From the adaption of chemotherapy in the 1990’s after the landmark meta-analysis (1) to the pivotal randomized trial pointing to “dealer’s choice” for platinum-doublet regimens (2), followed by treatment refinement using molecular profiling and targeted therapy for defined sub-populations (3,4), we now have the emergence of a new era to treat advanced non-small cell lung cancer (NSCLC). Checkpoint inhibitor therapy has moved from 2nd line and beyond salvage therapy, to first-line therapy in advanced NSCLC with the results of the KEYNOTE-189 trial (5) on the heels of KEYNOTE-024 (6). Coupled with the recent presentations of KEYNOTE-042 (7) and KEYNOTE-407 (8) and other published front-line checkpoint inhibitor studies including CheckMate-026 (9), CheckMate-227 (10), and I Mpower150 (11), I will put into context the results of KEYNOTE-189 in the present state of clinical practice.

The KEYNOTE-189 study randomized metastatic non-squamous NSCLC patients without sensitizing EGFR or ALK aberrations who had not received prior treatment for metastatic disease in a double-blind fashion 2:1 to either platinum-pemetrexed with 200 mg pembrolizumab or placebo every 3 weeks for 4 cycles, followed by pembrolizumab or placebo for a total of 35 cycles with pemetrexed (5). Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance score of 0–1 and the absence of symptomatic central nervous system metastases, history of noninfectious pneumonitis that required the use of glucocorticoids, active autoimmune disease, or active use of systemic immunosuppressive treatment. Patients were also excluded if they had received more than 30 Gy of radiotherapy to the lung in the previous 6 months prior to enrollment. Programmed death-ligand 1 (PD-L1) immunohistochemical expression [tumor proportion score (TPS), ≥1% vs. <1%], choice of platinum-based drug (cisplatin vs. carboplatin), and smoking history (never vs. former or current) were patient randomization stratification factors. Investigators could choose between cisplatin 75 mg/m$^2$ or carboplatin (area under the concentration-time curve, 5 mg per milliliter per minute), while pemetrexed was dosed at 500 mg/m$^2$. Radiographic response was assessed by RECIST 1.1 criteria (12). The two primary end points were overall survival (OS) (any cause of death from the time of randomization) and progression-free survival (PFS) (as assessed by earliest event, either by independent central radiologic review or any cause of death, from the time from randomization). The study allowed crossover for patients in the placebo-combination group who had verified disease progression.

Overall, 965 patients were screened for enrollment. The main reasons for exclusion prior to randomization included: presence of an activating epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) aberration, ECOG performance status score ≥2, lack of written, informed consent, and active central nervous system metastasis and/or carcinomatous meningitis. Enrollment of 616 patients occurred between February 26, 2016 and March 6, 2017 at 118 sites, mostly from Europe and North America. A TPS score ≥1% was present in 63% of these
patients. The effective crossover rate to immunotherapy for the placebo-combination group was 41.3%, including 67 patients receiving pembrolizumab monotherapy after disease progression and an additional 18 patients receiving immunotherapy outside of the KEYNOTE-189 trial.

At 12 months, the estimated proportion of patients out of the intention-to-treat (ITT) population who were alive was 69.2% (95% CI, 64.1 to 73.8) in the pembrolizumab-combination group and 49.4% (95% CI, 42.1 to 56.2) in the placebo-combination group. The median OS was not reached in the pembrolizumab-combination group, while it was 11.3 months (95% CI, 8.7 to 15.1) in the placebo-combination group (HR for death =0.49; 95% CI, 0.38 to 0.64; P<0.001). The benefit of the pembrolizumab-combination was observed across the three TPS cutoffs of <1%, 1–49%, and ≥50%, with 12-month OS rates, 61.7% vs. 52.2%; (HR =0.59; 95% CI, 0.38 to 0.92), 71.5% vs. 50.9%; (HR =0.55; 95% CI, 0.34 to 0.90), and 73.0% vs. 48.1% (HR =0.42; 95% CI, 0.26 to 0.68); respectively. There were also statistically significant differences for median PFS and overall response rate (ORR) favoring the pembrolizumab-combination. The 95% CI for the ORR for the placebo-combination was in line with the ORR for induction platinum-pemetrexed in a similar patient population of non-squamous NSCLC (13). Diarrhea and rash, grade 3 febrile neutropenia, and acute kidney injury were observed more frequently in the pembrolizumab-combination group. There were also three cases of pneumonitis (immune-mediated AE) that led to death in the pembrolizumab-combination group.

While not unique to this particular study and prevalent in other present-day randomized phase III trials in oncology, one questions why the study designers use an unequal allocation rather than a 1:1 randomization scheme. Unequal randomization schemes are less efficient, requiring 12% more patients, have issues with validity as they can produce a biased belief in patients, caregivers, and investigators after randomization allocation to the investigational arm (14). One could argue that 2:1 randomization to the pembrolizumab-combination provides added safety information about this regimen, however, there are a number of pembrolizumab plus chemotherapy trials in NSCLC and other cancers that completed or were ongoing at the time of KEYNOTE-189’s conduct.

Nonetheless, KEYNOTE-189’s results show significant improvement in OS for the pembrolizumab-combination group. How is clinical practice impacted by the results of this study, in the context of the other recent readouts of combination studies with immunotherapy in NSCLC? First, a high-level overview of the results, and where applicable, critiques of six of these studies follow below.

KEYNOTE-407 is similar to the KEYNOTE-189 study design, except it allowed only a squamous NSCLC population and evaluated a chemotherapy backbone of carboplatin with either paclitaxel or nab-paclitaxel with or without pembrolizumab (8). Interestingly, the study appropriately had a 1:1 randomization design. Overall and similar to KEYNOTE-189, both the co-primary endpoints of PFS and OS were met in KEYNOTE-407, irrespective of the TPS score.

KEYNOTE-024 allowed both non-squamous and squamous NSCLC without EGFR or ALK aberrations, TPS ≥50%, and randomized patients 1:1 to either single agent pembrolizumab or investigator’s choice of platinum-doublet therapy (6). The primary endpoint was PFS, while OS was a secondary endpoint. Crossover to pembrolizumab at disease progression was allowed. Pembrolizumab significantly improved PFS and OS compared with chemotherapy.

KEYNOTE-042 allowed both non-squamous and squamous NSCLC without EGFR or ALK aberrations, any PD-L1+, and randomized patients 1:1 to either single agent pembrolizumab or either carboplatin and pemetrexed or carboplatin and paclitaxel (7). The primary endpoint was OS with evaluation of TPS scores of ≥50%, ≥20%, and ≥1%; and pembrolizumab significantly improved OS for all three of these TPS cutoffs. However, this OS benefit is driven by high TPS scores, and an ad-hoc analysis for TPS 1–49%, showed no significant OS benefit for pembrolizumab. It is important to highlight that this trial was conducted outside the United States (US) and did not allow crossover to pembrolizumab. Thus, depending on the treatment options at the site of enrollment, patients assigned to the chemotherapy arm may not have been offered a checkpoint inhibitor at disease progression—or what is considered a standard of care 2nd line option in the US.

CheckMate-026 allowed both non-squamous and squamous NSCLC patients without EGFR or ALK aberrations, ≥1% PD-L1+, and randomized patients 1:1 to either single agent nivolumab or investigator’s choice of a platinum doublet (9). The primary endpoint was PFS for those with ≥5% PD-L1+, and crossover to nivolumab at disease progression was allowed. This randomized phase III study did not meet its primary endpoint and also did not demonstrate a statistically different OS for patients with ≥1% PD-L1+. 

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CheckMate-227 allowed both non-squamous and squamous NSCLC patients without EGFR or ALK aberrations, any PD-L1+, and randomized patients 1:1:1 to receive nivolumab plus ipilimumab, nivolumab monotherapy, or chemotherapy (if PD-L1 was ≥1%); or randomized 1:1:1 to receive nivolumab plus ipilimumab, nivolumab plus chemotherapy, or chemotherapy (if PD-L1 was <1%) (10). The trial did not allow crossover which may have impacted subsequent access to checkpoint inhibitor therapy depending on the location where the patient was enrolled. This study had two co-primary endpoints (I) PFS with nivolumab plus ipilimumab versus chemotherapy based on tumor mutational burden (TMB) with a pre-specified cutoff of ≥10 mutations per megabase and (II) OS with nivolumab plus ipilimumab versus chemotherapy in a patient population selected on the basis of the PD-L1 expression level. The publication did not report on the second co-primary endpoint (OS), and at the interim analysis the data safety and monitoring board committee recommended that the study continue. This was most likely recommended because the OS differences between the compared groups were not statistically significant to warrant halting the trial. Surprisingly, only 58% of those randomized were able to get a TMB result and the publication only reported that PFS, the less clinically meaningful co-primary endpoint, was met. The outcome for the more clinically important co-primary endpoint (OS) remains unknown at the time of this editorial submission. Interestingly, both the publication and study protocol are silent on any objectives evaluating OS in the nivolumab plus chemotherapy arm. This calls into question why a study treatment that affects 1/3 of all enrolled patients with PD-L1+ <1% (177 of 550) does not assess the nivolumab plus chemotherapy’s impact on OS compared with either of the other randomized cohorts. In the article’s discussion, the authors explain that the 42% failure rate for obtaining a TMB score was primarily due limited availability of sufficient quantity or quality of tumor specimens. This explanation is further unpalatable since these are samples from subjects enrolled on an international phase III trial, not routine clinical practice, with a protocol screening mandate that either archival or a recent tumor biopsy be submitted to a third party for PD-L1 status determination. In fact, 1,649 of the randomized patients had tumor available to undergo TMB testing, yet only 1,004 of them had a TMB result (1,004 of 1,739 randomized patients). After stating that TMB can be expected for 80–95% of patient samples undergoing testing, the supporting reference for this attestation is the website address of the vendor that markets the TMB test (10).

IMpower150 allowed both non-squamous and squamous NSCLC patients, any PD-L1+, and randomized patients 1:1:1 to receive bevacizumab plus carboplatin and paclitaxel (BCP), atezolizumab plus carboplatin and paclitaxel (ACP), or atezolizumab plus bevacizumab and carboplatin and paclitaxel (ABC) (11). The trial did not allow crossover which may have impacted subsequent access to checkpoint inhibitor therapy depending on where the patient was enrolled. This study had two co-primary endpoints limited to patients without EGFR or ALK aberrations (I) PFS (as assessed by investigators according to RECIST criteria) and PFS for patients who had a high expression of effector T-cell (Teff) gene signature in tumor and (II) OS. These primary endpoints prioritized evaluating ABC versus BCP before analyzing ACP versus BCP. The study met its primary endpoints showing superiority of ABC versus BCP. The publication did not report on the results of ACP, so we do not know if or how much added benefit bevacizumab provides compared with BCP. This could have cost and additional toxicity implications for patients treated with ABCP relative to other immunotherapy and chemotherapy combinations.

Beyond PD-L1, TMB, and Teff signature, recent preclinical data has demonstrated that the composition of the gut microbiome can have predictive features on how patients treated with immunotherapy may fare. This has been followed by a provocative publication, showing inferior survival in patients with NSCLC that received antibiotic therapy (which can alter the host gut microbiome) within 30 days of initiating checkpoint inhibitor treatment for their cancer (15). Other theranostics, such as cell-free tumor DNA are also being explored for cancer treatment identification and monitoring (16,17). An additional point to mention is the observation that RECIST 1.1 criteria is insufficient to determine tumor progression in patients receiving these class of agents (immune-response consensus criteria are needed) and that OS remains the main barometer for efficacy (18).

In conclusion, the therapeutic landscape for NSCLC has changed dramatically in the last 20 years. Based on the contemporary results of these recent phase III trials, KEYNOTE-189 and KEYNOTE-407 point to OS superiority for first-line treatment of metastatic NSCLC without EGFR or ALK aberrations and TPS <50% using pembrolizumab plus chemotherapy or ABCP (based on IMpower150) in any PD-L1+. This comes with a caveat, that if ACP also shows an OS advantage over BCP, then ACP would be favored over ABCP in that population.
Keeping in mind cost and toxicity when combining multiple agents, single agent pembrolizumab demonstrates OS superiority for metastatic NSCLC patients without EGFR or ALK aberrations having a TPS score ≥50%. The next phase of debate will be finding the most cost-effective combination therapy versus single agent or immunotherapy combination treatment for first-line treatment in this disease in order to move OS curves higher and further to the right.

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Footnote
Conflicts of Interest: Dr. GJ Weiss reports personal fees and other from Circulogene, personal fees from Paradigm, personal fees and other from Angiex, personal fees from Igynta, personal fees from Pfizer, personal fees from Merck, personal fees from IDEA Pharma, personal fees from GLG Council, other from Cambridge Healthcare Institute, personal fees from Novartis, other from Tesaro, other from Nantworks, outside the submitted work; in addition, Dr. GJ Weiss has a patent PCT/US2011/020612 issued.

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