Position of an international panel of lung cancer experts on the decision for expansion of approval for pembrolizumab in advanced non-small-cell lung cancer with a PD-L1 expression level of ≥1% by the USA Food and Drug Administration

Immune-checkpoint inhibitors (ICIs) have transformed the therapeutic landscape of advanced non-small-cell lung cancer (NSCLC) and now represent the new first-line standard of care (SoC), either in combination with platinum-based chemotherapy, achieving a survival benefit independent of histology and programmed death ligand-1 (PD-L1) expression levels [1–4], or as monotherapy in patients whose tumors express PD-L1 in ≥50% of the tumor cells [5, 6]. Recently, the phase III KEYNOTE 042 trial reported that pembrolizumab monotherapy (200 mg every 3 weeks for up to 35 cycles) in patients with a PD-L1 tumor proportion score (TPS) of at least 1% significantly improved overall survival (OS) compared with investigators' choice of platinum-based chemotherapy [16.7 months versus 12.1 months, hazard ratio (HR) 0.81; 95% confidence interval (CI) 0.71–0.93; $P = 0.0018$] [7]. Based on these results, the USA Food and Drug Administration (FDA) expanded the originally approved indication of pembrolizumab in the first-line setting to all patients with PD-L1 TPS ≥1%, without *EGFR* or *ALK* aberrations (https://www.fda.gov/drugs/fda-expands-pembrolizumab-indication-first-line-treatment-nsclc-tps-1). The European Medicines Agency has not made any definitive recommendation. With this statement, we would like to raise our concerns regarding the possibility of a broad adoption of pembrolizumab monotherapy as standard treatment for all patients with PD-L1 TPS ≥ 1%.

In the KEYNOTE 042 trial [7], 1274 advanced NSCLC patients with tumors with PD-L1 ≥ 1% were enrolled, and randomization was stratified by PD-L1 expression level (≥50% versus 1% to 49%). When the study was designed in 2014, the primary end point was OS in the subgroup of patients with PD-L1 ≥ 50%. In 2015, after enrollment of 662 patients, based on the OS benefit of the second-line pembrolizumab in PD-L1 ≥ 1% tumors in the KEYNOTE 010 trial [8], the protocol was amended and OS in patients with TPS ≥ 1% became a co-primary end point. Later, in April 2017, and after enrollment was completed, a new amendment was introduced and the final co-primary end points were OS in patients with PD-L1 TPS of ≥50%, ≥20%, and ≥1% in the intent-to-treat (ITT) population [7]. Pembrolizumab achieved a longer OS compared with chemotherapy in all three PD-L1 populations, without improvement in the secondary end points of progression-free survival and objective response rate [7]. Of note, nearly half (46.6%) of the patients enrolled had a TPS of ≥50%, which represents a potential bias for the over-performing efficacy of pembrolizumab in the ITT population. In the pre-defined OS analysis by PD-L1 expression, a survival benefit from pembrolizumab was not seen in the PD-L1 1% to 49% subgroup (median OS 13.4 versus 12.1 months, HR 0.92, 95% CI 0.77–1.11) [7]. This suggests that the observed benefit with pembrolizumab is largely driven by the 'high PD-L1 expression' group, in which the HR for OS benefit mirrors that from a similar population in the KEYNOTE 024 trial, (0.69 and 0.63, respectively), [6, 7].

Another important concern in KEYNOTE 042 is that crossover from the chemotherapy arm to pembrolizumab upon progression was not allowed per protocol. The trial enrolled patients from 9 December 2014 to 6 March 2017, during which at least four large randomized clinical trials [8–11] had already reported a survival benefit with second-line ICIs, including the KEYNOTE 010 trial published in 19 December 2015 [8]. Interestingly, crossover was allowed in the KEYNOTE 024 trial, although recruitment started in May 2012 [5]. Despite this evidence, only 20% of patients in the KEYNOTE 042 trial received an approved second-line immunotherapy [7]. Crossover is desirable in settings where a drug has already proven benefit in a subsequent line of therapy and attempts are being made to advance it to an earlier line [12], such as the KEYNOTE 042 trial, which tested a similar question: pembrolizumab upfront or as a sequential strategy for PD-L1 TPS ≥ 1% tumors. Therefore, the treatment received by patients in the control arm of KEYNOTE 042 should be considered suboptimal by current standards.

One of the major concerns about the efficacy of the first-line immunotherapy in patients not selected by high PD-L1 expression, is that ICIs may underperform compared to chemotherapy, as evidenced in the CHECKMATE 026 trial with nivolumab [13]. In KEYNOTE 042, analysis of OS data clearly shows that the effect of pembrolizumab across the ITT population is heterogeneous. In the overall population (PD-L1 ≥ 1%), survival curves cross approximately seven months after treatment initiation, with chemotherapy performing better than pembrolizumab during the first 6 months from randomization. This pattern is also repeated for the subgroup of patients with PD-L1 expression of 1% to 49% [7], suggesting that a substantial number of patients progress rapidly and die within the first six months of treatment without obtaining any meaningful benefit from immunotherapy. A similar observation has been reported in the phase III MYSTIC trial. In MYSTIC, first-line durvalumab did not improve OS compared with standard chemotherapy in patients with NSCLC and ≥25% PD-L1 expression. The OS curves also crossed beyond 6 months from randomization [14]. These data also highlight the potential risk of hyper-progressive disease with ICIs in a largely unselected patient population. Notably, this risk has not been observed among patients treated with the combination of ICIs and chemotherapy [2, 4].

Two randomized phase III trials in the first-line setting have reported survival benefit with the combination of platinum-based chemotherapy and pembrolizumab compared with chemotherapy alone in patients with non-squamous (KEYNOTE 189) [2, 3] and squamous (KEYNOTE 407) [4] histology, regardless of PD-L1 status, including the subset of tumors with PD-L1 expression of 1-49%. In both trials of chemo-immunotherapy combinations, the OS curves separate early and the corresponding HRs for survival are similar independent of histology [non-squamous: HR 0.62 (0.42–0.92) and squamous: HR 0.57 (0.36–0.90)] [3, 4]. Thus, in patients whose tumors have a PD-L1 TPS of 1% to 49%, the combination of chemotherapy and immunotherapy should be the standard of care.

Some clinicians may argue that pembrolizumab monotherapy could represent an effective and better-tolerated alternative to the more toxic chemo-immunotherapy combination, mainly in the frail population, such as elderly patients or patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2. However, KEYNOTE 042 only enrolled patients suitable for chemotherapy, with an ECOG PS 0-1 and median age was 63 years [7]. A recent pooled analysis reported survival benefit with pembrolizumab compared with chemotherapy in patients aged ≥75 years [15]. Yet, only a randomized clinical trial may define the real benefit in these specific populations.

From a regulatory aspect, it is likely that the recent FDA approval was given on the basis of comparable efficacy and better tolerability of pembrolizumab compared with chemotherapy, especially for the PD-L1 1% to 49% subgroup. Nevertheless, new drug approvals, based only on *P* values, without consideration to the dynamic evolution of survival curves, are challenging. In the era of personalized medicine, grouping all patients together based on a solitary—and rather imperfect—biomarker, without attempting to identify confounding determinants of efficacy, may represent a step back in our efforts to implement precision oncology. As an illustrative example, crossing survival curves in the historical IPASS study [16] prompted further investigation to identify potential determinants of efficacy of epidermal growth factor receptor inhibitors, leading to the identification of activating *EGFR* mutations as a robust predictive biomarker.

Finally, financial toxicity is an important issue with novel anticancer therapies. To preserve the sustainability of our health care systems, it is important to apply robust biomarkers for proper patient selection to achieve cost-effective strategies. In this sense, the Magnitude of Clinical Benefit Scale, developed by the European Society for Medical Oncology (ESMO), is a useful tool for the evaluation of new anti-cancer treatments. According to this scale (Form 2A, MCBS version 1.1, [17]), pembrolizumab in the ITT population of the KEYNOTE 042 trial receives a score of 2, which translates into a treatment without substantial clinical benefit, unlikely to affect clinical practice. On the contrary, in patients with PD-L1 ≥ 50% from the KEYNOTE 024 trial, pembrolizumab receives a score of 5, illustrating the difference on the magnitude of clinical benefit between the two trials and the value of a robust biomarker.

In conclusion, despite the statistically positive results of the KEYNOTE 042 trial, we are concerned that pembrolizumab monotherapy may not represent the best treatment strategy for patients with tumor PD-L1 of 1% to 49%, as they may be harmed by rapid progression on treatment. Until trials can further guide us to better identify which patients can benefit from single-agent pembrolizumab, the combination of chemotherapy with ICIs should be considered the SoC for the PD-L1 TPS 1-49% subgroup.

G. Mountzios[1*], J. Remon[2], S. Novello[3], N. Blais[4], R. Califano[5,6], T. Cufer[7], A. M. Dingemans[8], S. V. Liu[9], N. Peled[10], N. A. Pennell[11], M. Reck[12], C. Rolfo[13], D. Tan[14], J. Vansteenkiste[15], H. West[16] & B. Besse[17,18]

[1]Department of Medical Oncology, Henry Dunant Hospital Center, Athens, Greece; [2]Department of Medical Oncology, CIOCC HM Delfos Hospital, Barcelona, Spain; [3]Department of Oncology, University of Turin, AOU San Luigi, Orbassano, Italy; [4]Centre Hospitalier Universitaire de Montréal, University of Montreal, Montreal, Canada; [5]Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester; [6]Division of Cancer Sciences, University of Manchester, Manchester, UK; [7]University Clinic Golnik, Medical Faculty Ljubljana, Slovenia; [8]Department of Respiratory Medicine, Maastricht University Medical Center, Maastricht and Erasmus Medical Center, Rotterdam, The Netherlands; [9]Lombardi Comprehensive Cancer Center, Georgetown University, Washington, USA; [10]Soroka Medical Center and Ben-Gurion University, Beer-Sheva, Israel; [11]Hematology and Medical Oncology, Cleveland Clinic Taussig Cancer Institute, Cleveland, USA; [12]Lung Clinic Grosshansdorf, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany; [13]Greenebaum Comprehensive Cancer Center, University of Maryland School of Medicine, Baltimore, USA; [14]Division of Medical Oncology, National Cancer Centre, Singapore; [15]Respiratory Oncology Unit, University Hospital KU Leuven, Leuven, Belgium; [16]Department of Medical Oncology, City of Hope Comprehensive Cancer Center, Duarte, USA; [17]Cancer Medicine Department, Institut Gustave Roussy, Villejuif; [18]Université Paris-Saclay, Orsay, France
(*E-mail: gmountzios@gmail.com)

Funding

None declared.

Disclosure

GM received honoraria/consultancy from AstraZeneca, Roche, Pfizer, BMS, MSD, Takeda, Boehringer, Merck, Novartis, Amgen; received travel fees from AstraZeneca, Roche, Pfizer, BMS, MSD, Takeda, Boehringer, Merck, Novartis, Astellas, Pierre Fabre. JR: Other from MSD (advisory), other from BOEHRINGER (advisory), other from PFIZER (advisory), personal fees and other from OSE IMMUNOTHERAPEUTICS (travel), other from BMS (travel and advisory), other from ASTRAZENECA (travel and advisory), other from ROCHE (travel), outside the submitted work. SN is a advisor/speaker bureau for Astra Zeneca, BI, Celgene, Eli Lilly, MSD, Takeda, Pfizer, Roche, BMS, Abbvie. NB is a consultant honorarium to Pfizer, AZ, BMS, Merck, BI, Novartis, Takeda, Sanofi, Roche; received research grants from CCTG, Astra Zeneca. RC received honoraria and consultancy fees from AstraZeneca, Boehringer Ingelheim, Lilly Oncology, Roche, Pfizer, MSD, BMS, Takeda, and Novartis. TC received honoraria for lectures and advisory board consultations from AstraZeneca. AMD is an advisory board member of BMS, MSD, Roche, Eli Lilly, Takeda, Pfizer, Boehringer Ingelheim (all institution); received research grant from BMS (institution); received research support from Abbvie (institution). SL is an advisory board/consultant of Apollomics, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, G1 Therapeutics, Genentech/Roche, Guardant Health, Heron, Ignyta, Inivata, Janssen, Lilly, Merck, Pfizer, Regeneron, Taiho (DSMB), Takeda/Ariad, Tempus; received research grant (institution) from Alkermes, AstraZeneca, Bayer, Blueprint, Bristol-Myers Squibb, Clovis, Corvus, Debiopharm, Esanex, Genentech/Roche, Ignyta, Lilly, Lycera, Merck, Molecular Partners, OncoMed, Pfizer, Rain Therapeutics. NP is an advisor for and honorarium from AstraZeneca, AID Genomics, Boehringer-Ingelheim, BMS, E.Lilly, MSD, Novartis, Pfizer, Roche,

NovellusDx, FMI, Gaurdant360. NP received consulting fees from AstraZeneca, Merck, Eli Lilly, BMS, and Cota. MR: Amgen, Abbvie, AstraZeneca, Boehringer-Ingelheim, BMS, Celgene, Lilly, Merck, MSD, Novartis, Pfizer, Roche; received institutional support for research from BMS. CR reports speaker from MSD and GuardantHealth, scientific advisor Mylan, institutional research collaboration Biomark Inc., non-remunerated collaboration with OncoDNA, and steering scientific committee for Oncopass. DT received honoraria from Merck, Pfizer, Novartis, Boehringer Ingelheim, Roche, Takeda; performed as a advisory-consultancy for Novartis, Bayer, Boehringer Ingelheim, Celgene, Astra Zeneca, Eli-lily, Loxo; received research grant from Novartis, Astra Zeneca, GlaxoSmithKline, Bayer, Pfizer; received travel/accommodation expenses from Merck, Pfizer, Novartis, Boehringer Ingelheim, Roche, Takeda. JV is a consultancy or advisory functions for AstraZeneca, BMS, Boehringer Ingelheim, MSD, Pfizer, Roche; is a lectures for AstraZeneca, Boehringer Ingelheim, MSD, Roche, BMS. HW received honoraria from Ariad, AstraZeneca, Boehringer-Ingelheim, BMS, Celgene, Genentech/Roche, LOXO, Merck, PharmaMar, Pfizer, Spectrum, Takeda; speakers bureau for AZ, Genentech/Roche, Merck. BB reports grants from Abbvie, grants from Amgen, grants from AstraZeneca, grants from Biogen, grants from Blueprint Medicines, grants from BMS, grants from Celgène, grants from Eli-Lilly, grants from GSK, grants from Ignyta, grants from IPSEN, grants from Merck KGaA, grants from MSD, grants from Nektar, grants from Onxeo, grants from Pfizer, grants from Pharma Mar, grants from Sanofi, grants from Spectrum Pharmaceuticals, grants from Takeda, grants from Tiziana Pharma, outside the submitted work.

References

1. Planchard D, Popat S, Kerr K et al. Metastatic non-small cell lung cancer: eSMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol 2018; 29(Supp 4): iv192–iv237.
2. Gandhi L, Rodríguez-Abreu D, Gadgeel S et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 2018; 378(22): 2078–2092.
3. Gadgeel S, Garassino MC, Esteban E et al. KEYNOTE-189: updated OS and progression after the next line of therapy (PFS2) with pembrolizumab (pembro) plus chemo with pemetrexed and platinum vs placebo plus chemo for metastatic nonsquamous NSCLC. J Clin Oncol 2019; 37(suppl; abstr 9013).
4. Paz-Ares L, Luft A, Vicente D et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. N Engl J Med 2018; 379(21): 2040–2051.
5. Reck M, Rodríguez-Abreu D, Robinson AG et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 2016; 375(19): 1823–1833.
6. Reck M, Rodríguez-Abreu D, Robinson AG et al. Updated analysis of KEYNOTE-024: pembrolizumab versus platinum-based chemotherapy for advanced non-small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater. J Clin Oncol 2019; 37(7): 537–546.
7. Mok TSK, Wu Y-L, Kudaba I et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet 2019; 393(10183): 1819–1830.
8. Herbst RS, Baas P, Kim D-W et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2016; 387(10027): 1540–1550.
9. Borghaei H, Paz-Ares L, Horn L et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 2015; 373(17): 1627–1639.
10. Brahmer J, Reckamp KL, Baas P et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 2015; 373(2): 123–135.
11. Fehrenbacher L, von Pawel J, Park K et al. Updated efficacy analysis including secondary population results for OAK: a randomized phase III study of atezolizumab versus docetaxel in patients with previously treated advanced non-small cell lung cancer. J Thorac Oncol 2018; 13(8): 1156–1170.
12. Haslam A, Prasad V. When is crossover desirable in cancer drug trials and when is it problematic?. Ann Oncol 2018; 29(5): 1079–1081.
13. Carbone DP, Reck M, Paz-Ares L et al. First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. N Engl J Med 2017; 376(25): 2415–2426.
14. Rizvi NA, Chul Cho B, Reinmuth N et al. Durvalumab with or without tremelimumab vs platinum-based chemotherapy as first-line treatment for metastatic non-small cell lung cancer: MYSTIC. Ann Oncol 2018; 29(Suppl 10): mdy511.005.
15. Nosaki K, Saka H, Hosomi Y et al. Safety and efficacy of pembrolizumab monotherapy in elderly patients with PD-L1–positive advanced non–small-cell lung cancer: pooled analysis from the KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042 studies. Lung Cancer 2019; 135: 188–195.
16. Fukuoka M, Wu Y-L, Thongprasert S et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). J Clin Oncol 2011; 29(21): 2866–2874.
17. Cherny NI, Dafni U, Bogaerts J et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Ann Oncol 2017; 28(10): 2340–2366.

doi:10.1093/annonc/mdz295
Published online 3 September 2019

International consensus for advanced bladder cancer: an opportunity between the lines

Every year, about half a million people in the world are diagnosed with bladder cancer [1], with the industrialized nations of North America and Europe leading the incidence and with a rising burden in the developing world. While urothelial cancer dominates, uncommon variant histologies challenge clinicians with their distinct characteristics and therapeutic response profiles. The pathological and prognostic diversity of bladder cancer, heterogeneity of presentations and overall aggressive nature of advanced bladder cancer pose unique and often demanding challenges to the patient and treating clinician. As a result, there exist considerable differences in the practice of bladder cancer care across the world with an urgent need to homogenise practice and outcomes.

The European Association of Urology (EAU) and European Society of Medical Oncology (ESMO) have recognized conflicting evidence and lacunae in the existing guidelines in advanced bladder cancer [2, 3]. The latest effort from the EAU and ESMO,