Axitinib

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 > 8.2.2. Targeted therapies

ATC codes: L01EK01

Indication	Renal cell carcinoma of kidney, except renal pelvis ICD11 code: 2C90.0
INN	Axitinib
Medicine type	Chemical agent
List type	Complementary
Formulations	**Oral > Solid > tablet:** 1 mg ; 3 mg ; 5 mg
EML status history	Application rejected in 2025 (TRS 1064)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Main patents have expired but secondary patents might remain active in some jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Tags	Cancer
Wikipedia	Axitinib
DrugBank	Axitinib

Expert Committee recommendation

The Expert Committee recognized that cancer is a growing societal, public health and economic problem globally, and it is responsible for nearly one in three premature deaths from noncommunicable disease. The proportion of patients with advanced stage at first presentation is still substantial. Solid tumours that are amenable to effective therapy using PD-1/PD-L1 immune checkpoint inhibitors are a major cause of the rising burdens with respect to lives lost. The Committee recalled previous applications for immune checkpoint inhibitors. In 2019 nivolumab and pembrolizumab were recommended for listing for treatment of metastatic melanoma, a relatively rare cancer for which these medicines are extremely effective. In 2021 and 2023, applications for immune checkpoint inhibitors for treatment of metastatic NSCLC were not recommended, despite recognition of their relevant efficacy in prolonging life, due to their high costs. The Committee noted the rapid pace of innovation in immuno-oncology and emphasized the importance of reducing inequities in cancer care by increasing access to immune checkpoint inhibitors, adopting multiple strategies. In consideration of the application, the Expert Committee: • appreciated the approach taken by the WHO Collaborating Centre on Evidence Synthesis and Evaluation of Novel Cancer Therapies at the University of Cologne, Germany to identify the PD-1/PD-L1 immune checkpoint inhibitor–indication pairings proposed for EML listing from among the many such medicines that are approved and

available, and considered that the approach taken was up-to-date, comprehensive, systematic, transparent and evidence based and provided a solid basis for its decision-making; • noted that all proposed pairings were approved by the European Medicines Agency for first-line treatment of adults for the therapeutic indications for which they are proposed, had evidence from randomized trials and received a score of four or higher on the European Society of Medical Oncology's Magnitude of Clinical Benefit Scale in the non-curative setting; • applied the EML principle for cancer medicines to demonstrate at least 4–6 months overall survival gain in randomized controlled trials; and • appreciated and took into consideration the review of the application undertaken by the EML Cancer Experts group and the Evidence to Decision frameworks that followed the GRADE approach prepared by the Secretariat. The Committee favoured pairings where the evidence strongly supported a large benefit-to-risk ratio. The Committee considered monotherapy more positively than combination therapy for indications where both are approved and a trade-off between additional efficacy, toxicity and cost would typically occur. The Expert Committee recommended the inclusion of: • pembrolizumab, atezolizumab and cemiplimab as first-line monotherapy of metastatic non-small cell lung cancer with high PD-L1 expression (≥ 50%). Listing is recommended for pembrolizumab with a square box as the class representative, and atezolizumab and cemiplimab as specified therapeutic alternatives; • pembrolizumab as first-line monotherapy for deficient mismatch repair/microsatellite instability-high metastatic colorectal cancer; • pembrolizumab, in combination with platinum-based chemotherapy, as first-line treatment of metastatic cervical cancer with PD-L1 expression ≥ 1%. The Committee considered that these recommendations for inclusion provide the best chance of minimizing financial harm and concentrating expenditure into the areas with the most favourable incremental gain in benefit-to-risk ratio. The Committee noted that the use of immune checkpoint inhibitors in adults with solid tumours that have predictive biomarkers (e.g. high PD-L1 expression for non-small cell lung cancer) rather than all patients is the highest priority, to enable greater access in settings where budgetary constraints may require prioritization of scenarios that offer the greatest clinical value. With the recommendation to list pembrolizumab for the above-mentioned indications, the Committee recommended changing the current square box listing of nivolumab as the class representative and pembrolizumab as the specified therapeutic alternative for metastatic melanoma, to make pembrolizumab the class representative with nivolumab as the specified therapeutic alternative. This is intended to signal to countries the possibility of aggregating procurement of a single molecule, pembrolizumab, for multiple cancer indications, which can influence price negotiations with manufacturers. Limiting procurement fragmentation by focusing on a select few immune checkpoint inhibitors is likely to facilitate central purchasing through competitive tendering and better competition from pembrolizumab biosimilars, thereby increasing access. In addition to its recommendations on which immune checkpoint inhibitors to prioritize for inclusion on the EML, the Committee also recognized the value of strategies to improve access, particularly in resource-constrained settings, as presented in the report from the EML cancer experts consultation meeting, and recommended their use. The Committee noted that these strategies were based on evaluation of available evidence and pragmatic considerations. The Committee considered the strategies to improve access to care in two components: clinical strategies and health-system strategies. The Committee acknowledged that, while clinical strategies (over which doctors and patients have greater control) and health-system strategies (requiring government-led policy legislations and reforms) should complement each other, clinical strategies can be implemented immediately and can rapidly benefit access. Clinical strategies – doctors and patients The Committee acknowledged the importance of patients being empowered to make an informed and consensual decision about their treatment, including through information on benefits, harms, accessibility and feasibility of care. This might require comparing alternatives that may differ from each other in one or more of the aforementioned factors. Strategies that can be considered to improve access include: dose optimization according to patient weight (weight-based dosing); rounding down doses to the closest vial size and strength (dose banding); or hybrid dosing regimens that combine the two; and if relevant, vial sharing. Additionally, longer intervals between treatment administration or shorter durations of treatment can also be considered. The Committee also noted that ongoing studies are investigating outcomes with ultra-low-dose immunotherapy. If the results are favourable, ultra-low-dose immunotherapy could be a viable strategy to further improve access. Health-system strategies – policy-makers To enable better value procurement through tendering and competition leading to increased access for individuals and health systems, the Committee recommended that national policies take advantage of similar clinical performance in different immune checkpoint inhibitors, regardless of their biological target (i.e. PD-1 or PD-L1). The Committee opted to

recommend four immune checkpoint inhibitors for non-small cell lung cancer using the square box listing, indicating interchangeability at the health-system level for this indication. The recommended medicines have different pharmacological properties but are considered therapeutic alternatives. Where no relevant difference exists in efficacy and safety data, the preferred medicine at the country level should be the one that is generally available at the lowest price. At the country level, the interpretation of the square box should be extensive (i.e. a class effect), potentially covering other equally effective and safe immune checkpoint inhibitors of assured quality where these are offered at an advantageous price. The Committee stressed the importance of effective strategies to encourage rapid entry of biosimilars of immune checkpoint inhibitors into markets. With pembrolizumab listed on the EML for multiple cancers, efforts should be prioritized on accelerating approval and procurement of pembrolizumab biosimilars over those of the other listed molecules. Ensuring a competitive market, with ideally more than four or five alternative suppliers, would foster market maturity, reduce prices, and strengthen the sustainability of access. This strategy is fully aligned with WHO's broader goal of encouraging generic and biosimilar competition as a central pathway to achieving equitable access to high-value cancer treatments. The Committee recognized the need for companion in-vitro diagnostic tests to identify patients eligible for treatment with the recommended immune checkpoint inhibitors. It noted that access to diagnostic capacity is limited in less-resourced settings and may be a barrier to appropriate and optimal use of these medicines. However, the Committee highlighted that this scenario was more variable in middle-income countries, where testing for molecular alterations is more readily available and the price associated with tests is a small fraction of the price associated with treatment. The Committee recognized that the requirement for companion diagnostics adds additional cost but offers a pathway to limit inappropriate use of immune checkpoint inhibitors (i.e. outside of recommended indications) and serves to prevent the waste of resources with non-essential or lower-value use. The Committee considered that countries could apply their own affordability criteria in determining which (if any) of the recommended immune checkpoint inhibitors could be reasonably incorporated into national EMLs and reimbursement schemes. In addition, the Committee considered that countries could apply their own feasibility criteria in assessing health-system readiness for implementing immune checkpoint inhibitors, in terms of diagnostic infrastructure, health-care worker training in immuno-oncology, resources for the management of immune-mediated side-effects and monitoring capabilities, to ensure their safe and effective use. The Committee recognized that the implementation of recommendations concerning immune checkpoint inhibitors will progress at different speeds, largely reflecting the capacity of individual healthcare systems. In low-income countries, limited resources, infrastructure challenges, and demographic factors such as a predominantly young population may significantly delay the adoption of these medicines. By contrast, upper- and lower-middle-income countries are expected to introduce them more rapidly. The Expert Committee did not recommend listing for the following immune checkpoint inhibitors for treatment of the specified conditions: • cemiplimab, durvalumab plus tremelimumab, nivolumab plus ipilimumab, or pembrolizumab – each in combination with chemotherapy – for the treatment of oncogenic-driver wild-type metastatic non-small cell lung cancer regardless of PD-L1 expression; • tislelizumab in combination with chemotherapy for oncogenic-driver wild-type metastatic non-small cell lung cancer with ≥ 50% PD-L1 expression; • nivolumab plus ipilimumab for the treatment of dMMR/MSI-H phenotype metastatic colorectal cancer or metastatic melanoma; • dostarlimab in combination with chemotherapy for dMMR/MSI-H phenotype metastatic endometrial cancer; • pembrolizumab or nivolumab, in combination with chemotherapy, for first-line treatment of metastatic ERBB2-negative gastric or gastro-oesophageal junction adenocarcinoma with ≥ 1% or ≥ 5% PD-L1 expression, respectively; • durvalumab in combination with chemotherapy for first-line treatment of biliary tract cancer regardless of PD-L1 expression; • durvalumab monotherapy, durvalumab plus tremelimumab, or atezolizumab plus bevacizumab for first-line treatment for metastatic hepatocellular carcinoma regardless of PD-L1 expression; • pembrolizumab in combination with chemotherapy for first-line treatment of metastatic head and neck squamous cell carcinoma; • pembrolizumab, nivolumab, or nivolumab plus ipilimumab, each in combination with chemotherapy, for first-line treatment of metastatic oesophageal squamous cell cancer; • nivolumab plus ipilimumab, pembrolizumab plus axitinib, or pembrolizumab plus lenvatinib for the first-line treatment of metastatic renal cell carcinoma regardless of PD-L1 expression; • pembrolizumab in combination with chemotherapy for first-line treatment of triple-negative breast cancer with PD-L1 expression CPS ≥ 10. The reasons for not to recommending inclusion of these pairings included

prioritization of monotherapy over combination therapy, magnitude of overall survival gains of fewer than 4–6 months, limited or absence of mature overall survival data, unfavourable benefit-to-risk profiles, uncertainty about optimal immune checkpoint inhibitor and tyrosine kinase inhibitor positioning (i.e. in sequence or in combination) and uncertainty about optimal use across different patient cohorts which may vary with the immunogenicity of tumour types.

Background

Applications for the inclusion of PD-1/PD-L1 immune checkpoint inhibitors on the EML for the treatment of non-small cell lung cancer were reviewed by the Expert Committee in 2019, 2021 and 2023. On each occasion, inclusion was not recommended. In 2019, the 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 non-small cell lung cancer 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 non-small cell lung cancer 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 effect 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 (2). 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 that may require specialized management in certain cases. 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 non-small cell lung cancer in practice. However, their 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 (3). In 2023, the Committee acknowledged possible improvement in quality of life in addition to improved overall survival associated with the use of pembrolizumab compared with platinum-based chemotherapy in patients with advanced or metastatic non-small cell lung cancer expressing high levels of PD-L1. The Committee noted that longer follow-up data were available, with overall survival benefits maintained over a 5-year period. The Committee also noted that atezolizumab and cemiplimab showed similar benefits in prolonging median overall survival compared with platinum-based chemotherapy in the same patient population, although 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 (4). 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 class when compared with platinum-based chemotherapy. 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 dose and duration of treatment, with ongoing trials

investigating use of lower doses or for a shorter duration. 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 (4). 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 for a large proportion of the global population. The Committee also noted the need to select patients that could benefit from treatment 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 could lead to additional wasted resources, both public and private (4). The Committee recognized the risk at the country level of listing immune checkpoint inhibitors on the EML, 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 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 high prices of immune checkpoint inhibitors and PD-L1 testing, as well as the high prevalence of non-small cell lung cancer. The Committee recognized that the opportunity costs of providing immune checkpoint inhibitors at current prices for the treatment of patients with non-small cell lung cancer 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 the proportion of patients eligible for treatment would help foster the development of solutions that facilitate access, without bankrupting the health-care budget (4). 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 (2).

Public health relevance

Cancer is responsible for nearly one in three premature deaths from noncommunicable disease. It was the leading cause of death in 57 countries worldwide in 2019, and may surpass cardiovascular disease as the leading cause of death globally by the end of this century (5). According to GLOBOCAN, in 2022, about 20 million new cancer cases and almost 10 million cancer deaths were estimated to have occurred. In 2050, the number of new cases is likely to reach about 35 million, an increase of 77%. Since demographic transitions are an important driver of the cancer burden, the absolute increase in cancer cases is predicted to be greatest in countries with high and very high Human Development Indices (HDI), i.e. countries with higher incomes according to the World Bank Classification, and generally older populations. However, relative increases will be highest in medium and low HDI countries, with increases of nearly 100% and 142%, respectively (6). This more rapid increase in cancer cases, in conjunction with the disproportionally high cancer death burden in low- and middle-income countries accounting for 70.6% of all cancer deaths (7–8), projects a substantial worsening of the already existing global inequality in cancer care as a consequence. Reasons for the high mortality to incidence ratio (70% versus 60%) in low- and middle-income countries include late-stage presentation, barriers to health-care access, and low availability and prohibitively high prices of cancer medicines (8–10). However, data from high-income countries also show that a substantial proportion of cancers are at an advanced stage at first presentation (11). Consequently, a holistic approach is necessary to reduce the global cancer burden effectively, including improved availability, access and affordability of disease-stage appropriate medical oncology treatments and palliative care measures.

Benefits

Based on a prioritized selection of eight immune checkpoint inhibitors and 12 cancer types, the applicants conducted multiple systematic reviews of randomized controlled trials comparing treatments based on immune checkpoint inhibitors with the established standard of care in the palliative first-line setting. Patient-relevant

outcomes of interest were overall survival, progression-free survival, quality of life and higher grade (≥ 3) adverse events. Biliary tract carcinoma irrespective of PD-L1 expression One randomized controlled trial of durvalumab plus chemotherapy versus chemotherapy alone was identified that evaluated treatment of unresectable advanced or metastatic biliary tract carcinoma (TOPAZ-1 (12, 13)). Of 685 randomized participants, 341 received durvalumab plus chemotherapy and 344 received chemotherapy. Durvalumab 1500 mg was administered intravenously on day 1, in combination with gemcitabine 1000 mg/m2 and cisplatin at 25 mg/m2 body-surface area on days 1 and 8, of eight 21-day cycles. After a median follow-up of 22.9 months, there was moderate-certainty evidence that durvalumab-containing regimens likely increase overall survival (hazard ratio (HR) for death 0.76, 95% confidence interval (CI) 0.64 to 0.91; one randomized controlled trial, 685 participants). In absolute terms, 56 versus 47 people per 100, respectively, on durvalumab plus chemotherapy or chemotherapy alone were alive at 1 year, 34 versus 24 people per 100 were alive at 1.5 years, and median overall survival gain was 3.6 months. After a median follow-up of 16.4 months, there was moderate-certainty evidence that durvalumab-containing regimens likely increased progression-free survival (HR for disease progression or death 0.75, 95% CI 0.63 to 0.89; one randomized controlled trial, 685 participants). In absolute terms, 12 versus 6 people per 100 were without disease progression at 1 year. There was moderate-certainty evidence that durvalumab-containing regimens likely have little to no effect on health-related quality of life (mean difference (MD) from baseline 0.88, 95% CI –1.80 to 3.65; one randomized controlled trial, 646 participants). Cervical cancer with PD-L1 expression ≥ 1% One randomized controlled trial of pembrolizumab plus platinum-based chemotherapy versus platinum-based chemotherapy alone was identified that evaluated treatment of metastatic cervical cancer (Keynote-826 (14–16)). Of 617 participants randomized, 548 had PD-L1 expression of CPS ≥ 1%. After a median follow-up of 39.1 months, there was high-certainty evidence that pembrolizumab-containing regimens increase overall survival (HR for death 0.60, 95% CI 0.49 to 0.74; one randomized controlled trial, 548 participants). In absolute terms, 57 versus 39 people per 100, respectively, on pembrolizumab plus platinum-based chemotherapy or platinum-based chemotherapy alone were alive at 2 years, 46 versus 27 people per 100 were alive at 3 years and median overall survival gain was 11.0 months. There was high-certainty evidence that pembrolizumab-containing regimens increase progression-free survival (HR for disease progression or death 0.60, 95% CI 0.48 to 0.75; one randomized controlled trial, 548 participants). In absolute terms, 52 versus 34 people per 100 were without disease progression at 1 year. There was high-certainty evidence that pembrolizumab-containing regimens have little to no effect on health-related quality of life (MD from baseline 1.30, 95% CI –3.02 to 5.62; one randomized controlled trial, 519 participants). Deficient mismatch repair/microsatellite instability-high colorectal cancer One randomized controlled trial of pembrolizumab monotherapy versus fluoropyrimidine-based chemotherapy was identified that evaluated treatment of deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) metastatic colorectal cancer irrespective of PD-L1 expression (Keynote-117 (17–19)). Of 307 randomized participants, 153 received pembrolizumab monotherapy and 154 received the comparator treatment (modified FOLFOX6, modified FOLFOX6 plus bevacizumab, modified FOLFOX6 plus cetuximab, FOLFIRI, FOLFIRI plus bevacizumab, or FOLFIRI plus cetuximab). After a median follow-up of 44.5 months, there was low-certainty evidence that pembrolizumab may increase overall survival (HR for death 0.74, 95% CI 0.53 to 1.03; one randomized controlled trial, 307 participants). In absolute terms, 60 versus 50 people per 100, respectively, on pembrolizumab monotherapy or fluoropyrimidine-based chemotherapy were alive at 3 years, and median overall survival gain was 12.9 months. There was low-certainty evidence that pembrolizumab may increase progression-free survival (HR for disease progression or death 0.59, 95% CI 0.45 to 0.79; one randomized controlled trial, 307 participants). In absolute terms, 57 versus 39 people per 100 were without disease progression at 3 years. There was low-certainty evidence that pembrolizumab may have little to no effect on health-related quality of life (MD from baseline 8.96, 95% CI 4.24 to 13.69; one randomized controlled trial, 292 participants). dMMR/MSI-H endometrial cancer One randomized controlled trial of dostarlimab plus carboplatin and paclitaxel versus carboplatin and paclitaxel was identified that evaluated treatment of dMMR/MSI-H primary advanced or recurrent endometrial cancer (RUBY (20–23)). Of 494 participants randomized, 118 had dMMR-MSI-H tumours. After a median follow-up of 36.6 months, there was low-certainty evidence that dostarlimab-containing regimens may result in a large increase in overall survival (HR for death 0.32, 95% CI 0.17 to 0.63; one randomized controlled trial, 118 participants). In absolute terms, 84 versus 57 people per 100, respectively, in the dostarlimab arm or carboplatin arm were alive at 2 years and 78 versus 46 people per 100 were alive at 3 years. Median overall

survival was not reached in the dostarlimab arm and was 31.4 months in the chemotherapy arm. An estimated median overall survival gain of 66.7 months was calculated by the applicants, using the HR and baseline risk estimate from the comparator arm. There was moderate-certainty evidence that dostarlimab-containing regimens likely increase progression-free survival (HR for disease progression or death 0.28, 95% CI 0.16 to 0.50; one randomized controlled trial, 118 participants). In absolute terms, 67 versus 24 people per 100 were without disease progression at 1 year. There was low-certainty evidence that dostarlimab-containing regimens may increase health-related quality of life (MD from baseline 9.38, 95% CI 5.45 to 13.31; one randomized controlled trial, 115 participants). Human epidermal growth factor receptor 2-negative gastric and gastro-oesophageal junction adenocarcinoma with PD-L1 expression CPS ≥ 1/CPS ≥ 5 Two randomized controlled trials of pembrolizumab plus chemotherapy versus chemotherapy alone (Keynote-859 (24, 25) and Keynote-062 (26–28)) and one randomized controlled trial of nivolumab plus chemotherapy versus chemotherapy alone (CheckMate 649 (29–31)) were identified that evaluated treatment of human epidermal growth factor receptor 2 (HER2)-negative gastric or gastro-oesophageal junction adenocarcinoma in patients with PD-L1 expression of CPS ≥ 1 (pembrolizumab) or CPS ≥ 5 (nivolumab). After a median follow-up of 30.2 months, there was low-certainty evidence that pembrolizumab-containing regimens may increase overall survival compared with chemotherapy (HR for death 0.78, 95% CI 0.68 to 0.89; two randomized controlled trials, 1742 participants). In absolute terms, 26 versus 18 people per 100, respectively, on pembrolizumab plus chemotherapy or chemotherapy alone were alive at 2 years, and median overall survival gain was 3.2 months. There was low-certainty evidence that pembrolizumab-containing regimens may increase progression-free survival (HR for disease progression or death 0.77, 95% CI 0.66 to 0.89; two randomized controlled trials, 1874 participants). In absolute terms, 14 versus 8 people per 100 were without disease progression at 2 years. There was low-certainty evidence that pembrolizumab-containing regimens may have little to no effect on health-related quality of life (MD from baseline 1.25, 95% CI –1.07 to 3.58; one randomized controlled trial, 1542 participants). After a median follow-up of 47.4 months, there was moderate-certainty evidence that nivolumab-containing regimens likely increase overall survival compared with chemotherapy (HR for death 0.70, 95% CI 0.61 to 0.81; one randomized controlled trial, 955 participants). In absolute terms, 31 versus 19 people per 100, respectively, on nivolumab-containing regimens or chemotherapy were alive at 2 years and median overall survival gain was 4.8 months. There was low-certainty evidence that nivolumab-containing regimens may increase progression-free survival (HR for disease progression or death 0.70, 95% CI 0.60 to 0.81; one randomized controlled trial, 955 participants). In absolute terms, 21 versus 11 people per 100 were without disease progression at 2 years. There was moderate-certainty evidence that nivolumab-containing regimens likely have little to no effect on health-related quality of life (MD from baseline 6.42, 95% CI 0.67 to 12.17; one randomized controlled trial, 797 participants). Head and neck squamous cell carcinoma with PD-L1 expression combined positive score ≥ 1 One randomized controlled trial of pembrolizumab as monotherapy or in combination with platinum-based chemotherapy versus platinum-based chemotherapy and cetuximab was identified that evaluated treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (Keynote-048 (32–35)). Of 882 randomized participants, 301 received pembrolizumab monotherapy, 281 received pembrolizumab-based chemotherapy and 300 received the comparator treatment. PD-L1 expression combined positive score (CPS) ≥ 1 was equally distributed in intervention and comparator arms and was found in about 85% of participants. Data extracted compared pembrolizumab-based chemotherapy versus cetuximab-based chemotherapy only, as this was the only combination that satisfied the inclusion criteria applied by the applicants. After a median follow up of 45 months, there was moderate-certainty evidence that pembrolizumab-containing regimens likely increase overall survival (HR for death 0.64, 95% CI 0.53 to 0.78; one randomized controlled trial, 477 participants). In absolute terms, 32 versus 17 people per 100, respectively, on pembrolizumab-based chemotherapy or cetuximab-based chemotherapy were alive at 2 years, 21 versus 9 people per 100 were alive at 3 years and median overall survival gain was 6.0 months. After a median follow-up of 11.9 months, there was low-certainty evidence that pembrolizumab-containing regimens may have little to no effect on progression-free survival (HR for disease progression or death 0.82, 95% CI 0.67 to 1.00; one randomized controlled trial, 477 participants). In absolute terms, 16 versus 11 people per 100 were without disease progression at year. There was moderate-certainty evidence that pembrolizumab-containing regimens likely result in little to no difference in health-related quality of life (MD from baseline 0.40, 95% CI -3.80 to 4.60;

one randomized controlled trial, 527 participants). Hepatocellular carcinoma irrespective of PD-L1 expression Two randomized controlled trials of atezolizumab plus bevacizumab versus sorafenib (IMbrave 150 (36–38)), and durvalumab as monotherapy or in combination with chemotherapy versus sorafenib (HIMALAYA (39–41)) were identified that evaluated treatment of hepatocellular carcinoma. For the comparison of atezolizumab-containing regimens versus sorafenib, after a median follow-up of 15.6 months, there was moderate-certainty evidence that atezolizumab-containing regimens likely increase overall survival (HR for death 0.66, 95% CI 0.52 to 0.85; one randomized controlled trial, 501 participants). In absolute terms, 55 versus 40 people per 100, respectively, on atezolizumab-containing regimens or sorafenib were alive at 1.5 years and median overall survival gain was 6.9 months. There was moderate-certainty evidence that atezolizumab-containing regimens likely increase progression-free survival (HR for disease progression or death 0.65, 95% CI 0.53 to 0.81; one randomized controlled trial, 501 participants). In absolute terms, 36 versus 21 people per 100 were without disease progression at 1 year. There was moderate-certainty evidence that atezolizumab-containing regimens likely have little to no effect on health-related quality of life (MD from baseline 2.54, 95% CI –1.31 to 6.39; one randomized controlled trial, 481 participants). For the comparison of durvalumab monotherapy versus sorafenib, after a median follow-up of 47.9 months, there was low-certainty evidence that durvalumab may increase overall survival (HR for death 0.86, 95% CI 0.74 to 1.01; one randomized controlled trial, 778 participants). In absolute terms, 38 versus 33 people per 100, respectively, on durvalumab monotherapy or sorafenib were alive at 2 years, 20 versus 15 people per 100 were alive at 4 years and median overall survival gain was 2.3 months. After a median follow-up of 32.4 months, there was moderate-certainty evidence that durvalumab monotherapy likely results in little to no difference in progression-free survival (HR for disease progression or death 1.02, 95% CI 0.88 to 1.19; one randomized controlled trial, 778 participants). In absolute terms, 32 versus 33 people per 100 were without disease progression at 1 year. There was moderate-certainty evidence that durvalumab monotherapy likely has little to no effect on health-related quality of life (MD from baseline 4.30, 95% CI 0.41 to 8.19; one randomized controlled trial, 778 participants). For the comparison of durvalumab plus tremelimumab versus sorafenib, after a median follow-up of 48.2 months, there was moderate-certainty evidence that durvalumab plus tremelimumab likely increases overall survival (HR for death 0.78, 95% CI 0.67 to 0.92, one randomized controlled trial, 782 participants). In absolute terms, 42 versus 33 people per 100, respectively, on durvalumab plus tremelimumab or sorafenib were alive at 2 years, 23 versus 15 people per 100 were alive at 4 years and median overall survival gain was 3.9 months. After a median follow-up of 32.7 months, there was low-certainty evidence that durvalumab plus tremelimumab may increase progression-free survival (HR for disease progression or death 0.90, 95% CI 0.77 to 1.05; one randomized controlled trial, 782 participants). In absolute terms, 37 versus 33 people per 100 were without disease progression at 1 year. There was moderate-certainty evidence that durvalumab plus tremelimumab likely has little to no effect on health-related quality of life (MD from baseline –0.35, 95% CI –4.21 to 3.51; one randomized controlled trial, 782 participants). Malignant melanoma Five randomized controlled trials of ipilimumab plus nivolumab for the treatment of malignant melanoma were identified. Three randomized controlled trials included patients irrespective of PD-L1 expression and BRAF V600 mutation status (ABC (42, 43), CheckMate 067 (44, 45) and CheckMate 069 (46, 47)), and two randomized controlled trials included patients irrespective of PD-L1 mutation status and with BRAF V600-mutant disease (DREAMseq/EA6134 (48, 49) and SECOMBIT (50)). A total of 1537 participants were randomized: 639 to ipilimumab plus nivolumab and 898 to one of the control regimens. Among randomized participants, 346 receiving ipilimumab plus nivolumab and 422 receiving a control regimen had a BRAF V600 mutation. A vast majority of participants included in this review did not have brain metastases. Ipilimumab was administered at a dose of 3 mg/kg and nivolumab at a dose of 1 mg/kg on day 1 of four 3-week cycles. Subsequently, patients received nivolumab 3 mg/kg on day 1 of 2-week cycles. Treatment continued for: up to 2 years of nivolumab administration; until disease progression; until development of unacceptable toxicity; or on withdrawal of consent. Ipilimumab plus nivolumab was compared with: ipilimumab monotherapy 3 mg/kg on day 1 of four 3-week cycles (CheckMate 067 and CheckMate 069); nivolumab monotherapy 3 mg/kg on day 1 of 2-week cycles (ABC and CheckMate 067); BRAF/MEK inhibitor combination dabrafenib 150 mg twice daily and trametinib 2 mg once daily (DREAMseq); and BRAF/MEK inhibitor combination encorafenib 450 mg once daily and binimetinib 45 mg twice daily (SECOMBIT). For the comparison of ipilimumab plus nivolumab versus immune-checkpoint inhibitor monotherapy, after a median follow-up of 34.6 months, there was moderate-certainty evidence that ipilimumab plus nivolumab likely increases overall survival (HR for death

0.68, 95% CI 0.50 to 0.93; three randomized controlled trials, 1133 participants). In absolute terms, 64 versus 52 people per 100, respectively, on ipilimumab plus nivolumab or immune-checkpoint inhibitor monotherapy were alive at 2 years, 49 versus 35 people per 100 were alive at 5 years and median overall survival gain was 12.8 months. After a median follow-up of 35.7 months, there was low-certainty evidence that ipilimumab plus nivolumab may increase progression-free survival (HR for disease progression or death 0.50, 95% CI 0.31 to 0.82; two randomized controlled trials, 1087 participants). In absolute terms, 49 versus 24 people per 100 were without disease progression at 2 years. There was moderate-certainty evidence that ipilimumab plus nivolumab likely results in little to no difference in health-related quality of life (MD from baseline -1.08, 95% CI –3.44 to 1.28; one randomized controlled trial, 758 participants). For the comparison of ipilimumab plus nivolumab versus BRAF/MEK inhibitors for BRAF V600-mutant disease, after a median follow-up of 32.2 months, the evidence was very uncertain about the effect of ipilimumab plus nivolumab on overall survival (HR for death 0.73, 95% CI 0.42 to 1.27; one randomized controlled trial, 138 participants). In absolute terms, 73 versus 65 people per 100, respectively, on ipilimumab plus nivolumab or BRAF/MEK inhibitors were alive at 2 years and 64 versus 54 people per 100 were alive at 5 years. Median overall survival was not reached in either group. The evidence was very uncertain about the effect of ipilimumab plus nivolumab on progression-free survival. Pooled 2-year progression-free survival rates were 40.1% versus 23.9% (two randomized controlled trials, 403 participants). Health-related quality of life was not reported. Oncogenic driver wild-type non-small cell lung cancer with high PD-L1 expression (tumour proportion score ≥ 50%) Five randomized controlled trials of atezolizumab (IMpower 110 (51, 52) and IPSOS (53)), cemiplimab (EMPOWER-Lung1 (54–56)) and pembrolizumab (Keynote-024 (57–59) and, Keynote-042 (60, 61)) were identified that evaluated treatment, as monotherapy, of non-small cell lung cancer without oncogenic driver mutations (EGFR, ALK) and PD-L1 expression ≥ 50%. All studies were global, multicentre, unblinded phase III randomized controlled trials comparing immune-checkpoint inhibitor monotherapy with the established standard of care for non-small cell lung cancer, with the exception of IPSOS, which was conducted in a patient setting where no clearly established standard treatment exists (patients ineligible for platinum-based chemotherapy). Patients with squamous cell or non-squamous cell tumours that were negative for EGFR or ALK driver mutations were eligible for inclusion. After median follow-up of 60.7 months, there was moderate-certainty evidence that pembrolizumab monotherapy likely increases overall survival compared with platinum-based doublet chemotherapy (hazard ratio (HR) for death 0.66, 95% CI 0.57 to 0.76; two randomized controlled trials, 904 participants). In absolute terms, 45 versus 30 people per 100, respectively, on pembrolizumab monotherapy or platinum-based doublet chemotherapy were alive at 2years and 22 versus 10 people per 100 were alive at 5 years and median overall survival gain was 6.3 months. There was low-certainty evidence that pembrolizumab monotherapy may increase progression-free survival (HR for disease progression or death 0.66, 95% CI 0.39 to 1.12; two randomized controlled trials, 904 participants). In absolute terms, 35 versus 21 people per 100 were without disease progression at 1 year. There was low-certainty evidence that pembrolizumab monotherapy may increase health-related quality of life (MD from baseline 7.85, 95% CI 2.51 to 13.19; one randomized controlled trial, 297 participants). After median follow-up of 35.6 months, there was low-certainty evidence that atezolizumab monotherapy may increase overall survival compared with chemotherapy (HR for death 0.79, 95% CI 0.54 to 1.09; two randomized controlled trials, 280 participants). In absolute terms, 39 versus 30 people per 100, respectively, on atezolizumab monotherapy or chemotherapy were alive at 2 years and median overall survival gain was 3.7 months. There was low-certainty evidence that atezolizumab monotherapy may increase progression-free survival (HR for disease progression or death 0.63, 95% CI 0.48 to 0.84; two randomized controlled trials, 280 participants). In absolute terms, 34 versus 18 people per 100 were without disease progression at 1 year. Health-related quality of life for atezolizumab was not reported. After median follow-up of 35.0 months, there was moderate-certainty evidence that cemiplimab monotherapy likely increases overall survival compared with platinum-based doublet chemotherapy (HR for death 0.63, 95% CI 0.52 to 0.77; one randomized controlled trial, 712 participants). In absolute terms, 50 versus 34 people per 100, respectively on cemiplimab monotherapy or platinum-based doublet chemotherapy were alive at 2 years, 40 versus 23 people per 100 were alive at 3 years and median overall survival gain was 8.0 months. There was moderate-certainty evidence that cemiplimab monotherapy likely increases progression-free survival (HR for disease progression or death 0.56, 95% CI 0.47 to 0.67; one randomized controlled trial, 712 participants). In absolute terms, 24 versus 8 people per 100 were

without disease progression at 1 year. There was moderate-certainty evidence that cemiplimab monotherapy likely results in little to no difference in health-related quality of life (MD from baseline 5.03 (95% CI 2.11 to 7.96; one randomized controlled trial, 563 participants). Oncogenic driver wild-type non-small cell lung cancer irrespective of PD-L1 expression Eight randomized controlled trials of (i) pembrolizumab plus platinum-based chemotherapy (Keynote-021 (62, 63), Keynote-189 (64–66) and Keynote-407 (67–69)); (ii) cemiplimab plus platinum-based chemotherapy (EMPOWER-Lung3 (70–72)); (iii) ipilimumab plus nivolumab plus chemotherapy (CheckMate 9LA (73–75)); (iv) durvalumab plus tremelimumab plus chemotherapy (POSEIDON (76, 77)); and (v) tislelizumab plus platinum-based chemotherapy (RATIONALE-307 (78–80) and RATIONALE-304 (81–84)), each versus platinum-based doublet chemotherapy, were identified that evaluated treatment of non-small cell lung cancer without oncogenic driver mutations (EGFR, ALK) irrespective of PD-L1 expression. All studies were global multicentre phase III randomized controlled trials, except for Keynote-021, which was a phase I/II randomized controlled trial. Keynote-189, Keynote-407 and EMPOWER-Lung3 were double-blinded, comparing immune-checkpoint inhibitor-based regimens with an active chemotherapeutic backbone and placebo. Keynote-021, CheckMate 9LA, POSEIDON and CheckMate 9LA were unblinded. All studies followed the same basic structure of comparing the addition of an immune-checkpoint inhibitor or immune-checkpoint inhibitor-doublet to platinum-based chemotherapy with platinum-based chemotherapy alone. After a median follow-up of 59.8 months, there was moderate-certainty evidence that pembrolizumab-containing regimens likely increase overall survival compared with platinum-based doublet chemotherapy (HR for death 0.66, 95% CI 0.58 to 0.74; three randomized controlled trials, 1298 participants). In absolute terms, 48 versus 33 people per 100, respectively, on pembrolizumab-containing regimens or platinum-based doublet chemotherapy were alive at 2 years, 22 versus 10 people per 100 were alive at 5 years and median overall survival gain was 6.3 months. There was high-certainty evidence that pembrolizumab-containing regimens increase progression-free survival (HR for disease progression or death 0.55, 95% CI 0.48 to 0.64; three randomized controlled trials, 1298 participants). In absolute terms, 43 versus 21 people per 100 were without disease progression at 1 year. There was moderate-certainty evidence that pembrolizumab-containing regimens may result in little to no difference in health-related quality of life (MD from baseline 5.00, 95% CI 2.13 to 7.87; two one randomized controlled trials, 1156 participants). After a median follow-up of 28.4 months, there was moderate-certainty evidence that cemiplimab-containing regimens likely increase overall survival compared with platinum-based doublet chemotherapy (HR for death 0.65, 95% CI 0.51 to 0.82; one randomized controlled trial, 466 participants). In absolute terms, 43 versus 27 people per 100, respectively, on cemiplimab-containing regimens or platinum-based doublet chemotherapy were alive at 2 years and median overall survival gain was 6.9 months. There was high-certainty evidence that cemiplimab-containing regimens increase progression-free survival (HR for disease progression or death 0.55, 95% CI 0.44 to 0.68; one randomized controlled trial, 466 participants). In absolute terms, 37 versus 16 people per 100 were without disease progression at 1 year. There was high-certainty evidence that cemiplimab-containing regimens do not increase health-related quality of life (MD from baseline 0.61, 95% CI –2.23 to 3.45; one randomized controlled trial, 466 participants). After a median follow-up of 54.5 months, there was low-certainty evidence that ipilimumab plus nivolumab-containing regimens may increase overall survival compared with platinum-based doublet chemotherapy (HR for death 0.74, 95% CI 0.63 to 0.87; one randomized controlled trial, 719 participants). In absolute terms, 37 versus 26 people per 100, respectively, on ipilimumab plus nivolumab-containing regimens or platinum-based doublet chemotherapy were alive at 2 years, 20 versus 11 people per 100 were alive at 5 years and median overall survival gain was 3.9 months. There was moderate-certainty evidence that ipilimumab plus nivolumab-containing regimens likely increase progression-free survival (HR for disease progression or death 0.70, 95% CI 0.59 to 0.83; one randomized controlled trial, 719 participants). In absolute terms, 31 versus 19 people per 100 were without disease progression at 1 year. There was moderate-certainty evidence that ipilimumab plus nivolumab-containing regimens have little to no effect on health-related quality of life (MD from baseline 4.70, 95% CI –3.26 to 12.66; one randomized controlled trial, 646 participants). After a median follow-up of 63.4 months, there was low-certainty evidence that durvalumab plus tremelimumab-containing regimens may increase overall survival compared with platinum-based doublet chemotherapy (HR for death 0.77, 95% CI 0.65 to 0.92; one randomized controlled trial, 675 participants). In absolute terms, 31 versus 22 people per 100, respectively, on durvalumab plus tremelimumab-containing regimens or platinum-based doublet chemotherapy were alive at 2 years, 13 versus 7 people per 100 were alive at 5 years and median overall survival gain was 3.5 months. After a

median follow-up of 10.3 months, there was moderate-certainty evidence that durvalumab plus tremelimumab-containing regimens likely increase progression-free survival (HR for disease progression or death 0.72, 95% CI 0.60 to 0.86; one randomized controlled trial, 675 participants). In absolute terms, 23 versus 13 people per 100 were without disease progression at 1 year. Health-related quality of life was not reported. After a median follow-up of 16.4 months, there was low-certainty evidence that tislelizumab-containing regimens may increase overall survival compared with platinum-based doublet chemotherapy (HR for death 0.80, 95% CI 0.62 to 1.02; two randomized controlled trials, 694 participants). In absolute terms, 75 versus 69 people per 100, respectively, on tislelizumab-containing regimens or platinum-based doublet chemotherapy were alive at 1 year and median overall survival gain was 4.5 months. There was high-certainty evidence that tislelizumab-containing regimens increase progression-free survival (HR for disease progression or death 0.51, 95% CI 0.40 to 0.66; two randomized controlled trials, 694 participants). In absolute terms, 37 versus 14 people per 100 were without disease progression at 1 year. There was moderate-certainty evidence that tislelizumab-containing regimens likely result in little to no difference in health-related quality of life (MD from baseline 3.70, 95% CI –0.06 to 7.46; two randomized controlled trials, 687 participants). Oesophageal squamous cell carcinoma with PD-L1 expression CPS ≥ 1/CPS ≥ 10 One randomized controlled trial of pembrolizumab plus chemotherapy versus chemotherapy alone (Keynote-590 (85–87)) and one of nivolumab plus chemotherapy or ipilimumab plus nivolumab versus chemotherapy alone (CheckMate 648 (88, 89)) were identified that evaluated treatment of advanced oesophageal squamous cell carcinoma. The review included only the subgroup of participants in Keynote-590 with PD-L1 expression CPS ≥ 10, and the subgroup of participants in CheckMate 648 with PD-L1 expression on tumour cells (TC) ≥ 1%, in line with the prioritization framework. After a median follow-up of 22.6 months, there was low-certainty evidence that pembrolizumab plus chemotherapy may increase overall survival compared with platinum-based chemotherapy in patients with PD-L1 expression CPS ≥ 10 (HR for death 0.57, 95% CI 0.43 to 0.75; one randomized controlled trial, 286 participants). In absolute terms, 34 versus 15 people per 100, respectively, on pembrolizumab plus chemotherapy or platinum-based chemotherapy were alive at 2 years and median overall survival gain was 6.6 months. There was low-certainty evidence that pembrolizumab-containing regimens may increase progression-free survival (HR for disease progression or death 0.53, 95% CI 0.40 to 0.60; one randomized controlled trial, 286 participants). In absolute terms, 17 versus 4 people per 100 were without disease progression at 2 years. There was low-certainty evidence that pembrolizumab-containing regimens may have little to no effect on health-related quality of life (MD from baseline -1.95, 95% CI –7.72 to 3.82; one randomized controlled trial, 274 participants). After a median follow-up of 39.5 months, there was low-certainty evidence that nivolumab plus chemotherapy may increase overall survival compared with platinum-based chemotherapy in patients with PD-L1 expression TC ≥ 1% (HR for death 0.59, 95% CI 0.46 to 0.76; one randomized controlled trial, 315 participants). In absolute terms, 29 versus 12 people per 100, respectively, on nivolumab plus chemotherapy or platinum-based chemotherapy were alive at 2 years, 26 versus 10 people per 100 were alive at 3 years, and median overall survival gain was 6.3 months. There was moderate-certainty evidence that nivolumab plus chemotherapy likely increases progression-free survival (HR for disease progression or death 0.67, 95% CI 0.51 to 0.89; one randomized controlled trial, 315 participants). In absolute terms, 21 versus 10 people per 100 were without disease progression at 1 year. There was moderate-certainty evidence that nivolumab plus chemotherapy likely has little to no effect on health-related quality of life (MD from baseline 3.44, 95%–CI –0.03 to 6.91; one randomized controlled trial, 522 participants). After a median follow up of 39.7 months, there was low-certainty evidence that ipilimumab plus nivolumab may increase overall survival compared with platinum-based chemotherapy in patients with PD-L1 expression TC ≥ 1% (HR for death 0.62, 95% CI 0.48 to 0.80; one randomized controlled trial, 315 participants). In absolute terms, 27 versus 12 people per 100, respectively, on ipilimumab plus nivolumab or platinum-based chemotherapy were alive at 2 years, 24 versus 10 people per 100 were alive at 3 years and median overall survival gain was 5.6 months. There was low-certainty evidence that ipilimumab plus nivolumab may have little to no effect on progression-free survival (HR for disease progression or death 1.04, 95% CI 0.79 to 1.36; one randomized controlled trial, 315 participants). In absolute terms, 9 versus 10 people per 100 were without disease progression at 1 year. There was moderate-certainty evidence that ipilimumab plus nivolumab likely has little to no effect on health-related quality of life (MD from baseline 1.91, 95% CI -1.70 to 5.51; one randomized controlled trial, 529 participants). Renal cell carcinoma irrespective of PD-L1 expression Two

randomized controlled trials of ipilimumab plus nivolumab versus sunitinib (BOINIKK (90–92), CheckMate 214 (93–95)) and two randomized controlled trials of pembrolizumab plus axitinib or lenvatinib versus sunitinib (Keynote-426 (96–100), CLEAR (101–104)) were identified that evaluated treatment of renal cell carcinoma. For the comparison of ipilimumab plus nivolumab versus sunitinib, after a median follow-up of 92.6 months, there was low-certainty evidence that ipilimumab plus nivolumab may increase overall survival (HR for death 0.72, 95% CI 0.62 to 0.84; two randomized controlled trials, 1178 participants). In absolute terms, 69 versus 60 people per 100, respectively, on ipilimumab plus nivolumab or sunitinib were alive at 2 years, 48 versus 36 people per 100 were alive at 5 years and median overall survival gain was 13 months. There was low-certainty evidence that ipilimumab plus nivolumab may result in little to no difference in progression-free survival (HR for disease progression or death 0.96, 95% CI 0.66 to 1.40; two randomized controlled trials, 1169 participants). In absolute terms, 45 versus 43 people per 100 were without disease progression at 1 year. There was low-certainty evidence that ipilimumab plus nivolumab may increase health-related quality of life (MD from baseline 6.28, 95% CI 2.60 to 9.96; one randomized controlled trial, 923 participants). For the comparison of pembrolizumab plus axitinib or lenvatinib versus sunitinib, after a median follow-up of 59.2 months, there was low-certainty evidence that pembrolizumab-containing regimens may increase overall survival (HR for death 0.83, 95% CI 0.72 to 0.94; two randomized controlled trials, 1573 participants). In absolute terms, 72 versus 67 people per 100, respectively, on pembrolizumab-containing regimens or sunitinib were alive at 2 years, 44 versus 37 people per 100 were alive at 5 years and median overall survival gain was 9.6 months. After a median follow-up of 37.1 months, there was moderate-certainty evidence that pembrolizumab-containing regimens likely increase progression-free survival (HR for disease progression or death 0.54, 95% CI 0.33 to 0.86; two randomized controlled trials, 1573 participants). In absolute terms, 64 versus 43 people per 100 were without disease progression at 1 year. There was moderate-certainty evidence that pembrolizumab-containing regimens likely have little to no effect on health-related quality of life (MD from baseline −0.34, 95% CI −2.78 to 2.10; two randomized controlled trials, 1546 participants). Triple-negative breast cancer with PD-L1 expression ≥ 10% One randomized controlled trial of pembrolizumab plus chemotherapy versus chemotherapy was identified that evaluated treatment of advanced/metastatic triple-negative breast cancer (Keynote-355 (105–107)). Of 847 participants randomized, 323 had PD-L1 CPS ≥ 10% and among those with PD-L1 CPS ≥ 10, 220 received pembrolizumab plus chemotherapy and 103 received chemotherapy. Chemotherapy was the investigator’s choice of nab-paclitaxel, paclitaxel or gemcitabine plus carboplatin. After a median follow-up of 44.1 months, there was low-certainty evidence that pembrolizumab-containing regimens may increase overall survival compared with chemotherapy alone (HR for death 0.73, 95% CI 0.55 to 0.95; one randomized controlled trial, 323 participants). In absolute terms, 45 versus 34 people per 100, respectively, on pembrolizumab regimens or chemotherapy were alive at 2 years, 34 versus 23 people per 100 were alive at 3 years and median overall survival gain was 6.0 months. There was low-certainty evidence that pembrolizumab-containing regimens may increase progression-free survival (HR for disease progression or death 0.66, 95% CI 0.50 to 0.88; one randomized controlled trial, 323 participants). In absolute terms, 38 versus 23 people per 100 were without disease progression at 1 year. There was moderate-certainty evidence that pembrolizumab-containing regimens likely have little to no effect on health-related quality of life (MD from baseline –1.80, 95% CI –7.33 to 3.73; one randomized controlled trial, 317 participants).

Harms

Biliary tract carcinoma irrespective of PD-L1 expression There was high-certainty evidence that durvalumab-containing regimens result in little to no difference in grade ≥ 3 adverse events (risk ratio (RR) 0.98, 95% CI 0.91 to 1.06; one randomized controlled trial, 680 participants). Cervical cancer with PD-L1 expression ≥ 1% There was moderate-certainty evidence that pembrolizumab-containing regimens likely increase grade ≥ 3 adverse events (RR 1.09, 95% CI 1.01 to 1.19; one randomized controlled trial, 616 participants). dMMR/MSI-H colorectal cancer There was low-certainty evidence that pembrolizumab monotherapy may reduce grade ≥ 3 adverse events (RR 0.72, 95% CI 0.61 to 0.85; one randomized controlled trial, 296 participants). dMMR/MSI-H endometrial cancer There was low-certainty evidence that dostarlimab-containing regimens may increase grade ≥ 3 adverse events (RR 1.20, 95% CI 1.06 to 1.36; one randomized controlled trial, 487 participants). HER2-negative gastric and gastro-oesophageal junction adenocarcinoma with PD-L1 expression CPS ≥ 1/CPS ≥ 5 There was low-certainty

evidence that pembrolizumab-containing regimens may increase grade ≥ 3 adverse events (RR 1.11, 95% CI 1.01 to 1.23; two randomized controlled trials, 2066 participants). There was low-certainty evidence that nivolumab-containing regimens may increase grade ≥ 3 adverse events (RR 1.35, 95% CI 1.23 to 1.49; one randomized controlled trial, 1549 participants). Head and neck squamous cell carcinoma with PD-L1 expression CPS ≥ 1 There was moderate-certainty evidence that pembrolizumab-containing regimens likely result in little to no difference in grade ≥ 3 adverse events (RR 1.02, 95% CI 0.95 to 1.10; one randomized controlled trial, 563 participants). Hepatocellular carcinoma irrespective of PD-L1 expression For the comparison of atezolizumab plus bevacizumab versus sorafenib, there was very-low-certainty evidence that atezolizumab plus bevacizumab may result in little to no difference in grade ≥ 3 adverse events (RR 1.11, 95% CI 0.97 to 1.28; one randomized controlled trial, 485 participants). For the comparison of durvalumab monotherapy versus sorafenib, there was low-certainty evidence that durvalumab monotherapy may reduce grade ≥ 3 adverse events (RR 0.73, 95% CI 0.64 to 0.85; one randomized controlled trial, 762 participants). For the comparison of durvalumab plus tremelimumab versus sorafenib, there was moderate-certainty evidence that durvalumab plus tremelimumab likely results in little to no difference in grade ≥ 3 adverse events (RR 0.98, 95% CI 0.87 to 1.10; one randomized controlled trial, 762 participants). Malignant melanoma For the comparison of ipilimumab plus nivolumab versus immune-checkpoint inhibitor monotherapy, there was high-certainty evidence that ipilimumab plus nivolumab increases grade ≥ 3 adverse events (RR 2.37, 95% CI 2.03 to 2.77; three randomized controlled trials, 1137 participants). For the comparison of ipilimumab plus nivolumab versus BRAK/MEK inhibitors for BRAF V600-mutant disease, there was low-certainty evidence that ipilimumab plus nivolumab may increase grade ≥ 3 adverse events (RR 1.26, 95% CI 0.94 to 1.69; two randomized controlled trials, 394 participants). Oncogenic driver wild-type non-small cell lung cancer with high PD-L1 expression (TPS ≥ 50%) There was moderate-certainty evidence that pembrolizumab monotherapy likely reduces grade ≥ 3 adverse events (risk ratio (RR) 0.49, 95% CI 0.37 to 0.66; two randomized controlled trials, 1555 participants). There was low-certainty evidence that atezolizumab monotherapy may reduce grade ≥ 3 adverse events (RR 0.81, 95% CI 0.54 to 1.22; two randomized controlled trials, 996 participants). There was low-certainty evidence that cemiplimab monotherapy may reduce grade ≥ 3 adverse events (RR 0.89, 95% CI 0.76 to 1.03; one randomized controlled trial, 699 participants). Oncogenic driver wild-type non-small cell lung cancer irrespective of PD-L1 expression There was moderate-certainty evidence that pembrolizumab-containing regimens likely result in little to no difference in grade ≥ 3 adverse events (RR 1.08, 95% CI 1.00 to 1.16; three randomized controlled trials, 1286 participants). There was moderate-certainty evidence that cemiplimab-containing regimens likely increase grade ≥ 3 adverse events (RR 1.39, 95% CI 1.06 to 1.81; one randomized controlled trial, 465 participants). There was low-certainty evidence that ipilimumab plus nivolumab-containing regimens may increase grade ≥ 3 adverse events (RR 1.21, 95% CI 1.05 to 1.40; one randomized controlled trial, 707 participants). There was moderate-certainty evidence that durvalumab plus tremelimumab-containing regimens likely result in little to no difference in grade ≥ 3 adverse events (RR 1.05, 95% CI 0.92 to 1.21; one randomized controlled trial, 664 participants). There was very-low-certainty evidence that tislelizumab-containing regimens may increase grade ≥ 3 adverse events (RR 1.11, 95% CI 0.93 to 1.34; two randomized controlled trials, 687 participants). Oesophageal squamous cell carcinoma with PD-L1 expression CPS ≥ 1/CPS ≥ 10 There was low-certainty evidence that pembrolizumab plus chemotherapy may result in little to no difference in grade ≥ 3 adverse events (RR 1.03, 95% CI 0.97 to 1.10; one randomized controlled trial, 740 participants). There was low-certainty evidence that nivolumab plus chemotherapy may increase grade ≥ 3 adverse events (RR 1.33, 95% CI 1.11 to 1.61; one randomized controlled trial, 614 participants). There was low-certainty evidence that ipilimumab plus nivolumab may reduce grade ≥ 3 adverse events (RR 0.91, 95% CI 0.73 to 1.13; one randomized controlled trial, 626 participants). Renal cell carcinoma irrespective of PD-L1 expression For the comparison of ipilimumab plus nivolumab versus sunitinib, there was low-certainty evidence that ipilimumab plus nivolumab may reduce grade ≥ 3 adverse events (RR 0.82, 95% CI 0.64 to 1.04; two randomized controlled trials, 1223 participants). For the comparison of pembrolizumab plus axitinib or lenvatinib versus sunitinib, there was moderate-certainty evidence that pembrolizumab-containing regimens likely increase grade ≥ 3 adverse events (RR 1.11, 95% CI 1.04 to 1.18; two randomized controlled trials, 1546 participants). Triple-negative breast cancer with PD-L1 expression ≥ 10% There was moderate-certainty evidence that pembrolizumab-containing regimens likely result in little to no difference in grade ≥ 3 adverse events (RR 1.06, 95% CI 0.97 to 1.15; one randomized controlled trial, 843 participants).

Cost / cost effectiveness

No evidence was presented in the application on costs or cost–effectiveness of the various interventions. A separate report, prepared by Arianna Schouten, Knowledge Ecology International, presented an analysis of financial implications of pembrolizumab and nivolumab and the potential impact of their inclusion on the EML (108). The report highlighted that immune checkpoint inhibitors are still prohibitively expensive, especially in low- and middle-income countries. The report explored the financial and policy landscape surrounding these medicines and discussed strategic pathways that can support improved affordability and access. Key patents for pembrolizumab and nivolumab are set to expire between 2028 and 2033, and subsequent market entry of biosimilars presents an important opportunity to reduce costs. Pembrolizumab has broader indications and a stronger biosimilar pipeline, and so is expected to face greater pricing pressure, potentially leading to price reductions of up to 60%. Nivolumab, with fewer indications and a less competitive pipeline, may see more moderate reductions of between 25% and 40%. However, biosimilar entry may be delayed by evergreening strategies employed by originator companies. These include the development of subcutaneous formulations (109), which can secure new patents and extend market exclusivity beyond the original expiry dates – potentially up to 2039 in the case of pembrolizumab. These strategies affect competition and may hinder timely access to biosimilars, especially in high-revenue markets. Policy-makers must weigh the trade-offs between supporting biosimilar intravenous formulations and newer subcutaneous versions that may prolong exclusivity. The report highlighted that despite sharing many common treatment indications and potentially acting as within-class treatment alternatives, there has been limited within-class market competition, with spending on individual immune checkpoint inhibitors remaining relatively stable over time. Factors identified that may contribute to the lack of within-class market competition include market segmentation based on indication, the role of biomarkers and limited direct head-to-head comparative studies of individual immune checkpoint inhibitors. Current pricing levels often exceed national cost–effectiveness thresholds and may still exceed these thresholds despite potential price reductions following biosimilar entry. Thus, the report emphasizes the importance of a multifaceted strategy to address price and competition and improve affordability and access. Additional strategies include a supportive policy environment favouring the uptake of biosimilars, pooled procurement mechanisms to make use of collective bargaining and reduce prices, and voluntary and compulsory licensing to overcome patent barriers and facilitate early access. The report concludes that inclusion of immune checkpoint inhibitors on the WHO EML can play an important role in catalysing global and national efforts to achieve equitable access by signalling the public health importance of immune checkpoint inhibitors and legitimizing and enabling policy and procurement strategies.
Price and cost–effectiveness data for the proposed immune checkpoint inhibitors were collected by the WHO Secretariat and included in the Evidence to Decision framework documents prepared by the Secretariat. Overall, the wholesale and retail prices for the proposed immune checkpoint inhibitors are still high across different World Bank income settings. Resource requirements to implement immune checkpoint inhibitor treatment were judged to be large for all medicine–indication pairings. Cost–effectiveness studies were identified for each medicine–indication pairing but were limited to high-income and upper-middle-income settings. The reported incremental cost–effectiveness ratios were usually higher than corresponding willingness-to-pay thresholds, with few exceptions (e.g. pembrolizumab for dMMR/MSI-H colorectal cancer (110–113)).

WHO guidelines

WHO guidelines for the treatment of solid tumours are not currently available.

Availability

No information was presented in the application on the availability of the proposed medicines. The Evidence to Decision tables prepared by the Secretariat provided information about the availability of the proposed immune checkpoint inhibitors. Across the board, it was determined that they were probably not available in most settings. In each case, the medicines were approved for use in many countries, however access outside of high-income countries was deemed limited. Data on the availability, out-of-pocket costs, and accessibility of pembrolizumab for

melanoma, non-small cell lung cancer, colorectal cancer and renal cell carcinoma were available from the 2023 update to the ESMO Global Consortium Study (114). These data provide indirect evidence regarding the extent of immune checkpoint inhibitor availability across World Bank income settings. The study found that nivolumab and pembrolizumab for melanoma were almost always available to patients in high- and most upper-middle-income countries at no cost or on a subsidized basis. However, in low- and lower-middle-income countries, if available, these medicines were generally only available with full out-of-pocket costs paid by patients. Substantial discrepancies in accessibility of nivolumab and pembrolizumab were fund between higher and lower income countries.

Other considerations

The EML cancer experts group reviewed the application and provided its advice for the Expert Committee, as summarized below. Biliary tract carcinoma irrespective of PD-L1 expression The group did not support the inclusion of durvalumab plus chemotherapy for treatment of biliary tract cancer because of a small median overall survival gain (3.6 months, 95% CI 1.1 to 6.4 months) which was below the accepted EML threshold. Cervical cancer with PD-L1 expression ≥ 1% The group supported the inclusion of pembrolizumab plus chemotherapy (without bevacizumab) for the treatment of cervical cancer with PD-L1 expression ≥ 1% based on a median overall survival gain of 11 months (95% CI 5.8 to 17.2 months) based on long-term follow-up (median 39.1 months). The group considered that the subgroup analysis comparing overall survival in patients with or without concomitant bevacizumab found no meaningful difference between treatment groups (HR 0.63, 95% CI 0.47 to 0.87 and HR 0.74, 95% CI 0.53 to 1.04, respectively). dMMR/MSI-H colorectal cancer The group supported the inclusion of pembrolizumab as monotherapy for dMMR/MSI-H colorectal cancer based on a median overall survival gain of 12.9 months (95% CI −1.07 to 32.3 months) based on long-term follow-up (median 44.5 months). Additional benefits identified include a small increase in health-related quality of life and a moderate decrease in adverse events compared with chemotherapy. The group did not support the inclusion of nivolumab plus ipilimumab for this indication because the added value of ipilimumab and nivolumab together was judged to be limited. Furthermore, the group had concerns about the price of two versus one immune checkpoint inhibitors and the additional burden of procuring and administering multiple medicines. dMMR/MSI-H endometrial cancer The group did not support the inclusion of dostarlimab plus chemotherapy for treatment of dMMR/MSI-H endometrial cancer. It noted that the calculated increase in median overall survival was extremely large (66.7 months, 95% CI 18.4 to 153.3 months), and that dostarlimab may be associated with a small improvement in health-related quality of life. However, the group had concerns over the price and duration of treatment, which would be prohibitively high in most settings. The group also noted that data for pembrolizumab plus chemotherapy were promising but immature at this time. It also raised concerns over lack of access to backbone chemotherapy (carboplatin and paclitaxel) in some settings. HER2-negative gastric and gastro-oesophageal junction adenocarcinoma with PD-L1 expression CPS ≥ 1/CPS ≥ 5 The group did not support the inclusion of pembrolizumab plus chemotherapy or nivolumab plus chemotherapy for treatment of HER2-negative gastric and gastro-oesophageal junction adenocarcinoma with PD-L1 expression CPS ≥ 1 (pembrolizumab) or CPS ≥ 5 (nivolumab) because of affordability concerns, limited median overall survival gains, little to no difference in health-related quality of life and possible increases in adverse events. Head and neck squamous cell carcinoma with PD-L1 expression CPS ≥ 1 The group did not support the inclusion of pembrolizumab chemotherapy for treatment of head and neck squamous cell carcinoma with PD-L1 expression CPS ≥ 1. The group noted that the medicines offer a moderate overall survival gain of 6 months. However, it considered that patients often have worse performance status (e.g. ECOG 2/3) outside of clinical trials and, in such patients, pembrolizumab has been associated with less pronounced improvements in overall survival (115). Hepatocellular carcinoma irrespective of PD-L1 expression The group did not support the inclusion of atezolizumab plus bevacizumab, durvalumab monotherapy, or durvalumab plus tremelimumab for treatment of hepatocellular carcinoma. All trials compared immune checkpoint inhibitors with sorafenib, a tyrosine kinase inhibitor that is not currently listed as an essential medicine and may be the best treatment option and thus may not be an appropriate comparator. Only atezolizumab plus bevacizumab met the EML threshold for overall survival gain. The duration of follow-up and median overall survival gains varied across the trials. The group interpreted this heterogeneity as a factor that limited the generalizability of benefit across the medicines. Malignant

melanoma The cancer experts did not support the inclusion of nivolumab plus ipilimumab for treatment of malignant melanoma irrespective of PD-L1 expression or BRAF V600-mutation status. The group judged that combination therapy, when compared with monotherapy, had long-lasting and large benefits in overall survival (median overall survival 12.8 months after median follow-up of 34.6 months). However, this benefit was offset by concerns regarding the increased price and adverse events with combination therapy compared with nivolumab or pembrolizumab monotherapy (already included on the EML). Despite being beneficial, the group considered that the addition of ipilimumab to nivolumab would present a further challenge in a number of settings (cost of two versus one immune checkpoint inhibitors and the additional burden of procuring and administering multiple medicines) and interfere with the priority of the large-scale adoption of nivolumab or pembrolizumab. Given the dominant role of pembrolizumab in the treatment of malignant melanoma and other cancers, the group proposed reversing the current listing of nivolumab as the class representative and pembrolizumab as the therapeutic alternative on the EML. The group also suggested that an application for pembrolizumab and nivolumab to be included on the EMLc for the treatment of malignant melanoma in children be sought in the future. Oncogenic driver wild-type non-small cell lung cancer The group supported the inclusion of pembrolizumab, atezolizumab and cemiplimab as monotherapy for oncogenic-driver wild-type non-small cell lung cancer with PD-L1 expression ≥ 50% but were unable to reach consensus on whether or not to support the inclusion of tislelizumab plus chemotherapy for this indication. Median overall survival benefits for pembrolizumab, atezolizumab, cemiplimab, and tislelizumab plus chemotherapy were 6.3 months, 3.7 months, 8.0 months and 4.5 months, respectively. The group noted that the survival gain with atezolizumab might have been underestimated, given that a proportion of trial participants received immune checkpoint inhibitors in the subsequent line of treatment. The group noted that evidence on and regulatory approval for tislelizumab monotherapy for non-small cell lung cancer is lacking. The group did not support the inclusion of cemiplimab plus chemotherapy, durvalumab plus tremelimumab plus chemotherapy, nivolumab plus ipilimumab plus chemotherapy or pembrolizumab plus chemotherapy for treatment of oncogenic-driver wild-type non-small cell lung cancer irrespective of PD-L1 expression. The decision to support the inclusion of monotherapy over combination therapy was based on the strong biological rationale that patients with increased PD-L1 expression are likely to benefit more and the potential to avoid cytotoxic effects from chemotherapy. The group raised concerns over the feasibility of using immune checkpoint inhibitors in low-income settings because of the need for companion diagnostic tests to identify patients eligible for treatment (i.e. with PD-L1 expression ≥ 50% and without targetable oncogenes). However, feasibility is more variable in middle-income settings where diagnostic testing is more readily available and the price of testing is a small fraction of the overall treatment cost. Some members of the group emphasized that immune checkpoint inhibitors for non-small cell lung cancer are likely not cost-effective in most settings, and their use risks diverting resources at the expense of other essential medicines. However, by supporting the inclusion only of monotherapy in patients with high PD-L1 expression, countries can be guided in prioritizing these medicines for the indications and in the populations for whom the benefits would be the largest. Oesophageal squamous cell carcinoma with PD-L1 expression CPS ≥ 1/CPS ≥ 10 The group did not support the inclusion of pembrolizumab plus chemotherapy for treatment of oesophageal squamous cell carcinoma with PD-L1 expression ≥ 10%. It also did not support the inclusion of nivolumab plus chemotherapy or nivolumab plus ipilimumab plus chemotherapy for treatment of oesophageal squamous cell carcinoma with PD-L1 expression ≥ 1%. The group judged that the gains in overall survival with these combinations were moderate in size, but that the benefits were offset by the price, uncertainty in response durability, the unclear role of PD-L1 expression as a predictive biomarker and the potential for increased harms associated with poorer prognosis at baseline. The group considered that pembrolizumab, nivolumab and nivolumab plus ipilimumab are likely the least cost-effective options for this indication when compared with tislelizumab and toripalimab, for which separate applications were evaluated. Renal cell carcinoma irrespective of PD-L1 expression The group did not support the inclusion of nivolumab plus ipilimumab, pembrolizumab plus axitinib, or pembrolizumab plus lenvatinib for treatment of renal cell carcinoma versus sunitinib because of heterogeneity in the trial results and concerns over cost–effectiveness outside of high-income countries. There was also uncertainty about the optimal immune checkpoint inhibitor and tyrosine kinase inhibitor positioning (e.g. in sequence or in combination). The group noted that the addition of a tyrosine kinase inhibitor to pembrolizumab monotherapy probably increased adverse events. Triple-negative breast cancer with PD-L1 expression ≥ 10% The group did not support the inclusion of pembrolizumab plus chemotherapy for treatment of triple-negative breast

cancer because of heterogeneity in trial results, concerns over cost–effectiveness outside of high-income countries and feasibility due to diagnostic requirements. The group judged that the overall survival gain were moderate (6.0 months), but also noted evidence from a phase III trial of chemotherapy with or without atezolizumab for early relapsing unresectable locally advanced or metastatic triple-negative breast cancer, which found no overall survival benefit with atezolizumab-based treatment (116). Strategies to improve access to immune checkpoint inhibitors The group emphasized the importance of strategies to improve access to cancer medicines and discussed a number of strategies including: the potential for a pharmacological class effect and interchangeability of immune checkpoint inhibitors; reduced intensity of dosing and overall treatment duration; vial sharing; biosimilars; pooled procurement; and licensing strategies to improve access and reduce global inequities. Interchangeability of immune checkpoint inhibitors In the absence of head-to-head randomized trials, the group considered strong biological rationale and indirect evidence supporting the potential for recommending different immune checkpoint inhibitors as therapeutic alternatives and therapeutically equivalent, to set up tendering mechanisms for procurement agencies and hospitals (117, 118). PD-1 and PD-L1 inhibitors act to prevent the same immunological interaction that occurs between the PD-1 receptor on T-cells and the PD-L1 protein on tumour cells, which otherwise suppresses the immune system's ability to attack tumour cells (119). In consideration of metastatic non-small cell lung cancer, the group highlighted the effects of pembrolizumab, atezolizumab and cemiplimab on overall survival, and considered that any differences in trial results may be attributed to differences in the study design and population, and not to inherent differences between the medicines (51, 56, 58, 61). Therefore, the cancer experts supported the inclusion, suggesting pembrolizumab be listed as the class representative, with atezolizumab and cemiplimab as therapeutic alternatives. The group proposed that in cases where pembrolizumab, atezolizumab or cemiplimab are not available or affordable, other immune checkpoint inhibitors could also be considered as therapeutic alternatives at the country level since they act on the same immunological pathway. However, the magnitude of clinical benefit should also be taken into consideration and therapeutic equivalence may therefore be limited to cancer medicines and indications in which the magnitude of benefit is large and the evidence is mature. These medicines should be prioritized for procurement. The group highlighted the need to improve current standards for regulatory approval and suggested comparative adaptive trials as the new standard to prove equivalence and interchangeability among the various immune checkpoint inhibitors. This research should include head-to-head randomized trials – as recently suggested by the United States Food and Drug Administration – to reduce heterogeneity in study designs and enable comparisons (120). The PERLA trial is one example of a head-to-head randomized trial that provided evidence for similar efficacy of dostarlimab combined with chemotherapy and pembrolizumab combined with chemotherapy in previously untreated metastatic non-squamous non-small cell lung cancer (121). With indirect evidence, heterogeneity in techniques and tests measuring levels of predictive biomarkers limits confidence in indirect comparisons of immune checkpoint inhibitors. Finally, post-approval studies can provide important information on optimal treatment doses, schedules, duration and positions (e.g. first- versus second-line) (119). Reduced intensity treatment The group acknowledged growing evidence supporting the use of reduced-intensity treatment with many molecules used to treat several types of cancer (122). Among immune checkpoint inhibitors, evidence indicates that much lower doses of both nivolumab and pembrolizumab provide maximal binding to their receptors, and that such binding is maintained for considerably longer than the registered dosing intervals of 2 or 4 weeks for nivolumab and 3 or 6 weeks for pembrolizumab. A 2012 study investigated the binding of nivolumab to receptors on circulating T-cells at 8 weeks after a range of doses (0.1–10 mg/kg given every 2 weeks) and found no significant difference in receptor occupancy (123). The doses evaluated in cohorts of 10–20 patients were 3.3%, 10.0%, 33.3%, 100.0% and 333.3% of the clinically approved dose used in clinical trials evaluating the medicine. Only one outlier was found in 11 patients which had reduced binding at the very lowest dose of 0.1 mg/kg. A 2024 study collected 122 serial peripheral blood mononuclear cell samples at multiple time points from 19 patients receiving nivolumab at different doses and at varying frequencies (every 4 to 12 weeks) (124). Receptor occupancy on CD4+ and CD8+ T-cells was measured at 4, 8 and 12 weeks after doses of 40 mg, 240 mg and 480 mg. No consistent differences were found in receptor binding either as a function of dose or time. Serum nivolumab concentration was measured as a function of time after these doses; although serum concentrations were higher with higher doses, the median serum concentration of low-dose (40 mg) nivolumab remained higher

than the minimal effective concentration of 1.5 microgram/mL for 3 months. In a phase II study, 168 patients with advanced renal cell cancer were randomized to receive nivolumab doses of 0.3 mg/kg, 2 mg/kg and 10 mg/kg every 3 weeks (125). No significant difference was seen in response rate, progression-free survival or overall survival between treatment groups, yet the dose taken forward for phase III trials was 3 mg/kg every 2 weeks. A 2023 randomized phase III superiority study compared low-dose nivolumab (20 mg flat dose once every 3 weeks) combined with chemotherapy with chemotherapy alone in 151 patients with advanced head and neck squamous cell carcinoma (126). The approved dose of nivolumab for this indication is 240 mg every 2 weeks. Thus, every 6 weeks there was an intensity reduction between the on-label and low-dose of about 94% (40 mg versus 720 mg). The median overall survival at 1-year was 10.1 months and 6.7 months in the nivolumab and chemotherapy arms, respectively. The consistent results of the target binding, pharmacokinetic and clinical studies provide substantial evidence in support of an alternative dosing strategy for nivolumab. This is especially important in settings where full-dose treatment is not attainable (e.g. due to out-of-pocket costs). The approved doses of pembrolizumab are 2 mg/kg or a flat dose of 200 mg every 3 weeks, or double those doses given every 6 weeks. In a phase I study, an ex-vivo IL-2 PD-1 receptor modulation assay was used to study pembrolizumab receptor engagement after doses of 1 mg/kg, 3 mg/kg or 10 mg/kg every 2 weeks (127). PD-1 target engagement remained high during multiple courses of therapy and independent of dose. Intrapatient escalating doses of 0.005–10 mg/kg were given to patients and, with a terminal half-life of 2–3 weeks, measurements of serum concentration suggest that receptor inhibition would be maintained for at least 2 months after doses as low as 0.3 mg/kg. The NVALT-30 trial evaluated low-dose pembrolizumab (300 mg every 6 weeks or 100 mg every 3 weeks, with or without chemotherapy) and standard dose pembrolizumab (400 mg every 6 weeks or 150–200 mg every 3 weeks) for treatment of stage IV non-small cell lung cancer (128). A pre-planned interim analysis found a non-significant difference in 1-year overall survival between dosing arms which met the predetermined criterion for continuing the trial. Weight-based instead of fixed doses were shown to maintain treatment effectiveness while reducing treatment costs for non-small cell lung cancer in retrospective cohort studies and this dosing has been implemented in several countries (129–131). Reduced-intensity treatment strategies include dose reduction, rounding and banding, longer intervals between administrations, and shorter duration of treatment. Multiple trials are investigating early cessation of treatment, extended dosing intervals and lower doses as reduced-intensity treatment strategies for immune checkpoint inhibitors (132, 133). The cancer experts' group considered that promising data were available for nivolumab and pembrolizumab based on dose-finding phase I and II studies (125–127, 134, 135), and pharmacokinetic and pharmacodynamic studies (123, 124, 133, 136–140). However, limited data were available that demonstrated similarity with registered doses based on long-term overall survival from comparative randomized trials, as well as for other immune checkpoint inhibitors. The group considered that reduced-intensity treatment has the potential to significantly reduce the cost of immune checkpoint inhibitor treatment, without substantial reduction in efficacy. The group recommended that emerging evidence from ongoing and future dose-optimization trials should be closely monitored. Vial size and sharing Immune checkpoint inhibitors are typically provided in single-use vials with fixed concentrations and unused portions often go to waste if the entire vial is not needed for an individual patient's dose. Vial sharing is a practical approach to cut costs and improve access. Vial sharing allows for precise doses to be administered without wastage, particularly in weight-based regimens (141). Some regions have strict rules about the sharing of single-use vials due to contamination risks. However, controlled hospital settings with proper aseptic techniques can mitigate these concerns. Such a strategy may also require coordination in scheduling and pharmacy preparation to ensure vials are used efficiently with multiple patients within the drug stability timeframes. Biosimilars, pooled procurement and licensing strategies The group agreed with and endorsed the findings of the report describing an analysis of financial implications of pembrolizumab and nivolumab and the potential impact of their inclusion on the EML (108), elaborated in Costs/cost-effectiveness subsection above. Alternative models for stimulating medicine innovation The group highlighted that the high prices of new cancer medicines are not justified by production costs, disease rarity or magnitude of benefit. Efforts to use collective purchasing power through negotiations with procurement or reimbursement authorities, or through price controls, have had limited success in moderating excessive prices and disparities in access. The group noted various innovative models for medicines development. These included proposals aimed at: facilitating rapid entry of generics in developing countries by offering a system of rewards for originator companies (142); and investigating alternative models for funding and investment that delink the costs

of research development and the price of health products (143, 144).

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