Nivolumab

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: L01FF01

Indication	Other specified malignant neoplasms of bronchus or lung ICD11 code: 2C75.Y
INN	Nivolumab
Medicine type	Biological agent
List type	Complementary
Formulations	Parenteral > General injections > IV: 10 mg per mL concentrate solution for infusion
EML status history	Application rejected in 2019 (TRS 1021)
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.
Tags	Cancer
Wikipedia	Nivolumab
DrugBank	Nivolumab

Expert Committee recommendation

The Committee endorsed the recommendations of the EML Cancer Medicine Working Group with regard to the proposed threshold of four to six months of overall survival benefit as a guiding principle for prioritizing cancer medicines for inclusion on the EML, and applied this principle to the consideration of the immune checkpoint inhibitors. The Committee noted that there were no treatment options for metastatic melanoma currently included on the Model List. The Committee recommended the addition of nivolumab and pembrolizumab to the complementary list of the EML, for use as first-line monotherapy for treatment of patients with unresectable and metastatic melanoma on the basis of evidence of significantly increased overall survival for patients that met the recommended threshold for benefit, and in the absence of other EML-listed treatment options. Listing should be for nivolumab with a square box indicating pembrolizumab as a therapeutically equivalent alternative. The Committee noted that nivolumab was scored as 4/5 on the ESMO-MCBS v1.1 for this indication. The Committee considered that more mature data would be necessary before listing of these medicines could be considered for use in adjuvant indications of radically resected melanoma. The Committee did not recommend listing of atezolizumab, nivolumab or pembrolizumab for treatment of patients with metastatic NSCLC at this time, as the Committee considered that their precise place in the treatment/ immunotherapy of this condition is still evolving. 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 three years, and considered that data from longer follow up would better capture the actual magnitude of benefit. By the time of the next Committee meeting in 2021, more mature data will 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 landscape of clinical development of cancer immunotherapy still has some areas of uncertainty with regard to the optimal time for introduction of treatment (first- or second-line), appropriate patient selection, and whether or not use of ICIs in combination with other medicines is superior. The Committee expressed concern about the potential budget impact of oncology medicines, which could be an impediment to access, and countries may not be able to list these medicines on their national EMLs. Therefore, the Committee recommended that WHO engage stakeholders to find ways to facilitate better access and affordability as a high priority through avenues such as the Medicines Patent Pool, WHO prequalification and collaborative registration procedures. The Committee also recommended ongoing activities of the EML Cancer Medicines Working Group to include identification of obstacles to access and affordability of cancer medicines, and pricing data collection.

Background

The application requested the addition of atezolizumab, nivolumab and pembrolizumab to the complementary list of the EML: Atezolizumab: As second-line therapy in locally advanced or metastatic non-small cell lung carcinoma (NSCLC) after chemotherapy. Nivolumab: Early and advanced stage melanoma; As second-line therapy after chemotherapy failure in locally advanced or metastaticNSCLC, regardless of PD-L1 status Pembrolizumab: Early and advanced stage melanoma; As first-line therapy in NSCLC expressing PD-L1≥50%, in second-line after chemotherapy failure for NSCLC PD-L1≥1% Atezolizumab, nivolumab and pembrolizumab belong to the class of PD-1/ PDL1 immune-checkpoint inhibitors (ICI) and had not previously been considered for inclusion on the EML. The EML currently includes cytotoxic chemotherapies for NSCLC, but there are no alternative medicines currently on the EML for the treatment of metastatic melanoma.

Public health relevance

Lung cancer is the most diagnosed and the leading cause of death for cancer worldwide, with an estimated 2 million new cases and 1.7 million deaths in 2018 (1). Lung cancer is a highly lethal malignancy, with an economic impact estimated around US$ 8 billion productivity lost in the BRICS countries (2). Moreover, in the absence of a wide coverage of an effective screening programme in place on global scale, lung cancer diagnoses occur in advanced stage in more than 60% of cases, with highly regional variability (3–5). Over 80% of lung cancers are classified as non-small cell lung cancer (NSCLC). Although targeted therapies have redefined the therapeutic landscape for some patients, these therapies are ineffective in patients whose tumours lack the particular genetic mutations/ alterations, constituting the majority of NSCLC patients. For this reason, ICI therapy is becoming part of the treatment of such patients, in an attempt to improve survival and quality of life. The ICIs targets are the immune-competent cells, such as T-lymphocytes and antigen-presenting cells, releasing a tumourinduced immunosuppressant milieu (e.g. PD-1, PD-L1) or strengthening the immune-activating signals of the immune response (e.g. GITR, pro- inflammatory interleukins, interferon-gamma) (6). The availability of ICIs in NSCLC addresses an unmet need for patients considered to have a poor prognosis in advanced stages, in the absence of an indication of targeted therapy. Melanoma is the most lethal form of skin cancer. In 2018, nearly 300 000 new cases were diagnosed worldwide, with over 60 000 deaths (1). As a cancer related to the exposure to sunlight, melanoma demonstrates greater variation in incidence rates across different ethnic groups and is more commonly found among fair-skinned Caucasian populations. Incidence of melanoma peaks at the 7th decade of life; however, though half of the diagnoses are in patients aged between 55 and 74 years, melanoma is the most common cancer diagnosed in adolescents and young adults 20–29 years and the most commonly diagnosed cancers in young adults worldwide (7). Early detection and resection of melanoma is the most effective treatment strategy, with a traditionally poor prognosis for metastatic disease (8).

Benefits

NSCLC (first-line) Pembrolizumab The Phase III KEYNOTE-024 study evaluated pembrolizumab as first-line treatment in patients with advanced NSCLC showing PD-L1 expression ≥50%, in the absence of epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) translocations (non-oncogene-driven NSCLC) (9). Approximately 30% of screened patients had tumour PD-L1 expression ≥50%. 305 patients were randomized to receive 200 mg pembrolizumab every three weeks (up to two years) or 4-6 cycles of standard platinum-doublet chemotherapy. Patients in the chemotherapy group were permitted to cross over to the pembrolizumab group if they experienced disease progression. In the intentionto- treat population, progression-free survival (PFS) and overall survival (OS) were significantly longer in the pembrolizumab group than the chemotherapy group (PFS: hazard ratio (HR) 0.50, 95%CI 0.37 to 0.68; p<0.001; OS: HR 0.60, 95%CI 0.41 to 0.89; p=0.005). Health-related quality of life measures also favoured pembrolizumab (10). 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 to 0.86), with a median OS of 30.0 months (95%CI 18.3–not reached) in the pembrolizumab arm and 14.2 months (95%CI 9.8 to 19.0) in the chemotherapy arm; the Kaplan-Meier estimate of OS at 12 months was 70.3% (95%CI 62.3% to 76.9%) for the pembrolizumab group and 54.8% (95%CI 46.4% to 62.4%) for the chemotherapy group (11). Eighty-two patients, allocated to the chemotherapy arm, crossed over to receive pembrolizumab upon meeting eligibility criteria. In term of magnitude of benefit, pembrolizumab provided a gain of median OS of +15.8 months and +15.5% at one year. Based on the KEYNOTE-024 trial results, the clinical benefit of pembrolizumab in the first-line setting measured with the European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 received a score of 4 (12). The first-line use of pembrolizumab was investigated in NSCLC other than PD-L1>50%, to assess if the benefit was conserved in unselected populations of patients. The Phase III KEYNOTE-042 trial randomized patients with NSCLC EGFR/ALK wild type showing PD-L1≥1%, both adenocarcinoma and squamous NSCLC, to receive either pembrolizumab 200 mg every three 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% (13). 1274 patients were randomized: 637 to each arm. 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, 95%CI 0.56 to 0.85), consistent with the results of Keynote-024 for the PD-L1 enriched population. The median OS (up to approximately 38 months) with the PD-L1 inhibitor was 20.0 months vs 12.2 months with chemotherapy. The HR for OS was 0.77 (95%CI 0.64 to 0.92) and 0.81 (95%CI 0.71 to 0.93) for PD-L1 ≥20% and ≥1%, respectively. In patients with limited expression of PD-L1 (1–49%) the stratified analysis of survival showed that OS reached 17.7 vs 13.0 months in PD-L1 ≥20% and 16.7 and 12.1 in PD-L1 ≥1%, respectively in these sub-populations. However, an exploratory analysis of KEYNOTE-042 showed that the survival advantage associated with pembrolizumab vs chemotherapy in patients with a tumour proportion score between 1% to 49% was not relevant (median OS: 13.4 vs 12.1 months; HR 0.92, 95%CI 0.77 to 1.11). The overall benefit might be driven by the enriched population with high expression of PD-L1 as the preponderance of the OS benefit was seen in patients with ≥50%, the only sub-group gaining more than six months overall survival. NSCLC (second-line) Pembrolizumab The KEYNOTE-010 trial randomized 1034 patients with previously-treated squamous (22% of the population) and non-squamous (70%) NSCLC with PDL1 expression of at least 1% of tumour cells to receive pembrolizumab (2 mg/kg or 10 mg/kg, every three weeks) or docetaxel 75 mg/m2 every three weeks (14). Approximately two thirds of NSCLC patients screened met the PD-L1 threshold of 1%, and 28% showed high expression (≥50%), consistent with previous findings in 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 to 0.88; 10 mg/kg, HR 0.61, 95%CI 0.49 to 0.75). Median overall survival was 10.4 months (95%CI 9.4 to 11.9) for the pembrolizumab 2 mg/kg group, 12.7 months (10.0 to 17.3) for the pembrolizumab 10 mg/kg group, and 8.5 months (95%CI 7.5 to 9.8) for the docetaxel group. One-year overall survival was 43.2% vs 52.3% vs 34.6%. Based on the KEYNOTE-010 trial results, the clinical benefit of pembrolizumab in the second-line setting measured with the ESMO-MCBS v1.1 was scored at 5/5 (12). In patients with a PD-L1 tumour proportion score of ≥50%, the greatest benefit was observed for OS for pembrolizumab 2 mg/kg vs docetaxel with HR 0.54 (95%CI 0.38 to 0.77; p=0.0002), and for pembrolizumab 10 mg/kg vs docetaxel HR 0.50 (95%CI 0.36 to 0.70; p<0.0001). Median OS was 14.9 months and 17.3 months for the 2 mg/kg and 10 mg/kg arms respectively, longer than the chemotherapy arm (8.2 months). After the primary analysis, crossover from docetaxel to pembrolizumab was allowed. 36 months overall survival rate was 23% for the pembrolizumab groups (pooling the two dose arms) vs 11% for docetaxel (15). Nivolumab The role of nivolumab as second-line treatment of NSCLC has been investigated two Phase III clinical trials: CheckMate-017 and CheckMate-057. In CheckMate-017, 272 patients with squamous NSCLC were randomized to receive nivolumab 3 mg/kg every two weeks, or docetaxel, at a dose of 75 mg/m2 every three weeks (16). The median OS was 9.2 months (95%CI 7.3 to 13.3) in the nivolumab group vs 6.0 months (95%CI 5.1 to 7.3) in the docetaxel group. The OS rate at one year was 42% (95%CI 34 to 50) in the nivolumab group vs 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 to 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 postprogression benefit persisting (17). The level of PD-L1 expression was neither prognostic nor predictive of any of the efficacy endpoints. Based on the CheckMate-017 trial results, the clinical benefit of nivolumab in the second-line setting in squamous cell NSCLC measured with the ESMO-MCBS v1.1 was scored at 5/5 (12). In CheckMate-057, 582 patients with non-squamous NSCLC (e.g. adenocarcinoma) were randomized to nivolumab or docetaxel (18). Nivolumab improved OS compared to 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 (95%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 sub-group analysis did not favour nivolumab over docetaxel in the EGFR-mutated NSCLC population (oncogene-driven disease, HR 1.18) (19). Moreover, the EGFR wildtype populations seemed to derive the greatest benefit, with HR 0.66 (95%CI 0.51 to 0.86). Based on the CheckMate-057 trial results, the clinical benefit of nivolumab in the second-line setting in non-squamous cell NSCLC measured with the ESMO-MCBS v1.1 was scored at 5/5 (12). In an updated analysis of CheckMate-017 and CheckMate-057, pooled two-year OS favoured nivolumab in both squamous and non-squamous NSCLC (squamous: 29%, 95%CI 24% to 34% vs 16%, 95%CI 12% to 20%; non-squamous: 23%, 95%CI 16% to 30% vs 8%, 95%CI 4% to 13%) (20). 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 vs 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). Among nivolumab-treated patients, 37% of confirmed responders with squamous NSCLC and 34% with nonsquamous NSCLC had ongoing responses after two years' minimum follow up and no patient in docetaxel group had an ongoing response. Consistent with the primary analyses, two-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. 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 two years' minimum follow-up was 0.38 (95%CI 0.24 to 0.60) for patients with nonsquamous NSCLC. Atezolizumab The Phase III OAK trial randomized 850 immuno-oncology naive patients with advanced squamous and non-squamous NSCLC previously treated with one or two lines of chemotherapy to receive atezolizumab 1200 mg fixed dose every three weeks or standard docetaxel 75 mg/m² every three weeks (21). Treatment was administered until unacceptable toxicity or disease progression. Atezolizumab could be continued beyond disease progression if clinical benefit was demonstrated despite evidence of radiological disease progression on computerized tomography (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. OS was improved in the ITT study population with atezolizumab, reaching a median OS of 13.8 months (95%CI 11.8 to 15.7) vs docetaxel (9.6 months, 95%CI 8.6 to 11.2), with HR 0.73 (95%CI 0.62 to 0.87, p=0.0003). Based on the OAK trial results, the clinical benefit of atezolizumab in the second-line setting measured with the ESMO-MCBS v1.1 was scored at 5/5 (12). Sub-group analysis showed a greater magnitude of benefit in patients with higher PD-L1 expression, both assessed on tumour cells (TC) or immuneinfiltrating 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 to 0.93, p=0.0102) and +5.5 months in TC2/3 or IC2/3 population (HR 0.67, 95%CI 0.49 to 0.90, p=0.0080). Metastatic melanoma Pembrolizumab The role of pembrolizumab was investigated in randomized trials and cohort studies for metastatic or unresectable locally-advanced melanoma as monotherapy, both in BRAF-mutated and wild-type tumours. The Phase I Keynote-001 trial evaluated pembrolizumab 2 mg/kg and 10 mg/kg every two weeks in patients with advanced melanoma (22). Around one third of the population was pre-treated with ipilimumab. The overall response rate during receipt of therapy, across all doses, based on assessment by the investigator according to immune-related response criteria was 38%. An updated analysis showed an estimated five-year OS rate of 34% in all patients enrolled (pre-treated with chemotherapy, targeted agents or ipilimumab) and 41% in treatment-naive patients (23). Median OS was 23.8 months (95%CI 20.2 to 30.4) and 38.6 months (95%CI 27.2–not reached) in pre-treated and treatment-naive patients, respectively with a five-year PFS rates of 21% and 29%. The Phase II Keynote-002 trial assessed the efficacy and safety of pembrolizumab 2 mg/kg or 10 mg/kg every three weeks vs investigator-choice chemotherapy (paclitaxel plus carboplatin, paclitaxel, carboplatin, dacarbazine, or oral temozolomide) in patients with ipilimumab-refractory melanoma (1:1 randomization, n=540 patients) (24, 25). Median OS was 13.4 months for 2 mg/ kg, 14.7 months for 10 mg/kg, and 11.0 months for chemotherapy. 18-months OS rates were 40%, 44%, and 36%; 24-months rates were 36%, 38%, and 30%. HR for OS was 0.86 (95%CI 0.67 to 1.10) for 2 mg/kg and 0.74 (95%CI 0.57 to 0.96) for 10 mg/kg, with no difference between doses (0.87, 95%CI 0.67 to 1.12). The benefit was consistent across the sub-groups, of age (younger or older than 65 years), plasma lactate dehydrogenase (LDH) normal or elevated, sex and BRAF status (mutant or wild-type). Based on the Keynote-002 trial results, the clinical benefit of pembrolizumab for melanoma in the second-line setting measured with the ESMO-MCBS v1.1 was scored at 3/5 (12). The Phase III Keynote 006 trial assessed pembrolizumab (10 mg/kg every two weeks or every three weeks) as first-line therapy for advanced melanoma, versus ipilimumab (3 mg/kg), the standard of care at the time of the investigation (26, 27). Median OS was not reached in either pembrolizumab group and was 16.0 months with ipilimumab (HR 0.68, 95%CI 0.53 to 0.87 for pembrolizumab every two weeks vs ipilimumab and 0.68, 95%CI 0.53 to 0.86 for pembrolizumab every 3 weeks vs ipilimumab). 24-month OS rate was 55% in the two- and threeweek group, and 43% in the

ipilimumab group, showing limited differences between pembrolizumab dosing schedules. Nivolumab The CheckMate 037 trial assessed the efficacy and safety of nivolumab (3 mg/kg every two weeks) in ipilimumab-progressing patients, compared with standard chemotherapy (dacarbazine, paclitaxel combined with carboplatin every three weeks) (28). Confirmed objective responses were reported in 31.7% (95%CI 23.5 to 40.8) in the nivolumab group versus 10.6% (95%CI 3.5 to 23.1) in the chemotherapy arm. However overall survival did not differ between arms, being 15.74 (12.88 to 19.88) in the nivolumab group and 14.39 (11.66 to 18.17) in the investigator's choice group (HR 0.95, 95%CI 0.73 to 1.24) (29). CheckMate 066 tested nivolumab first-line versus dacarbazine, showing a gain in OS of 73% vs 42% at 1 year (30, 31). Response rates also favoured nivolumab, 40% vs 14%. Three-year OS survival rates were 51.2% (95%CI 44.1% to 57.9%) and 21.6% (95%CI 16.1% to 27.6%), respectively. The median OS was 37.5 months (95%CI 25.5 months to not reached) in the nivolumab group and 11.2 months (95%CI 9.6 to 13.0 months) in the dacarbazine group (HR 0.46, 95%CI 0.36 to 0.59), with a net benefit of OS of +26.3 months. CheckMate 067 tested the combination treatment of the two ICIs nivolumab and ipilimumab against nivolumab monotherapy and ipilimumab alone in a 1:1:1 ratio (32, 33). Median PFS was 11.5 months (95%CI 8.9 to 16.7) with nivolumab plus ipilimumab, compared with 2.9 months (95%CI 2.8 to 3.4) with ipilimumab (HR 0.42; 99.5% CI, 0.31 to 0.57) and 6.9 months (95%CI 4.3 to 9.5) with nivolumab (HR for the comparison with ipilimumab, 0.57, 99.5%CI 0.43 to 0.76, p<0.001). A subgroup analysis according to PD-L1 expression was performed. Patients with tumours positive for PD-L1, achieved a median PFS of 14.0 months in the nivolumab-plus-ipilimumab group and in the nivolumab group, but in patients with PD-L1–negative tumours, PFS was longer with the combination therapy than with nivolumab alone (11.2 months (95%CI 8.0 to not reached) vs 5.3 months (95%CI 2.8 to 7.1)). The four-year follow-up updated results confirmed the earlier findings: median OS was not reached (95%CI 38.2 to not reached) in the nivolumab plus ipilimumab group, 36.9 months (95%CI 28.3 to not reached) in the nivolumab group, and 19.9 months (95%CI 16.9 to 24.6) in the ipilimumab group. The results of sub-group analyses suggested that the greatest benefit with the combination of nivolumab and ipilimumab versus nivolumab alone may occur in the context of negative PD-L1 tumour expression. In the subgroup of patients with PD-L1–positive tumours, both nivolumab alone and nivolumab plus ipilimumab resulted in a similar prolongation of PFS compared to ipilimumab alone. This finding suggested the role of immunotherapy as monotherapy in "inflamed tumours", showing high expression of PD-L1 and a role of combination therapy for "non-inflamed" tumours, for which the combination ICI could derive a major benefit, acting synergistically on different steps of immune activation. The clinical benefit of nivolumab for first-line treatment of metastatic melanoma measured with the ESMO-MCBS v1.1 was scored at 4/5 (12). Early stage (resected) melanoma The discussion around the role of immunotherapy in the adjuvant setting of melanoma is ongoing, with data of OS expected to confirm the optimal strategy of care, particularly between the ipilimumab and the PD-1 blockers, including the safety profile. Pembrolizumab Pembrolizumab was assessed as an adjuvant agent in the Phase III Keynote 054 trial, for patients with stage III resected melanoma. Patients were randomized to receive pembrolizumab 200 mg every three weeks for 18 doses or placebo (n=1019) (34). Pembrolizumab showed a superior relapse-free survival rate, from 61% to 75.4% at 12 months (HR 0.57, 95%CI 0.43 to 0.74); the data were consisted across the PD-L1 pre-specified sub-groups. Nivolumab The CheckMate-238 trial compared high-dose ipilimumab versus nivolumab 3 mg/kg every two weeks up to 12 months (35). Patients with resected stage III and IV, with no evidence of disease (NED) derived major benefit from nivolumab: relapse-free survival at 12 months was 70.5% and 60.8%, respectively (HR 0.65, 95%CI 0.51 to 0.83). At 24-months follow-up, nivolumab was shown to be superior with +13% of relapse-free survival (35, 36). The benefit was consistent across the sub-groups of PD-L1 expression, in PD-L1 less than 5% or 5% and more.

Harms

NSCLC first-line Pembrolizumab In Keynote 024, 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, of which 53.3% vs 26.6% were Grade 3 (moderate-severe) to Grade 5 (toxic death) in the chemotherapy and pembrolizumab groups, respectively. The treatment discontinuation rate was slightly higher in the chemotherapy arm (10.7%) than the ICI arm (7.1%) due to these TRAEs (9). TRAEs for pembrolizumab were consistent with an immune-mediated process, 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, 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 pre-medication 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. In Keynote 042, despite a

longer duration of treatment exposure, Grades 3 to 5 TRAEs occurred much less often with pembrolizumab than with chemotherapy (17.8% vs 41.0%) (13). Grades 3 to 5 immune-related adverse events and infusion reactions occurred more frequently among patients treated with pembrolizumab than with chemotherapy (8.0% vs 1.5%). The respective rates of treatment discontinuation (9.0% vs 9.4%) and treatment-related deaths (2.0% vs 2.3%) were comparable between treatment arms. NSCLC second-line Pembrolizumab In the Keynote-010 trial the safety profile favoured pembrolizumab with less Grade 3–5 adverse events, 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 (14). There was no difference in the efficacy or safety of pembrolizumab at 2 or 10 mg/kg. Nivolumab In the CheckMate-017, treatment-related adverse events, including haematologic and non-haematologic 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% were Grade 3 or 4; in the docetaxel group, this occurred in 86% of the patients of which 55% were Grade 3 or 4 (16). The safety profile was consistent with the class side-effects, with no new signals of safety, namely the most frequently reported TRAEs with nivolumab were fatigue and asthenia and for docetaxel were neutropenia (33%; 10% febrile neutropenia), fatigue (33%), alopecia (22%), nausea (23%) and peripheral neuropathy (11%). Respectively 3% and 10% of patients discontinued the treatment for an adverse event in the ICI and CT arm. In the CheckMate-057, the safety profile and pattern of adverse events in non-squamous NSCLC patients were consistent with the data from squamous population: treatment-related adverse events were observed in 69%/10%/5% in nivolumab arm and 88%/54%/15% in docetaxel arm for any Grade/Grade 3-4/ discontinuation rate, respectively (18). Atezolizumab In the Phase III OAK trial, tolerability was better with atezolizumab, with 15% of 609 patients treated with atezolizumab experiencing a Grade 3–4 treatmentrelated toxicity compared with 43% of 578 patients treated with docetaxel (21). Fatigue (87 patients (14%)), nausea (53 patients (9%)), decreased appetite (52 patients (9%)), and asthenia (51 patients (8%)) were the most common atezolizumab-related adverse events of any grade. Metastatic melanoma Pembrolizumab Safety analysis showed a higher incidence of Grade 3–4 TRAEs in patients receiving chemotherapy (26%) vs pembrolizumab (11% in the 2mg/kg group, 14% in the 10 mg/kg group) (24). The most common serious TRAEs observed in the combined pembrolizumab treatment groups were diarrhoea and pneumonitis. There were no treatment-related deaths. Treatment interruption as a result of TRAEs was needed in 15 (8%) of 178 patients treated with pembrolizumab 2 mg/kg, 15 (8%) of 179 patients treated with pembrolizumab 10 mg/kg, and 30 (18%) of 171 patients treated with chemotherapy. TRAEs led to permanent treatment discontinuation in five (3%) patients given pembrolizumab 2 mg/kg, 12 (7%) given pembrolizumab 10 mg/kg, and 10 (6%) patients given chemotherapy. In the Keynote 006 trial, around two thirds of the study population experienced a TRAE; however, Grade 3 to 5 adverse events that were attributed to a study drug by investigators occurred in 13.3% of patients receiving pembrolizumab every two weeks, 10.1%, every three weeks and 19.9% of patients receiving ipilimumab, respectively, with a safety profile favourable of the PD-1 blocker over CTLA-4 inhibitor (26). The rate of permanent discontinuation of a study drug because of TRAEs was lower in each pembrolizumab group than in the ipilimumab group (4.0%, 6.9%, and 9.4%, respectively). Nivolumab In the CheckMate 066 trial, treatment-related Grade 3/4 adverse events occurred in 15.0% (31 of 206) of nivolumab-treated patients and in 17.6% (36 of 205) of dacarbazine-treated patients (30, 31). In the CheckMate 238 trial, nivolumab showed a major tolerability and better safety profile with 14.4%/9.7% Grade 3 and 4 adverse events/treatmentrelated discontinuation, compared with 45.6%/42.6% in the ipilimumab arm (32, 33). Early stage (resected) melanoma No data were presented in the application regarding the safety of immune checkpoint inhibitors for melanoma in the early/resected stage setting.

Cost / cost effectiveness

NSCLC The application presented a cost-effectiveness analysis of first-line pembrolizumab in advanced non-oncogene driven NSCLC expressing high levels of PD-L1 (37). Data of safety and efficacy were derived from the Keynote 024 trial (13). The analysis was conducted from the perspective of a United States third-party public health care payer (updated to US$, year 2016 values). Pembrolizumab would be expected to result in an incremental cost of US$ 98 281 per quality adjusted life year (QALY) gained or an incremental cost of US$ 78 873 per life year (LY) gained. Including cost of PD-L1 testing had a very small impact on the model results. With a five-year time horizon, the ICER was US$ 99 998/LY and US$ 122 024/QALY; with a 10-year time horizon, the ICER was US$ 83 065 and US$ 103 101/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. In the second-line setting, a cost-effectiveness analysis was presented for pembrolizumab versus docetaxel in the enriched population with PDL1> 50%. Base case results for PD-L1 positive (TPS ≥50%) patients treated with pembrolizumab showed a mean survival of 2.25 years (38). 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 US$ 168 619/QALY, which is costeffective in the United States using a threshold of three times GDP per capita. Melanoma The cost-effectiveness of nivolumab for the treatment of advanced melanoma patients has been investigated in the United Kingdom. A Markov state-transition model was developed to estimate the lifetime costs and benefits of nivolumab versus ipilimumab and dacarbazine for BRAF mutation-negative patients and versus ipilimumab, dabrafenib, and vemurafenib for BRAF mutationpositive patients (39). Nivolumab was the most cost-effective treatment option in BRAF mutation-negative and mutation-positive patients, with incremental cost-effectiveness ratios of £ 24 483 and £ 17 362 per QALY, respectively. A similar analysis was performed for pembrolizumab in advanced melanoma in Portugal (40). A cost-effectiveness model was developed to analyse the costs and consequences of treatment with pembrolizumab compared to treatment with ipilimumab in patients with advanced melanoma not previously treated with ipilimumab. Pembrolizumab increased life expectancy in 1.57 undiscounted life-years (LYs) and was associated with an increase in costs versus that of ipilimumab. The estimated incremental cost-effectiveness ratio was € 47 221 per QALY and € 42 956 per LY. The authors concluded that considering the usually accepted thresholds in oncology, pembrolizumab is a cost-effective alternative for treating patients with advanced melanoma in Portugal.

WHO guidelines

None available.

Availability

Atezolizumab (trade name Tecentriq, Genetech Inc.) is available as a 60 mg/mL injection solution for intravenous use as 840 mg/14 mL and 1,200 mg/20 mL single-dose vials. Nivolumab (trade name Opdivo, Bristol-Myers Squibb) is available as a 10 mg/mL injection solution for intravenous use as 40 mg/4 mL, 100 mg/10 mL and 240 mg/24 mL single-dose vials. Pembrolizumab (trade name Keytruda, Merck Sharp & Dohme) is available as 50 mg lyophyilized powder for intravenous injection and as a 25 mg/ mL injection solution for intravenous use as 100 mg/4mL single-dose vial.

Other considerations

As a result of the Keynote-024 trial, pembrolizumab was approved by the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) as first-line therapy for patients with NSCLC with high PD-L1 expression (PD-L1≥50%) as assessed by immunohistochemistry. 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 (20–22). The PD-L1 IHC 22C3 pharmDx assay is the companion diagnostic of pembrolizumab first-line 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 as a reliable specimen to assess the PD-L1 status, reducing the need of more invasive procedures and increasing the likelihood to have an informative specimen in term of prediction to treatment response with few cytology materials. Pembrolizumab as monotherapy is indicated in the first-line 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, and in association with chemotherapy for the first-line treatment of NSCLC, regardless of PD-L1 status. Moreover, pembrolizumab is indicated for the first-line treatment of metastatic melanoma, with no biomarker for patients’ selection. Patients are treated with pembrolizumab until disease progression or unacceptable toxicity. Comments on the application were received from the WHO Department of Management of NCDs, Disability, Violence and Injury Prevention. The technical unit advised that it not support inclusion of these medicines on the EML at this time, though noting with great interest the emerging data on long-term outcomes in this clinically relevant class of medicines.

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