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EDITORIAL

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[1] 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)[2]. 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[3]. In 2012, Topalian and colleagues[4] 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[4], 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[5]. 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 ($P < 0.001$)[6], 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[7], and ipilimumab single-agent therapy eked out a niche as adjuvant treatment in high-risk resected melanoma[8], which has since been upheld by a five-year OS HR of 0.72 (95% CI 0.58–0.88, P=0.001)[9]. While optimal duration of treatment remains

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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.

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[9]. 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[10]. Atezolizumab found a role in initial treatment of cisplatin-ineligible patients with advanced urothelial carcinoma with an ORR of 23%[11], although the drug missed its primary endpoint of survival in those that had progressed on platinum-based chemotherapy.[12] More recently, checkpoint inhibitors have been explored as neoadjuvant therapy with promising results in head and neck squamous cell carcinoma[13] and NSCLC[14], 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

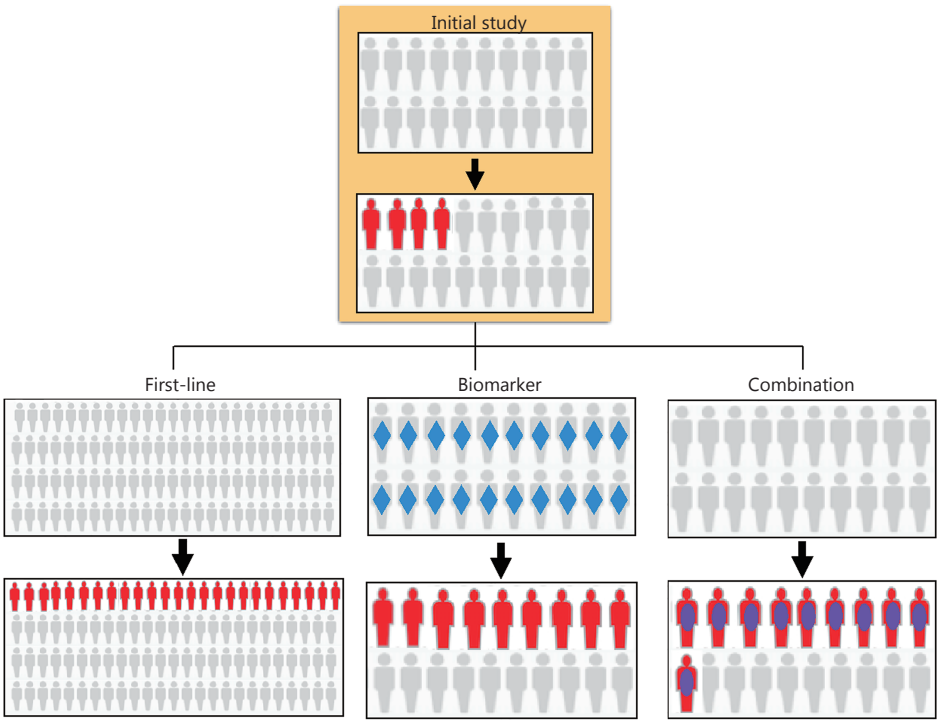

Figure 1 Strategies to improve immune checkpoint inhibitor overall response rates. Grey=unselected population. Red=responders. Blue diamond=biomarker positive. Purple oval=combination responder. Hypothetical representation modeled after pembrolizumab studies in non-small cell lung cancer with initial response rate 20%, first-line unselected 25%, first-line biomarker selected 50%, combination-therapy 55%.

initial nivolumab trial did not identify colorectal cancer (CRC) responders, by selecting for mismatch-repair deficiency, Diaz and colleagues[15] 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[15]. 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[16] 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)[17]. Carbone and colleagues[18] 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[19]. 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)[18,20]. 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

Table 2 Published clinical trials utilizing first-line immune checkpoint inhibitors

Lead author, year	Study type	Solid tumor type	Intervention	Biomarker	Outcome*
Carbone 2017[18] CheckMate-026	Open-label, phase 3	Advanced NSCLC	Nivolumab *vs.* chemotherapy	PD-L1≥1% (28-8 IHC)	PFS 4.2 m *vs.* 5.9 m
Hui 2017[39] KEYNOTE-001	Open-label, phase 1b	Advanced NSCLC	Pembrolizumab	PD-L1≥1% (22C3 IHC)	ORR 27% OS 22.1 m
Hellmann 2017[25] CheckMate-012	Open-label, phase 1	Advanced NSCLC	Nivolumab+ipilimumab	PD-L1 stratified (28-8 IHC)	ORR 38–47% (PD-L1≥1%=ORR 57%)
Balar 2017[11]	Open-label, phase 2	Advanced urothelial	Atezolizumab	PD-L1 stratified (SP142)	ORR 23% (No PD-L1 association)
Langer 2016[36] KEYNOTE-021	Open-label, phase 2	Advanced NSCLC	Platinum doublet +/- pembrolizumab	PD-L1 stratified (22C3 IHC)	ORR 55% *vs.* 29%
Reck 2016[17] KEYNOTE-024	Open-label, phase 3	Advanced NSCLC	Pembrolizumab *vs.* chemotherapy	PD-L1≥50% (22C3 IHC)	PFS 10.3 m *vs.* 6.0 m
Nghiem 2016[10]	Open-label, phase 2	Advanced Merkel cell	Pembrolizumab	None	ORR 56%
Reck 2016[34]	Randomized-controlled, phase 3	Extensive SCLC	Etoposide/platinum +/- ipilimumab	None	OS 11.0 m *vs.* 10.9 m NS
Postow 2015[23] CheckMate-069	Open-label, phase 1	Advanced melanoma, BRAF-WT	Nivolumab +ipilimumab	None	ORR 61%
Robert 2015[6] CheckMate-066	Randomized-controlled, phase 3	Advanced melanoma, BRAF-WT	Nivolumab *vs.* dacarbazine	None	12 m OS 72.9% *vs.* 42.1%
Aglietta 2014[35]	Open-label, phase 1b	Advanced pancreatic	Tremelimumab +gemcitabine	None	ORR 5.9% OS 7.4 m
Reck 2013[33]	Randomized-controlled, phase 2	Extensive SCLC	Paclitaxel/carboplatin +/- ipilimumab (phased/concurrent)	None	OS 9.9 m *vs.* 12.9 m *vs.* 9.1 m

*All results are significant unless otherwise noted. IHC: immunohistochemistry. m: month, NS: not significant. ORR: overall response rate. OS: overall survival. PD-L1: programmed death ligand-1. PFS: progression-free survival. SCLC: small cell lung cancer. WT: wild-type.

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[21,22].

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%[23], further substantiated by a 2-year OS improvement of 63.8% compared to 53.6%[24]. However, when this approach was adopted in NSCLC, three out of every four patients discontinued treatment due to toxicity or progression[25]. This similarly was reflected in Antonia and colleagues[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[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%[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[29], but require further clinical validation. While there were initial concerns that concurrent treatment may antagonize an immune response, work by Galluzzi and colleagues[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[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, 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% ($P < 0.001$) and PFS of 16.8 months *vs.* 5.6 months, consistent with a HR of 0.52 (95% CI 0.42–0.65, $P < 0.001$)[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[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[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[35].

The combination of chemotherapy and checkpoint inhibition in more immunogenic cancers has been more encouraging. In late 2016, Langer and colleagues[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%)[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[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[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.

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