Durvalumab

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 8. Immunomodulators and antineoplastics > 8.2. Antineoplastics and supportive medicines > 8.2.3. Immunomodulators

ATC codes: L01FF03

Indication	Other specified malignant neoplasms of bronchus or lung ICD11 code: 2C75.Y
INN	Durvalumab
Medicine type	Biological agent
List type	Complementary
Formulations	Parenteral > General injections > IV: 120 mg per 2.4 mL in vial ; 500 mg per 10 mL in vial
EML status history	Application rejected in 2023 (TRS 1049)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Wikipedia	Durvalumab
DrugBank	Durvalumab

Expert Committee recommendation

The Expert Committee recognized that PD-1/PD-L1 immune checkpoint inhibitor therapy has become part of the standard treatment for patients with NSCLC with tumours that do not express targetable oncogenes based on improvements in overall survival that meet the established thresholds for possible inclusion on the Model List. The Committee acknowledged possible improvement in quality of life in addition to improved overall survival associated with the use of pembrolizumab, when compared with platinum-based chemotherapy in patients with advanced/metastatic NSCLC expressing high levels of PD-L1. The Committee noted that longer follow-up data were now available, with overall survival benefits maintained over a 5-year period. The Committee also noted that atezolizumab and cemiplimab showed similar benefits, that is, prolonging median overall survival compared with platinum-based chemotherapy in patients with advanced/metastatic NSCLC and high PD-L1 expression, although the available follow-up data were shorter than for pembrolizumab. For durvalumab as consolidation therapy in locally advanced disease, data also suggested a meaningful benefit. However, the Committee considered that the data were less mature and required further evaluation over time. The Committee acknowledged that individual immune checkpoint inhibitors may differ in their efficacy and safety profiles but considered that an overall net benefit could be assumed for the entire class when compared with platinum-containing chemotherapies. The Committee considered that in principle, the availability of several interchangeable immune checkpoint inhibitors could boost competition and favour access. However, the Committee noted that uncertainty remained about the optimal medicine dose and duration of treatment, with ongoing clinical trials investigating the use of immune checkpoint inhibitors in various cancers at lower doses or for a shorter duration (49). The Committee commended these studies and recommended that such trials be promoted and publicly funded to confirm if lower doses and shorter duration of treatment were indeed associated with non-inferior survival outcomes, similar or lower toxicity and lower costs, and offered a pathway to more affordable and widespread access. The Committee noted that prices of immune checkpoint inhibitors have remained prohibitively

high in most settings. In the absence of true competition, the Committee remained concerned that this situation would continue to contribute to serious inequities between rich and poor countries and patients, which would result in negligible availability and unaffordable prices of these medicines for a large proportion of the global population. The Committee also noted the need to select patients that could benefit from immune checkpoint inhibitors based on PD-L1 expression. Affordable access to necessary diagnostics would add an extra burden on countries and listing these medicines without being able to target their use to those patients who would benefit most from them could lead to additional waste of resources, both public and private. The Committee reiterated the importance for WHO to continue to tackle the high prices of cancer medicines and welcomed the news of progress being made in the establishment of the WHO Technical Advisory Group on Pricing Policies for Medicines to increase affordable access to essential and priority medicines. The Committee recognized the risks at the country level of listing immune checkpoint inhibitors on the WHO Model List, including financial risks based on the current costs of procurement, opportunity costs associated with diverting resources from other diseases, treatments or preventive programmes (e.g. smoking cessation, clean air), and limited feasibility because of barriers to the timely access to diagnostics. The Committee considered that the potential financial impact associated with procurement and appropriate use of immune checkpoint inhibitors could be a significant risk to the financial sustainability of health budgets in many low- and middle-income countries. This was especially true if these countries aimed to provide universal treatment coverage, given the current high prices of immune checkpoint inhibitors and PD-L1 testing, as well as the high prevalence of NSCLC. The Committee recognized that the opportunity costs of providing immune checkpoint inhibitors at current prices for the treatment of patients with NSCLC would be substantial for many health systems. The Committee considered that an assessment of various scenarios based on different assumptions on procurement price, capacity to administer and proportion of patients eligible for treatment would help foster the development of solutions that facilitated access without bankrupting the health care budget. The Committee recalled the recommendation made in 2019 to include nivolumab pembrolizumab on the EML for treatment of metastatic melanoma (1). The Committee noted that the magnitude of benefit of immune checkpoint inhibitors for melanoma far exceeded the benefit seen in lung cancer. The Committee proposed that countries with access to these medicines for melanoma and with sufficient resources to increase the number of patients that could be treated could consider the use of immune checkpoint inhibitors as first-line treatment of metastatic, non-oncogene-addicted NSCLC, in patients with high PD-L1 expression, as a high-priority for expansion. Based on these considerations, the Expert Committee did not recommend the inclusion of PD-1/PD-L1 immune checkpoint inhibitors on the EML for the first-line treatment of metastatic NSCLC with PD-L1 expression ≥ 50% (pembrolizumab, atezolizumab, cemiplimab), nor for locally advanced, unresectable NSCLC with PD-L1 expression ≥ 1% after chemoradiotherapy (durvalumab).

Background

Applications for the inclusion of PD-1/PD-L1 immune checkpoint inhibitors on the EML for the treatment of NSCLC were reviewed by the Expert Committee in 2019 and 2021. On each occasion, inclusion was not recommended. In 2019, inclusion of pembrolizumab, nivolumab and atezolizumab was not recommended as the Committee considered that the precise place of these medicines in the treatment of this condition was still evolving (i.e. immunotherapy alone or in combination with chemotherapy). The Committee noted the evidence of efficacy in the treatment of patients with metastatic NSCLC with these agents. The Committee observed that the duration of follow-up of the single studies for first-line and second-line immunotherapy in trials for lung cancer was generally shorter than 3 years, and considered that data from longer follow-up would better demonstrate the magnitude of benefit. The Committee expressed the hope that by the time of the 2021 Committee meeting, more mature data would be available for metastatic NSCLC and also for use of these agents in locally advanced non-resectable disease, and as adjuvant therapy. Furthermore, the Committee noted that the clinical development of cancer immunotherapy still had some areas of uncertainty about the optimal time for introduction of treatment (first- or second-line), appropriate patient selection (i.e. use of biomarkers) and whether or not the use of immune checkpoint inhibitors in combination with other medicines was superior to monotherapy. The Committee expressed concern about the potential impact of oncology medicines on health budgets, which could be an impediment to access, and the fact that countries may not be able to list these medicines on their national EMLs because of their high price (1). In 2021, the Committee acknowledged that atezolizumab, durvalumab, nivolumab and pembrolizumab were associated with a relevant median overall survival benefit as first-line treatment, well over the EML threshold of 4 to 6 months, based on evidence from several randomized trials. The Committee also noted that the addition of PD-1/PD-L1 immune checkpoint inhibitors to conventional chemotherapy was associated with modest increases in toxicity which may require specialized management in selected case. Overall, the Committee considered that these medicines had a favourable benefit-to-harm ratio and acknowledged that they had substantially improved outcomes for the treatment of NSCLC in practice. However, inclusion of was not

recommended as the Committee considered that at current prices, these medicines were prohibitively expensive in many settings. The issue of treatment costs and appropriate use of these medicines is further complicated by the need for diagnostic testing to identify patients most likely to benefit from treatment, uncertainties about the optimal duration of treatment, the significant disease burden and the likely large eligible patient population. The Committee considered that the financial implications of listing PD-1/PD-L1 immune checkpoint inhibitors for this indication would result in unsustainable expenditures for many patients and health systems (2). The PD-1 immune checkpoint inhibitor nivolumab (with a square box indicating pembrolizumab as a therapeutic alternative) was added to the EML in 2019 for first-line monotherapy in patients with unresectable and metastatic melanoma (1).

Public health relevance

Lung cancer is a leading cause of morbidity, disability and death worldwide (3). In 2020, 2.2 million people were diagnosed with lung cancer, corresponding to 11.4% of all cancers diagnosed; 1.8 million people died from this disease, constituting 18% of all cancer-related deaths. The economic impact of lung cancer is estimated to be around US$ 8 billion in productivity lost in developing countries (4). In the absence of a wide coverage of effective screening programmes globally, more than 60% of lung cancer cases are diagnosed when the disease is locally advanced or metastatic, with some regional variability (5). More than 80% of the lung cancers are classified as NSCLC (6). Targeted therapies have redefined treatment for patients with genomic alterations in driver oncogenes including: epidermal growth factor (EGFR) mutations, anaplastic lymphoma kinase rearrangements, ROS1 rearrangements, BRAF mutations, human epidermal growth factor receptor 2 (HER2) mutations, or amplifications, and neurotrophic tyrosine kinase 1-3 fusions. However, the greatest proportion of NSCLC, both squamous and non-squamous histology type, do not have specific pathogenic genomic alterations that can be treated with targeted medicines, including EGFR, anaplastic lymphoma kinase gene or ROS1 (7). Historically, patients with non-oncogene-addicted NSCLC have experienced poor survival outcomes because of a lack of therapeutic options in advanced disease settings. For non-oncogene-addicted NSCLC, the treatments currently included in the EML are all chemotherapies and are associated with a median overall survival of about 12 months.

Benefits

Advanced and metastatic NSCLC expressing high levels of PD-L1 (≥ 50%) Pembrolizumab The phase III KEYNOTE-024 study evaluated pembrolizumab as first-line treatment in 305 participants with previously untreated, advanced NSCLC with tumour PD-L1 expression ≥ 50% and no sensitizing mutation of the EGFR gene or translocation of the anaplastic lymphoma kinase gene (8–10). Participants were randomized to receive 200 mg pembrolizumab every 3 weeks for up to 35 cycles (154 patients) or four to six cycles of standard platinum doublet chemotherapy (151 patients). Patients in the chemotherapy group with progressive disease were permitted to cross over to pembrolizumab. The effective crossover rate was 66% (99/151; 83 on-study and 16 outside the study). At a median follow-up of 5 years, median overall survival was 26.3 months (95% confidence interval (CI) 18.3 to 40.4 months) for pembrolizumab and 13.4 months (95% CI 9.4 to 18.3 months) for chemotherapy (hazard ratio (HR) 0.62, 95% CI 0.48 to 0.81). Progression-free survival was 7.7 versus 5.5 months (HR 0.50, 95% CI 0.39 to 0.65), with 3- and 5-year progression-free survival rates of 22.8% and 12.8% with pembrolizumab and 4.1% and 0.0% with standard chemotherapy (10). The health-related quality of life analysis showed a clinically meaningful and significant improvement favouring patients treated with pembrolizumab (11). Fewer participants treated with pembrolizumab had deterioration in the QLQ-LC13 composite endpoint than participants given chemotherapy: 31% (46/151) versus 39% (58/148). Time to deterioration was longer with pembrolizumab than with chemotherapy: median not reached (95% CI 8.5 months to not reached) versus 5.0 months (95% CI 3.6 months to not reached); HR 0.66, 95% CI 0.44 to 0.97). Compliance with quality of life questionnaires was 90% at baseline and about 80% at 15 weeks. Atezolizumab The phase III IMpower110 study evaluated atezolizumab as first-line treatment in 554 participants with previously untreated metastatic EGFR or anaplastic lymphoma kinase wild type NSCLC with tumour PD-L1 expression of ≥ 1% (12). Patients were randomized to receive atezolizumab 1200 mg every 3 weeks (277 patients) or four to six cycles of platinum-based chemotherapy (277 patients). Crossover from the chemotherapy group to the atezolizumab group was not permitted. At the interim analysis after median follow-up of 15.7 months, atezolizumab monotherapy was associated with longer overall survival and progression-free survival, compared with chemotherapy. The overall survival for atezolizumab and chemotherapy in the population with high-PD-L1 expression (≥ 50%) was 20.2 months and 13.1 months, respectively (HR 0.59, 95% CI 0.40 to 0.89). Progression-free survival in the population with high-PD-L1 expression was 8.1 and 5 months in the atezolizumab and chemotherapy arms, respectively (stratified HR 0.63, 95% CI 0.45 to 0.88). Investigator-assessed confirmed response was higher with atezolizumab than with chemotherapy (38.3% versus 28.6%) in the population with high-PD-L1 expression. Investigator-assessed confirmed response rates did not differ significantly between treatment arms in the populations with any (≥ 1%) or high or intermediate (≥

5%) PD-L1 expression. In an updated analysis with a median follow-up of 31.3 months, the median overall survival for atezolizumab versus chemotherapy in the high or intermediate PD-L1 expression group was 19.9 months versus 16.1 months (stratified HR 0.87, 95% CI 0.66 to 1.14). An exploratory overall survival analysis in the high PD-L1 expression group showed a median overall survival of 20.2 months with atezolizumab and 14.7 months with chemotherapy, consistent with the primary analysis (13). Prespecified analysis of quality-of-life patient-reported outcomes for the high PD-L1 expression population included evaluation of the time to confirmed deterioration as a secondary endpoint and change from baseline in global health status, functioning and lung cancer symptoms. The mean baseline scores for global health status, physical functioning and role functioning were moderate, the symptom burden was low and all were similar in both arms. No differences in time to deterioration were seen between arms for cough (HR 0.98, 95% CI 0.48 to 2.03), chest pain (HR 1.02, 95% CI 0.47 to 2.22), dyspnoea (HR 0.96, 95% CI 0.57 to 1.60) and three-symptom composite score (HR 0.92, 95% CI 0.59 to 1.44). No clinically meaningful worsening in dyspnoea, cough or chest pain was seen with atezolizumab versus chemotherapy. Fatigue and nausea/vomiting scores numerically improved immediately with atezolizumab and were maintained to week 48 (14). Cemiplimab The open-label phase III EMPOWER-lung 1 study compared cemiplimab monotherapy with platinum doublet chemotherapy in the first-line treatment of 710 patients with advanced NSCLC with tumour PD-L1 expression of ≥ 50% (15). Patients were randomized to receive cemiplimab 350 mg every 3 weeks for up to 36 cycles (356 patients) or four to six cycles of platinum-based chemotherapy (354 patients). Crossover from chemotherapy to cemiplimab was allowed following disease progression. Thus, 74% (150/203) of patients who progressed on chemotherapy received cemiplimab as a crossover treatment; 32% (50/158) of patients who progressed on cemiplimab received extended treatment with the addition of chemotherapy. The primary endpoints were overall survival and progression-free survival; quality of life was a secondary endpoint. At a median follow-up of 10.8 months, median overall survival was not reached (95% CI 17.9 months to not evaluable) with cemiplimab versus 14.2 months (95% CI 11.2 to 17.5 months) with chemotherapy (HR 0.57, 95% CI 0.42 to 0.77). Median progression-free survival was 8.2 months with cemiplimab compared with 5.7 months with chemotherapy (HR 0.54, 95% CI 0.43 to 0.68). Cemiplimab appeared to improve, or not have a detrimental effect on, quality of life. Clinically meaningful effects (mean difference of scores of more than 5 points) were observed on social functioning and global health status and quality of life: differences in least-square means +5.27 (95% CI 2.41 to 8.13, two-sided nominal P = 0.0003) and +5.03 (95% CI 2.11 to 7.96, two-sided nominal P = 0.0008), respectively. Fatigue (least-square mean −8.6), appetite loss (−7.52), alopecia (−18.57) and constipation (−5.7) also favoured cemiplimab. For all other symptoms assessed, cemiplimab had similar quality-of-life effects as chemotherapy, with no detrimental effects (16). Locally advanced, unresectable NSCLC with PD-L1 expression ≥ 1% Durvalumab The phase III PACIFIC trial evaluated durvalumab versus placebo as consolidation therapy in 713 patients with stage III locally advanced, unresectable NSCLC, irrespective of tumour PD-L1 expression, who did not have disease progression after at least two cycles of platinum-based chemoradiotherapy (17–19). Patients were randomized 2:1 to receive durvalumab 10 mg/kg every 2 weeks for up to 12 months (476 patients) or matching placebo (237 patients). At an interim analysis after median follow-up of 14.5 months, median progression-free survival was 16.8 months versus 5.6 months in the durvalumab and placebo groups, respectively (HR 0.52, 95% CI 0.42 to 0.65) (17). Analysis after median follow-up of 25.2 months showed the 24-month overall survival rate was 66.3% versus 55.6% in the durvalumab and placebo groups, respectively (HR 0.68, 99.73% CI 0.47 to 0.997) (18). Analysis after median follow-up of 34.2 months reported median overall survival rates of 47.5 months with durvalumab versus 29.1 months with placebo (stratified HR 0.68, 95% CI 0.53 to 0.87), corresponding to 5-year overall survival rates of 42.9% with durvalumab versus 33.4% with placebo. Median progression-free survival was 16.9 months with durvalumab versus 5.6 months with placebo (HR 0.52, 95% CI 0.42 to 0.65), corresponding to an estimated 5-year progression-free survival rate of 33.1% with durvalumab versus 19.0% with placebo. An exploratory analysis based on the level of tumour PD-L1 expression showed that patients seemed to derive greater benefit when PD-L1 expression was ≥ 1% (HR for overall survival 0.61, 95% CI 0.44 to 0.85) than when PD-L1 expression was < 1% (HR for overall survival 1.15, 95% CI 0.75 to 1.75) (19). Health-related quality of life was also reported in the PACIFIC trial (20, 21). After median follow-up of 25.2 months, 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 patient-reported outcomes 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, no clinically important between-group differences were found in time to deterioration of prespecified key patient-reported outcome endpoints. Real-world studies evaluating durvalumab The PACIFIC-R study was an international, retrospective study of patients who started durvalumab within an early access programme between September 2017 and December 2018 (22). Median progression-free survival was 21.7 months; it was longer in patients with PD-L1 expression ≥1% compared with < 1% (22.4 months versus 15.6 months). Overall survival data were not reported. A cohort study in Germany based on an expanded access programme of

durvalumab reported data on 121 patients (23). With a median follow-up of 25.1 months, median progression-free survival was 20.1 months and median overall survival was not reached. At 12 and 18 months, rates of progression-free survival were 56% and 53%, while overall survival rates at 12 and 24 months were 79% and 66%. The data were consistent with the PACIFIC trial. A multicentre real-world cohort study in Canada included 141 patients treated with chemoradiotherapy plus durvalumab consolidation and compared the outcome with a historical cohort of 121 patients treated with chemoradiotherapy and no consolidation. Median follow-up was 15.8 months in the durvalumab cohort and 51.5 months in the historical cohort. Overall survival improved with durvalumab, with a median overall survival not reached versus a median overall survival of 26.9 months in the historical control cohort (HR 0.56, 95% CI 0.37 to 0.85). Overall survival rates at 12-months were 92.5% for the durvalumab group and 78.5% for the historical cohort (HR 0.56, 95% CI 0.37 to 0.85) (24). A cohort study in the Republic of Korea reported data on 61 patients, 21 of whom had received durvalumab consolidation and 40 had received no consolidation treatment after chemoradiotherapy. More than half of the patients did not meet the criteria of the PACIFIC study; however, they still received consolidation durvalumab in real-world practice. Median progression-free survival was not reached in the durvalumab group versus 9.6 months in the observation group. Durvalumab treatment was associated with favourable progression-free survival also in the subgroup of patients who did not meet the criteria of the PACIFIC study (not reached versus 6.4 months). Overall survival data were not reported (25). An observational cohort study across the Veterans Health Administration in the United States included patients with stage III NSCLC who had received concurrent chemoradiotherapy, with or without durvalumab: 1006 patients who had received durvalumab and 989 who had not. The addition of durvalumab was associated with higher progression-free survival (HR 0.62, 95% CI 0.55 to 0.70) and overall survival (HR 0.57, 95% CI 0.50 to 0.66) (26). Another cohort study analysed data from the United States National Cancer Database for patients diagnosed with clinical stage III NSCLC between 2015 and 2017 with follow-up to the end of 2018 who were treated with chemoradiation. The cohort included 23 811 patients, of whom 1297 (5.4%) had received durvalumab. The use of immunotherapy was associated with longer overall survival (HR 0.74, 95% CI 0.67 to 0.82), corresponding to a 3-year overall survival rate of 52% versus 44% (27).

Harms

The safety of pembrolizumab was evaluated in KEYNOTE-024 study (8–10). The rate of adverse events among patients in the pembrolizumab arm was 76.6% versus 90.0% among patients in the chemotherapy arm, corresponding to a proportion of moderate-severe adverse events of 31.2% versus 53.3%. Toxicity led to treatment discontinuation in 13.6% and 10.7% in the pembrolizumab and chemotherapy arms, respectively, and resulted in toxic death in 1.3% and 2%, respectively. The most common adverse events with pembrolizumab were diarrhoea, fatigue, pyrexia and pruritus, all reported in 10–15% of the patients, and generally of low-to-moderate grade. Immune-related adverse events were reported in 34.4% of patients, of which 13.6% were moderate to severe and one case of fatal pneumonitis. The most common immune-related events were thyroiditis (11%, but less than 1% were moderate to severe) and pneumonitis. In the IMpower110 study, the adverse events of any grade with atezolizumab and chemotherapy were reported in 90.2% and 94.7% of participants, respectively. Grade 3 and 4 adverse events were reported in 30.1% and 52.5% of participants in the atezolizumab and chemotherapy arms, respectively, while grade 5 adverse events were reported in 3.8% and 4.2%. The most frequent grade 3 and 4 adverse events were anaemia, neutropenia and thrombocytopenia. Hepatic laboratory abnormalities, rash and hypothyroidism were the most reported immune-mediated adverse events (≥ 5% in each group). Grade 3 or 4 immune-mediated adverse events occurred in 6.6% and 1.5%, with no grade 5 event reported (12). The EMPOWER-lung 1 study assessed the overall safety profile of cemiplimab (15). In total, adverse events were reported in 43% and 40% of patients in the cemiplimab and chemotherapy arms, respectively, of which 14% and 39% were moderate-to-severe events and 3% and 2% were fatal events. The most common toxicities observed with cemiplimab were poor appetite, transaminitis and anaemia, all occurring in 5% of the patients, and generally grade 1–2. Treatment with chemotherapy was associated with anaemia (30%, with 14% grade 3, i.e. haemoglobin < 8 g/dL), nausea (25%), peripheral neuropathy (10%) and hyporexia (14%). The safety of durvalumab was evaluated in the PACIFIC study (19). The most frequent adverse reactions were cough (40.2% versus 30.3% in the placebo arm), upper respiratory tract infections (26.1% versus 11.5% in the placebo arm) and rash (21.7% versus 12.0% in the placebo arm). The most frequent grade 3/4 adverse reaction was pneumonia (6.5% versus 5.6% in the placebo arm). The overall incidence of grade 3/4 adverse reactions was 12.8% in the durvalumab arm versus 9.8% in the placebo arm. Radiation pneumonitis occurred in 33.9% patients in the durvalumab arm and 24.8% patients in the placebo arm, including grade 3 (3.4% versus 3.0%) and grade 5 (1.1% versus 1.7%). Grade 5 (fatal) immune-mediated pneumonitis occurred in 0.8% patients on durvalumab versus 1.3% patients on placebo. In the combined safety database with durvalumab monotherapy (3006 participants with multiple tumour types), immune-mediated pneumonitis occurred in 92 (3.1%) patients, including grade 3 in 25 (0.8%) patients, grade 4 in two (<

0.1%) patients and grade 5 in six (0.2%) patients. Of the 92 patients with immune-mediated pneumonitis, 69 received high-dose corticosteroid treatment and durvalumab was discontinued in 38 patients. Other immune-related adverse reactions reported in less than 1% of patients treated with durvalumab monotherapy in clinical trials were myasthenia gravis, myocarditis, myositis, polymyositis, meningitis, encephalitis and Guillain–Barre syndrome. No overall differences in safety were reported between older (≥ 65 years) and younger patients (28). The phase II PACIFIC-6 clinical trial was designed to evaluate the safety and benefit of durvalumab after sequential chemoradiotherapy, in a single-arm prospective cohort (29). The study enrolled 117 patients. The median progression-free survival was 10.9 months with a 12-month progression-free survival rate of 49.6% and an overall survival rate of 84.1%. Grade 3/4 toxicity occurred in 18.8% of patients. Two patients (1.7%) experienced Grade 5 (fatal) adverse events. Safety and efficacy appeared consistent with findings from the PACIFIC trial.

Cost / cost effectiveness

Pembrolizumab The application identified six cost–effectiveness studies of first-line pembrolizumab versus chemotherapy for NSCLC with high levels of PD-L1 (30–35). All but one of the studies (34) were from high-income country settings. Incremental cost–effectiveness ratios per quality-adjusted life year (QALY) gained were €84 097 in France, Sw.fr. 57 402 in Switzerland, US$ 103 128 in China, US$ 110 922 in China, Hong Kong SAR and US$ 97 621 in the United States. In the United Kingdom, the incremental cost–effectiveness ratio per end-of life adjusted QALY was US$ 52 000. A systematic review that evaluated the cost–effectiveness of pembrolizumab versus cemiplimab for NSCLC with high levels of PD-L1 in the United States reported an incremental cost–effectiveness ratio for pembrolizumab of US$ 114 246 per QALY gained (36). Atezolizumab The application identified two cost–effectiveness studies of first-line atezolizumab versus chemotherapy for NSCLC with high levels of PD-L1 (37, 38). Incremental cost–effectiveness ratios varied from US$ 52 415 per QALY gained (using a scenario involving a patient-assistance programme) to US$ 125 779 per QALY gained in China, and from US$ 123 424 to US$ 224 590 per QALY gained in the United States. Cemiplimab The application identified two cost–effectiveness studies of first-line cemiplimab versus chemotherapy for NSCLC with high levels of PD-L1, both from the United States perspective (39, 40). Incremental cost–effectiveness ratios ranged from US$ 40 390 to US$ 91 891 per QALY gained. Another study modelled the cost–effectiveness of cemiplimab, pembrolizumab and atezolizumab, from a United States health-sector perspective (41). The results suggested that first-line cemiplimab was a cost-effective option compared with first-line pembrolizumab (incremental cost–effectiveness ratios US$ 52 998 per QALY gained), and a dominant alternative versus first-line atezolizumab at a willingness-to-pay threshold of US$ 100 000 per QALY gained. Durvalumab The application identified seven cost–effectiveness studies of durvalumab as consolidation therapy in locally advanced NSCLC, from the perspective of China, Switzerland, United Kingdom and United States (42–48). Incremental cost–effectiveness ratios were US$ 55 285 to US$ 138 920 per QALY gained in the United States (depending on the payer perspective), £22 665 per QALY gained in the United Kingdom, Sw.fr. 66 131 to Sw.fr. 88 703 per QALY gained (depending on PD-L1 tumour expression), and ¥46 093 to ¥193 898 per QALY gained in China (depending on use of a patient assistance programme or retail prices).

WHO guidelines

WHO guidelines for treatment of NSCLC are not currently available.

Availability

Pembrolizumab, atezolizumab and cemiplimab have regulatory approval in multiple countries for the treatment of metastatic NSCLC. They have primary patent protection until 2028, 2029 and 2035, respectively. Durvalumab has regulatory approval in multiple countries for the treatment of locally advanced, unresectable NSCLC as consolidation therapy after platinum-based chemotherapy. It has primary patent protection until 2030. No biosimilar products are available.

Other considerations

The technical team in cancer in the WHO Department of Noncommunicable Diseases reviewed and provided comments on the application. The technical team was uncertain about the inclusion of immune checkpoint inhibitors on the EML at this time because, despite established evidence of meaningful clinical benefit of these medicines in NSCLC, there were concerns about the feasibility of introducing these medicines because of limited accessibility, limited availability of diagnostic testing, limited capacity to manage toxicities and overall implications for the budget of health systems. The technical team proposed that data from low- and middle-

income countries that could test and validate the effectiveness and feasibility of widespread use of immune checkpoint inhibitors would help stakeholders understand the implications of including this class of medicines in WHO Model List. These data can include evaluating ability to safely delivery these medicines, provide concomitant diagnostic services, manage toxicities and evaluate the effect on health expenditure. The EML Cancer Medicines Working Group reviewed the application but was not able reach a consensus to support or not the inclusion of PD-1/PD-L1 immune checkpoint inhibitors on the EML for first-line treatment of selected patients with metastatic NSCLC with PD-L1 expression ≥ 50%, whose tumours do not harbour a targetable oncogene. The Working Group acknowledged a relevant and meaningful survival benefit after long follow-up and a possible improvement of the quality of life associated with the use of pembrolizumab. The Group noted that atezolizumab and cemiplimab for the same indication, and durvalumab for locally advanced non-metastatic lung cancer with PD-L1 expression ≥ 1%, after prior chemotherapy and radiation therapy, provide similar benefits although the available trial data for these medicines have a shorter duration of follow-up duration. Several members of the Working Group were still uncertain about the implications at the country level of listing immune checkpoint inhibitors on the WHO Model List, including: the financial risks based on the current costs of procurement; the opportunity costs associated with diverting resources from other diseases or treatments; highly limited feasibility of use because of barriers to the timely access to diagnostics; and lack of information about the most cost-effective duration of treatment and dose. Predictive biomarkers, such as PD-L1 expression, are key to selecting patients with tumours that are more likely to respond to immune checkpoint inhibitors. It was also highlighted that, despite the approval of several checkpoint inhibitors, prices for these agents have remained prohibitively high in most settings, discounting is consistently limited by the production companies and biosimilar products cannot be expected to be available in most countries in the near future. Other Working Group members highlighted that a positive recommendation by WHO on immune checkpoint inhibitors for the treatment of NSCLC could guide countries in prioritizing these medicines for this specific indication, limiting their use for other cancers in which benefits were less relevant. The Model List can support national decision-making and inform national guidelines for clinical practice and guide the procurement and supply of medicines in the public sector. Working Group members also stressed that price competition should be facilitated for immune checkpoint inhibitors by allowing early utilization of more molecules in national markets. The Working Group also noted that the application did not consider camrelizumab, nivolumab/ipilimumab, sintilimab, sugemalimab or toripalimab. Most of these therapies have shown comparable improvement in disease control compared with other immune checkpoint inhibitors under consideration. However, overall survival data were mature only for nivolumab/ipilimumab, with all other molecules tested in clinical trials with incomplete survival data.

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