The ascent of immune checkpoint inhibitors: is the understudy ready for a leading role?

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The recent approval of pembrolizumab as second-line treatment for any solid tumor with high-level microsatellite instability or mismatch repair deficiency agnostic of tissue and origin has shattered a glass ceiling for immune checkpoint inhibitors. No longer bound to a specific cancer diagnosis but rather a biomarker, pembrolizumab has heightened a burgeoning optimism towards the drug class. Yet how these agents should carve out additional indications is subject to fierce debate. While we know immune checkpoint inhibitors may not be A-list actors ready to carry first-line treatment plans on their own across all tumor types, can we enable these agents by carefully crafting a supporting cast and distribution strategy? Should they be reserved for leading roles only in certain niche markets defined by biomarkers? Or are they most successful as back-up when the show must go on and the best option is not available?

To date, there are six United States Food & Drug Administration approved immune checkpoint inhibitors, mostly indicated for second-line treatment (Table 1). Current targets include inhibitory T-cell receptors cytotoxic T-lymphocyte associated protein 4 (CTLA4) and programmed death-1 (PD-1) as well as transmembrane protein PD-1 ligand (PD-L1); although others are under investigation, such as stimulatory OX40 and inhibitory B7-H3, lymphocyte activation-3 (LAG3), and T-cell immunoglobulin and mucin-domain containing-3 (TIM3). By blocking receptors or ligands that dampen immune activity (or activating receptors or ligands that promote it), checkpoint inhibitors ideally reinvigorate or expand T-cell anticancer response. In 2012, Topalian and colleagues published the results of a basket trial with PD-1 inhibitor BMS-936558, now known as nivolumab, which suggested significant responses in a small subset of heavily-pretreated patients with an overall response rate (ORR) of 28% in advanced melanoma, 18% in non-small cell lung cancer (NSCLC), and 28% in renal cell carcinoma; although there were no responders in castration-resistant prostate and colorectal cancer. The responses in this trial were remarkably durable; 20 of 31 responses lasted one year or longer, and five-year follow up of the CA209-003 cohort of NSCLC reported earlier this year revealed 16 survivors, four times as many that would be expected based on estimates from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) Program. These data are grossly characteristic of the literature for single-agent checkpoint inhibitors used as salvage therapy, and while an ORR of 20% is somewhat underwhelming, the chance of durable responses in cancers with otherwise poor prognosis has led to considerable effort to magnify ORR to demonstrate overall survival (OS) benefit.

There have been three main strategies to this end in checkpoint inhibitor clinical trials (Figure 1). One strategy has been to change the population treated by altering the sequence of checkpoint inhibitor single-agent therapy, which has seen variable success in the first-line setting (Table 2). In unselected patients with advanced melanoma, nivolumab bested dacarbazine with an ORR of 40% vs. 13.9% and 12-month OS of 72.9% opposed to 42.1%, reflected in a hazard ratio (HR) of 0.43 with a 95% confidence interval (CI) of 0.34–0.56 (P < 0.001), although it may be argued the efficacy of chemotherapy in melanoma is relatively low. Tremelimumab nevertheless failed to beat standard-of-care chemotherapy in previously untreated melanoma, and ipilimumab single-agent therapy eked out a niche as adjuvant treatment in high-risk resected melanoma, which has since been upheld by a five-year OS HR of 0.72 (95% CI 0.58–0.88, P=0.001). While optimal duration of treatment remains...
unknown for most checkpoint inhibitors, this study was unique in that dosing was set at every 3 weeks for 4 doses followed by every 3 months for up to 3 years only. It is one of the first randomized, placebo-controlled trials to show durable survival benefit in a capped treatment setting.

In cancer types other than melanoma, single-agent first-line checkpoint inhibitors have had mixed results. Pembrolizumab boasted an ORR of 56% in Merkel cell carcinoma in a study of 26 patients, although it is not yet approved for this use. Atezolizumab found a role in initial treatment of cisplatin-ineligible patients with advanced urothelial carcinoma with an ORR of 23%, although the drug missed its primary endpoint of survival in those that had progressed on platinum-based chemotherapy. More recently, checkpoint inhibitors have been explored as neoadjuvant therapy with promising results in head and neck squamous cell carcinoma and NSCLC, although these studies require validation in larger cohorts. So far, adjustments in therapy sequencing of single-agent checkpoint inhibitors have been restricted to immunotherapy-favorable cancer subtypes, but even so, there has been no consistent evidence of first-line survival benefit in all-comers outside of melanoma. Given the extremely high cost of checkpoint inhibitors and unclear duration for which to continue treatment when given first-line, it is likely this approach will continue to be closely scrutinized by providers, payers, and drug regulatory agencies.

Another approach has been to identify a group of patients more likely to respond via biomarker selection. Although the

Table 1: Current United States Food & Drug Administration approved indications for immune checkpoint inhibitors

| Agent     | Target | Indication                  | Treatment line                  | Year |
|-----------|--------|-----------------------------|---------------------------------|------|
| Atezolizumab | PD-L1 | NSCLC, advanced             | Second                          | 2016 |
|           |        | Urothelial carcinoma, advanced | Second                          | 2016 |
| Avelumab   | PD-L1 | Merkel cell carcinoma       | First/second                    | 2017 |
|           |        | Urothelial carcinoma, advanced | Second                          | 2017 |
| Durvalumab | PD-L1 | Urothelial carcinoma, advanced | Second                          | 2017 |
| Ipilimumab | CTLA4  | Melanoma, advanced          | Second                          | 2011 |
|           |        | Melanoma, advanced          | First (+ nivolumab)             | 2015 |
|           |        | Melanoma, stage III         | Adjuvant                        | 2015 |
| Nivolumab  | PD-1   | Melanoma, advanced          | Second                          | 2014 |
|           |        | Melanoma, advanced          | First (+ ipilimumab)            | 2015 |
|           |        | NSCLC, advanced             | Second                          | 2015 |
|           |        | RCC, advanced               | Second                          | 2015 |
|           |        | Classic Hodgkin’s lymphoma  | Fourth                          | 2016 |
|           |        | H&N SCC, recurrent or advanced | Second                         | 2016 |
|           |        | Urothelial carcinoma, advanced | Second                          | 2017 |
| Pembrolizumab | PD-1 | Melanoma, advanced          | Second                          | 2014 |
|           |        | NSCLC                       | Second if PD-L1 overexpressed ≥1% | 2015 |
|           |        | Melanoma, advanced          | First                           | 2015 |
|           |        | H&N SCC, advanced           | Second                          | 2016 |
|           |        | NSCLC                       | First if PD-L1 overexpressed ≥50% | 2016 |
|           |        | Classic Hodgkin’s lymphoma  | Fourth                          | 2017 |
|           |        | Urothelial carcinoma, advanced | Second                          | 2017 |
|           |        | NSCLC, non-SCC              | First (+ pemetrexed and carboplatin) | 2017 |
|           |        | MSI-high cancer             | Second                          | 2017 |

CTLA4: cytotoxic T-lymphocyte associated protein 4. H&N: head and neck. MSI: microsatellite instable. NSCLC: non-small cell lung cancer. PD-1: programmed death-1 checkpoint inhibitor. PD-L1: programmed death ligand-1. SCC: squamous cell carcinoma.
initial nivolumab trial did not identify colorectal cancer (CRC) responders, by selecting for mismatch-repair deficiency, Diaz and colleagues achieved an ORR of 71% in refractory CRC patients treated with pembrolizumab. Although the trial followed only 11 patients with mismatch-repair deficient CRC for 20 weeks, HR was 0.10 for progression (P < 0.001) and 0.22 for death (P=0.05) compared to mismatch repair-proficient CRC. This trial was instrumental in the approval of pembrolizumab as second-line treatment for any solid tumor with high-level microsatellite instability or mismatch repair deficiency.

Some success, albeit not as profound, has been seen with tumor PD-L1 immunohistochemistry (IHC) with the 22C3 assay as a means for enriching patient selection in previously-treated NSCLC. Using a PD-L1 cut point of 50% that was validated prospectively, Garon and colleagues achieved an ORR of 45.2% that was more than double that of non-selected patients treated with pembrolizumab, which was reflected in a progression-free survival (PFS) of 6.3 months as opposed to 3.7 months in the unselected population. This approach was evaluated in the first-line setting with KEYNOTE-024, which compared patients with advanced NSCLC with PD-L1 expression of 50% or greater randomized to pembrolizumab vs. platinum-based chemotherapy. Those treated with pembrolizumab had an ORR of 44.8% vs. 27.8% with chemotherapy, reflected in a median PFS of 10.3 months vs. 6.0 months and OS HR of 0.6 (95% CI 0.41–0.89, P=0.005) Carbone and colleagues attempted a similar study with nivolumab in advanced NSCLC enriched by PD-L1 selection in CheckMate-026, yet this study did not show a benefit to the PD-1 inhibitor as PFS was 4.2 months with nivolumab vs. 5.9 months with standard chemotherapy. As pembrolizumab and nivolumab are similar drugs, it has been suggested that the selected cut point and PD-L1 IHC staining with the 28-8 assay may have been problematic. Given the results of the PACIFIC trial, which is discussed below, it is also worth considering whether previous radiotherapy played a role in these discordant results. The KEYNOTE-024 study did not publish whether its patients received prior radiotherapy, although the KEYNOTE-001 study had roughly similar representation compared to all three arms of the CheckMate-026 study (43% vs. 38%–40%, respectively). Additional investigation into this topic may be considered. Ultimately, it is clear PD-L1 staining represents a helpful biomarker, but additional efforts may and should be taken to further hone...
patient selection, especially considering that other markers of response, such as infiltration of T-cell subsets and tumor mutation burden, do not always correlate strongly with PD-L1 expression.

A third strategy to enhance outcomes has been to add a second agent to a checkpoint inhibitor. In advanced melanoma, CheckMate-069 added nivolumab to ipilimumab as first-line therapy and increased ORR to 61%\textsuperscript{23}, further substantiated by a 2-year OS improvement of 63.8% compared to 53.6%\textsuperscript{24}. However, when this approach was adopted in NSCLC, three out of every four patients discontinued treatment due to toxicity or progression\textsuperscript{25}. This similarly was reflected in Antonia and colleagues\textsuperscript{26} evaluation of durvalumab and tremelimumab in NSCLC, which had only 25% of patients able to continue treatment. This is being evaluated further in the MYSTIC trial, which compares first-line durvalumab monotherapy and durvalumab in combination with tremelimumab vs. platinum-based standard-of-care chemotherapy in metastatic NSCLC. While the trial did not meet its primary endpoint of PFS, OS data for durvalumab monotherapy and durvalumab combined with tremelimumab are expected in 2018\textsuperscript{27}. In small cell lung cancer (SCLC), the combination of nivolumab and ipilimumab in the second-line setting fared somewhat better, although the ORR of approximately 20% was accompanied by grade 3–4 reactions in 30%\textsuperscript{28}. Attention since has been directed towards combining checkpoint inhibitors with other treatments with non-overlapping toxicities, such as radiation and chemotherapy. Other inhibitors of tumor-mediated immune suppression outside of the immune checkpoint, such as indoleamine 2, 3-dioxygenase-1 (IDO-1) inhibitors, also have been combined
with checkpoint inhibitors with encouraging preliminary results\textsuperscript{20}, but require further clinical validation. While there were initial concerns that concurrent treatment may antagonize an immune response, work by Galluzzi and colleagues\textsuperscript{30,31} has revealed the opposite. Certain types of chemotherapy, including 5-fluorouracil, cisplatin, doxorubicin, gemcitabine, paclitaxel, and topotecan, as well as radiation, may heighten antigenicity and adjuvanticity and improve immunostimulation by suppressing regulatory T-cells and recruitment of immunosuppressive immune cells. In a retrospective review of the KEYNOTE-001 trial, Shaverdian and colleagues\textsuperscript{20} noted that PFS with pembrolizumab was significantly longer in patients who had previously received radiotherapy vs. those who did not receive radiotherapy, leading to a respective OS of 10.7 months vs. 5.3 months with a HR of 0.58 (95% CI 0.36–0.94, \textit{P}=0.026). This hypothesis was explored prospectively in the PACIFIC trial, in which locally advanced NSCLC patients who had received definitive concurrent chemotherapy and radiotherapy were randomized to durvalumab or placebo for up to 12 months. Patients receiving durvalumab had increased ORR of 28.4% vs. 16.0% (\textit{P}<0.001) and PFS of 16.8 months vs. 5.6 months, consistent with a HR of 0.52 (95% CI 0.42–0.65, \textit{P}<0.001).\textsuperscript{32}

Even so, chemotherapy in combination with checkpoint inhibitors has been shown to have suboptimal results in less immunogenic cancers. In SCLC, the combination of phased ipilimumab with paclitaxel and carboplatin first-line had some efficacy with OS 12.9 months vs. 9.9 months, although concurrent ipilimumab with chemotherapy performed worse with an OS of 9.1 months\textsuperscript{33}. Ipilimumab since has been combined with etoposide and platinum in a phased approach in extensive-stage SCLC with the addition of maintenance ipilimumab vs. placebo; unfortunately, there was no significant OS benefit\textsuperscript{34}. In pancreatic cancer, tremelimumab has been combined with gemcitabine as first-line therapy in metastatic disease, but despite being tolerable, the median OS of 7.4 months failed to show significant survival benefit beyond that expected for gemcitabine alone\textsuperscript{35}.

The combination of chemotherapy and checkpoint inhibition in more immunogenic cancers has been more encouraging. In late 2016, Langer and colleagues\textsuperscript{36} published the results of KEYNOTE-021, a study in which patients received pembrolizumab in addition to platinum-doublet chemotherapy as first-line treatment for non-squamous NSCLC. The combination therapy group had an ORR of 55% compared to 29% of the chemotherapy only group, with similar grade 3 or higher toxicities and percentages of patients discontinuing the study due to adverse events (10%)\textsuperscript{36}. Subset analysis by PD-L1 staining revealed that patients with less than 1% and 50% or more PD-L1 staining benefited more from combination treatment than chemotherapy, while patients with 1%–49% PD-L1 staining did not. These results potentially could be explained by the small number of patients who were then broken down into smaller groups based on PD-L1 staining. The results from the CheckMate-227 study, in which patients with stage IV NSCLC were randomized among first-line nivolumab, nivolumab plus ipilimumab, and nivolumab with platinum-doublet chemotherapy compared to control arm platinum-doublet chemotherapy, have yet to be reported\textsuperscript{37}. Interestingly, NSCLC patients treated with checkpoint inhibitors in the salvage setting that progress and go on to other chemotherapy may have improved outcomes compared to those that do not receive checkpoint inhibitors. A retrospective review found disease control in 78% vs. 60% refractory NSCLC patients, respectively, with an odds ratio for partial response of 0.30 is for those without prior exposure to immunotherapy\textsuperscript{38}. Further investigation into sequencing therapies is warranted.

How checkpoint inhibitor clinical trials strategize to optimize outcomes via reaching new populations of patients, more carefully selecting patients, and combining and sequencing therapies helps us understand the efficacy of these agents. From the success of first-line therapy in advanced melanoma and metastatic NSCLC, the gains in survival in adjuvant ipilimumab in locally advanced melanoma and maintenance durvalumab in locally advanced NSCLC, and the rare but durable efficacy as salvage treatment in a variety of immunogenic cancers, it is obvious immune checkpoint inhibitors have progressed far beyond an understudy role. Yet as seen in the negative CheckMate-026 study, checkpoint inhibitors still require careful guidance and may not be ready to lead treatment plans unconditionally. Questions remain regarding optimal duration of therapy, the limits of durable response, and optimal combinations and treatment sequencing. Moreover, in a world with spiraling healthcare costs, the high price of these agents cannot be ignored. Nevertheless, checkpoint inhibitors are rising stars who have not yet reached their full potential. Much remains to be seen.

**Conflict of interest statement**

No potential conflicts of interest are disclosed.

**References**

1. United States Food and Drug Administration. FDA grants
accelerated approval to pembrolizumab for first tissue/site agnostic indication. [Accessed 15 June 2017]. Available from: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm560040.htm.

2. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012; 12: 252-64.

3. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity. 2013; 39: 1-10.

4. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti- PD-1 antibody in cancer. N Engl J Med. 2012; 366: 2443-54.

5. American Association for Cancer Research. Five-year survival rate for nivolumab-treated advanced lung cancer patients. 2017. [Accessed 18 October 2017]. Available from: http://www.aacr.org/Newsroom/Pages/News-Release-Detail.aspx?ItemID=1031-.WefyZ0yZOYU.

6. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015; 372: 320-30.

7. Ribas A, Kefford R, Marshall MA, Punt CJ, Haanen JB, Marmol M, et al. Phase III randomized clinical trial comparing tremelimumab with standard-of-care chemotherapy in patients with advanced melanoma. J. Clin. Oncol. 2013; 31: 616-22.

8. Eggermont AM, Chiarion-Sileni V, Grob JJ, Dummer R, Wolchok JD, Schmiidt H, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. Lancet Oncol. 2015; 16: 522-30.

9. European Society of Medical Oncology. Ipilimumab for melanoma: new data show survival benefit in the adjuvant setting and dose–response in metastatic disease. [Accessed 18 October 2017]. Available from: http://www.esmo.org/Conferences/Past-Conferences/ESMO-2016-Congress/News-Articles/Ipilimumab-for-melanoma-New-data-show-survival-benefit-in-the-adjuvant-setting-and-dose-response-in-metastatic-disease.

10. Nghiem PT, Bhatia S, Lipson EJ, Kudchadkar RR, Miller NJ, Annamalai L, et al. PD-1 blockade with pembrolizumab in advanced merkel-cell carcinoma. N Engl J Med. 2016; 374: 2542-52.

11. Balar AV, Galsky MD, Rosenberg JE, Powles T, Petrylak DP, Bellmunt J, et al. Atezolizumab as first-line treatment in cisplatin- ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet. 2017; 389: 67-76.

12. Roche. Roche provides update on phase III study of Tecentriq® (atezolizumab) in people with previously treated advanced bladder cancer. 2017. [Accessed 16 October 2017]. Available from: https://www.roche.com/media/store/releases/med-cor-2017-05-10.htm.

13. Uppaluri R, Zolkind P, Lin TX, Nussenbaum B, Jackson RS, Rich J, et al. Neoadjuvant pembrolizumab in surgically resectable, HPV negative, locally advanced head and neck squamous cell carcinoma (HNSCC). In: 2017 ASCO Annual Meeting, Abstract number 6012. Chicago, IL: American Society of Clinical Oncology (ASCO), 2017.

14. Chaft JE, Forde PM, Smith KN, Anagnostou V, Cottrell TR, Taube JM, et al. Neoadjuvant nivolumab in early-stage, resectable non-small cell lung cancers. In: 2017 ASCO Annual Meeting, Abstract number 8505. Chicago, IL: American Society of Clinical Oncology (ASCO), 2017.

15. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med. 2015; 372: 2509-20.

16. Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med. 2015; 372: 2018-28.

17. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csáosi T, Fulop A, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med. 2016; 373: 1823-33.

18. Carbone DP, Reck M, Paz-Ares L, Creelan B, Horn L, Steins M, et al. First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. N Engl J Med. 2017; 376: 2415-26.

19. Garon EB. Cancer immunotherapy trials not immune from imprecise selection of patients. N Engl J Med. 2017; 376: 2483-5.

20. Shaverdian N, Lisberg AE, Bornayyan K, Veruttipong D, Goldman JW, Formenti SC, et al. Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial. Lancet Oncol. 2017; 18: 895-903.

21. Tumeck PC, Harview CL, Yearley JH, Shintaku IP, Taylor EJM, Robert L, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature. 2014; 515: 568-71.

22. Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science. 2015; 348: 124-8.

23. Postow MA, Chesney J, Pavlick AG, Robert C, Grossmann K, McDermott D, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med. 2015; 372: 2006-17.

24. Hodi FS, Chesney J, Pavlick AC, Robert C, Grossmann KF, McDermott DF, et al. Combined nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial. Lancet Oncol. 2016; 17: 1558-68.

25. Hellmann MD, Rizvi NA, Goldman JW, Gettinger Scott N, Borghaei Hossein, Brahmer Julie R, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. Lancet Oncol. 2017; 18: 31-41.

26. Antonia S, Goldberg SB, Balmanoukian A, Chaft JE, Sanborn RE, Gupta A, et al. Safety and antitumour activity of durvalumab plus tremelimumab in non-small cell lung cancer: a multicentre, phase 1b study. Lancet Oncol. 2016; 17: 299-308.

27. AstraZeneca. AstraZeneca reports initial results from the ongoing MYSTIC trial in stage IV lung cancer. [Accessed 17 October 2017]. Available from: https://www.astrazeneca.com/media-centre/press-releases/2017/astrazeneca-reports-initial-results-from-the-ongoing-
Antonia SJ, López-Martin JA, Bendell J, Ott PA, Taylor M, Eder JP, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. Lancet Oncol. 2016; 17: 883-95.

Hamid O, Bauer TM, Spira AI, Smith DC, Olszanski AJ, Tarhini AA, et al. Safety of epacadostat 100 mg bid plus pembrolizumab 200 mg Q3W in advanced solid tumors: Phase 2 data from ECHO-202(KEYNOTE-037). In: 2017 ASCO Annual Meeting. Abstract number 3012. Chicago, IL: American Society of Clinical Oncology (ASCO), 2017.

Galluzzi L, Buqué A, Kepp O, Zitvogel L, Kroemer G. Immunological effects of conventional chemotherapy and targeted anticancer agents. Cancer Cell. 2015; 28: 690-714.

Galluzzi L, Buqué A, Kepp O, Zitvogel L, Kroemer G. Immunogenic cell death in cancer and infectious disease. Nat Rev Immunol. 2017; 17: 97-111.

Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. N Engl J Med. 2016; 375: 1728-38.

Reck M, Bondarenko I, Luft A, Serwatowski P, Barlesi F, Chacko R, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial. Ann Oncol. 2013; 24: 73-83.

Reck M, Luft A, Szczesna A, Havel L, Kim SW, Akerley W, et al. Phase III randomized trial of ipilimumab plus etoposide and platinum versus placebo plus etoposide and platinum in extensive-stage small-cell lung cancer. J Clin Oncol.

Aglietta M, Barone C, Sawyer MB, Moore MJ, Miller WH Jr, Bagalà C, et al. A phase I dose escalation trial of tremelimumab (CP-675, 206) in combination with gemcitabine in chemotherapy-naive patients with metastatic pancreatic cancer. Ann Oncol. 2014; 25: 1750-5.

Langer CJ, Gadgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, Powell SF, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol. 2016; 17: 1497-508.

Paz-Ares L, Brahmer J, Hellman MD, Reck M, O’Byrne K, Borghaei H, et al. CheckMate 227: A randomized, open-label phase 3 trial of nivolumab, nivolumab plus ipilimumab, or nivolumab plus chemotherapy versus chemotherapy in advanced non-small cell lung carcinoma. Abstract number 144TIP. Geneva, Switzerland: European Lung Cancer Conference (ELCC), 2017.

Rothschild S. Response to salvage chemotherapy following exposure to PD-1/PD-L1 inhibitors in patients with NSCLC. Abstract number 91PD_PR. Geneva, Switzerland: European Lung Cancer Conference (ELCC).

Hui R, Garon EB, Goldman JW, Leighl NB, Hellmann MD, Patnaik A, et al. Pembrolizumab as first-line therapy for patients with PD-L1-positive advanced non-small cell lung cancer: a phase 1 trial. Ann Oncol. 2017; 28: 874-81.