

EDITORIAL



Implementation of the ESMO-Magnitude of Clinical Benefit Scale: real world example from the 2022 Israeli National Reimbursement Process

In recent years there has been a surge in the number of new medications for the treatment of cancer.^{1,2} Many of these agents are truly innovative and transformative and their incorporation into routine practice has improved outcomes for many patients. These medications often come with a high and ever-increasing price tag, however, making it unsustainable even for the wealthiest health systems to afford all new medications and new indications for established therapies.³⁻⁵ The rising prices of effective drugs have led to the development of the ‘Cost-Effective but Unaffordable’ paradox.⁶ In order to optimize the balance between improving patient outcomes and maintaining economic sustainability,⁷ many health care systems implemented Health Technology Assessment (HTA) mechanisms to select which new therapies provide enough patient benefit to justify the cost of incorporating them into national insurance coverage schemes.

Several tools aim to provide objective methods for the evaluation of the magnitude of clinical benefit generated by novel cancer drugs and indications such as the European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS⁸), the American Society of Clinical Oncology-Value Framework (ASCO-VF⁹) or the overall value of an intervention such as the National Comprehensive Cancer Network evidence blocks.¹⁰ Irrespective of the scale that is used, conclusions from these scales may be confounded by biases deriving from study design, study implementation or data analysis.¹¹ Thus, in addition to the formal scales, the evaluation of the magnitude of clinical benefit requires a careful assessment of the evidence for potential biases that may have generated exaggerated or reduced benefit or underestimated potential harms. Given the acknowledged limitation of the generalizability of the knowledge gained from clinical trials,¹¹ the appraisal of clinical benefit may also be influenced by ‘real world data’ and the experience of physicians who actively work in the relevant field.

THE ‘THERAPEUTIC BASKET OF SERVICES’: HTA PROCESS IN ISRAEL

The Israeli health system is universal and allows accessible health care to all Israeli citizens. To safeguard economic sustainability, however, not all licensed medications or specific indications are reimbursed. In order to be

reimbursed and provided free of charge, licensed drugs, technologies or indications for the treatment of cancer must also be approved by the HTA process of the Ministry of Health (MOH).¹² The HTA process is undertaken on an annual basis by the ‘health basket’ committee of the MOH,¹³ which includes physicians, administrators representing the payers and prominent public figures representing the public. Each year the government allocates a limited budget dedicated for financing new drugs and technologies for the following year. The health basket committee evaluates and ranks all candidate drugs and technologies to select those to be reimbursed within the allocated budget. These budget constraints mandate a thorough evaluation of each candidate, as well as a method to compare between them. As drugs and technologies may be part of any field of medicine, the comparison is extremely difficult, especially when comparing and choosing from diverse fields such as oncology and hematology on the one hand and preventive medicine, diabetes and hypertension on the other hand. In most recent years ~30% of the budget expansion was allocated to oncology new drugs,¹⁴ however this was smaller in 2021 (8%), due to COVID-19 considerations and also a significant allocation for the treatment of diabetes which had a very large budget impact.

Three tiers lead to the final decision: (i) scientific evaluation of each new drug/indication/technology by experts in the specific field relevant for the application who submit a ranked listing of new therapies irrespective of cost (i.e. medical oncologists rank drugs and technologies candidates for solid cancer treatment, hematologists review candidates in hematological diseases, etc.); (ii) financial evaluation by the MOH including the total budget impact of incorporating the new therapy; (iii) final evaluation by the health basket committee.

PROFESSIONAL SUBMISSION OF CANCER MEDICATIONS TO THE HTA BODY IN ISRAEL

For solid tumor oncology submissions, ranked listing is developed by the Israeli Society of Clinical Oncology and Radiotherapy (ISCORT) together with the National Council for the Prevention, Detection and Treatment of Malignant Diseases (The National Council) which is a body appointed by the MOH, using a two-step structured method.

- (i) Evaluation and ranking of candidate medications/indications in each specialty field by the dedicated expert group of ISCORT (breast, thoracic, gastrointestinal,

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etc.). The ranking is informed by ESMO-MCBS scores and by independent review of the data.

- (ii) Submissions from the subspecialty groups are considered by a steering committee of ISCORT and the National Council to formulate a single ranking list for solid tumor oncology. The ranking is also informed by ESMO-MCBS scores, and the expert input of the subspecialty groups.

THE RANKED LISTING OF CANDIDATES FOR THE 2022 UPDATE OF THE BASKET OF SERVICES

For the year 2022, 77 new indications for 41 drugs were submitted by the MOH for evaluation (Table A1). The most common drugs were targeted therapies (26, 63%) followed by immune checkpoint inhibitors (ICIs) (7, 17%), chemotherapies (4, 10%) hormonal therapies (2, 5%) and antibody-drug conjugates (2, 5%). The most common indications were targeted therapies (35, 45%) and ICIs (30, 39%). A total of 42 of the 77 indications (55%) were recommended for reimbursement by the professional oncology societies; 30 (39%) indications were recommended for reimbursement from the allocated budget expansion and a further 12 indications (15.5%), which were alternatives to previously approved medications, were recommended for reimbursement but without added cost to the overall budget (Table A2). Treatments with curative intent were given the highest priority. Most submissions for potentially curative intent were recommended for funding (6 of 8, 75%), compared with only 36 of 69 (52%) indications for non-curative treatment. With one exception, the therapies with curative potential that were incorporated in the ranking achieved an ESMO-MCBS score of A.

The thirty interventions recommended for reimbursement from the allocated budget expansion were ranked for prioritization. Five adjuvant treatments with curative intent were ranked above treatments with non-curative intent. With three exceptions, all non-curative indications in the top 30 list were scored by the ESMO-MCBS v1.1 as three or above. The exceptions were: (i) olaparib as maintenance therapy for BRCA-mutated, unresectable or metastatic pancreatic cancer (ESMO-MCBS v1.1 score 2) was ranked 20/30, because it delayed the need for further chemotherapy which the ISCORT GI-group members considered as a patient benefit not captured by the POLO study design endpoints; (ii) ipilimumab and nivolumab after progression on a single agent ICI in advanced melanoma (ESMO-MCBS v1.1 not scorable) was ranked lowly (24/30). It was strongly endorsed by the melanoma specialty group since it is a common off-label clinical practice, though it is not yet supported by any prospective randomized study and (iii) the study supporting the indication of pembrolizumab for patients with BCG-unresponsive high-risk, non-muscle invasive bladder cancer¹⁵ (ranked 30/30) was a single-arm de-escalation study in the curative setting which is a design that is not scorable using ESMO-MCBS v1.1.

This shortcoming is being addressed in the draft version 2.0 which is currently in validation testing.

Indications 26-29 were of targeted therapies in rare clinical scenarios with a proven biomarker, tested in early, non-randomized clinical trials, but showing promising efficacy together with a strong biological rationale for their activity. These included sotorasib for non-small-cell lung cancer (NSCLC) harboring KRAS G12C mutation,¹⁶ amivantamab and mobocertinib for NSCLC harboring epidermal growth factor receptor (EGFR) exon 20 insertion^{17,18} and pemigatinib for cholangiocarcinoma harboring fibroblast growth factor receptor 2 (FGFR2) alterations.¹⁹ Evidence for benefit for these indications was derived from single-arm studies with surrogate outcomes of overall response rate and duration of survival. The steering committee considered the rarity of certain driver mutations impacting the feasibility of conducting large registration trials, and accordingly ranked drugs with high response rate and durable response in this setting above what would be dictated by the ESMO-MCBS score.

To enhance the value and contain the total budget impact and thus allow inclusion of more drugs, the committee members recommended narrowing some of the indications requested by the sponsors (Table A1). Some of these recommendations were inferred from the indirect comparisons of clinical trials, planned and *post hoc* subgroup analyses and biological understanding of mechanisms of actions. Thus, the final list recommended that coverage for the use of ICIs in urothelial, esophageal and gastric cancers should be restricted to programmed death-ligand 1-positive tumors only.

The 12 indications for which reimbursement decisions did not require additional budget allocation (Table A2) were all for indications where there was little or no added marginal benefit compared with other agents already fully covered by the national insurance scheme, but where listing of an alternative may have a positive economic impact by the introduction of competitive pricing. Since equally effective therapies were already covered by the national insurance scheme, these 12 indications were not ranked for added clinical benefit.

CONCLUSIONS

Unlike other countries (e.g. Australia, Germany, Austria, France, Canada, Hungary and UK), where submissions are considered on an *ad hoc* basis, the HTA process in Israel is an annual process whereby all new candidate technologies are considered simultaneously and competitively for funding from constrained budget expansion. Since the annual health basket evaluation mechanism allows only one opportunity for drugs to be reimbursed each year, the ranking process presented here is, to our knowledge, the only annual formal national ranking of all new cancer drugs. Ultimately, this process is not the final determinate. The list and the considerations underlying its development will be presented to the central HTA committee where all the data

are reviewed and where value, cost and total budget impact of each indication are additional considerations in the determination of the new therapies to be included in the “free for user” basket of services. This very hands-on experience highlights many of the difficulties challenging HTA processes globally, illustrates the value of incorporating the ESMO-MCBS as part of the process, but also points to the limitations of data objectification where uncertainty regarding the veracity and generalizability of the available data is high. Among the non-curative therapies in addition to the ESMO-MCBS score, clinical experience from the perspective of the members of the relevant subspecialty faculty groups was also influential.

As the ESMO-MCBS score may be influenced by bias introduced in study design, implementation and data analysis,²⁰ scoring needs to be considered along with a careful and critical scrutiny for biases that may have influenced the scores. The high prevalence of licensing approvals based on surrogate endpoints or on single-arm studies using surrogate outcomes has generated a higher than ever level of uncertainty to the evaluation of true clinical benefit.²¹ Whereas clinical expertise and experience may be useful in adjudicating on this uncertainty, the adjudication process may also be confounded by confirmation bias, optimism bias, recall bias and the seduction of new technologies.

We presented here the formal recommendation of the ISCOR and the National Council for 2022 reimbursement of cancer medications in Israel. The ranking itself, as well as the detailed description of the process of its generations, using the ESMO-MCBS score, may be useful for other countries and organizations dealing with the daunting process of implementing the best clinical care while maintaining a financially sustainable approach.

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APPENDIX 1

The formal recommendations of the Israeli Society of Clinical Oncology and Radiotherapy (ISCORT) and the National Council for the Detection, Prevention and Treatment of Malignant Diseases for the 2022 Health Basket Committee

Table A1. The formal recommendations for the 2022 Health Basket Committee					
Rank	Drug	Indication	Main outcome	Comments/specific recommendations	ESMO-MCBS v1.1 score
Medications with curative potential (adjuvant/neoadjuvant)					
1	Tagrisso/osimertinib	Adjuvant therapy after tumor resection in adult patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations.	HR for DFS 0.17		A
2	Opdivo/nivolumab	Adjuvant treatment of patients with MIUC who are at high risk of recurrence after undergoing radical resection of MIUC.	HR for DFS 0.53	Recommended for PD-L1-positive tumors only.	A
3	Opdivo/nivolumab	Adjuvant treatment of completely resected esophageal or GEJ cancer with residual pathologic disease in patients who have received neoadjuvant chemoradiotherapy.	HR for DFS 0.6		A
4	Tecentriq/atezolizumab	Adjuvant treatment following resection and platinum-based chemotherapy for patients with NSCLC whose tumors have PD-L1 expression of $\geq 1\%$ on tumor cells.	HR for DFS 0.66	Recommended for stages II-IIIa only without EGFR or anaplastic lymphoma kinase alteration.	A
5	Keytruda/pembrolizumab	Treatment of patients with high-risk early stage triple-negative breast cancer in combination with chemotherapy as neoadjuvant treatment, followed by pembrolizumab as a single agent as adjuvant treatment after surgery.	HR for EFS 0.63 pCR increase from 51% to 65%		A
Medications for metastatic disease: life prolongation and/or improved quality of life					
6	Keytruda + Lenvima/ pembrolizumab + lenvatinib	Pembrolizumab in combination with lenvatinib is indicated for treatment of patients with advanced endometrial carcinoma who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation.	HR for OS 0.62, 11.4-18.3 months		4
7	Opdivo/nivolumab	In combination with chemotherapy is indicated as first-line treatment in patients with advanced or metastatic esophageal adenocarcinoma with PD-L1 CPS $>5\%$.	Nivolumab data: CPS $>5\%$: HR 0.71 for OS, 3.5 months absolute benefit Pembrolizumab data: CPS >10 : HR for OS 0.62, 4 months absolute benefit	All three indications were considered as a class effect and recommended only for patients with CPS $>5\%$ for nivolumab or $>10\%$ for pembrolizumab, where most of the effect was seen.	4
	Opdivo/nivolumab	In combination with chemotherapy is indicated as first-line treatment in patients with advanced or metastatic gastric cancer or GEJ cancer with PD-L1 CPS $>5\%$.			3
	Keytruda/pembrolizumab	Treatment of patients with locally advanced or metastatic esophageal or GEJ (tumors with epicenter 1-5 cm above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation in combination with chemotherapy.			
8	Ayvakit/avapritinib	Treatment of adults with unresectable or metastatic GIST harboring a PDGFRA exon 18 mutation, including PDGFRA D842V mutations.	No phase III but 91% RR, very rare disease	Will require additional costs for molecular testing.	3
9	Braftovi/encorafenib	In combination with cetuximab, indicated for the treatment of metastatic colorectal cancer with BRAF V600E mutation after prior systemic therapy.	HR for OS 0.65, absolute benefit 3.6 months	Recommended for the 2021 health basket but not approved.	3
10	Padcev/enfortumab	Treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a PD-1 or PD-L1 inhibitor, and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting.	HR for OS 0.7, absolute benefit 4 months		3

Continued

Table A1. Continued

Rank	Drug	Indication	Main outcome	Comments/specific recommendations	ESMO-MCBS v1.1 score
11	Lynparza/olaparib	Treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA1/2 or ATM-mutated metastatic castration-resistant prostate cancer who have progressed following prior treatment with enzalutamide or abiraterone.	HR for PFS 0.34, 4 months absolute benefit		4
12	Bavencio/avelumab	Maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma that has not progressed with first-line platinum-containing chemotherapy.	HR 0.69 for OS, 7 months absolute benefit		4
13	Gavreto/pralsetinib	Treatment of metastatic RET fusion-positive NSCLC.	Rare condition, no phase III, RR 80%, DOR 11 months		3
13	Gavreto/pralsetinib	Treatment of adult and pediatric patients ≥ 12 years of age with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate) OR with advanced or metastatic RET-mutant medullary thyroid cancer who require systemic therapy.	Rare disease, no phase II. RR 60%-80% with durable responses		3
14	Enhertu/trastuzumab deruxtecan	Treatment of patients with unresectable or metastatic HER2-positive breast cancer who have received at least one prior anti-HER2-based regimen in the metastatic setting.	HR for PFS 0.28. It is not yet approved by either EMA or FDA		4
15	Imfinzi/durvalumab	Imfinzi in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of patients with extensive-stage SCLC.	HR 0.75 for OS, 8% higher 2-years survival		3
15	Tecentriq/atezolizumab	Tecentriq in combination with carboplatin and etoposide is indicated for the first-line treatment of adult patients with extensive stage SCLC.	HR for OS 0.76		3
16	Lynparza/olaparib Rubraca/rucaparib Zejula/niraparib	Maintenance treatment of patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response to platinum-based chemotherapy.	~15% PFS benefit after 2 years	Considered as a class effect. Already reimbursed for BRCA1/2 or HRD tumors.	3
17	Enhertu/trastuzumab deruxtecan	Treatment of patients with locally advanced or metastatic HER2 positive gastric or GEJ adenocarcinoma who have received prior trastuzumab-based regimen.	Phase II trial, HR for OS 0.59, absolute benefit 4 months		4
18	Tabrecta/capmatinib Tepmetko/tepotinib	Treatment of adult patients with metastatic NSCLC whose tumors have a mutation that leads to mesenchymal-epithelial transition exon 14 skipping.	Rare condition, no phase III data, RR 50%-70% for ~12 months	Considered as a class effect.	3
19	Tukysa/tucatinib	Tukysa is indicated in combination with trastuzumab and capecitabine for the treatment of adult patients with HER2-positive locally advanced or metastatic breast cancer who have received at least two prior anti-HER2 treatment regimens.	HR 0.48 for PFS, 2 months absolute benefit but 24% difference at 1 year for patients with brain metastases	Recommended only for patients with brain metastases.	3
20	Lynparza/olaparib	Maintenance treatment of adult patients with deleterious or suspected deleterious gBRCAm metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen.	HR 0.53 for PFS, 3.6 months absolute benefit but compared with placebo, improves quality of life		2
21	Erleada/apalutamide Xtandi/enzalutamide	Treatment of adult men with metastatic hormone-sensitive prostate cancer in combination with androgen deprivation therapy.	HR 0.43 for OS	Recommended only for low volume disease or high volume but low tolerance to abiraterone that is already reimbursed for this indication.	4

Continued

Table A1. Continued					
Rank	Drug	Indication	Main outcome	Comments/specific recommendations	ESMO-MCBS v1.1 score
22	Libtayo/cemiplimab	As monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic basal cell carcinoma who have progressed on or are intolerant to a hedgehog pathway inhibitor.	Phase II only, RR 31%, durable responses		3
23	Tecentriq/atezolizumab	Tecentriq, in combination with cobimetinib and vemurafenib, is indicated for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.	Based on PFS gain	Recommended only for patients with aggressive disease: brain metastases or elevated high-density lipoprotein.	3
24	Opdivo/nivolumab	In combination with ipilimumab, is indicated for the treatment of patients with advanced (unresectable or metastatic) melanoma.	Based on clinical experience, guidelines and retrospective data. Not yet approved by EMA or FDA. Randomized, controlled trial results pending	Recommended as a clinical need in order to allow addition of ipilimumab upon progression on nivolumab.	Not scorable
25	Qinlock/ripretinib	Treatment of adult patients with advanced GIST who have received prior treatment with ≥ 3 kinase inhibitors, including imatinib.	HR for PFS 0.15		3
26	Rybrevant/amivantamab	Treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutation, whose disease has progressed on or after platinum-based chemotherapy.	Rare condition, no phase III, RR 40%, DOR 11.1 months		3
27	Pemazyre/pemigatinib	Monotherapy for the treatment of adults with locally advanced or metastatic cholangiocarcinoma, with a FGFR2 fusion or rearrangement, who have progressed after at least one prior line of systemic therapy.	No phase III, RR 35.5%, DOR 7.5 months		3
28	Sotorasib	Treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic NSCLC, as determined by an approved test, who have received at least one prior systemic therapy.	On phase II trial, ORR 37%, DOR 11.1 months		3
29	Exkivity/mobocertinib	Treatment of adult patients with EGFR exon 20 insertion mutation-positive, metastatic NSCLC, who have received prior platinum-based chemotherapy.	Rare condition, no phase III, RR 43%, DOR 14 months		3
30	Keytruda/pembrolizumab	Treatment of patients with BCG-unresponsive high-risk, non-muscle invasive bladder cancer with carcinoma <i>in situ</i> with or without papillary tumors who are ineligible for, or have elected not to undergo cystectomy.	Bladder preservation due to 41% complete response		Not scorable

ATM, Ataxia-Telangiectasia Mutated; CPS, combined positive score; DFS, disease-free survival; DOR, duration of response; ESMO-MCBS, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; EFS, event free survival; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; FDA, Food and Drug Administration; FGFR2, fibroblast growth factor receptor 2; gBRCAm, germline BRCA mutation; GEJ, gastroesophageal junction; GIST, gastrointestinal stromal tumor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; HRD, homologous recombination deficiency; MIUC, muscle invasive urothelial carcinoma; NSCLC, non-small-cell lung cancer; OS, overall survival; pCR, pathologic complete response; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PDGFRA, platelet-derived growth factor receptor alpha; PFS, progression-free survival; RET, rearranged during transfection; RR, response rate; SCLC, small-cell lung cancer.

Table A2. Additional medications without additional cost			
Drug	Indication	Main outcome	ESMO-MCBS v1.1
Lorviqua/lorlatinib	Treatment of adult patients with metastatic NSCLC whose tumors are ALK-positive.	As least as good as second generation ALK inhibitor	4
Nerlynx/neratinib	Advanced or metastatic breast cancer—Nerlynx in combination with capecitabine is indicated for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting.	Improved RMST-PFS of 2.2 months, median PFS gain 0.1 month	1
Keytruda/pembrolizumab	Treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma.	ORR 56%, CR 24%	3
Keytruda/pembrolizumab	Treatment of patients with recurrent or metastatic cutaneous squamous cell carcinoma that is not curable by surgery or radiation.	ORR 50%, CR 17%	3
Keytruda/pembrolizumab	Pembrolizumab in combination with chemotherapy, is indicated for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS >10) as determined by a validated test.	HR for PFS 0.65 for patients with CPS >10	3
Vitakvi/larotrectinib	Vitakvi as monotherapy is indicated for the treatment of adult and pediatric patients with solid tumors that display a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment options.	ORR 75%, DOR 35 months	3
Xtandi/enzalutamide	Treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer.	Similar efficacy to apalutamide with different toxicity profile	3
Cabometyx/cabozantinib	Cabometyx, in combination with nivolumab, is indicated for the first-line treatment of advanced renal cell carcinoma in adults.	Only for medium- and high-risk patients	4
Lenvima/lenvatinib	In combination with pembrolizumab is indicated as first-line treatment of patients with advanced renal cell carcinoma.	ORR 70%	4
Opdivo/nivolumab	Cabometyx, in combination with nivolumab, is indicated for the first-line treatment of advanced renal cell carcinoma in adults.	Only for medium- and high-risk patients	4
Keytruda/pembrolizumab	In combination with lenvatinib is indicated as first-line treatment of patients with advanced renal cell carcinoma.	Only for medium- and high-risk patients	4
PHESGO (combination injection trastuzumab pertuzumab)	PHESGO is indicated for use in combination with chemotherapy for the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory or early-stage breast cancer (either >2 cm in diameter or node-positive) as part of a complete treatment regimen for early breast cancer.	Similar efficacy and toxicity profile to Herceptin	B

ALK, anaplastic lymphoma kinase; CPS, combined positive score; CR, complete response; DOR, duration of response; ESMO-MCBS, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; NSCLC, non-small-cell lung cancer; ORR, overall response rate; PD-L1, programmed death-ligand 1; PFS, progression-free survival; RMST, restricted mean survival time; TNBC, triple-negative breast cancer.