Application for the inclusion of the anti-PD1 immune-checkpoint inhibitors in the WHO Model list of ESSENTIAL MEDICINES for the treatment of "non-oncogene- addicted" (EGFR, ALK, and ROS1 wild type) locally advanced and metastatic non-small cell lung cancer (NSCLC).

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European Society for Medical Oncology (ESMO)

3. International Nonproprietary Name (INN, generic name) of the medicine

3.1 Pembrolizumab

3.2 Nivolumab

3.3 Atezolizumab

3.4 Durvalumab

These medicines belong to the class of PD-1/ PD-L1 immune-checkpoint inhibitors (ICI), which are immune-therapy agents for the treatment of NSCLC. ICIs are in addition, registered drugs for the treatment of numerous other tumour types. However, this application aims to address the priority indications for tumours with a cogent public health interest where the role of ICIs is definite, for the indications with no controversies and debates ongoing, for which a valuable role in cancer treatment has been established and widely agreed by the oncology experts and scientific societies.

4. Formulation proposed for inclusion, including adult and paediatric (1, 2)

4.1 Pembrolizumab (trade name Keytruda) is a humanised monoclonal anti-programmed cell death-1 (PD-1) antibody (IgG4/kappa isotype with a stabilising sequence alteration in the Fc region) produced in Chinese hamster ovary cells by recombinant DNA technology. One vial of powder contains 50 mg pembrolizumab. After reconstitution, 1 mL concentrate contains 25 mg pembrolizumab. It presents as a white to off-white lyophilised powder. For adults, the recommended schedule is 200 mg IV every 3 weeks or 400 mg every 6 weeks. For paediatric use, the suggested schedule is 2 mg/kg (not to exceed 200 mg) for colorectal cancer harbouring DNA mismatch repair deficiency.

4.2 Nivolumab (trade name Opdivo) a human IgG4 anti-PD1 antibody available as 10 mg/mL concentrate for solution for infusion: each mL concentrate contains 10 mg nivolumab, one vial of 4 mL contains 40 mg nivolumab, one vial of 10 mL contains 100 mg nivolumab, one vial of 24 mL contains 240 mg nivolumab. It is to be administered as an intravenous infusion over 30 or 60 minutes, depending on the dose. The infusion is administered through a sterile, non-pyrogenic, low protein binding in-line filter with a pore size of 0.2-1.2 µm. The recommended dose of nivolumab is 240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes. For paediatric patients with body weight less than 40 kg, the total volume of infusion must not exceed 4 mL/kg of body weight: The safety and effectiveness of nivolumab have been established in paediatric patients age 12 years and older with mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

4.3 Atezolizumab (trade name Tecentriq) is available at Tecentriq 840 mg concentrate for solution for infusion. One 14 mL vial of concentrate contains 840 mg of atezolizumab. Atezolizumab is an Fc-engineered, humanised IgG1 anti-programmed death-ligand 1 (PD-L1) monoclonal antibody produced in Chinese hamster ovary cells by recombinant DNA technology. PD-L1 and PD-L2 are the natural ligands of PD-1. The use is intended as intravenous. The recommended dose of atezolizumab monotherapy is 1,200 mg administered intravenously every 3 weeks, as 840 mg administered intravenously every 2 weeks, or 1,680 mg administered intravenously every 4 weeks. No data is available for the use of atezolizumab in the paediatric setting.

4.4 Durvalumab (trade name Imfinzi) is available as a concentrate for infusion in the form of one vial of 2.4 mL of concentrate containing 120 mg of durvalumab and one vial of 10 mL of concentrate containing 500 mg of durvalumab. Durvalumab is produced in mammalian (Chinese hamster ovary) cells by recombinant DNA technology and is a fully human, immunoglobulin G1kappa (IgG1κ) monoclonal antibody that selectively blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1). Durvalumab does not induce antibody-dependent cell-mediated cytotoxicity (ADCC). The recommended dose of durvalumab is 10 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks, until disease progression or unacceptable toxicity, or a maximum of 12 months, through an intravenous line containing a sterile, low-protein binding 0.2 or 0.22 micron in-line filter. The safety and efficacy of durvalumab in children and adolescents aged below 18 years of age have not been established, and no data are available.

5. International availability - sources, if possible, manufacturers and trade names

In this submission, we will consider the indications for ICIs in NSCLC scored as European Society for Medical Oncology- Magnitude of Clinical Benefit Scale (ESMO-MCBS) grade 4 or 5 in Non-Curative settings and for which no controversies exist (3).

5.1 Pembrolizumab as monotherapy is indicated in the frontline treatment of advanced EGFR and ALK wild type NSCLC showing PD-L1 hyperexpression i.e., PD-L1≥50% and for the second-line treatment of advanced NSCLC with a PD-L1 tumour expression ≥1% after platinum-containing chemotherapy failure. Moreover, it is EMA-approved in association with chemotherapy for the frontline treatment of NSCLC, regardless PD-L1 status. In melanoma, it is approved by EMA for the frontline treatment of metastatic melanoma, with no biomarker for patients' selection, and as monotherapy for the adjuvant treatment of adults with stage III melanoma and lymph node involvement who have undergone complete resection. Other indications include patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV, patients with locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy, locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10. Finally, pembrolizumab is indicated for recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1≥ 50% and who are progressing on or after platinum-containing chemotherapy, as monotherapy, or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy for the first-line treatment of metastatic or unresectable recurrent HNSCC in adults whose tumours express PD-L1 with a CPS ≥ 1 and in combination with axitinib for the first-line treatment of advanced renal cell carcinoma in adults. Additional indications approved by FDA include patients with MSI-H or dMMR metastatic solid tumours, including and not limited to colorectal cancer, for the first-line treatment of patients with NSCLC expressing PD-L1 [tumour proportion score (TPS) ≥1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumour aberrations, for the treatment of patients with recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) that is not curable by surgery or radiation, for the treatment of patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy and at least 1 other prior line of therapy (accelerated approval), for the treatment of adult and paediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma (MCC, accelerated approval), for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumours express PD-L1 (CPS ≥1) as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy (accelerated approval), for the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the oesophagus whose tumours express PD-L1 (CPS ≥10) as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy, for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumours express PD-L1 (CPS ≥1) as determined by an FDA-approved test (accelerated approval), for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib (accelerated approval), for the treatment of adult and paediatric patients with unresectable or metastatic tumour mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumours, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options (accelerated approval).

Patients are treated with pembrolizumab until disease progression or unacceptable toxicity. The use of pembrolizumab has been tested in some clinical trials (e.g., KEYNOTE-024 trial, see below) for up to 35 cycles and in other trials up to progressive disease or maximal tolerance, with the optional clinical decision to stop the treatment after 35 cycles and resume in case of progressive disease, where applicable. Atypical responses (i.e., an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed (4). It is currently recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed. ICI treatment can be continued for 4-8 weeks after the evidence of disease progression at CT scan, in patients without clinical evidence of disease worsening and/or reporting improvement of cancer- related symptoms and quality of life, as these patients can experience temporarily pseudo progression. In this submission for NSCLC, we will consider the indications of NSCLC scored as ESMO-MCBS grade 4 or 5 and for which no controversies exist in the indications, namely the use frontline in NSCLC expressing PD-L1≥50%, the use frontline in combination with cytotoxic chemotherapy in NSCLC irrespective of PD-L1 expression and the use in the second line after chemotherapy failure for NSCLC PD-L1≥1%, all in the setting of advanced disease.

5.2 Nivolumab is indicated as monotherapy for the treatment of locally advanced or metastatic NSCLC after prior chemotherapy in adults, regardless of PD-L1 status. Nivolumab is also approved for the treatment of patients with melanoma (BRAF wild-type and BRAF mutated) as frontline treatment as monotherapy or in combination with ipilimumab in the advanced disease setting and as monotherapy for the resected high-risk melanoma (e.g., involved lymph nodes at presentation and stage IV resected (NED) melanoma), as adjuvant agent. The same discussion provided for pembrolizumab on the pseudo progression pattern of tumour response is applicable to nivolumab (4), as a class effect observed with different ICI. For nivolumab use in the adjuvant setting, the maximum treatment duration is 12 months. Treatment with nivolumab in the metastatic setting, either as a monotherapy or in combination with ipilimumab, is currently continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient. Other registered indications for nivolumab are advanced renal cell carcinoma (RCC) after prior therapy in adults, frontline RCC in combination with ipilimumab for patients with intermediate or high risk renal cancer, for adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant and treatment with BV, for recurrent or metastatic HNSCC in adults progressing on or after platinum-based therapy and for locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy. FDA approved nivolumab additionally for patients with MSI-H or dMMR metastatic solid tumours, for the treatment of Hepatocellular carcinoma patients previously treated with sorafenib, for the treatment of patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based chemotherapy. Nivolumab combined to ipilimumab has been FDA-approved for previously treated MSI-H/dMMR metastatic colorectal cancer and for the first-line treatment of adult patients with metastatic NSCLC whose tumours express PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumour aberration. Recently, FDA approved nivolumab combined to low dose ipilimumab given with two cycles of platinum-doublet chemotherapy for the first-line treatment of adult patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumour aberrations, irrespective of histology or PD-L1 expression. In this submission for NSCLC, we will consider the indications of NSCLC scored as ESMO-MCBS grade 4 or 5 and for which no controversies exist in the indications, namely the use in the second line after chemotherapy failure, regardless PD-L1 status (all comers).

5.3 Atezolizumab is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. Atezolizumab monotherapy is also registered for adult patients with locally advanced or metastatic urothelial carcinoma after prior platinum-containing chemotherapy or in patients considered cisplatin ineligible and whose tumours have a PD-L1 expression ≥ 5%, as well as in combination with nab-paclitaxel for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease. FDA additionally approved atezolizumab for the first-line treatment of adult patients with metastatic NSCLC whose tumours have high PD-L1 expression (PD-L1 stained ≥50% of tumour cells [TC ≥50%] or PD-L1 stained tumour-infiltrating immune cells [IC] covering ≥10% of the tumour area [IC ≥10%]), with no EGFR or ALK genomic tumour aberrations and in combination with bevacizumab, paclitaxel, and carboplatin, for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumour aberrations. It has also been FDA-approved in combination with paclitaxel protein-bound and carboplatin for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumour aberrations. Other FDA approvals include in combination with carboplatin and etoposide for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC), in combination with bevacizumab for the treatment of patients with unresectable or metastatic HCC who have not received prior systemic therapy, in combination with cobimetinib and vemurafenib for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. It is recommended that patients are treated with atezolizumab until loss of clinical benefit or unmanageable toxicity. In this submission we will consider the evidence supporting the inclusion of atezolizumab for the treatment in NSCLC.

5.4 Durvalumab as monotherapy is indicated by EMA for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy. Additionally, FDA approved durvalumab for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy (accelerated approval), for the treatment of adult patients with unresectable, Stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy irrespective of tumour PD-L1 expression, and in combination with etoposide and either carboplatin or cisplatin, as first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC). In this submission we will consider the evidence supporting the inclusion of durvalumab for maintenance therapy in patients with PD-L1-expressing locally advanced NSCLC, after platinum chemoradiotherapy.

Different schedules of ICIs have been proposed for the treatment of patients presenting with advanced or metastatic disease: time-limited, non-time-limited (e.g. up to disease progression or patient's tolerance) and optional time-limited (according to physician's choice in patients achieving a complete response or sustained response). Treatment with ICI can be continued until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression (optional time-limited schedule). It may well be that ICI administration only have to be administered for a defined period of time. Accordingly, several clinical trials are ongoing for a shorter schedule of ICI (time-limited), but none of these has provided robust data to stop treatment before 24 months, and results are awaited. This specific limit is acknowledged for pembrolizumab, in which a clear indication to stop treatment at 24 months in patients without disease progression is reported. However, the same acknowledgment is reported for ICI in several clinical trials ongoing, with an optional stop of treatment and the possibility to resume, as appropriate. Durvalumab, on the contrary, is administered to patients with unresectable stage III NSCLC until disease progression or unacceptable toxicity, or a maximum of 12 months.

6. Whether listing is requested as an individual medicine or as an example of a therapeutic group?

Therapeutic group.

7. Information supporting the public health relevance.

Lung cancer. Lung cancer is the most diagnosed and the first cause of death for cancer worldwide, estimating 2 million new cases and 1.7 related deaths in 2018, according to Global Cancer Observatory 2018 (5). Lung cancer is a highly lethal malignancy, with an economic impact estimated around $8 billion productivity lost in the BRICS countries (6). Moreover, in the absence of a wide coverage of an effective screening programme in place on global scale, lung cancer diagnoses occur in advanced stages (i.e. III and IV, TNM 8th) in more than 60% of cases, with highly regional variability (7-9). Lung cancer is the leading cause of cancer-related mortality in the United States and worldwide. Over 80% of the lung cancers are classified as NSCLC. Although targeted therapies have redefined the therapeutic landscape for patients with molecularly druggable NSCLC (e.g. epidermal growth factor receptor [EGFR] mutations, anaplastic lymphoma kinase [ALK] rearrangements, ROS1 rearrangements, BRAF mutations, HER2 mutations or amplifications, NTRK1-3 fusions), these therapies are ineffective in those tumours lacking such genetic alterations, the majority of NSCLC patients. However, ICI therapy has become part of the treatment of such patients, which has led to improvements in survival and quality of life. The ICI target and reactivate the immune-competent cells, i.e. T-lymphocytes and antigen-presenting cells, by inhibiting the immunosuppressive ligand PD-L1 or its receptor, PD-1, in the tumour-induced immunosuppressant milieu or by strengthening the immune-activating signals of immune-response (e.g. GITR, pro- inflammatory interleukins, interferon-gamma) (10). The approval of ICIs in NSCLC addresses an unmet need for patients considered to have a poor prognosis in advanced stage, in the absence of an indication of targeted therapy.

8. PD-1 and PD-L1 immune-checkpoint inhibitors for the treatment of non-oncogene driven NSCLC.

The use of ICIs represented a landmark achievement for the treatment of advanced lung cancer, particularly after the approval of ICI for the treatment of metastatic disease, with various patients' enrichments per predictive biomarkers (i.e. PD-L1 IHC, microsatellite/ DNA mismatch repair status, tumour mutational burden), both frontline and in pre-treated patients. For this application, we selected the indications for ICI showing the most valuable and durable results with a public health relevance and no controversies debated on the appropriate use, namely a) the frontline indication of pembrolizumab as ICI monotherapy in PD-L1≥50% NSCLC patients, b) the frontline indication of pembrolizumab as ICI in combination with cytotoxic chemotherapy in NSCLC patients irrespective of PD-L1 expression and c) second line, selected (pembrolizumab) or not selected (nivolumab, atezolizumab) per PD-L1 expression (3, 11).

9. Treatment details

All the drugs are used in NSCLC, as:

- Frontline (pembrolizumab, atezolizumab) in metastatic NSCLC expressing high levels of PD-L1.

- Frontline (pembrolizumab) in combination with cytotoxic chemotherapy in metastatic squamous and non-squamous NSCLC irrespective of tumour PD-L1 expression.

- As frontline consolidation (durvalumab) for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy.

- After chemotherapy failure, as second line regimen, in PD-L1 positive (pembrolizumab) or non-PD-L1 selected patients (nivolumab, atezolizumab) in NSCLC. Both the indications are intended for squamous and non-squamous histology NSCLC.

10. Summary of comparative effectiveness in a variety of clinical settings. Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data).

The data are provided by the ESMO Guidelines (12) for the management of advanced lung cancer and implemented with the use of other clinical guidelines, where available, and a manual research of databases (Medline, Scopus, Ovid, Google Scholar) and the relevant abstracts manually retrieved from the oncology meetings (ESMO, ASCO, ESMO Asia, ELCC, WLCC) for lung cancer. The ESMO Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development (13). The relevant literature has been selected by the expert authors, reporting the levels of evidence (I-V) and the grades of recommendations (A-E), adapting the Infectious Diseases Society of America-United States Public Health Service Grading System. ESMO-MCBS v1.1 is used to calculate scores for new therapies/indications approved by the EMA since 1 January 2016, with 4 or 5 and A, B considered as valuable scores to suggest priority medicines in advanced and curative setting, respectively (3).

10.1 Treatment of non- oncogene driven NSCLC as described Sep 2020 in the ESMO NSCLC Guideline (12)

10.1A Frontline treatment with pembrolizumab as monotherapy in PD-L1-high, EGFR/ALK wild type NSCLC.

First-line treatment of EGFR- and ALK-negative high PD-L1 NSCLC (PD-L1≥50% TPS, tested with IHC). Lung cancers were previously considered poorly immunogenic, with minimal benefit seen in historical studies of cytokine modulation or vaccines. However, the recent development of ICI showed that immunotherapy can play an important role in the treatment of patients with lung cancer. The phase 3 KEYNOTE-024 study has established the role for pembrolizumab as first-line treatment in patients with treatment-naive, advanced NSCLC showing PD-L1 expression ≥ 50%, in absence of EGFR mutation or ALK translocations (non-oncogene-driven NSCLC). In KEYNOTE-024, 1934 EGFR and ALK wild type NSCLC patients were screened to identify 500 patients (30%) with tumour PD-L1 expression ≥50%. The companion diagnostics for pembrolizumab in this trial was PD-L1 IHC 22C3 PharmD assay, a qualitative IHC assay using monoclonal mouse anti-PD-L1, Clone 22C3 intended for use in the detection of PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) samples. PD-L1 protein expression in NSCLC is determined by using TPS, which is the percentage of viable tumour cells showing partial or complete membrane staining at any intensity (14). Of these patients, 305 patients were randomised to receive 200 mg pembrolizumab every 3 weeks (up to 2 years) or 4-6 cycles of standard platinum-doublet chemotherapy. All efficacy measures favoured pembrolizumab, including objective response rate (ORR 45% versus 28%), PFS (hazard ratio (HR) 0.5, 95% confidence interval (CI) 0.37–0.68, p<0.001] and OS (HR 0.6, 95% CI 0.41–0.89, p = 0.005). Safety and quality of life (QoL) also favoured pembrolizumab. In the intention-to-treat population, based on 189 events of progression or death in the first survival report, median PFS was 10.3 months (95% CI, 6.7 to not reached) in the pembrolizumab group and 6.0 months (95% CI, 4.2 to 6.2) in the chemotherapy group. At the time of the second interim analysis, 108 deaths had occurred. The estimated percentage of patients who were alive at 6 months was 80.2% (95% CI, 72.9 to 85.7) in the pembrolizumab group and 72.4% (95% CI, 64.5 to 78.9) in the chemotherapy group. An updated survival report with a 25.2 months median follow-up, confirmed the superiority of pembrolizumab over chemotherapy: the HR for OS was 0.63 (95% CI, 0.47–0.86; nominal p=0.002), median (95% CI) OS was 30.0 (18.3–not reached) months in the pembrolizumab arm and 14.2 (9.8–19.0) months in the chemotherapy arm; the Kaplan-Meier estimate of OS at 12 months was 70.3% (95% CI, 62.3%–76.9%) for the

pembrolizumab group and 54.8% (95% CI, 46.4%–62.4%) for the chemotherapy group (15). Eighty-two patients, allocated to the chemotherapy arm, crossed over to receive pembrolizumab upon meeting eligibility criteria. In term of effect size, pembrolizumab provided a gain of median OS of +15.8 months and +15.5% at 1 year. Treatment-related adverse events (TRAE) occurred in 73.4% of the patients in the pembrolizumab group and in 90.0% of the patients in the chemotherapy group. 53.3% vs 26.6% were grade 3 (moderate- severe) to grade 5 (toxic death) per CTCAE (16) in the chemotherapy and ICI, respectively, resulting in a slightly higher treatment discontinuation rate because of treatment-related adverse events in the chemotherapy arm (10.7%) than the ICI arm (7.1%). TRAEs for ICI were consistent with an immune-mediated process against "the self", meaning an autoimmune event or an immune-activation syndrome, the most common being hypo- and hyper-thyroidism (9% and 8%, all grade 1 and 2 per CTCAE, non-severe events not leading to discontinuation of therapy and registered as laboratory transient and not clinically relevant alterations of plasma thyroid hormones), diarrhoea (in 14.3% of the patients), fatigue (10.4%), and pyrexia (10.4%) in the pembrolizumab group; for chemotherapy, the bone marrow toxicity (anaemia in 44.0%) and traditional systemic TRAEs were observed (nausea in 43.3% and fatigue in 28.7%); anti-emetic premedication was allowed per protocol, consistent with institutional and international guidelines for moderately to highly-emetogenic platinum-containing CT regimens in the standard of care arm.

At the 2019 World Conference on Lung Cancer (WCLC) (Abstract OA14.01), with more than 3 years of median follow-up, the median OS length among patients in the pembrolizumab arm was 26.3 months vs 14.2 months in the chemotherapy arm. The 36-month OS rate was 43.7% in the pembrolizumab arm vs 24.9% in the chemotherapy arm. Despite longer mean treatment duration in the pembrolizumab arm (11.1 vs 4.4 months), grade 3–5 treatment-related adverse events were less frequent with pembrolizumab vs chemotherapy (15).

As for the last update, ESMO 2020 Virtual Congress (Abstract LBA51), KEYNOTE-024 data were updated with median follow-up of 5 years, (55.1-68.4 months), and a 55% cross-over rate to pembrolizumab arm. They revealed that pembrolizumab treated patients exhibit a consistent and significant OS significant improvement (pembrolizumab 31.9% vs 16.3% chemotherapy), and fewer grade 3-5 adverse events - pembrolizumab 31.2% vs 53.3% chemotherapy (17).

The health-related quality of life (QoL) analysis showed a clinically meaningful and significant improvement of QoL (18). The European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 items (QLQ-C30), the EORTC Quality of Life Questionnaire Lung Cancer 13 items (QLQ-LC13), and the European Quality of Life 5 Dimensions-3 Level (EQ-5D-3L) questionnaire were used to assess the prespecified exploratory endpoint of pembrolizumab versus chemotherapy on patient-reported outcomes (PROs). Least-squares mean baseline-to-week-15 change in QLQ-C30 GHS/QOL score was 6.9 (95% CI 3.3 to 10.6) for pembrolizumab and −0.9 (−4.8 to 3.0) for chemotherapy, for a difference of 7.8 (2.9 to 12.8; p=0.0020). Fewer pembrolizumab treated patients had deterioration in the QLQ-LC13 composite endpoint than chemotherapy treated patients (46 [31%] of 151 patients vs 58 [39%] of 148 patients). Time to deterioration was longer with pembrolizumab than with chemotherapy (median not reached [95% CI 8.5 to not reached] vs 5.0 months [3.6 to not reached]; HR 0.66, 95% CI 0.44–0.97; p=0.029).

As a result of KEYNOTE-024, pembrolizumab was approved by the FDA and EMA as first-line therapy for patients with NSCLC with high PD-L1 expression (PD-L1≥50%) as assessed at immuno-histochemistry. In the approval trial, the PD-L1 expression was assessed in FFPE tumour samples at a central laboratory with the use of the commercially available PD-L1 IHC 22C3 pharmDx assay (Dako) on histology specimens. However, the assessment of PD-L1 IHC of cytology cell-block was as reliable as the histology assessment, in independent assessments (19-21). The PD-L1 IHC 22C3 pharmDx assay is the companion diagnostic of pembrolizumab frontline with the threshold of "high expression" PD-L1 tumour proportion score of ≥50%. This finding is clinically relevant since the collection of a histology sample may be challenging in lung cancer diagnosis, particularly when bronchoscopy with fine-needle aspirations is used. In detail, cell block cytology is a technique used in cytopathology (in addition to smears) for evaluation of tissue from fine needle aspirations or fluid aspiration for which the cells in solution are then concentrated via centrifuge from cytological specimens into paraffin blocks that can be cut and stained by the same methods used for histopathology. Based on this evidence, the use of the cell block is considered a reliable specimen to assess the PD-L1 status, reducing the need for more invasive procedures and increasing the likelihood of having an informative specimen in terms of prediction treatment response with few cytology materials.

A cost-effectiveness analysis has been provided for the indication of pembrolizumab frontline in advanced non-oncogene driven PD-L1 high NSCLC (22). The work aimed to measure was the incremental cost-effectiveness ratio (ICER), expressed as cost per quality-adjusted life-year (QALY) gained and the incremental cost per life-year (LY) gained. Data of safety and efficacy were derived from KEYNOTE-024 trial (23). The analysis was conducted from the perspective of a US third-party, public healthcare payer (updated to $US, year 2016 values). Pembrolizumab would be expected to result in an incremental cost of $US98,281/ QALY gained or an incremental cost of $US78,873/LY gained. Including the cost of PD-L1 testing has a very small impact on the model results. With a 5-year time horizon, the ICER was $US99,998/LY and $US122,024/QALY; with a 10-year time horizon, the ICER was $US83,065 and

$US103,101/QALY. Base-case results indicated that, compared with standard of care over a 20-year time horizon, pembrolizumab would be expected to result in an additional 1.31 LYs and an additional 1.05 QALYs gained.

Grade of Evidence and Level of Recommendation. Based on the KEYNOTE-024 trial, confirmed at a 3-year follow-up updated survival analysis, pembrolizumab is a new standard as first-line option for patients with advanced NSCLC, and PD-L1 expression ≥50% who do not otherwise have contraindications to ICI (such as severe and active autoimmune disease, organ transplantation recipient treated with immunosuppressing drugs, active infectious disease i.e. active hepatitis B or C, HIV or acute infections like pneumonia) [grade of evidence and level of recommendation: I,A; European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: 5/5].

The frontline use of ICI has also been investigated in NSCLC other than PD-L1>50%, to assess if the benefit was conserved in unselected populations of patients. The phase 3 clinical trial KEYNOTE-042 randomized NSCLC EGFR/ALK wild type showing PD-L1≥1%, both adenocarcinoma and squamous NSCLC, to receive either pembrolizumab 200 mg every 3 weeks or standard chemotherapy (paclitaxel plus carboplatin or pemetrexed plus carboplatin), stratifying per PD-L1 expression at three thresholds of PD-L1: ≥ 50%, ≥20% and ≥1%. In total 1274 patients were randomized: 637 to each arm (23). 599 patients (47.0%) had PD-L1 ≥50%, 818 (64.2%) had ≥20%. Pembrolizumab improved OS in NSCLC patients with PD-L1≥ 50% (HR 0.69), consistent with the results of KEYNOTE-024 for the PD-L1 enriched population. Indeed, the HR for OS was 0.69 (95% CI 0.56 – 0.85), 0.77 (95% CI 0.64 – 0.92) and 0.81 (95% CI 0.71 – 0.93) for PD-L1 ≥50, ≥20% and ≥1%, respectively. However, the preponderance of the OS benefit was driven by patients with PD-L1 ≥50%, the only subgroup gaining more than +6 months of OS, while no significant increase was seen in those patients with 1%–49% as in the exploratory analysis of survival, where OS was showed to be 13.4 versus 12.1 months in this subpopulation (HR 0.92, 95% 0.77-1.11).

The same hypothesis was tested in the phase 3 CheckMate 026 trial, in patients with untreated, advanced NSCLC and PD-L1≥1%, randomized to nivolumab or platinum-doublet standard chemotherapy (24). Patients were stratified as PD-L1<5% and PD-L1≥5%. Patients received nivolumab (administered intravenously at a dose of 3 mg/kg every 2 weeks) or platinum-based chemotherapy (administered once every 3 weeks for up to 6 cycles). The trial failed to demonstrate a superiority of ICI over chemotherapy in unselected NSCLC patients. In the primary efficacy analysis population (patients with a PD-L1 expression level of ≥ 5%), there was no difference in PFS between the treatment groups. The median PFS was 4.2 months (95% CI, 3.0 to 5.6) in the nivolumab group and 5.9 months (95% CI, 5.4 to 6.9) in the chemotherapy group (HR for disease progression or death, 1.15; 95% CI, 0.91 to 1.45; p=0.25). The median OS in the primary efficacy analysis population was 14.4 months (95% CI, 11.7 to 17.4) in the nivolumab group and 13.2 months (95% CI, 10.7 to 17.1) in the chemotherapy group (HR for death, 1.02; 95% CI, 0.80 to 1.30). Similar results regarding PFS and OS were found for all the patients randomised, regardless of PD-L1 expression. Nivolumab was not associated with a longer PFS than chemotherapy. Overall, these results confirm the benefit of pembrolizumab in the first-line setting seen in KEYNOTE-024, restricted to patients with high PD-L1 expression (≥50%).

10.1B Atezolizumab Monotherapy for the first-line treatment of adult patients with metastatic NSCLC whose tumours have high PD-L1 expression (PD-L1 stained ≥50% of tumour cells [TC ≥50%] or PD-L1 stained tumour-infiltrating immune cells [IC] covering ≥10% of the tumour area [IC ≥10%]), with no EGFR or ALK genomic tumour aberrations.

Atezolizumab is an active PD-L1 inhibitor that has been evaluated in phase II (24, 25) studies for previously treated patients without EGFR or ALK genomic tumour alterations. The promising results for high PD-L1 expression subset were confirmed for OS benefit in a phase III study for previously treated patients (26).

The efficacy and safety of atezolizumab in the first-line was tested in the IMpower110 Study, a randomised, phase 3 trial, multicentric trial for untreated Non-Squamous, metastatic, NSCLC, EGFR or ALK wild type, whose tumour expressed PDL1 by SP142, a PD-L1 specific assay. Primary endpoint was OS and secondary endpoints included: PFS, response rate (RR) and duration of response (DoR), PFS in PD-L1 and blood-based tumour mutational burden (TMB) (27).

IMpower110 randomised 572 patients, age >18 years, ECOG 0 or 1, in a 1:1 ratio, to receive atezolizumab 1200 mg intravenously or platinum-based chemotherapy (4 or 6 cycles) once every 3 weeks. Chemotherapy regimens were tailored according to tumour histology-non squamous NSCLC received either cisplatin (75 mg/m2) or carboplatin (area under the concentration−time curve [AUC], 6) in addition to pemetrexed (500 mg/m^2) intravenously; patients with squamous NSCLC received a regimen of cisplatin (75 mg/m^2) plus gemcitabine (1250 mg/m^2) or a regimen of carboplatin (AUC, 5) plus gemcitabine (1000 mg/m^2) intravenously.

Randomisation was stratified according to sex, ECOG performance-status score, histologic type, and PD-L1 status (≥1% PD-L1 expression on tumour cells and any level of PD-L1 expression on tumour-infiltrating immune cells vs. <1% PD-L1 expression on tumour cells and ≥1% PD-L1 expression on tumour-infiltrating immune cells). Assessment for PD-L1 was tested across 3 different assays: SP-142, 22C3 and SP263.

Radiologic assessment occurred at baseline, every 6 weeks for 48 weeks, and every 9 weeks thereafter, until progression according to RECIST 1.1 or loss of clinical benefit for patients in the atezolizumab group who were treated beyond disease progression, withdrawal of consent, or death, whichever occurred first. Importantly, cross-over was not allowed to the atezolizumab group.

Of note, OS was tested hierarchically for EGFR and ALK NSCLC: high PD-L1 expression (≥50% of tumour cells or ≥10% of tumour-infiltrating immune cells), then high and intermediate PD-L1 expression (≥5% of tumour cells or tumour infiltrating immune cells), and then any PD-L1 expression (≥1% of tumour cells or tumour-infiltrating immune cells; intention-to-treat population).

At the interim analysis, median follow-up of 15.7 months (Sept. 10, 2018), atezolizumab monotherapy revealed both longer OS (primary endpoint) and PFS, as compared to chemotherapy arm. The PFS benefit was respectively 8.1 vs 5.0 months (stratified HR), for disease progression or death, 0.63; 95% CI, 0.45 to 0.88). Among patients with EGFR and ALK wild-type tumours who had high or intermediate PD-L1 expression, PFS was 7.2 months in the atezolizumab group and 5.5 months in the chemotherapy group (stratified HR for disease progression or death, 0.67; 95% CI, 0.52 to 0.88). The OS for atezolizumab and chemotherapy arm was respectively 20.2 months vs. 13.1 months; (HR for death, 0.59; 95% [CI], 0.40 to 0.89; P = 0.01) in the high-score PD-L1 staining population, according to pre-planned interim analysis.

As OS testing did not meet its threshold in the TC2/3 or IC2/3 wild-type population (PD-L1 expression of 5% or greater by TCs or ICs), OS was not tested in this population.

Regarding safety profile, the atezolizumab and chemotherapy arms adverse events (AE) respectively occurred as follows: any grade AE 90.2% vs 94.7%, Grade 3 and 4 AE 30.1% vs 52.5%, Grade 5 AE 3.8% vs 4.2%. The most frequent Grade 3 and 4 AE were anaemia, neutropenia, and thrombocytopenia.

Hepatic laboratory abnormalities, rash, and hypothyroidism were the most commonly reported immune-mediated adverse events (≥5% in either group). Grade 3 or 4 immune-mediated adverse events occurred in 6.6% and 1.5%, with no Grade 5 event reported.

PRO analysis prespecified endpoints to IMPOWER110 PD-L1 high concerning to time to confirmed deterioration (TTD) in QLQ-LC13 lung cancer symptoms (secondary endpoint) and change from baseline (BL) in global health status (GHS), functioning and lung cancer symptoms -exploratory endpoints (28). Questionnaires completion rates were QLC-C30 (90% atezolizumab, 86% chemo), QLC-LC13 (89% atezolizumab, 85% chemo), and remained >80% at most visits. Mean BL scores for GHS, physical functioning, and role functioning were moderate, symptom burden was low, and all were similar in both arms. “No differences in TTD were seen between arms for cough (HR, 0.98; 95% CI: 0.48, 2.03), chest pain (HR, 1.02; 95% CI: 0.47, 2.22), dyspnoea (HR, 0.96, 95% CI: 0.57, 1.60), and 3-symptom composite score (HR, 0.92; 95% CI: 0.59, 1.44). Mean change in physical function from baseline to week 42 was slightly improved with atezolizumab and greater or similar to chemotherapy. No clinically meaningful worsening in dyspnoea, cough or chest pain was seen with atezolizumab vs chemotherapy. Fatigue and nausea or vomiting scores numerically improved immediately with atezolizumab and were maintained to week 48” (28).

Considering the regulatory agencies process, atezolizumab has not been EMA approved, however, FDA atezolizumab label and its “List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools)”, VENTANA PD-L1(SP142) immunohistochemistry assay is currently considered as the reference (29).

The 7.1 months absolute OS gain favouring atezolizumab for high PD-L1 expression (≥50% expression of PD-L1 on TC3 or ≥10% expression on tumour-infiltrating IC3), EGFR and ALK wild-type metastatic NSCLC, is aligned with the clinical benefit required by WHO EML Model for cancer medicines analysis prioritisation. Thus, ESMO Guidelines consider an option for the population of the study [I, A; not EMA-approved], “with formal caution of a subgroup analysis compared with trial design and ITT using only TC >50% [I, B]” (12).

10.1C Use of immune-checkpoint inhibitor pembrolizumab in combination with cytotoxic chemotherapy in first line for unselected NSCLC patients without actionable oncogenic driver. KEYNOTE-189 (Non-Squamous) and KEYNOTE-407.

The efficacy and safety of pembrolizumab in combination with chemotherapy for untreated advanced non-squamous NSCLC, without sensitising EGFR/ALK alterations, regardless of PD-L1 TPS, was tested in the KEYNOTE-189 Study. This double-blind, randomised clinical trial, assigned 616 patients, performance status ECOG 0-1, to receive 4 cycles of chemotherapy (pemetrexed + platinum-based compound), with 200 mg of pembrolizumab or saline placebo, both administered intravenously every 3 weeks for up to 35 cycles in a 2:1 ratio (30).

Criteria for treatment cessation include radiologic progression, unacceptable toxic effects, investigator decision, or patient withdrawal of informed consent. Randomisation was stratified according to PD-L1 expression (tumour

proportion score, ≥1% vs. <1%), choice of platinum-based drug (cisplatin vs. carboplatin), and smoking history (never vs. former or current).

Even though not a formal PD-L1 threshold requirement for treatment, the PD-L1 expression was assessed by means of the companion test 22C3 pharmDx assay (Agilent), where the TPS refers to the percentage of membranous staining by immunohistochemistry in the tumour cells specimen. Co-primary endpoints of this study were PFS and OS. Participants were allowed to cross-over after progression in the placebo arm to receive pembrolizumab.

Efficacy was assessed in the intention-to-treat population, and Kaplan–Meier method was used to estimate OS and PFS, and radiologic assessment for progression followed the RECIST 1.1 criteria.

The study demonstrated a statistically significant PFS improvement in the pembrolizumab-treated group compared with the placebo- 8.8 months (95% CI, 7.6 to 9.2) vs 4.9 months (95% CI, 4.7 to 5.5) in the placebo-combination group (HR for progression or death, 0.52; 95% CI, 0.43 to 0.64; P<0.001). Likewise, there was a statistically significant improvement for OS, NR vs 11.3 months (95% CI, 8.7 to 15.1), [HR for death, 0.49; 95% CI, 0.38 to 0.64; P<0.0010].

Following PD-L1 stratification criteria, the pembrolizumab-chemotherapy arm exhibited efficacy across all subgroups analysed, including those with a PD-L1 tumour proportion score of less than 1% (12-month OS rate, 61.7% vs. 52.2%; HR for death, 0.59; 95% CI, 0.38 to 0.92), a score of 1 to 49% (12-month OS rate, 71.5% vs. 50.9%; HR, 0.55; 95% CI, 0.34 to 0.90), and a score of 50% or greater (12-month OS rate, 73.0% vs. 48.1%; HR, 0.42; 95% CI, 0.26 to 0.68).

Response rates were also higher in the pembrolizumab combination group 47.6% (95% CI, 42.6 to 52.5), compared to 18.9% (95% CI, 13.8 to 25.0) in the placebo-combination group (P<0.001), and consistent across all PD-L1 subgroups, notably greater in the subgroup PD-L1 ≥50% (61.4% vs. 22.9%).

The KEYNOTE-189 update was recently published, at a median follow up of 23.1 (18.6 to 30.9) months, and confirmed a sustained clinical and statistically meaningful benefit in terms of efficacy and safety; median OS was 22.0 (19.5 to 25.2) months in the pembrolizumab combination group and 10.7 (8.7 to 13.6) months in the placebo-combination group (HR, 0.56; 95% CI, 0.45 to 0.70), a 10.3 months absolute gain. The estimated 24-month OS rates were 45.5% and 29.9%, respectively (Ref. x). Median PFS was 9.0 (8.1 to 9.9) months and 4.9 (4.7 to 5.5) months in the pembrolizumab and placebo-combination groups, respectively (HR, 0.48; 95% CI, 0.40 to 0.58) with estimated 24-months PFS rates were 20.5% and 1.5%. Notably, the study update confirmed the benefit for OS and PFS across all PD-L1 Tumour Proportional Scores (31).

Considering safety, the most frequent adverse events in the KEYNOTE-189 were nausea (55.6 vs 52% in placebo, grade ≥3 3.5% both arms), anaemia (46.2% vs 46.5% in placebo, grade ≥3 16.3% vs 15.3%), fatigue (40.7% vs 38.1%, grade ≥3 5.7% vs 2.5% in placebo). Rates of adverse events were similar for carboplatin and cisplatin. The proportion of patients that discontinued all trial drugs because of adverse events was greater in the pembrolizumab plus chemotherapy arm compared to placebo-combination (13.8% vs 7.9%). Also, the discontinued pembrolizumab rate was higher for pembrolizumab (20.2% vs 10.4%). Overall, the immune-related adverse events of interest occurred in the pembrolizumab (any grade 22.7%, grade ≥3 8.9%) or placebo (any grade 11.9%, grade ≥3 (4.5%). The most frequent immune-related AE were hypothyroidism (any grade 6.7%, grade ≥3 0.5%), pneumonitis (any grade 4.4%, grade ≥3 2.7%), hyperthyroidism (any grade 4%, grade ≥3 0%), Infusion reaction (any grade 2.5%, grade ≥3 0.2%), colitis (any grade 2.2%, grade ≥3 0.7%).

A KEYNOTE-189 patient-related outcomes (PRO) analysis was conducted and recently published (3). Key PRO endpoints were change from baseline to week 12 (during chemotherapy) and week 21 (following chemotherapy) in QLQ-C30 global health status/quality of life (GHS/QOL) score, and time to deterioration in cough, chest pain, or dyspnoea. With the purpose of measuring the domains, EORTC Quality-of-Life Questionnaire- Core 30 (QLQ-C30) and Lung Cancer 13 (QLQ-LC13), and EuroQoL 5D (EQ-5D) were collected at cycles 1–5, every 3 cycles thereafter during year 1, and every 4 cycles during years 2–3 until disease progression while on study treatment; and at treatment discontinuation and the 30-day safety follow up visit. PRO endpoints and a measure of minimum effect were well defined from baseline to weeks 12 and 21 in the QLQ-C30 GHS/QOL scale, and time to deterioration (defined as the time to the first onset of a ≥10-point increase from baseline. Conversely, there was no statistical power to calculate the PROs; p values for these analyses are nominal, and all are two-sided. There was no adjustment for multiplicity, also.

The compliance rate for PRO questionnaires at baseline and week 30 were 89% in pembrolizumab plus chemo vs 90% chemo plus placebo, and 76% pembrolizumab plus chemo vs 72% chemo plus placebo, respectively. The results for time to deterioration (mean) in cough, chest pain, or dyspnoea was not reached (95% CI 10·2 months to not reached) in the pembrolizumab plus chemo group versus 7·0 months (4·8 to not reached) in the placebo plus chemo group (HR 0·81 [95% CI 0·60−1·09], p=0·16. The score changes from baseline were generally favourable for the pembrolizumab plus chemo group than in the control group for most functional and symptom scales at week 21. Also, at week 21, deterioration in GHS/QOL was less frequent in patients in the pembrolizumab plus pemetrexed– platinum group (105 [26%] patients) than in the placebo plus pemetrexed–platinum group (75 [38%] patients), with similar results

on all QLQ-C30 functional and symptom scales. Importantly, symptom scale scores for dyspnoea and pain improved in the pembrolizumab plus pemetrexed–platinum group and worsened or remained stable in the placebo group.

According to ESMO Guidelines update 2020, "pembrolizumab in combination with pemetrexed and a platinum-based Chemotherapy (KEYNOTE-189) should be considered a standard option in metastatic non-squamous NSCLC [I, A; ESMO-MCBS v1.1 score: 4]" (12).

NICE technology appraisal guidance [(TA557) 10 Jan 2019] calculated that incremental cost-effectiveness ratio (ICER) was less than £50,000 per QALY gained, and concluded that "ICERs were not all clearly within the range usually considered a cost-effective use of resources" and decided "not to recommend pembrolizumab combination for routine use in adults with untreated, metastatic, non-squamous NSCLC whose tumours have no EGFR- or ALK-positive mutations." Conversely, the pembrolizumab combination for use within the Cancer Drugs' Fund, was considered an option for untreated, metastatic non-squamous NSCLC, EGFR and ALK negative tumours if the treatment does not exceed 2 years and under the managed access agreement. Notably, the uncertainty concerning the OS gain derived from data published in 2018, and did not review its 'cost-effectiveness after the last published OS update in 2020 (32).

The efficacy and safety of pembrolizumab in combination with chemotherapy for untreated advanced squamous NSCLC, without sensitising EGFR/ALK alterations, regardless of PD-L1 TPS, was tested in the KEYNOTE-407 Study. As squamous cell carcinoma frequently lacks oncogene driver aberrations that predict response to the recently developed target therapies, this treatment shed light on a specific scenario that accounts for 30% of NSCLC. To test whether the addition of pembrolizumab to chemotherapy is both effective and safe, the clinical trial KEYNOTE-407 compared pembrolizumab plus chemotherapy (carboplatin and either paclitaxel or nanoparticle albumin-bound [nab] with placebo plus chemotherapy (carboplatin and either paclitaxel or nab-paclitaxel) (33). x

Eligibility criteria and study design included patients age>18 years with untreated metastatic Squamous NSCLC, any PD-L1 TPS expression - IHC 22C3 pharmDx assay (Agilent Technologies), as the companion test. A total of 559 patients were randomised and double-blinded, assigned, in a 1:1 ratio, to receive 200 mg of pembrolizumab or saline placebo on day 1 for up to 35 cycles. For the first 4 cycles, all the patients also received carboplatin (at a dose calculated to produce an area under the concentration–time curve of 6 mg per mL per minute) on day 1 and either paclitaxel (200 mg/m^2) on day 1 or nab-paclitaxel (100 mg/m^2) on days 1, 8, and 15. All treatments were administered intravenously in 3-week cycles. Cross over was allowed to patients with confirmed disease progression. Randomisation was stratified according to PD-L1 tumour proportion score, the percentage of tumour cells with membranous PD-L1 staining (63.1% of patients), choice of taxane (paclitaxel for 60.1%), and geographic region of enrolment (East Asia 19% vs. the rest of the world 81%).

Radiologic assessment occurred at weeks 6, 12, and 18 and then every 9 weeks through week 45 and every 12 weeks. In this regard, the treatment was continued until radiographic disease progression following RECIST 1.1 criteria, unacceptable toxicity, investigator's decision to discontinue the treatment, or withdrawal of patient consent. Importantly, patients who had radiographic disease progression, but were clinically stable could continue treatment at the discretion of an investigator until disease progression was confirmed by imaging performed within 28 days after the first radiologic image showing progression.

The intention-to-treat efficacy analysis occurred with a medium 7.8 (0.1 to 19.1) months follow up period. The median OS was 15.9 months (95% [CI], 13.2 to not reached) in the pembrolizumab-combination group and 11.3 months (95% [CI], 9.5 to 14.8) in the placebo-combination group (HR for death, 0.64; 95% CI, 0.49 to 0.85; P<0.001), and a 1-year Kaplan-Meier estimate of 65.2% pembrolizumab arm vs 48.3% placebo arm. Overall, the results reveal an OS benefit gain of 4.6 months, reducing of death by 36%, and favouring the addition of pembrolizumab in comparison with to standard of care chemotherapy. The OS benefit extends to all PD-L1 staining subgroups, including PD-L1<1%. The PFS benefit of the pembrolizumab combination was 6.4 months (95% CI, 6.2 to 8.3) in the pembrolizumab-combination group and 4.8 months (95% CI, 4.3 to 5.7) in the placebo-combination group (HR for disease progression or death, 0.56; 95% CI, 0.45 to 0.70; P<0.001). Of note, PFS benefit was observed in all prespecified subgroups with incremental improvements with increasing PD-L1 TPS. The response rate was 57.9% (95% CI, 51.9 to 63.8) in the pembrolizumab arm, and 38.4% (95% CI, 32.7 to 44.4) in the placebo arm. Likewise, OS and PFS, the response rate favoured pembrolizumab in all PD-L1 stratified subgroups.

Considering the safety profile of pembrolizumab in combination to chemotherapy, 98.2% of pembrolizumab combination patients group vs 97.9% in the placebo group experienced any grade of adverse event (AE), where anaemia, alopecia and neutropenia were the most common in both arms. Adverse events grade ≥3AE occurred in 69.8% of pembrolizumab arm patients, and 68.2% in the placebo arm, anaemia, and neutropenia occurring in more than 10%. Of interest, pneumonitis and autoimmune hepatitis were the grade ≥3 that occurred more frequently in the pembrolizumab arm. Toxicity led to dose reduction of chemotherapy in 22.7% and 17.5%, respectively; led to the discontinuation of any treatment component in 23.4% and 11.8%; and led to the discontinuation of all treatment components in 13.3% and 6.4%. The most frequent AEs reported were anaemia, alopecia and neutropenia in both

arms. grade ≥3 AE that occurred in at least 10% of patients were anaemia and neutropenia. Particularly, pneumonitis and autoimmune hepatitis grade ≥3 AE occurred more frequently in the pembrolizumab group.

According to ESMO Guidelines UPDATE 2020, the results from KEYNOTE-407 place the combination of pembrolizumab plus carboplatin and paclitaxel or nab-P as a standard choice in patients with metastatic squamous NSCLC [I, A; ESMO-MCBS v1.1 score: 4].

NICE technology appraisal guidance [(TA600) 11 September 2019] concluded that "The long-term OS benefit with pembrolizumab combination therapy was uncertain because of the very short duration of the interim data from KEYNOTE-407". The committee decided that "the ICER was not within the range usually considered a cost-effective use of resources" and that the further OS data is required to reduce cost-effectiveness uncertainty (34).

10.1D Use of frontline consolidation durvalumab for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy.

Approximately 25% to 30% of patients with NSCLC are diagnosed with locally advanced or stage III disease. A proportion of these patients may experience the curative benefits of combined chemotherapy and surgery or concurrent chemotherapy and radiation therapy. Unfortunately, the majority of patients with Stage III NSCLC have unresectable disease. Despite treatment with Platinum-based CT concurrently with definitive RT at a minimum of 60 Gy, locoregional disease control is followed by regional and systemic relapse resulting in a median OS of less than 2 years for these patients and a 5-year survival of 15%.

The efficacy of durvalumab was evaluated in the PACIFIC Study, a randomised, double-blind, placebo-controlled, multicentric study in 713 patients with locally advanced, unresectable NSCLC, irrespective of tumour PD-L1 expression (35). Patients had completed at least 2 cycles of definitive platinum-based chemotherapy with radiation therapy within 1 to 42 days prior to initiation of the study and had an ECOG performance status of 0 or 1, without any clinical or radiological evidence of disease progression. Patients were randomised 2:1 to receive 10 mg/kg durvalumab (n = 476) or placebo (n = 237) via intravenous infusion every 2 weeks for up to 12 months or until unacceptable toxicity or confirmed disease progression. Randomisation was stratified for gender, age (<65 years vs. ≥65 years), and smoking status (smoker vs. non-smoker). Patients with disease control at 12 months were given the option to be re-treated upon disease progression. Where available, archival tumour tissue specimens taken prior to chemoradiation therapy were retrospectively tested for PD-L1 expression on tumour cells (TC) using the VENTANA PD-L1 (SP263) IHC assay (available in 63% of patients). The two primary endpoints of the study were PFS and OS. Disease characteristics were as follows: Stage IIIA (53%), Stage IIIB (45%), histological sub-groups of squamous (46%), non-squamous (54%). Of 451 patients with PD L1 expression available, 67% were TC ≥1% [PD-L1 TC 1-24% (32%), PD L1 TC≥ 25% (35%)] and 33% were TC < 1%.

The study demonstrated a statistically significant improvement in PFS in the durvalumab -treated group compared with the placebo group [HR = 0.52 (95% CI: 0.42, 0.65), p < 0.0001] as well as in OS [HR = 0.68 (95% CI: 0.53, 0.87), p = 0.00251]. The improvements in PFS and OS were consistently observed in all predefined subgroups analysed, including ethnicity, age, gender, smoking history, EGFR mutation status and histology. As of January 31, 2019, 48.2% of patients had died (44.1% and 56.5% in the durvalumab and placebo groups, respectively). The median duration of follow-up was 33.3 months. The updated OS remained consistent with that previously reported (stratified HR = 0.69 [95% CI: 0.55–0.86]); the median OS was not reached with durvalumab but was 29.1 months with placebo. The 12-, 24- and 36-month OS rates with durvalumab and placebo were 83.1% versus 74.6%, 66.3% versus 55.3%, and 57.0% versus 43.5%, respectively. All secondary outcomes examined showed improvements consistent with previous analyses (36).

Additional post-hoc subgroup analyses were conducted to evaluate the efficacy by tumours PD-L1 expression (≥25%, 1-24%, ≥1%, <1%) and for patients whose PD-L1 status cannot be established. A significant benefit from durvalumab was observed only in the PDL1 TC>1% population, both for OS (HR 0.53, 95% CI 0.36-0.77, median OS Not Reached vs 29.1 months) and PFS (HR 0.46, 95% CI 0.33-0.64, median PFS 17.8 vs 5.6 months), while in the PD-L1-negative population there was no statistically significant improvement in either OS (HR 1.36 (0.79, 2.34)) or PFS (0.73 (0.48, 1.11)). Recently, an exploratory analysis of outcomes by tumour cell (TC) PD-L1 expression from the PACIFIC trial was published (37). In total, 709 patients of whom received at least 1 dose of study treatment durvalumab (n = 473) or placebo (n = 236). Some 451 (63%) were PD-L1-assessable: 35%, 65%, 67%, 33%, and 32% had TC ≥25%, <25%, ≥1%, <1%, and 1%–24%, respectively. As of 31 January 2019, median follow-up was 33.3 months. Durvalumab improved PFS versus placebo (primary-analysis data cut-off, 13 February 2017) across all subgroups [HR, 95% CI; medians]: TC ≥25% (0.41, 0.26–0.65; 17.8 versus 3.7 months), <25% (0.59, 0.43–0.82; 16.9 versus 6.9 months), ≥1% (0.46, 0.33–0.64; 17.8 versus 5.6 months), <1% (0.73, 0.48–1.11; 10.7 versus 5.6 months), 1%–24% [0.49, 0.30–0.80; not reached (NR) versus 9.0 months], and unknown (0.59, 0.42–0.83; 14.0 versus 6.4 months). Durvalumab improved

OS across most subgroups (31 January 2019 data cut-off; HR, 95% CI; medians): TC ≥25% (0.50, 0.30–0.83; NR versus 21.1 months), <25% (0.89, 0.63–1.25; 39.7 versus 37.4 months), ≥1% (0.59, 0.41–0.83; NR versus 29.6 months), 1%–24% (0.67, 0.41–1.10; 43.3 versus 30.5 months), and unknown (0.60, 0.43–0.84; 44.2 versus 23.5 months), but not <1% (1.14, 0.71–1.84; 33.1 versus 45.6 months). Safety was similar across subgroups. Accordingly, a PFS benefit with durvalumab was observed across all subgroups, and OS benefit across all but TC <1%, according to a post hoc subgroup analysis. For this reason, EMA label restricts durvalumab prescription only to "tumours expressing PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy", whether PD-L1 expression is not a requirement in the FDA Durvalumab label (38).

A recent 4-year OS update (20 Mar 2020, median follow up, 34.2 months [range, 0.2–64.9]), confirmed a sustained benefit for PFS (stratified HR 0.55, 95% CI 0.44–0.67; median 17.2 vs 5.6 months) and OS (stratified HR 0.71, 95% CI 0.57–0.88). Median OS for the durvalumab arm was 47.5 months vs 29.1 months, placebo. The 48-month OS rates were 49.6% vs 36.3% for durvalumab vs placebo, and PFS rates were 35.3% vs 19.5% respectively (36, 39).

Patient-reported symptoms, function and health-related quality of life (HRQoL) were collected using the EORTC QLQ-C30 and its lung cancer module (EORTC QLQ-LC13). As of 22 March,2018, the median follow-up was 25·2 months (37). More than 79% of patients given durvalumab and more than 82% of patients given placebo completed questionnaires up to week 48. Between baseline and 12 months, the prespecified longitudinal PROs of interest, cough dyspnoea, chest pain, fatigue, appetite loss, physical functioning and global health status or quality of life remained stable with both treatments, with no clinically relevant changes from baseline. Generally, there were no clinically important between-group differences in time to deterioration of prespecified key PRO endpoints.

The safety of durvalumab (10 mg/kg) has been evaluated in the PACIFIC Study population, in which the most frequent adverse reactions were cough (40.2% vs 30.3% in placebo), upper respiratory tract infections (26.1% vs 11.5% in placebo) and rash (21.7% vs 12.0% in placebo). The most frequent grade 3-4 adverse reaction was pneumonia (6.5% vs 5.6% in placebo). The overall incidence of grade 3 or 4 adverse reactions was 12.8% in the durvalumab arm vs 9.8% in placebo. Radiation pneumonitis occurred in 161 (33.9%) patients in the IMFINZI-treated group and 58 (24.8%) in the placebo group, including grade 3 (3.4% vs 3.0%) and grade 5 (1.1% vs 1.7%). Overall, durvalumab is most commonly associated with immune-mediated adverse reactions. In the combined safety database with durvalumab monotherapy, (n = 1889 multiple tumours types), immune-mediated pneumonitis occurred in 79 (4.2%) patients, including Grade 3 in 12 (0.6%), grade 4 in 1 (< 0.1%) patient, and grade 5 in 5 (0.3%) patients. Forty-five of the 79 patients received high-dose corticosteroid treatment, whereas durvalumab was discontinued in 26 patients. Resolution occurred in 42 patients. Immune-mediated pneumonitis occurred more frequently in patients in the PACIFIC Study who had completed treatment with concurrent chemoradiation within 1 to 42 days prior to initiation of the study (10.7%), than in the other patients in the combined safety database (2.0%). It occurred in 51 (10.7%) patients in the durvalumab-treated group and 16 (6.8%) patients in the placebo group, including grade 3 in 8 (1.7%) patients on durvalumab vs. 6 (2.6%) patients on placebo. Grade 5 (fatal) pneumonitis occurred in 4 (0.8%) patients on IMFINZI vs. 3 (1.3%) patients on placebo. Other immune-related adverse reactions reported in less than 1% of patients treated with durvalumab monotherapy in clinical trials (n = 1889) were myasthenia gravis, myocarditis, myositis, polymyositis, meningitis, encephalitis and Guillain-Barre syndrome. No overall differences in safety were reported between elderly (≥65 years) and younger patients. Recently, preliminary real-world data confirmed favourable PFS in durvalumab-treated patients with unresectable stage III lung cancer, though at a grade 3 radiation pneumonitis rate of 14.3% (40).

A decision-analytic microsimulation model was developed in order to compare chemoradiotherapy versus chemoradiation followed by durvalumab consolidation therapy until progression or for a maximum of 1 year for potential budgetary consequences. Simulated conditions were matched to those of the PACIFIC phase 3 randomised clinical trial and reasonable treatment strategies for metastatic NSCLC. Among 2 million simulated patients, durvalumab consolidation therapy was cost-effective compared with no consolidation therapy at a $100,000 per quality-adjusted life-year willingness-to-pay threshold, with an estimated incremental cost-effectiveness ratio of $67,421 per quality-adjusted life-year, and would contribute an additional $768 million to national cancer spending in year 1. The annual budgetary consequence would then decrease to $241 million in year 5. Durvalumab consolidation therapy represents an indication where expensive immunotherapies can be cost-effective, as treating with immunotherapy earlier in the course of cancer progression can provide significant value, despite having a substantial budgetary consequence (41). In another study by SAKK, a Markov model based on the 3-year follow-up data of the PACIFIC trial was used in order to compare consolidation durvalumab with observation, using published utility values and assessed costs for treatment strategies from the perspective of the Swiss health care payers. In the unselected/PD-L1-positive patients, durvalumab showed an incremental effectiveness of 0.76/1.18 quality-adjusted life-year (QALY) and incremental costs of Swiss Francs (CHF) 67,239/78,177, resulting in incremental cost-effectiveness ratios of CHF 88,703/66,131 per QALY gained, respectively. The most influential factors for the incremental cost-effectiveness ratio were the utility before first progression, costs for durvalumab, and the HR for OS under durvalumab versus observation. The cost-effectiveness of durvalumab was better than CHF 100,000 per QALY gained in 75% of the simulations in probabilistic sensitivity analysis [7]. NICE recently stipulated that durvalumab has the potential to be cost-effective compared with standard

care, but more evidence from the ongoing trial is needed to address the uncertainties. Overall, these results confirm the benefit of durvalumab at an earlier stage of advanced lung cancer, in unresectable stage III disease, especially in the PDL1-positive cohort, with a reported median OS not reached at 3 years of follow up and a 3-year survival rate of 57%.

ESMO Guidelines for "Early and Locally Advanced Non-Small-Cell Lung Cancer (NSCLC) Treatment" Recommendations was recently updated, 04 May 2020, following EMA approval, recommend durvalumab consolidation treatment for unresectable Stage III NSCLC {[I, A; ESMO-MCBS v1.1 score: 4] (42).

10.1E Use of immune-checkpoint inhibitors in second line for NSCLC without actionable oncogenic driver after the failure of platinum- containing first line standard chemotherapy.

In the few years since benefit was shown with PD-1 blockade in lung cancers, three PD-1/ PD-L1 therapies have been approved by the FDA and the EMA in the second-line setting. The three approved therapies in the immunotherapy-naive, second-line setting include the PD-1 blockers pembrolizumab, nivolumab and the PD-L1 blocker atezolizumab. Each has been approved based on phase 3 studies demonstrating improved OS compared to docetaxel, the standard of care chemotherapy in second line for NSCLC patients failing the platinum-containing frontline chemotherapy (43, 44). Overall, there are no major differences in terms of efficacy or safety among these three therapies to inform a single optimal choice, and no head-to-head comparative studies have been conducted, accordingly the selection should be based on the availability, accessibility and procurement in place for these medicines. There are two key distinctions between the three approved therapies, which can affect choice and use: (i) PD-L1 expression in the tumour: nivolumab and atezolizumab are approved in patients with previously treated, advanced NSCLC irrespective of PD-L1 expression, while pembrolizumab is approved only in patients with PD-L1 >1% TPS. (ii) Schedule of administration: pembrolizumab is approved to be given in the dose of 200 mg every 3 weeks or 400 mg every 6 weeks, nivolumab is given in the dose of 240 mg once every 2 weeks, whereas atezolizumab can be given in the doses of 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks, based on current EMA approval. Of note, the FDA has recently approved a 4-weekly schedule for nivolumab for lung cancer. Overall, any of these three therapies represents reasonable standard therapy for most patients with advanced, previously treated, immunotherapy-naive NSCLC.

Pembrolizumab. The KEYNOTE-010 trial randomised 1033 patients with previously treated squamous (22% of the population) and non-squamous NSCLC with PD-L1 expression on at least 1% of tumour cells to receive pembrolizumab (tested at two doses, 2 mg/kg or 10 mg/kg, every 3 weeks) or docetaxel 75 mg/m^2 every 3 weeks (45) 66% of NSCLC patients screened resulted eligible for the PD-L1 threshold of 1% and 28% showed a high expression (≥ 50%), consistently with previous findings (KEYNOTE-024). Patients were stratified in PD-L1 1-49% and PD-L1 ≥ 50%. OS was longer for pembrolizumab versus docetaxel (2 mg/ kg, HR 0.71, 95% CI 0.58 - 0.88; p< 0.001; 10 mg/kg, HR 0.61, 95% CI 0.49 - 0.75; p< 0.001), with a 2-year OS rate of 14.5% versus 30.1% (2 mg/kg group) [I, A; ESMO-MCBS v1.1 score: 5/5]. In patients with a PD-L1 tumour proportion score of ≥ 50%, the greatest benefit was observed for OS for pembrolizumab 2 mg/kg versus docetaxel with HR 0.54 (95% CI 0.38– 0.77; p=0.0002), and for pembrolizumab 10 mg/kg versus docetaxel HR 0.50 (0.36–0.70; p<0.0001). Indeed, median OS was 14.9 – 17.3 for the 2 mg/kg and 10 mg/kg arms, longer than chemotherapy arm (8.2 months). The safety profile favoured pembrolizumab with less grade 3-5 AE, namely 16% vs 35% in the chemotherapy arm, and decreased appetite (14%) and fatigue (14%) for ICI and neutropenia (14%), alopecia. (33%), anaemia (13%) and oral mucositis (14%) for chemotherapy. There was no difference in the efficacy or safety of pembrolizumab at 2 or 10 mg/kg.

Long term outcomes from KEYNOTE-010 were recently published (46). Pembrolizumab continued to improve OS over docetaxel in the PD-L1 TPS ≥ 50% and ≥ 1% groups (HR, 0.53; 95% CI, 0.42 to 0.66; P < .00001; and HR, 0.69; 95% CI, 0.60 to 0.80; P < .00001, respectively) after a 42.6-month median follow-up. Estimated 36-month OS rates were 34.5% versus 12.7% and 22.9% versus 11.0%, respectively. Grade 3-5 treatment-related adverse events occurred in 16% versus 37% of patients, respectively. Seventy-nine of 690 patients completed 35 cycles/2 years of pembrolizumab; 12-month OS and PFS rates after completing treatment were 98.7% (95% CI, 91.1% to 99.8%) and 72.5% (95% CI, 59.9% to 81.8%), respectively. Seventy-five patients (95%) had objective response (RECIST v1.1, blinded independent central review) and 48 (64%) had ongoing response. Grade 3-5 treatment-related adverse events occurred in 17.7% of patients. Fourteen patients received second course pembrolizumab: 5 completed 17 cycles, 6 (43%) had partial response, and 5 (36%) had stable disease.

A cost-effectiveness analysis has been provided for pembrolizumab versus docetaxel in the enriched population with PD-L1> 50% in the second second-line setting. Base case results project for PD-L1 positive (TPS ≥50%) patients treated with pembrolizumab a mean survival of 2.25 years (47). For docetaxel, a mean survival time of 1.07 years was estimated. Expected QALYs were 1.71 and 0.76 for pembrolizumab and docetaxel, respectively. The incremental cost per QALY gained with pembrolizumab vs docetaxel is $168,619/QALY, which is cost-effective in the US using a threshold of 3-times GDP per capita

Nivolumab. The role of nivolumab as standard ICI in second-line treatment of NSCLC has been established based on two phase 3 clinical trials, CheckMate-017 and CheckMate-057. In CheckMate-017, 272 patients with squamous NSCLC were randomised to receive nivolumab 3 mg/kg every 2 weeks, or docetaxel, at a dose of 75 mg/m2 every 3 weeks (29). The median OS was 9.2 months (95% CI, 7.3 to 13.3) in the nivolumab group as compared with 6.0 months (95% CI, 5.1 to 7.3) in the docetaxel group. The OS rate at 1 year was 42% (95% CI, 34 to 50) in the nivolumab group versus 24% (95% CI, 17 to 31) in the docetaxel group. OS was improved in those who received nivolumab (HR 0.59, 95% CI 0.44–0.79, p<0.001). The rate of confirmed objective response was higher with nivolumab than with docetaxel (20% [95% CI, 14 to 28] vs. 9% [95% CI, 5 to 15]; p=0.008). The median PFS was 3.5 months (95% CI, 2.1 to 4.9) in the nivolumab group and 2.8 months (95% CI, 2.1 to 3.5) in the docetaxel group, consistent with the mechanism of action of ICIs, where atypical patterns of response are described (pseudo progression) and long-lasting post-progression benefit persisting (14). Interestingly, across the prespecified expression levels (1%, 5%, and 10%), PD-L1 expression was neither prognostic nor predictive of any of the efficacy endpoints. Treatment-related adverse events, including hematologic and nonhematologic events, occurred less frequently with nivolumab than with docetaxel: in the nivolumab group, 58% of the patients had events of any grade of which 7% grade 3 or 4; in the docetaxel group, this occurred in 86% of the patients of which 55% were grade 3 or 4. The safety profile was consistent with the class- side effects with no new signals of safety, namely the most frequently reported treatment-related adverse events with nivolumab were fatigue and asthenia and for docetaxel were neutropenia (33%; 10% febrile neutropenia), fatigue (33%), alopecia (22%), and nausea (23%), peripheral neuropathy (11%). Three % and 10% of patients discontinued the treatment for an adverse event in ICI and chemotherapy arm, respectively.

In CheckMate-057, 582 patients with non-squamous NSCLC (e.g. adenocarcinoma) were randomised to nivolumab or docetaxel (48). Nivolumab improved OS versus docetaxel: at the time of interim analysis, median OS was 12.2 months (95% CI, 9.7 to 15.0) for nivolumab and 9.4 months (95% CI, 8.1 to 10.7) for docetaxel, with a HR of 0.73 (96% CI, 0.59 to 0.89; p=0.002). One-year OS rates were 51% (95% CI, 45 to 56) and 39% (95% CI, 33 to 45) for nivolumab and docetaxel, respectively. The survival HRs per subgroup analysis did not favour nivolumab over docetaxel in the EGFR mutated NSCLC population (oncogene- driven disease, HR=1.18) (31). Moreover, the EGFR wild type populations seemed to derive the greatest benefit, with an HR=0.66 (0.51–0.86). The safety profile and pattern of adverse events in non-squamous NSCLC patients were consistent with the data from the squamous population: treatment-related adverse events were observed in 69%/ 10%/5% in the nivolumab arm and 88%/ 54%/15% in docetaxel arm for any grade/ grade 3-4/ discontinuation rate, respectively.

In a recent update of CheckMate-017 and CheckMate-057, pooled 2-year OS favoured nivolumab in both squamous (29% [95% CI, 24% to 34%] vs 16% [95% CI, 12% to 20%]) [ESMO Guidelines strength of evidence and level of recommendation I, A; ESMO-MCBS v1.1 score: 5/5] and non-squamous NSCLC (23% [95% CI, 16% to 30%] versus 8% [95% CI, 4% to 13%]) [I, A; ESMO-MCBS v1.1 score: 5/5] (32). In the pooled analysis of OS in the intention-to-treat population (n = 854) with squamous (n = 272 [31.9%]) and non-squamous (n = 582 [68.1%]) NSCLC, median OS was 11.1 months (95% CI, 9.2 to 13.1 months) with nivolumab versus 8.1 months (95% CI, 7.2 to 9.2 months) with docetaxel (HR, 0.72; 95% CI, 0.62 to 0.84). Higher PD-L1 expression levels were associated with greater OS benefit with nivolumab (HR, 0.42; 95% CI, 0.28 to 0.63) in patients with ≥50% PD-L1 expression, but a benefit was still observed in patients with <1% PD-L1 expression (HR, 0.78; 95% CI, 0.61 to 0.99). Interestingly, durable responses were observed with nivolumab: 37% of confirmed responders with squamous NSCLC and 34% with non-squamous NSCLC had ongoing responses after 2 years' minimum follow-up and no patient in docetaxel group had an ongoing response. Consistent with the primary analyses, 2-year OS benefit with nivolumab versus docetaxel was observed in patients with squamous NSCLC regardless of PD-L1 expression level. However, in patients with non-squamous NSCLC, higher levels of PD-L1 were associated with a greater magnitude of OS benefit with nivolumab, but NSCLC with PD-L1<1% still derived greater benefit from ICI than chemotherapy: in patients with ≥50% PD-L1 expression, the HR for OS on the basis of 2 years' minimum follow-up was 0.38 (95% CI, 0.24 to 0.60) for patients with non-squamous NSCLC.

Recently, investigators pooled data from four clinical studies of nivolumab in patients with previously treated NSCLC (CheckMate 017, 057, 063, and 003) to evaluate survival outcomes. Across all four studies, 4-year OS with nivolumab was 14% (95% CI 11–17) for all patients (n=664), 19% (15–24) for those with at least 1% PD-L1 expression, and 11% (7–16) for those with less than 1% PD-L1 expression. In CheckMate 017 and 057, 4-year OS was 14% (95% CI 11–18) in patients treated with nivolumab, compared with 5% (3–7) in patients treated with docetaxel. Nivolumab continued to show long-term OS and PFS benefit compared to docetaxel, with 5-year survival rates of 13.4% vs 2.6% and PFS rates of 8% vs 0%. The OS benefit with nivolumab compared with docetaxel was observed across subgroups, including patients with tumour PD-L1 expression < 1%. Survival subsequent to response at 6 months on nivolumab or docetaxel was longer than after progressive disease at 6 months, with HRs for OS of 0·18 (95% 0·12–0·27) for nivolumab and 0·43 (0·29–0·65) for docetaxel; for stable disease versus progressive disease, HRs were 0·52 (0·37–0·71) for nivolumab and 0·80 (0·61–1·04) for docetaxel. Long-term data did not show any new safety signals (49-51).

Atezolizumab. The phase 3 OAK trial evaluated 850 patients with advanced squamous and non- squamous NSCLC previously treated with one or two prior lines chemotherapy and ICI-naive, who were randomised 1:1 to atezolizumab 1200 mg fixed dose every 3 weeks or standard docetaxel 75 mg/m² every 3 weeks (26). Treatment was administered until unacceptable toxicity or disease progression. Atezolizumab could be continued beyond disease progression if clinical benefit demonstrated despite evidence of radiological disease progression at CT scan, to rule out atypical pattern of response (i.e. pseudo progression). No crossover to atezolizumab was allowed. Patients were stratified by PD-L1 expression (defined as IC0, IC1, IC2 and IC3 level), using the companion diagnostic VENTANA SP142 PD-L1 IHC assay (Ventana Medical Systems). TC1/2/3 or IC1/2/3 was defined as PD-L1 expression on 1% or more of tumour cells or tumour-infiltrating immune cells, TC2/3 or IC2/3 as PD-L1 expression on 5% of these cells; TC3 was defined as PD-L1 expression on 50% or more of tumour cells and IC3 as 10% or more of tumour-infiltrating immune cells; and TC0 or IC0 as PD-L1 expression less than 1%. OS was improved in the study population with atezolizumab, reaching a median OS of 13, 8 months [95% CI 11.8–15.7]) versus docetaxel (9.6 months [8.6–11.2]), with HR 0.73 [95% CI 0.62–0.87], p=0.0003). The subgroup analysis showed a greater magnitude of benefit in patients with higher PD-L1 expression, both assessed on tumour cells (TC) or immune- infiltrating cells (IC): the net benefit gain in TC1/2/3 or IC1/2/3 population was +5.4 months (HR 0.74 [95% CI 0.58–0.93], p=0.0102) and +5.5 months in TC2/3 or IC2/3 population (HR 0.67 (95% CI 0.49–0.90); p=0.0080). Tolerability was also better with atezolizumab, with 15% of patients experiencing a grade 3–4 treatment-related toxicity compared with 43% of those treated with docetaxel [I, A; ESMO-MCBS v1.1 score: 5/5].

The efficacy and safety of atezolizumab versus the efficacy and safety of docetaxel as second- or third-line treatment in patients with advanced NSCLC in the primary (n = 850) and secondary (n = 1225) efficacy populations of the randomised phase III OAK study (respectively referred to as the intention-to-treat [ITT] 850 [ITT850] and ITT1225) at a published updated data cut-off were assessed recently (35). Atezolizumab demonstrated an OS benefit versus docetaxel in the updated ITT850 (HR = 0.75, 95% CI: 0.64-0.89, p = 0.0006) and the ITT1225 (HR = 0.80, 95% CI: 0.70-0.92, p = 0.0012) after minimum follow-up times of 26 and 21 months, respectively. Improved survival with atezolizumab was observed across programmed death-ligand 1 and histological subgroups. Fewer patients receiving atezolizumab experienced grade 3 or 4 treatment-related adverse events (14.9%) than did patients receiving docetaxel (42.4%); no grade 5 AEs related to atezolizumab were observed.

The aforementioned OAK study results were recently updated during the ESMO 2020 Virtual Conference (Abstract 1271P) and confirm the sustained magnitude of benefit favouring atezolizumab vs docetaxel. The 4-year OS rates are 15.5% for atezolizumab vs 8.7% docetaxel, respectively, and across all PD-L1 expression subgroups. Of note, atezolizumab arm also consistently had less grade 3-4 treatment-related adverse events and AE leading to treatment withdrawal (52).

The PROs reflecting lung cancer symptoms, and QoL were collected using the European Organization for the Research and Treatment of Cancer (EORTC) quality-of-life questionnaire, QLQ-C30, and its lung cancer module, QLQ-LC13. The EORTC QLQ-C30 completion rate was as follows: baseline, 98.1% with atezolizumab and 96.5% with docetaxel-treated, and >80% for all cycles to cycles 27 and 23 in the atezolizumab arm and docetaxel arm, respectively and similar for EORTC QLQ-LC13 questionnaire. No differences in the (Time to deterioration) TTD were seen between treatment arms in HRQoL (HR, 0.94; 95% CI, 0.72-1.24; and no differences were seen between the treatment arms for the TTD for other lung cancer symptoms (i.e., dyspnoea [QLQLC13].

Authors concluded that “atezolizumab prolongs the time until patients with advanced NSCLC experience limitations in performing their day-to-day activities (physical function and role function) and improves patient HRQoL compared with docetaxel” and there were “modest treatment arm differences” (53).

11. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group.

The cost-effectiveness studies published for ICI frequently exhibit some aspects that are worth being recognised:

Often, HTA, governmental, and independent CE analysis in the literature were not updated according to the recent and mature OS benefit data. For instance, NICE analysis and decisions commonly reflected the uncertainty of OS immature data from interim analysis, where the CE threshold was not favourable to the medicine adoption considering the price negotiations. Some of those analyses occurred before the updated OS mature data, and further analysis will be required for the appraisal committee decision. Far beyond a comprehensive CE analysis, finance as one of the pillars for UHC goal also requires budget impact analysis, and the costs related to the investment for maintenance, and improvement to offer quality and timely diagnosis, the most appropriate treatment, and the expected follow up in terms. To deliver such tasks, workforce, capacity building, are also components to guarantee a feasible and universal access to medicines.

13. Overview:

NSCLC: factors that affect the choice of treatment in NSCLC that lacks a driver mutation include both the presence and the level of PD-L1 expression, the extent of disease, the histology, and whether or not the patient is suitable for chemotherapy combination. Historically, patients with PD-L1 expression ≥50% are typically offered monotherapy with the anti-PD-1 antibody pembrolizumab frontline due to mature confirming greater OS benefit and safety profile.

Of note, recently available mature data for OS emerged to address the specific PD-L1 expression <50%. For this specific scenario, the combination of a platinum-doublet chemotherapy and immunotherapy is currently considered as the standard of care for both squamous and non-squamous histologies. EGFR, ALK wild-type, irrespective to PD-L1 expression according to medical societies lung cancer guidelines (NCCN, ESMO).

In the second-line setting, nivolumab and atezolizumab exhibit mature data that allow confirming a safer toxicity profile and greater clinical meaningful OS benefit in comparison with standard chemotherapy. Nivolumab and atezolizumab can be prescribed regardless of PD-L1 expression; however, for pembrolizumab, a threshold of 1% is defined.

Molecular and IHC diagnosis is a vital component for the application of immunotherapy in NSCLC and involves at least PDL1 staining, EGFR and ALK analysis. The immunotherapy regimens often lack clinical benefit or have not been studied in oncogene aberrant tumours, not to mention the alternative availability of the existing specific and effective TKI treatments. In addition, PD-L1 expression is not only likely to improve the cost-effectiveness ratio, as in KEYNOTE-024 study, but also a requirement for some regimens' prescription according to the regulatory agencies' medicines labels, as previously described (1st and 2nd line pembrolizumab monotherapy, 1st Line atezolizumab, for example). Currently, there are validated immunohistochemistry companion tests defined for the regimens described. According to recent studies validating where the 3 different available biomarkers for NSCLC (22C3, SP263, and SP142), the study "consolidates the analytical evidence for interchangeability of the 22C3, and SP263 assays and lower sensitivity of the SP142 assay" (54).

In order to address feasibility for the aforementioned regimens' adoption, factors like the existing and required workforce and their expertise, capacity building standards, governance for the access to medicines chain, and finally the financial aspects should be previously evaluated to offer timely, quality, accurate and reliable pathology diagnosis and treatment without financial toxicity.

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Appendix 1:

Table 1. ICI Regimens Published and related outcomes. The ESMO-MCBS scores for immune-checkpoint inhibitors for NSCLC. Scores ≥4 and A is substantial.