rather rare, they can become life-threatening if not anticipated and managed appropriately. Therefore, physicians should aim to prevent, anticipate, detect, treat, and monitor any potential immunotherapy-related toxicity.[17]

In general, any organ or tissue can be involved, although some irAEs occur much more commonly than others. The most frequently occurring irAEs affect skin, colon, endocrine organs, the liver and the lungs.[18] If an irAE occurs, it is important to rule out alternative diagnoses (such as infections) and quickly treat according to the intensity of the toxicity. In general, ICIs should be continued with close monitoring as long as the toxicity remains grade 1 in severity, except for some neurologic, haematologic, and cardiac toxicities. On the other end of the spectrum, grade 4 irAEs should trigger a permanent discontinuation of immunotherapy, except for endocrinopathies that have been controlled by hormone replacement. IrAEs of grade 2 to 3 require a more nuanced approach with titration of immunosuppressive medications as patients recover over a variable time course. In case of grade 3 events, immunotherapy should be put on hold and the adverse events should be treated with corticosteroids, usually consisting of prednisone or methylprednisolone at a dose of 1-2 mg/kg per day for a period of two weeks. After this short treatment course, corticosteroids should be tapered continuously over a period of at least 4-6 weeks. If symptoms do not improve within 48-72 hours, infliximab can be offered to alleviate some toxicities. Also for grade 2 events, corticosteroids can be considered. When symptoms and/or laboratory values revert to ≤ grade 1, rechallenge with ICIs can be pursued. However, caution is advised, especially in patients with early-onset irAEs. As a rule of thumb, dose adjustments are not recommended. Rechallenge with PD-1/PD-L1 monotherapy may be offered in patients with toxicity from combined therapy with a CTLA-4 antagonist once recovered to ≤ grade 1 (*Figure 1*).[19,20]

Pneumonitis

In the case of immune-related pneumonitis of grade 2 (symptomatic and affecting more than one lob or 25-50% of lung parenchyma), immunosuppressive treatment should be started immediately. Ideally, a bacterial infection should be ruled out. However, if there is suspicion of infection, antibiotics should be administered in parallel with an immunosuppressive treatment. Furthermore, pneumocystis prophylaxis should be considered. If there is no improvement within 48 hours, an escalation to grade 3 is necessary. Patients with a grade 3 pneumonitis should be hospitalised and treatment should consist of high-dose corticosteroids while immunotherapy treatment should be permanently discontinued. When the patient's condition does not improve within 48 hours or there is no imaging improvement after two days, additional immunosuppressive strategies (infliximab or mycophenolate mofetil) should be implemented and non-invasive ventilation can be considered.[18,20]

Hepatitis

For grade 1 hepatitis, ICIs can be continued under close monitoring of transaminase levels. However, in the event of grade 2 transaminase increase (ALT or AST 3-5 x the upper limit of normal [ULN]) or total bilirubin elevation, ICIs should be withheld temporarily. Persistent grade 2 elevation, after having ruled out other causes, should be treated with prednisolone 1 mg/kg/day (or equivalent). Upon improvement, checkpoint inhibitor therapy may be resumed after corticosteroid tapering. If worsening or no improvement occurs despite initiation of corticosteroids, dosing should be increased to 2 mg/kg/day (methyl)prednisolone or equivalent and checkpoint inhibitor therapy permanently discontinued. For grade 3 (ALT or AST 5-20 x ULN) or 4 (ALT or AST > 20 x ULN) hepatitis, checkpoint inhibitor therapy should be permanently discontinued, and corticosteroids should be increased to 2 mg/kg/day (methyl)prednisolone or equivalent. If there is no response to corticosteroids within 3 days, mycophenolate mofetil should be added. If the patient remains refractory, etanercept (not infliximab) should be considered. Finally, consultation with a hepatologist and consideration of liver biopsy is recommended in steroid and mycophenolate-refractory cases.[18,20]

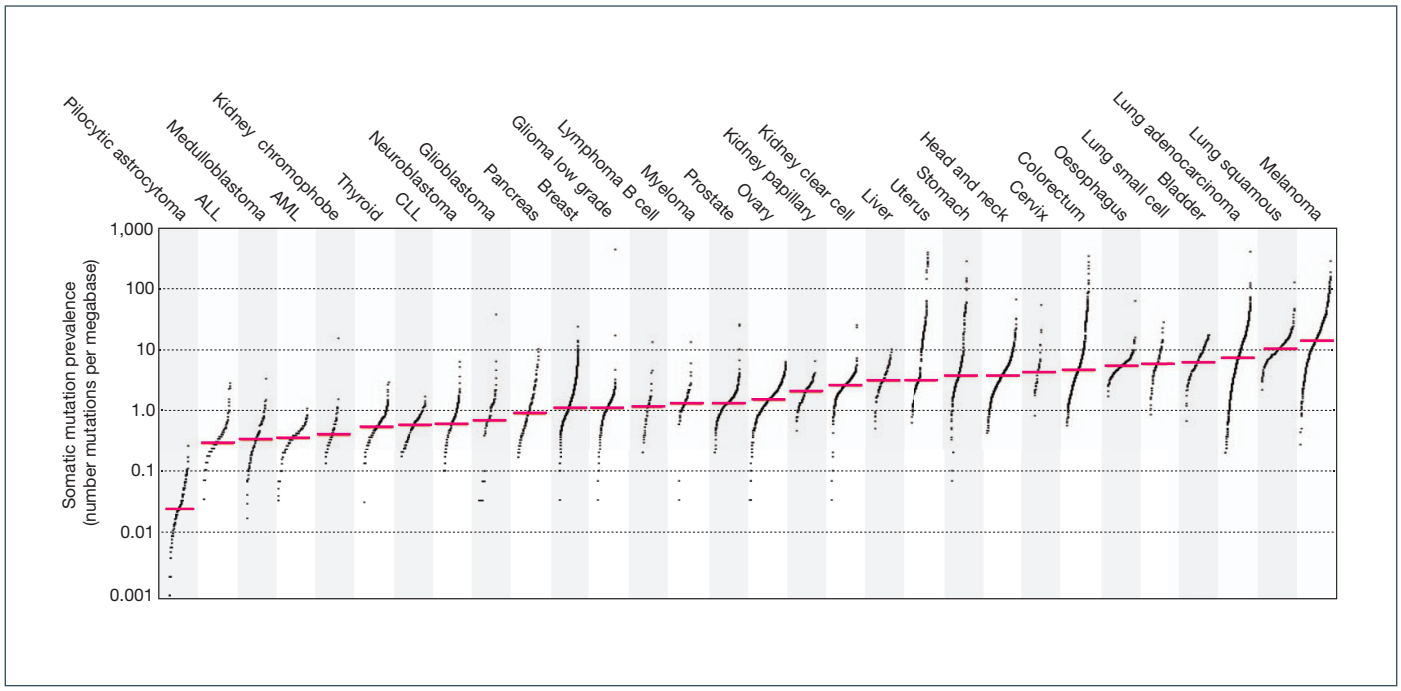

FIGURE 2. The prevalence of somatic mutations across human cancer types.[23]

Colitis

Gastro-intestinal toxicity from cancer immunotherapy is well described for anti-CTLA4 antibodies. In this, grade 2 colitis is defined as 4-6 liquid stools per day, while grade 3 is defined as more than 6 liquid stools per day. Especially for elderly patients with grade 2 colitis, it can become challenging to substitute this fluid loss by only drinking. For these patients, it is recommended to quickly administer fluids and electrolytes in a hospital environment. For grade 2 events, ICIs should be put on hold and steroids should be started. If there is no improvement within 72 hours, an escalation to grade 3 should be performed. In this phase, an addition of mycophenolate mofetil, infliximab or etanercept might become necessary. Colonoscopy should also be considered in grade 3 when other causes of diarrhoea (such as infections) cannot be excluded.[18,20]

FUTURE PROSPECTS OF IMMUNE THERAPEUTIC STRATEGIES AND BIOMARKERS

Biomarkers

In addition to the commonly used PD-L1 biomarker, the T-cell inflamed gene expression profile in the tumour microenvironment (TME) can predict the clinical response to anti-PD-1 across cancer types.[21] Furthermore, also mutation-derived neoantigens constitute important targets for immune attacks. The prevalence of somatic mutations is highly variable between and within cancer classes, ranging from about 0.001 per megabase (Mb) to more than 400 per Mb (*Figure 2*). While certain childhood cancers carry the fewest mutations, cancers related to chronic mutagenic exposures such as lung (tobacco smoking) and malignant melanoma (exposure to ultraviolet light) exhibited the highest prevalence.[22,23] Interestingly, a correlation was found between an increased mutational burden and the response to checkpoint inhibition of PD-1 and PD-L1.[24] However, it should be noted that high tumour mutational burden fails to predict response to anti-PD-1 in cancers where CD8 T-cell infiltration is not associated with neoantigen load.[25] Finally, also mismatch repair deficiency predicts the response of solid tumours to anti-PD-1.[26]

Future strategies

Several novel combination strategies are currently being explored to optimise the efficacy of immunotherapy in the treatment of lung cancer. First of all, a combination of radiation therapy and CTLA-4 blockade proved to induce systemic anti-tumour T-cells in chemotherapy-refractory metastatic NSCLC, where anti-CTLA-4 antibodies had failed to demonstrate significant efficacy alone or in combination with chemotherapy.[27]

Secondly, a phase Ib clinical trial demonstrated the feasibility, safety, and immunogenicity of the combination of personalised neoantigen vaccines (NEO-PV-01) and PD-1 inhibition in patients with advanced solid tumours, including NSCLC. Vaccine-induced T-cells persist over time, exhibit cytotoxic potential, and can migrate to tumours. In addition, epitope spread to non-vaccinating epitopes, and major pathologic tumour responses were

detected following vaccination.[28] Furthermore, also targeting indoleamine 2,3 dioxygenase (IDO) with a synthetic peptide vaccine was explored in patients with metastatic NSCLC. The vaccine was well tolerated with no severe toxicity occurring. A median OS of 25.9 months was demonstrated, and long-lasting partial response and stable disease was seen in 47% of patients.[29] A third potential novel strategy consists of tumour infiltrating lymphocyte (TIL) therapy. In this regard, a single-arm open-label phase I trial of TILs administered with nivolumab in 20 patients with metastatic NSCLC following initial progression on nivolumab monotherapy was conducted. Of 13 patients who progressed on nivolumab, most experienced an initial tumour regression at their first post-TIL CT-scan. Two patients achieved a complete response that was still ongoing after 1.5 years.[30]
Finally, several clinical trials are being conducted to treat lung cancer with CAR-T cell therapy. Although numerous advances in CAR-T cell therapy have been made in haematological tumours, the technology still entails considerable challenges in treating solid tumours, including on–target, off–tumour toxicity, paucity of tumour-specific antigen targets, T cell exhaustion in the tumour microenvironment, and low infiltration level of immune cells into solid tumour niches.[31]

CONCLUSION

The treatment paradigm for patients with advanced NSCLC has dramatically changed with the discovery of immunotherapy, resulting in better outcomes and fewer side effects compared to classic chemotherapy regimens. Multiple treatment options are now available for these patients, ranging from single-agent immunotherapy to combination regimens, including dual immune checkpoint inhibitor plus chemotherapy or immune checkpoint inhibitor plus chemotherapy plus anti–vascular endothelial growth factor drugs. However, special attention should go to the prevention, monitoring and appropriate treatment of immune-related adverse events, as this is crucial to prevent potentially fatal adverse events. Finally, many more exciting therapeutics are under active development and clinical investigation. In order to select the most suitable treatment for each individual patient, biomarkers will become of an even greater value in the future.

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LIBTAYO® (cemiplimab) – Abbreviated Prescribing Information – North Europe

▼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 adverse reactions.

PRESENTATION: 350 mg concentrate for solution for infusion. Each vial contains 350 mg of cemiplimab in 7 ml solution. **INDICATIONS*:** 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; •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; • for the first-line 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 cemiplimab in NSCLC, patients should be selected based on PD- L1 tumour expression using a validated test. **Recommended dose:** 350 mg LIBTAYO, every 3 weeks. Treatment may be continued until disease progression or unacceptable toxicity. **Administration:** LIBTAYO is for intravenous use only. It must be administered by intravenous infusion over 30 minutes. Other medicinal products should not be co-administered 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. **Special populations: Children:** Safety and efficacy in children below 18 years of age have not been established. **Elderly:** No dose adjustment is recommended. Data are limited in patients ≥75 years on cemiplimab monotherapy. **Renal impairment:** No dose adjustment is recommended. There are limited data in patients with severe renal impairment CLcr 15 to 29 ml/min. **Hepatic impairment:** No dose adjustment is recommended for patients with mild or moderate hepatic impairment. LIBTAYO has not been studied in patients with severe hepatic impairment and there are insufficient data in patients with severe hepatic impairment for dosing recommendations. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients. See full SmPC for the list of 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-related adverse reactions: Severe and fatal immune-related adverse reactions have been observed with LIBTAYO. These immune-related reactions may involve any organ system. Most immune-related reactions initially manifest during treatment with LIBTAYO; however, immune-related adverse reactions can occur after discontinuation of LIBTAYO. Immune-related 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-related adverse reactions. Immune- related adverse reactions should be managed with LIBTAYO treatment modifications, hormone replacement therapy (if clinically indicated), and corticosteroids. Evaluate patients for suspected immune-related adverse reactions to confirm an immune-related 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. The following immune related adverse reactions have been observed: - Immune-related pneumonitis, diarrhoea or colitis, nephritis: defined as requiring use of corticosteroids with no clear alternate aetiology, including fatal cases (for pneumonitis). 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-related pneumonitis should be ruled out), diarrhoea or colitis, or changes in renal function and manage with LIBTAYO treatment modifications, anti-diarrhoeal agents (if appropriate), and corticosteroids. - Immune-related hepatitis: defined as requiring use of corticosteroids with no clear alternate aetiology, including fatal cases. Monitor patients for abnormal liver tests prior to and periodically during treatment based on clinical evaluation and manage with LIBTAYO treatment modifications and corticosteroids. - Immune-related endocrinopathies: defined as treatment-emergent endocrinopathies with no clear alternate aetiology. *Thyroid disorders (Hypothyroidism/Hyperthyroidism/Thyroiditis):* Thyroiditis can present with or without an alteration in thyroid function tests. Thyroid disorders can occur at any time during the treatment. 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. Immune- related *Hypophysitis:*. Monitor patients for signs and symptoms of hypophysitis and manage with LIBTAYO treatment modifications, corticosteroids and hormone replacement. *Adrenal insufficiency:* Monitor patients for signs and symptoms of adrenal insufficiency during and after treatment and manage with LIBTAYO treatment modifications, corticosteroids and hormone replacement. *Type 1 Diabetes mellitus:* Immune-related type 1 diabetes mellitus, including diabetic ketoacidosis. Monitor patients for hyperglycaemia and signs and symptoms of diabetes based on clinical evaluation and manage with oral anti-hyperglycaemics or insulin and LIBTAYO treatment modifications.- Immune- related skin adverse reactions: defined as requiring use of systemic corticosteroids with no clear alternate aetiology, including severe cutaneous adverse reactions , 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. Monitor patients for evidence of suspected severe skin reactions and exclude other causes. 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 , and who had recent exposure to sulfa containing antibiotics. Manage patients with LIBTAYO treatment modifications and corticosteroids. - Other immune-related adverse reactions: Other fatal and life-threatening immune-related adverse reactions have been observed including paraneoplastic encephalomyelitis, meningitis and myositis. (see full SmPC for the list of other immune-related adverse reactions). Noninfective cystitis has been reported with other PD-1/PD-L1 inhibitors. Monitor patients for signs and symptoms of immune- related adverse reactions. Manage patients with LIBTAYO treatment modifications and corticosteroids. Solid organ transplant rejection has been reported in the post-marketing 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 which can be severe or life-threatening. Monitor patients for signs and symptoms 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. See SmPC for full list of patients excluded from clinical studies. **DRUG INTERACTIONS*:** No pharmacokinetic drug-drug interaction studies have been conducted with LIBTAYO. Use of systemic corticosteroids or other 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-related 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 following 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 breastfeed while being treated and for at least 4 months after the last dose. No clinical data are available on the possible effect of LIBTAYO on fertility. **UNDESIRABLE EFFECTS*:** Very common (≥ 1/10): upper respiratory tract infection, anaemia, decreased appetite, cough, nausea, diarrhoea, constipation, 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, abdominal pain, vomiting, stomatitis, colitis, hepatitis, arthritis, nephritis, aspartate aminotransferase increased, alanine aminotransferase increased, blood alkaline phosphatase increased, blood creatinine increased. Uncommon (≥ 1/1,000 to < 1/100): Sjogren's syndrome, immune thrombocytopenic purpura, adrenal insufficiency, thyroiditis, Type 1 diabetes mellitus, hypophysitis, meningitis, encephalitis, myasthenia gravis, paraneoplastic encephalomyelitis, chronic inflammatory demyelinating polyradiculoneuropathy, keratitis, myocarditis, pericarditis, muscular weakness, myositis, polymyalgia rheumatica, blood thyroid stimulating hormone increased, transaminases increased, blood bilirubin increased, blood thyroid stimulating hormone decreased. Additional immune-related adverse reactions observed in patients receiving combination therapy in clinical trials: vasculitis, Guillain-Barre syndrome and central nervous system inflammation each with the frequency of rare. **Please refer to the SmPC for full list of adverse reactions.** Health care professionals are asked to report any suspected adverse reactions via their national reporting system. **OVERDOSE:** In case of overdose, closely monitor patients for signs or symptoms of adverse reactions. Appropriate symptomatic treatment should be instituted. **MARKETING AUTHORISATION HOLDER:** Regeneron Ireland DAC., One Warrington Place, Dublin 2, Ireland. **LOCAL REPRESENTATIVE:** Sanofi or equivalent name/representative. **LEGAL CLASSIFICATION:** Prescription Only Medicine.

Abbreviated Prescribing Information based on the EU SmPC as of January 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 Genzyme, 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 januari 2022. Voor meer informatie zie de geregistreerde productinformatie.

Date of preparation: January 2022