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LEADING ARTICLE

Immune Checkpoint Blockade: The New Frontier in Cancer Treatment

Jeffrey M. Clarke[1] · Daniel J. George[2] · Stacey Lisi[3] · April K. S. Salama[4]

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Abstract
Immune checkpoint blockers have revolutionized cancer treatment in recent years. These agents are now approved for the treatment of several malignancies, including melanoma, squamous and non-squamous non-small cell lung cancer, renal cell carcinoma, urothelial carcinoma, and head and neck squamous cell carcinoma. Studies have demonstrated the significant impact of immunotherapy versus standard of care on patient outcomes, including durable response and extended survival. The use of immunotherapy-based combination therapy has been shown to further extend duration of response and survival. Immunotherapies function through modulation of the immune system, which can lead to immune-mediated adverse events (imAEs). These include a range of dermatologic, gastrointestinal, endocrine, and hepatic toxicities, as well as other less common inflammatory events. ImAEs are typically low grade and manageable when identified early and treated with appropriate measures. Identifying the right patient for the right therapy will become more important as new immunotherapies and immunotherapy-based combinations are approved and costs of cancer care continue to rise.

Key Points

Immunotherapies act differently from standard therapies: chemotherapy or targeted agents generally act directly on the tumor cells, whereas immunotherapies act on cancer cells indirectly by increasing activation of the immune system which ultimately leads to an anticancer immune response.

As cancer treatment continues to shift towards a more personalized approach, identifying predictive biomarkers will be essential to select patients who will benefit most from immunotherapy.

While single-agent immunotherapy is currently approved for several types of cancer, an area of important research consists in understanding how immunotherapy-based combination approaches may maximize clinical benefit.

✉ Jeffrey M. Clarke
jeffrey.clarke@duke.edu

[1] Division of Medical Oncology, Duke University School of Medicine, Duke Cancer Institute, DUMC 3198, Durham, NC 27710, USA

[2] Division of Medical Oncology, Duke University School of Medicine, Duke Cancer Institute, Duke Box 103861, Durham, NC 27710, USA

[3] Department of Pharmacy, Duke University Medical Center, Durham, NC 27710, USA

[4] Division of Medical Oncology, Duke University School of Medicine, Duke Cancer Institute, Duke Box 3198, Durham, NC 27710, USA

1 Introduction

Immunotherapies such as immune checkpoint blockers (ICBs) are an established therapeutic approach to cancer treatment. It is important that physicians and other healthcare stakeholders who influence treatment decisions involving patient care, reimbursement, and drug access understand how immunotherapies differ from traditional chemotherapies and targeted agents, and the importance of proper patient selection. Knowledge of the efficacy of single-agent and combination therapies and their associated safety profiles will help guide informed decisions.

Multiple therapeutic approaches exist for the treatment of cancer, each with a distinct mechanism of action. Traditional cytotoxic chemotherapy agents interfere with cell proliferation and division by inhibiting molecular mechanisms common across normal and malignant cells, thus directly, but nonspecifically, destroying both healthy and cancerous cells. Targeted agents, such as some tyrosine kinase inhibitors (TKIs), are generally designed to destroy cancer cells directly by targeting specific genetic alterations present in those cells. Conversely, immunotherapies act on cancer cells indirectly through the regulation of the immune system [1]. Over time, tumor cells can develop mechanisms to evade immune system recognition [2, 3]. One method for fighting malignancies is to increase activation of the immune system, which is required for successful destruction of cancer cells [2].

For decades, immunotherapies have been used as cancer treatments, including bacillus Calmette-Guérin in non-muscle invasive bladder cancer [4], high-dose interleukin-2 in metastatic renal cell carcinoma (RCC) and metastatic melanoma [5], and interferon α-2b in adjuvant treatment of melanoma [6]. However, their efficacy has been limited by researchers' lack of understanding regarding the processes underlying immune regulation. Since 2010, additional immunotherapies have received U.S. Food and Drug Administration (FDA) approval, including sipuleucel-T [7], approved for treatment of asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer; talimogene laherparepvec (T-VEC) [8], approved for the treatment of unresectable melanoma, recurrent after initial surgery; tisagenlecleucel, approved for the treatment of pediatric and young adult patients with B-cell precursor acute lymphoblastic leukemia [9]; axicabtagene ciloleucel, approved for the treatment of adult patients with large B-cell lymphomas [10]; and ICBs including ipilimumab [11], nivolumab [12], pembrolizumab [13], atezolizumab [14], avelumab [15], and durvalumab [16], approved for a wide range of malignancies, including melanoma, non-small cell lung cancer (NSCLC), RCC, urothelial carcinoma (UC), head and neck squamous cell carcinoma (HNSCC), Hodgkin lymphoma, Merkel cell carcinoma, microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) cancer, hepatocellular carcinoma, and gastric or gastroesophageal junction adenocarcinoma (Table 1). Although not yet approved by the FDA, durvalumab was recently added to the National Comprehensive Cancer Network (NCCN) guidelines for NSCLC as consolidation therapy for patients with unresectable stage III NSCLC who have received two or more cycles of definitive concurrent chemoradiation [70, 71].

ICBs act on cancer cells indirectly by removing the "brakes" that serve to regulate T lymphocytes, the main cells responsible for triggering an anticancer immune response [2, 11–16]. ICBs are an established class of immunotherapy that target negative regulators of T-cell activation, specifically the immune checkpoints, cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), programmed cell death-1 (PD-1), and programmed cell death ligand-1 (PD-L1). Inhibition of these immune checkpoint molecules prevents the downregulation of immune cells, leading to enhanced T-cell activity, which ultimately results in increased antitumor immunity [2].

2 Endpoints to Assess Clinical Outcomes Associated with ICBs

Currently, overall survival (OS) is the gold standard clinical endpoint used to demonstrate direct clinical benefit for novel anticancer agents in support of regular FDA approval [72]. Improvements in median OS associated with ICBs versus other therapies have been reported in several cancer types (Table 2), including RCC treated with nivolumab versus the targeted agent everolimus [28], NSCLC treated with either pembrolizumab or atezolizumab versus the chemotherapeutic agent docetaxel [42, 57], and UC treated with pembrolizumab versus chemotherapy [46]. However, as novel agents extend patient survival times, it becomes increasingly difficult to conduct long clinical trials in order to measure OS [75, 76]. Although the use of ICBs has improved survival in melanoma over standard chemotherapy, with some patients experiencing OS of 3 to 5 years [77, 78], when the follow-up is less than 1 year, median OS is usually not reached [22, 23, 39, 43]. Therefore, there is an interest in validating surrogate endpoints that can accurately predict survival benefit in clinical trials of immunotherapy and using these surrogate endpoints for drug approval [75].

The correlation between objective response rate (ORR), time to progression, disease-free survival, or progression-free survival (PFS) and OS is poorly understood [76, 79]. Some studies investigating ICBs in NSCLC, RCC, HNSCC, and UC have demonstrated increased OS in the absence of a PFS benefit [27, 28, 31, 42, 47, 57], whereas other trials in melanoma and NSCLC have demonstrated increased OS, as well as ORR and PFS, compared with standard of care (Table 2) [23, 43].

Several ICBs have gained FDA accelerated approval based on ORR, including atezolizumab, nivolumab, durvalumab, and avelumab in previously treated patients with UC [12, 14–16]; pembrolizumab in previously treated patients with HNSCC [13]; combination nivolumab plus ipilimumab in melanoma [80]; and pembrolizumab in NSCLC, as monotherapy or in combination with chemotherapy [13, 41, 52]. PFS has been investigated in several meta-analyses as a surrogate endpoint for OS in metastatic melanoma [75, 81], and has served as the basis for FDA approval of first-line pembrolizumab in patients with NSCLC [13].

Generally, ICBs have been shown to significantly improve ORR when compared with standard therapies, for example in patients with melanoma [22, 23, 39], RCC [28], and NSCLC with high PD-L1 expression [43] (Table 2). ICBs have also been shown to prolong duration of response (DOR) when compared with standard therapies (Table 2) [22, 23, 25, 39, 42, 43, 46]. The use of alternative endpoints as a surrogate for OS is an area of ongoing research, and further knowledge on this topic is likely to emerge in the near future.

3 Immunotherapeutics and Patient Selection

As the indications for approved ICBs expand, and new monotherapies and combination therapies come to market, the identification of biomarkers that predict benefit will be essential in selecting patients who will benefit most from immunotherapy.

Table 1 FDA-approved immunotherapies

Agent	Target	Approved Indication		Month and year	Efficacy That Led to FDA approval and subsequent label updates	OS Data (if available)	Trial Phase
Checkpoint blockers							
Ipilimumab (Yervoy®) [11]	CTLA-4	Unresectable or metastatic melanoma (adult patients)	1L+	Mar 2011	mOS: 10.1 mos. [103]	1-yr OS: 46% [103] 18-mo. OS: 33% [103] 2-yr OS: 24% [103]	3
		Unresectable or metastatic melanoma (pediatric patients)	1L+	July 2017	ORR: 12%[11]	1-yr OS: 67% [125]	1 [126] & 2 [125]
		Melanoma with pathologic involvement of regional lymph nodes	Adjuvant	Oct 2015	mRFS: 26.1 mos. [101]	5-yr OS: 65% [105]	3
Nivolumab (Opdivo®) [12]	PD-1	Unresectable or metastatic melanoma	2L, *BRAF* wt (after ipilimumab therapy) 3L, *BRAF* mut+(after BRAF inhibitor therapy and ipilimumab-therapy)	Dec 2014	ORR: 32% [31]	NA [31]	3
			1L, *BRAF* wt	Nov 2015	mOS: NR [30] mPFS: 5.1 mos. [30]	1-yr OS: 73% [30]	3
			1L, *BRAF* mut+	Jan 2016	mPFS: 6.9 mos. [44]	NA [44]	3
		Metastatic NSCLC	2L, squamous, after platinum-based therapy[a]	Mar 2015	mOS: 9.2 mos. [40]	1-yr OS: 42% [40, 127] 2-yr OS: 23% [127] 3-yr OS: 16% [127]	3
			2L, non-squamous, after platinum-based therapy[a]	Oct 2015	mOS: 12.2 mos. [33]	1-yr OS: 51% [33, 127] 18-mo. OS: 39% [33] 2-yr OS: 29% [127] 3-yr OS: 18% [127]	3
		Advanced RCC	2L, after prior anti-angiogenic therapy	Nov 2015	mOS: 25.0 mos. [20]	mOS (in patients treated beyond RECIST progression): 28.1 mos. [128]	3
		Relapsed or refractory classical Hodgkin lymphoma (adult patients)	After HSCT and brentuximab vedotin therapy	May 2016	ORR: 66% [12]	6-mo. OS: 99% [129]	1b&2
			4L+, including prior HSCT		ORR: 69% [12]		
		Recurrent or metastatic HNSCC	2L, after platinum-based therapy	Nov 2016	mOS: 7.5 mos. [35]	1-yr OS: 36% [35]	3
		Locally advanced or metastatic UC	2L after platinum-based therapy or 1L after neoadjuvant/adjuvant platinum-based therapy	Feb 2017	ORR: 20% [47]	mOS: 8.7 mos. [47]	2
		Metastatic, MSI-H or dMMR CRC (adult and pediatric patients)	2L+ (after therapy with fluoropyrimidine, oxaliplatin, and irinotecan)	July 2017	ORR: 28% [12]	mOS: NR [65] 1-yr OS: 73% [65]	2
		HCC	2L+ (after sorafenib)	Sept 2017	ORR: 14% [12]	mOS: 15.6 mos. [130] 1-yr OS: 60% [130] 18-mo. OS: 44% [130]	1/2

Table 1 (continued)

Ipilimumab + nivolumab (Yervoy® + Opdivo®) [12]	CTLA-4 PD-1	Unresectable or metastatic melanoma	1L+, *BRAF* wt	Sept 2015	ORR: 61% [94]	mOS (all patients): NR [102] mOS (*BRAF* mut+): 23.2 mos [102] 1-yr OS: 73% [102] 2-yr OS: 64% [102]	2
			1L+, *BRAF* wt and *BRAF* mut+	Jan 2016	mPFS: 11.5 mos. [44]	mOS: NR [131] 2-yr OS: 64% [131] 3-yr OS: 58% [131]	3
Pembrolizumab (Keytruda®) [13]	PD-1	Unresectable or metastatic melanoma	2L, *BRAF* wt (after ipilimumab therapy) 3L, *BRAF* mut+(after BRAF inhibitor therapy and ipilimumab-therapy)	Sept 2014	ORR: 26% [90]	1-yr OS: 58% (2 mg/kg q3w); 63% (10 mg/kg q3w) [90]	1
				Dec 2015	mPFS: 2.9 mos. [29] 6-mo. PFS: 34% (2 mg/kg q3w); 38% (10 mg/kg q3w) [29] 9-mo. PFS: 24% (2 mg/kg q3w); 29% (10 mg/kg q3w) [29]	mOS: 13.4 mos. (2 mg/kg q3w); 14.7 mos. (10 mg/kg q3w) [13]	2
			1L, *BRAF* wt and *BRAF* mut+	Dec 2015	mPFS: 4.1 mos. (10 mg/kg q3w); 5.5 mos. (10 mg/kg q2w) [132] 6-mo. PFS: 46% (10 mg/kg q3w); 47% (10 mg/kg q2w) [132]	mOS: NR [132] 1-yr OS: 68% (10 mg/kg q3w); 74% (10 mg/kg q2w) [132]	3
		Metastatic NSCLC	2L, after platinum-based therapy[a], PD-L1+ (high levels)	Oct 2015	ORR: 45% [37]	mOS: NR [37] mPFS: 6.3 mos. [37]	1
			2L, after platinum-based therapy[a], PD-L1+	Oct 2016	mOS: 10.4 mos. (2 mg/kg q3w); 12.7 mos. (10 mg/kg q3w) [21]	1-yr OS: 43% (2 mg/kg q3w); 52% (10 mg/kg q3w) [21]	2/3
			1L, PD-L1+ (high levels)	Oct 2016	mPFS: 10.3 mos. [28]	mOS: NR[28] 6-mo. OS: 80% [28]	3
		Recurrent or metastatic HNSCC	2L, after platinum-based therapy	Aug 2016	ORR: 16% [13]	mOS: 8 mos. [43][b] 6-mo. OS: 59% [43][b]	1b
		Relapsed or refractory classical Hodgkin lymphoma (adult and pediatric patients)	4L+, regardless of prior HSCT or brentuximab vedotin therapy	Mar 2017	ORR: 69% [133]	mOS: NR [133] 6-mo. OS: 100% [133]	2
		Locally advanced or metastatic UC	2L after platinum-based therapy or 1L after neoadjuvant/adjuvant platinum-based therapy	May 2017	mOS: 10.3 [23]	1-yr OS: 44% [23, 34, 134] 18-mo. OS: 33% [34]	3
			1L, cisplatin-ineligible	May 2017	ORR: 29% [13]	6-mo. OS: 67% [42]	2
		Unresectable or metastatic, MSI-H or dMMR solid tumors (adult and pediatric patients)	2L+ (with no satisfactory alternative treatment options)	May 2017	ORR: 40% [13]	mOS: NR [135] 6-mo. OS: 73% [135]	1b (2 studies) + 2 (3 studies)
		Unresectable or metastatic, MSI-H or dMMR CRC (adult and pediatric patients)	2L+ (after therapy with fluoropyrimidine, oxaliplatin, and irinotecan)		ORR: 36% [13]	mOS: NR [135] 6-mo. OS: 87% [135]	
		Recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma	2L+, PD-L1+ (after therapy with fluoropyrimidine, platinum, and, if appropriate, HER2 inhibitors)	Sept 2017	ORR: 13% [13]	mOS: 5.6 mos. [136][c] 1-yr OS: 23% [136]	2

Table 1 (continued)

Pembrolizumab (Keytruda®) [13] + pemetrexed/carboplatin	PD-1	Metastatic non-squamous NSCLC	1L	May 2017	ORR: 55% [38] mPFS: 13 mos. [38]	mOS: NR [137] 6-mo. OS: 92% [38] 1-yr OS: 77% [137] 18-mo. OS: 70% [137]	2
Atezolizumab (Tecentriq®) [14]	PD-L1	Locally advanced or metastatic UC	2L or 1L after neoadjuvant/adjuvant therapy	May 2016	ORR: 15% [46]	mOS: 7.9 mos. [46]	2
						mOS: 8.6 mos. [138][d]	3
			1L, cisplatin-ineligible	April 2017	ORR: 24% [14]	mOS: 15.9 mos. [69]	2
		Metastatic NSCLC	2L, after platinum-based therapy[a]	Oct 2016	mOS: 13.8 mos. [22]	1-yr OS: 55% [22] 18-mo. OS: 40% [22]	3
					mOS: 12.6 mos. [74]	NA [74]	2
Avelumab (Bavencio®) [15]	PD-L1	Metastatic Merkel cell carcinoma (adults and pediatric patients)	Any line of therapy	Mar 2017	ORR: 33% [15]	mOS: 11.3 mos. [104] 6-mo. OS: 69% [104]	2
		Locally advanced or metastatic UC	2L after platinum-based therapy or 1L after neoadjuvant/adjuvant platinum-based therapy	May 2017	ORR: 13% [15]	mOS: 7.7 mos. [41] 6-mo. OS: 55% [139] 1-yr OS: 40% [41]	1b
Durvalumab (Imfinzi®) [16]	PD-L1	Locally advanced or metastatic UC	2L after platinum-based therapy or 1L after neoadjuvant/adjuvant platinum-based therapy	May 2017	ORR: 17% [16]	mOS: 18.2 mo [45] 6-mo. OS: 64% [45] 9-mo. OS: 57% [45] 1-yr OS: 55% [45]	1/2
Immunotherapy other than checkpoint blockers							
Sipuleucel-T (Provenge®) [7]	APCs	Metastatic castrate-resistant (hormone-refractory) prostate cancer	Asymptomatic or minimally symptomatic	Apr 2010	mOS: 25.8 mos. [140]	3-yr OS: 32% [140]	3
Talimogene laherparepvec (Imlygic®) [8]	Unknown	Melanoma	Recurrent, after initial surgery	Oct 2015	DRR (CR+PR lasting ≥6mos.): 16% [141]	mOS: 23.3 mos. [141] 1-yr OS: 74% [141] 2-yr OS: 50% [141] 3-yr OS: 39% [141] 4-yr OS: 33% [141]	3
Tisagenlecleucel (Kymriah™) [9]	CAR-T (CD19)	B-cell precursor acute lymphoblastic leukemia (pediatric & young adult patients)	Refractory or in second or later relapse	Aug 2017	Overall remission rate: 83% [9]	6-mo. OS: 89% [142] 1-yr OS: 79% [142]	2
Axicabtagene ciloleucel (Yescarta™) [10]	CAR-T (CD19)	Large B-cell lymphomas: DLBCL, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma (adult patients)	Relapsed or refractory after at least two prior therapies (3L+)	Oct 2017	ORR: 72% [10] CR: 51% [10]	mOS: NR [143] 6-mo. OS: 80% [143]	2

APCs antigen-presenting cells, *CAR-T* chimeric antigen receptor-positive T cells, *CR* complete response, *CRC* colorectal cancer, *CTLA-4* cytotoxic T-lymphocyte-associated antigen-4, *DLBCL* diffuse large B-cell lymphoma, *dMMR* mismatch repair deficient, *DRR* durable response rate, *FDA* U.S. Food and Drug Administration, *HCC* hepatocellular carcinoma, *HNSCC* head and neck squamous cell carcinoma, *L* line of therapy, *mOS* median overall survival, *mPFS* median progression-free survival, *mRFS* median recurrence-free survival, *MSI-H* microsatellite instability-high, *mut+* mutation-positive, *NA* not available, *NR* not reached, *NSCLC* non-small cell lung cancer, *ORR* objective response rate, *OS* overall survival, *PD-1* programmed cell death-1, *PD-L1* programmed death ligand-1, *PFS* progression-free survival, *PR* partial response, *q2w* every 2 weeks, *q3w* every 3 weeks, *RCC* renal cell carcinoma, *RECIST* Response Evaluation Criteria in Solid Tumors, *UC* urothelial carcinoma, *wt* wild type

[a]Or after *EGFR*- or *ALK*-targeted agents in patients harboring those mutations

[b]A confirmatory phase 3 study (KEYNOTE-040) investigating pembrolizumab vs. standard treatment (methotrexate, docetaxel, or cetuximab) in patients with previously treated recurrent or metastatic HNSCC did not meet its primary endpoint of OS (HR = 0.81 [95% CI: 0.66–0.99], $P = 0.0204$; 1-yr. OS: 37% [pembrolizumab] vs. 27% [standard of care]; median OS: 8.4 mos. [pembrolizumab] vs. 7.1 mos. [standard of care]) [67, 68]

[c]Includes PD-L1+ and PD-L1- patients

[d]A confirmatory phase 3 study (IMvigor 211) investigating atezolizumab vs. chemotherapy (vinflunine, paclitaxel, or docetaxel) in patients with locally advanced or metastatic UC in the second-line setting did not meet its primary endpoint of OS (HR = 0.85 [95% CI: 0.73–0.99], $P = 0.038$; 1-yr. OS: 39% [atezolizumab] vs. 32% [chemotherapy]; median OS: 8.6 mos. [atezolizumab] vs. 8.0 mos. [chemotherapy]) [55, 69]

Table 2 Comparison of efficacy between checkpoint blockers as monotherapy and standard of care

Agent	Trial name/ number	Phase	Tumor Type	Median OS, months			ORR, %			Median DOR (range), months		
				ICB	Comparator	*P* value	ICB	Comparator	*P* value	ICB	Comparator	*P* value
Anti-CTLA-4												
Tremelimumab (investigational)	NCT00257205 [147]	3	Unresectable advanced melanoma (1L)	12.6	10.7[a]	0.127	11	10[a]	0.618	35.8	13.7[a]	0.0011
Anti-PD-1												
Nivolumab (FDA-approved)	CheckMate 037 [31] NCT01721746	3	Unresectable advanced or metastatic melanoma (2L+)	NA	NA	NA	32	11[b]	NA	NR (1.4+ – 10.0+)	3.5[b] (1.3+ – 3.5)	NA
	CheckMate 066 [30] NCT01721772	3	Unresectable advanced or metastatic melanoma, *BRAF* wt (1L)	NR	10.8[c]	<0.001	40	14[c]	<0.001	NR	6.0 (3 NR)[c]	NA
	CheckMate 017 [40] NCT01642004	3	Advanced squamous NSCLC (2L)	9.2	6.0[d]	<0.001	20	9[d]	0.008	NR (2.9 – 20.5+)	8.4[d] (1.4+ – 15.2+)	NA
	CheckMate 057 [33] NCT01673867	3	Advanced non-squamous NSCLC (2L)	12.2	9.4[d]	0.002	19	12[d]	0.02	17.2 (1.8 – 22.6+)	5.6[d] (1.2+ – 15.2+)	NA
	CheckMate 025 [20] NCT01668784	3	Advanced or metastatic clear-cell RCC (2L+)	25.0	19.6[e]	0.002	25	5[e]	<0.001	12.0 (0 – 27.6)	12.0[e] (0 – 22.2)	NA
	CheckMate 141 [35] NCT02105636	3	Platinum-refractory, recurrent HNSCC (2L+)	7.5	5.1[f]	0.01	13	6[f]	NA	NA	NA	NA
Pembrolizumab (FDA-approved)	KEYNOTE-002 [29] NCT01704287	2	Unresectable advanced or metastatic melanoma (ipilimumab-refractory, 2L+)	NA	NA	NA	23[g]	4[h]	<0.0001	NR[g] (5.8 – NR)	8.5[h] (2.8 – 9.5)	NA
	KEYNOTE-010 [21] NCT01905657	2/3	Advanced, PD-L1+ NSCLC (2L+)	10.4[i] 12.7[j]	8.5[d]	0.0008[i] <0.0001[j]	18[g]	9[d]	0005[i] 0002[j]	NR[g] (4.2 – 12.5)[g]	6.0[d] (2.7 – 6.1)	NA
	KEYNOTE-024 [28] NCT02142738	3	Metastatic, PD-L1+ (high levels) NSCLC (1L)	NR[k,l]	NR[j,k,l,m]	NA[k,l]	45	28[m]	NA	NR (1.9+ – 14.5+)	6.3[m] (2.1+ – 12.6+)	NA
	KEYNOTE-045 [23, 34, 134] NCT02256436	3	Advanced UC (platinum-refractory, 2/3L)	10.3	7.4[n]	0.0003	21	11[n]	0.001	NR (1.6+ – 24.6+)	4.4[n] (1.4+ – 24.0+)	NA
Anti-PD-L1												
Atezolizumab (FDA-approved)	POPLAR [74] NCT01903993	2	Locally advanced or metastatic NSCLC (platinum-refractory, 2/3L)	12.6	9.7[d]	0.040	15	15[d]	NA	14.3 (11.6 – NE)	7.2[d] (5.6 – 12.5)	.034
	OAK [22] NCT02008227	3	Locally advanced or metastatic NSCLC (platinum-refractory, 2/3L)	13.8	9.6[d]	0.0003	14	13[d]	NA	16.3 (10.0 – NE)	6.2[d] (4.9 – 7.6)	<.0001
	IMvigor 211 [138] NCT02302807	3	Locally advanced or metastatic UC (platinum-refractory, 2L+)	8.6	8.0[n]	0.038	13	13[n]	NA	21.7 (13.0 – 21.7)	7.4[n] (6.1 – 10.3)	NA

APCs antigen-presenting cells, *CTLA-4* cytotoxic T-lymphocyte-associated antigen-4, *DOR* duration of response, *FDA* U.S. Food and Drug Administration, *HNSCC* head and neck squamous cell carcinoma, *ICB* immune checkpoint blocker, *L* line of therapy, *NA* not available, *NE* not estimable/not evaluable, *NR* not reached, *NSCLC* non-small cell lung cancer, *ORR* objective response rate, *OS* overall survival, *PD-1* programmed cell death-1, *PD-L1* programmed death ligand-1, *RCC* renal cell carcinoma, *UC* urothelial carcinoma

[a] Comparator was investigator's choice single-agent chemotherapy: dacarbazine or temozolomide

[b] Comparator was investigator's choice chemotherapy: dacarbazine or carboplatin/paclitaxel

[c] Comparator was dacarbazine

[d] Comparator was docetaxel

[e] Comparator was everolimus

[f] Comparator was investigator's choice single-agent chemotherapy: methotrexate, docetaxel, or cetuximab

[g] Includes both 2-mg/kg and 10-mg/kg pembrolizumab treatment groups

[h] Comparator was investigator's choice chemotherapy: carboplatin/paclitaxel, paclitaxel, carboplatin, dacarbazine, or oral temozolomide

[i] 2 mg/kg pembrolizumab

[j] 10 mg/kg pembrolizumab

[k] OS at 6 months was 80% for pembrolizumab and 72% for chemotherapy ($P = 0.005$)

[l] At a median follow-up of 19.1 months, mOS was not reached with pembrolizumab and 14.5 months with chemotherapy ($P = 0.003$) [74]

[m] Comparator was investigator's choice chemotherapy: carboplatin/pemetrexed, cisplatin/pemetrexed, carboplatin/gemcitabine, cisplatin/gemcitabine, or carboplatin/paclitaxel

[n] Comparator was investigator's choice single-agent chemotherapy: paclitaxel, docetaxel, or vinflunine

The immunologic profile of the tumor can be taken into consideration when selecting appropriate patients. The level of PD-L1 expression within tumor cells and/or immune cells is associated with higher ORR or longer OS following treatment with PD-1/PD-L1 blockers in NSCLC and UC, pembrolizumab in HNSCC, and nivolumab in melanoma [23, 24, 27, 32, 41, 42, 44, 49, 54, 60, 62]. However, some patients with low or no levels of PD-L1 expression also respond to ICBs [27], indicating that PD-L1 expression is enriched for responders, but the absence of expression is not an absolute indicator of lack of benefit. Finally, some clinical trials in NSCLC have shown no strong correlation between outcome and baseline PD-L1 status [25].

To identify patients who may receive the most benefit from ICBs, a series of FDA-approved diagnostic assays has been developed to measure the level of PD-L1 expression in tumor and/or immune cells. These assays include one mandatory companion diagnostic with pembrolizumab monotherapy for patients with NSCLC or gastric/gastroesophageal junction adenocarcinoma (PD-L1 IHC 22C3 pharmDX, Dako) [82], and three complementary (optional) diagnostics: PD-L1 IHC 28–8 pharmDX (Dako) for nivolumab (non-squamous NSCLC, HNSCC, and UC) or nivolumab/ipilimumab combination (melanoma) [83], VENTANA PD-L1 SP142 assay for atezolizumab (UC and NSCLC) [84], and VENTANA PD-L1 SP-263 for durvalumab (UC) [85]. Therefore, PD-L1 testing should be used for patient selection only when planning to administer pembrolizumab in patients with NSCLC (except when pembrolizumab is used in first line [1 L] in combination with chemotherapy) or gastric/gastroesophageal junction adenocarcinoma [13]. Despite the development of FDA-approved assays for PD-L1 testing, some clinics use laboratory-developed tests, which can be less costly but can also increase the amount of testing variability [86]. Variability in PD-L1 testing can arise because of the type (tumor cells, immune cells, or a combination) and percentage cutoffs used for positivity, archival versus fresh tissue, primary versus metastatic biopsies, diversity of antibodies utilized, and tumor heterogeneity [86, 87]. Several comparative studies across different PD-L1 assays have been conducted, including collaborative studies between industry and academic institutions [88–91]. The outcomes of these studies have varied, with two studies showing concordance among assays [88, 90], one study showing equivalence for most assays [91], and one study revealing differences across all of the assays that do not support interchangeability [89]. Based on these preliminary findings, the PD-L1 assays that are currently available are not considered interchangeable.

The presence of tumors that harbor mutations in specific genes can influence therapy decisions. For example, the use of epidermal growth factor receptor (EGFR) TKIs is standard of care in patients with *EGFR*-mutation-positive NSCLC [92–94], and studies suggest that this population may not derive benefit from immunotherapy versus EGFR TKIs [95] or chemotherapy [96]. Therefore, the clinical benefit from monotherapy with anti-PD-1/PD-L1 antibodies remains suboptimal in *EGFR*-mutation-positive NSCLC, and novel combination and therapeutic approaches are needed [96]. The approval of anti-PD-1 therapy for the treatment of adult and pediatric patients with MSI-H or dMMR solid tumors (pembrolizumab) or colorectal cancer (pembrolizumab and nivolumab) that has progressed, underscores the importance of considering other biomarkers that are not specific to the immune checkpoint pathway when making ICB therapy decisions [13]. Patients with MMR deficiency are associated with a higher mutational burden and tumor neoantigen load than MMR-proficient patients, and these features could be driving clinical benefit of ICBs [33, 97, 98]. In fact, tumor mutational burden, known to enhance neoantigen formation, has been shown to be associated with increased response to ICBs, and in some cases improved OS as well, across tumor types such as melanoma [99, 100], NSCLC [101], and UC [54, 56, 102]. Baseline gene expression profiling has also been correlated with response to ICBs; specifically, interferon gamma (IFNγ) signature, which is indicative of an inflammatory tumor microenvironment, is associated with responsiveness to ICBs in several tumor types, including melanoma [103], UC [32, 54, 104, 105], NSCLC [58, 106], HNSCC [103], and gastric cancer [103].

Patients with autoimmune diseases raise concerns about the risk of immune-mediated toxicity associated with immunotherapy and are often excluded from clinical trials. However, as the use of immunotherapy continues to expand into a broader, real-world population, patients with preexisting autoimmune disorders or immune-mediated adverse events (imAEs) from prior immunotherapy are being considered [107, 108]. In one study, the use of the PD-1 blockers pembrolizumab or nivolumab in 119 patients with advanced melanoma and preexisting autoimmune disorders and/or imAEs from prior ipilimumab monotherapy resulted in an ORR of 37%, although approximately 10% of patients discontinued treatment because of imAEs [108].

Other factors that may influence immunotherapy treatment decisions include performance status, comorbidities that are incompatible with imAEs associated with these agents, and the presence of brain metastases. Although the majority of the clinical trials testing ICBs exclude patients with active brain metastases, pembrolizumab was administered to 36 patients with melanoma or NSCLC and untreated or progressive brain metastases in an investigator-initiated phase 2 trial. Relevant reduction in brain metastases was observed in 28% of patients, warranting further investigation of ICBs in this patient population [109]. In the phase 2 CheckMate 204 study, the combination of nivolumab and ipilimumab was administered to 75 patients with advanced melanoma and untreated brain metastases, and provided an intracranial ORR of 55% and an extracranial ORR of 49% [110].

Modern oncologic therapies are increasingly reliant on biomarkers within the tumor microenvironment. Personalized cancer care in the immediate future will have even greater dependence on predictive biomarkers for optimizing therapeutic options for patients. Therefore, the development and validation of novel biomarkers that identify patients who will benefit from anticancer treatments is critical. Biomarker assays are urgently needed, including assays for circulating biomarkers, which optimize test feasibility, convenience, and accuracy, and are non-invasive, preserving patient safety.

4 Pseudoprogression with ICBs

Measuring clinical outcomes associated with immunotherapies comes with a distinct set of challenges not observed with standard therapies. In some cases, the time required to establish an effective immune response may be delayed compared with standard therapies because of atypical responses reported with immunotherapies that are not observed with targeted agents or chemotherapy [111]. Pseudoprogression, also called tumor flare, is a distinct immune-related pattern of response caused by the infiltration of immune cells to the tumor site that can manifest in the form of an apparent increase in tumor size, the development of new lesions, or a mixed response such as progression and regression of different tumors in the same patient [112, 113]. The development of granulomatous changes in the lymph nodes resembling progression have also been described during immunotherapy treatment [114]. In studies investigating immunotherapies in patients with cancer, the prevalence of pseudoprogression can vary based on tumor type; for example, it has been reported to be 7% to 10% in melanoma [23, 113, 115], 5% to 7% in NSCLC [25, 27], 7% in UC [54], and 0% to 2% in HNSCC [44, 116].

Following the standard RECIST (Response Evaluation Criteria In Solid Tumors) v1.1 criteria [117], findings of pseudoprogression can be initially interpreted as disease progression and may lead to discontinuation of treatment before the potential clinical benefit of immunotherapy is fully realized [111, 112]. Studies have demonstrated that after initial apparent disease progression, some patients derive clinical benefit from continued administration of immunotherapy [22, 38, 57, 111, 118–121]. In a phase 3 study (CheckMate 025), 69% of patients with metastatic RCC treated with nivolumab beyond first progression subsequently demonstrated tumor reduction in target lesions, and almost half (48%) had a 30% reduction in tumor burden from baseline [111]. In another phase 3 study (CheckMate 037) investigating nivolumab in patients with advanced melanoma, 31% received treatment beyond progression, and 27% of these had a greater than 30% reduction in target lesions [22]. Similar findings were observed in 62 patients with recurrent or metastatic HNSCC treated with nivolumab beyond progression in the phase 3 CheckMate 141, with 24% of these patients experiencing tumor reduction [118], and in 137 patients with advanced or metastatic UC treated with atezolizumab beyond progression in the phase 2 IMvigor 210, with 33% experiencing tumor reduction [120]. In patients from IMvigor 210, prolonged survival was observed in subgroups of patients with favorable baseline prognostic characteristics (Eastern Cooperative Oncology Group performance status 0, lymph node-only disease, or no visceral metastases) [120]. Because of the unique responses observed with these agents, immune-related response criteria (irRC) have been developed to serve as a guide for the evaluation of antitumor responses with immunotherapies [113]. Based on survival analysis from patients with melanoma treated with pembrolizumab in the KEYNOTE 001 trial, the benefit of immunotherapy was underestimated in approximately 15% of patients when assessed by conventional RECIST v1.1 versus irRC [115]. Currently, irRC is often used in clinical trials of immunotherapy as a secondary approach for measuring responses, whereas standard RECIST is more prevalent in clinical practice.

According to the authors' personal experience, when treating long-term survivors who are experiencing a durable response from immunotherapy, it may be possible to incorporate treatment breaks followed by treatment rechallenge in cases of subsequent disease progression, although treatment breaks are not indicated in the label. In the KEYNOTE-006 study, 104 ipilimumab-naïve patients with advanced melanoma completed 2 years of pembrolizumab treatment: of these patients, 23%, 65%, and 12% had complete response (CR), partial response (PR), and stable disease (SD), respectively, at the time of completion of pembrolizumab treatment [122]. After a median follow-up of nearly 3 years, most (91%) of these 104 patients were progression-free, with ongoing CR, PR, and SD experienced by 22%, 62%, and 10% of patients, respectively [122]. Understanding the role of treatment breaks with immunotherapy is an area in need of further investigation.

5 Immunotherapy-Based Combination Approaches

Combination regimens, including two immunotherapies administered together or immunotherapy combined with either chemotherapy or targeted agents, may increase the number of patients with durable response or longer survival (Table 3). The PD-1/PD-L1 and CTLA-4 blockers target different pathways involved in immune regulation, and the combination of these agents enhances tumor response compared with monotherapy [141]. The initial approval of ipilimumab/nivolumab combination therapy for first-line treatment of melanoma was based on the high ORR reported with this combination versus single-agent ipilimumab in the CheckMate 069 study

(Table 3) [35], and was further supported by the phase 3 CheckMate 067 study, which showed significant improvements in median PFS [12, 24]. The accelerated approval of pembrolizumab plus chemotherapy (pemetrexed/carboplatin) for first-line treatment of non-squamous NSCLC was based on the high ORR reported with this combination versus pemetrexed/carboplatin alone in the KEYNOTE-021 trial (Table 3) [52]. Additional immunotherapy-based combination therapies are being tested in phase 3 studies (Table 4), and for some of these combination approaches, preliminary data are available (Table 3).

The concurrent use of immunotherapies in combination regimens, along with the supportive care required to manage increased toxicity, may contribute to the overall healthcare costs associated with these agents. Based on current labeling for the treatment of melanoma patients, ipilimumab and nivolumab are administered together only for the initial four doses; nivolumab is then given as monotherapy [12]. Alternative dosing regimens for ICBs used in combination are currently under investigation, with the goal of improving the safety profile while maximizing clinical benefit [125, 142, 143].

6 Adverse Events Associated with ICBs

By enhancing immune system function, ICBs can lead to adverse events (AEs) distinct from chemotherapy [144, 145], which include a range of dermatologic, gastrointestinal (GI), endocrine, and hepatic toxicities, as well as other less common inflammatory events [146]. Though imAE onset is variable, most occur during the initial months of therapy [11–16]. Whereas imAEs of any grade can occur in up to 90% of patients treated with ICBs as monotherapy [17, 20, 24, 36, 42, 43, 54, 56, 59, 62], the incidence of grade ≥ 3 imAEs can range from 1% to 10% with anti-PD-1/PD-L1 monotherapy [24, 43, 54, 56, 59, 62] and from 15% to 42% with anti-CTLA-4 monotherapy [17, 20, 24, 36]. Combination therapy with anti-CTLA-4 and anti-PD-1 antibodies is associated with a 40% to 45% incidence of grade ≥ 3 imAEs [24, 36]. Although infrequent, life-threatening imAEs can occur with ICBs [11–16].

Because severe imAEs can lead to treatment discontinuation, careful monitoring and prompt management are important to ensure patients continue to receive beneficial immunotherapy. Unlike chemotherapy, which can only be tolerated for shorter durations (e.g., 6 cycles), immunotherapy agents can be administered for up to 2 or 3 years in some cases [21, 147, 148]. Although recent analyses on cumulative toxicity associated with ICBs after long-term therapy are needed, an analysis conducted in 306 patients with advanced solid tumors treated for up to 22 months with nivolumab monotherapy in a phase 1 study showed no cumulative toxicity after a minimum of 14 months of follow-up [148]. In a pooled safety analysis of 282 patients with advanced melanoma who were treated with nivolumab monotherapy in two phase 3 and two phase 1 studies and who experienced new treatment-related imAEs, 85% did so within the first 16 weeks of treatment [149]. Based on a long-term safety analysis conducted in 95 patients with metastatic UC treated with atezolizumab in a phase 1a trial, most treatment-related AEs occurred within the first year after treatment initiation, with a 50% reduction in the incidence of these AEs during the second year [150]. Therefore, patient monitoring remains important with long-term therapy due to the rare occurrence of late-onset imAEs.

Guidelines for the management of imAEs have been proposed in expert reviews [144, 145, 151, 152] but are also available within the prescribing information for each agent and in brochures that can be downloaded from the manufacturers' websites [11–16, 153–157]. Most moderate and severe immune-mediated toxicities can be managed effectively with corticosteroids and can be resolved within 6 to 12 weeks [146]. For steroid-refractory cases, other immunosuppressive agents (e.g., mycophenolate mofetil or the tumor necrosis factor alpha antibody, infliximab) may be required to obtain control of the immune mediated toxicity [144, 145]. Patients developing moderate to severe imAEs may require integrated multidisciplinary care that should include specialists in gastroenterology, pulmonology, dermatology, neurology, ophthalmology, endocrinology, or rheumatology, depending on the type of toxicity [153, 155]. In addition, imAE awareness should be raised among healthcare providers outside the oncology team, such as emergency room physicians and nurses, who might be involved in managing patients receiving immunotherapy. In a real-world study investigating ipilimumab in 129 patients with metastatic melanoma, 26% of patients required corticosteroids for the management of AEs, and 5.4% were administered infliximab in the refractory setting [158]. In a large expanded-access program of nivolumab in combination with ipilimumab, which included 732 North American patients with advanced melanoma, grade 3/4 treatment-related AEs (TRAEs) occurred in 50% of patients, and 32% of the patients discontinued treatment due to TRAEs [159]. These results point to a safety profile consistent with clinical trial data.

7 Quality of Life Associated with ICBs

Although clinical outcomes for patients with cancer are often measured in terms of survival and response, patient-reported outcomes and health-related quality of life (HRQoL) are also important considerations from a patient perspective. Treatment with nivolumab or pembrolizumab has been shown to improve or maintain HRQoL compared with standard chemotherapy or targeted agents. An analysis of HRQoL from

Table 3 Summary of efficacy endpoints for select trials of combination approaches involving immune checkpoint blockers

Agent	FDA approval status[a]	Trial name/number	Phase	Tumor type	ORR and median DOR			
Anti-CTLA-4 + chemotherapy								
Ipilimumab + carboplatin/paclitaxel	No	CA184–041 [123] NCT00527735	2	Advanced NSCLC (1 L)		BORR	irBORR	mDOR
					Placebo + paclit/carbopl [$n = 66$]	14%	18%	NA
					Concurrent ipi[b] [$n = 70$]	21%	21%	NA
					Phased ipi[c] [$n = 68$]	32%	32%	NA
Anti-PD-1/PD-L1 + Anti-CTLA-4								
Nivolumab + ipilimumab	Yes	CheckMate 069 [36] NCT01927419	2	Unresectable advanced melanoma (1 L)		ORR		mDOR
					Ipi [$n = 47$]	11%	Ipi [$n = 5$]	NR
					Nivo + ipi [$n = 95$]	59%	Nivo + ipi [$n = 56$]	NR
					P value	<0.0001	–	–
Nivolumab + ipilimumab	Yes	CheckMate 067 [24, 37] NCT01844505	3	Unresectable advanced melanoma (1 L)		ORR		mDOR
					Nivo [$n = 316$]	44%	Nivo [$n = 138$]	NR
					Ipi [$n = 315$]	19%	Ipi [$n = 60$]	19.3 mos.
					Nivo + ipi [$n = 314$]	58%	Nivo + ipi [$n = 181$]	NR
					P value[e]	<0.001	–	–
Nivolumab + ipilimumab	No	CheckMate 214 [124] NCT02231749	3	Advanced or metastatic clear cell RCC		ORR		mDOR
					Nivo + ipi [$n = 550$]	39%	Nivo + ipi	NA
					Sun [$n = 546$]	32%	Sun	NA
					P value	0.0191		
Nivolumab + ipilimumab	No	CheckMate 012 [125, 126] NCT01454102	1	Recurrent advanced NSCLC (1 L)		ORR		mDOR
					Nivo + ipi q12wks [$n = 38$]	47%	Nivo + ipi q12wks [$n = 18$]	NR
					Nivo + ipi q6wks [$n = 39$]	38%	Nivo + ipi q6wks [$n = 15$]	NR
					Nivo + ipi [combined, $N = 77$]	43%	Nivo + ipi [combined, $N = 33$]	NR
Nivolumab + ipilimumab	No	CheckMate 032 [127] NCT01928394	1/2	Limited-stage or extensive-stage SCLC (recurrent, 2 L+)		ORR		mDOR
					Nivo [$n = 147$]	12%		NA
					Nivo + ipi [$n = 95$]	21%		NA
Nivolumab + ipilimumab	No	MAPS-2 [128] NCT02716272	2	Unresectable malignant pleural mesothelioma (2/3 L)		ORR		mDOR
					Nivo [$n = 63$]	18%	Nivo [$n = 11$]	7.4 mos.
					Nivo + ipi [$n = 62$]	26%	Nivo + ipi [$n = 16$]	7.9 mos.
Durvalumab + tremelimumab	No	Study 006 [129] NCT02000947	1b	Locally advanced or metastatic NSCLC (IMT-naïve)		ORR		mDOR
					Durva + treme [$n = 63$]	17%	Durva + treme [$n = 11$]	NR
Anti-PD-1/PD-L1 + chemotherapy								
Pembrolizumab + chemotherapy	Yes	KEYNOTE-021 [52, 53, 130] NCT02039674	2	Advanced non-squamous NSCLC (1 L)		ORR		mDOR
					Pembro + carbopl/pemetr [$n = 60$]	57%	Pembro + chemo [$n = 34$]	NR
					Carbopl/pemetr [$n = 63$]	32%	Chemo [$n = 20$]	NR
					P value	0.0029		NA
Pembrolizumab + chemotherapy	No	KEYNOTE-059 [131] NCT02335411	2	Advanced gastric or gastroesophageal cancer		ORR		mDOR
					Pembro (3 L+) [$n = 259$]	12%	Pembro (3 L+) [$n = 31$]	14.2 mos.
					Pembro + cispl/5-FU or cape (1 L) [$n = 25$]	60%	Pembro + cispl/5-FU or cape (1 L) [$n = 15$]	4.6 mos.
					Pembro (1 L, PD-L1+) [$n = 31$]	26%	Pembro (1 L, PD-L1+) [$n = 8$]	9.6 mos.
Nivolumab + chemotherapy	No	CheckMate 012 [132] NCT01454102	1	Advanced NSCLC (1 L)		ORR		mDOR
					Nivo 10 mg/kg + gem/cispl [$n = 12$]	33%	Nivo 10 mg/kg + gem/cispl [$n = 4$]	10.3 mos.
					Nivo 10 mg/kg + pemetr/cispl [$n = 15$]	47%	Nivo 10 mg/kg + pemetr/cispl [$n = 7$]	5.8 mos.
					Nivo 10 mg/kg + paclit/carbopl [$n = 15$]	47%	Nivo 10 mg/kg + paclit/carbopl [$n = 7$]	5.5 mos.
					Nivo 5 mg/kg + paclit/carbopl [$n = 14$]	43%	Nivo 5 mg/kg + paclit/carbopl [$n = 6$]	19.6 mos.
					Nivo + paclit/carbopl [combined, $n = 29$]	45%	Nivo + paclit/carbopl [combined, $n = 13$]	NA
					Nivo + chemo [combined, $N = 56$]	43%	Nivo + chemo [combined, $N = 24$]	NA
Atezolizumab + chemotherapy	Yes	NCT01633970 [133]	1b	Locally advanced or metastatic NSCLC (1 L)		ORR		mDOR
					Atezo + carbopl/ pemetr [$n = 25$]	64%	Atezo + carbopl + pemetr [$n = 16$]	NA
					Atezo + carbopl/ nab-paclit [$n = 26$]	46%	Atezo + carbopl + nab-paclit [$n = 12$]	NA
					Atezo + carbopl/ paclit [$n = 25$]	36%	Atezo + carbopl + paclit [$n = 9$]	NA

Table 3 (continued)

Agent	FDA approval status[a]	Trial name/number	Phase	Tumor type	ORR and median DOR			
					Atezo + chemo [combined, $N = 76$]	49%	Atezo + chemo [$n = 37$]	NA
Anti-PD-1 + immunotherapy								
Pembrolizumab + epacadostat (IDO1 inhibitor)	No	KEYNOTE-037 [134–137] ECHO-202 NCT02178722	1/2			ORR		mDOR
				Advanced melanoma [138]	Pembro + epa [$n = 63$]	56%	Pembro + epa [$n = 35$]	9.5+ mos.
				Recurrent or metastatic HNSCC (2 L+) [135]	Pembro + epa [$n = 38$]	34%	Pembro + epa [$n = 13$]	4.2+ mos.
				Advanced NSCLC (1 L–3 L) [134]	Pembro + epa [$n = 36$]	39%	Pembro + epa [$n = 14$]	6.2+ mos.
				Advanced RCC [136]	Pembro + epa [$n = 30$]	33%	Pembro + epa [$n = 10$]	6.2+ mos.
				Advanced UC (1 L+) [137]	Pembro + epa [$n = 40$]	35%	Pembro + epa [$n = 14$]	7.1+ mos.
Anti-PD-L1 + targeted therapy								
Avelumab + axitinib (VEGFR-TKI)	No	JAVELIN Renal 100 [139] NCT02493751	1b	Advanced RCC (1 L)		ORR		mDOR
					Avel + axitinib [$N = 55$]	58%	Avel + axitinib [$n = 32$]	NA

Agent	Trial name/ number	PFS and OS data (if available)						
Anti-CTLA-4 + chemotherapy								
Ipilimumab + carboplatin/paclitaxel	CA184-041 [123] NCT00527735			irPFS	PFS	OS	1-yr. OS	2-yr. OS
		Placebo + paclit/carbopl [$n = 66$]		4.6 mos.	4.2 mos.	8.3 mos.	39%	18%
		Concurrent ipi[b] [$n = 70$]		5.5 mos.	4.1 mos.	9.7 mos.	42%	16%
		Phased ipi[c] [$n = 68$]		5.7 mos.	5.1 mos.	12.2 mos.	50%	18%
		P value[d]		0.05	0.02	0.23	NA	NA
Anti-PD-1/PD-L1 + Anti-CTLA-4								
Nivolumab + ipilimumab	CheckMate 069 [36] NCT0192419		mPFS	1-yr. PFS	2-yr. PFS	mOS	1-yr. OS	2-yr. OS
		Ipi [$n = 47$]	3.0 mos.	16%	12%	NR	65%	54%
		Nivo + ipi [$n = 95$]	NR	53%	51%	NR	73%	64%
		P value	<0.0001	NA	NA	0.26	NA	NA
Nivolumab + ipilimumab	CheckMate 067 [24, 37] NCT01844505		mPFS	2-yr. PFS	3-yr. PFS	mOS	2-yr. OS	3-yr. OS
		Nivo [$n = 316$]	6.9 mos.	37%	32%	37.6 mos.	59%	52%
		Ipi [$n = 315$]	2.9 mos.	12%	10%	19.9 mos.	45%	34%
		Nivo + ipi [$n = 314$]	11.5 mos.	43%	39%	NR	64%	58%
		P value[e]	<0.001	NA	NA	<0.001	<0.001	NA
Nivolumab + ipilimumab	CheckMate 214 [124] NCT02231749		mPFS			mOS		
		Nivo + ipi [$n = 550$]	12.4 mos.			NR		
		Sun [$n = 546$]	12.3 mos.			32.9 mos.		
		P value	0.8498			0.0003		
Nivolumab + ipilimumab	CheckMate 012 [125, 126] NCT01454102		mPFS				1-yr. OS	
		Nivo + ipi q12wks [$n = 38$]	8.1 mos.				83%	
		Nivo + ipi q6wks [$n = 39$]	3.9 mos.				69%	
		Nivo + ipi [combined, $N = 77$]	8.0 mos.				76%	
Nivolumab + ipilimumab	CheckMate 032 [127] NCT01928394			3-mo. PFS			3-mo. OS	
		Nivo [$n = 147$]		18%			65%	
		Nivo + ipi [$n = 95$]		30%			64%	
Nivolumab + ipilimumab	MAPS-2 [128] NCT02716272		mPFS			mOS		
		Nivo [$n = 63$]	4.0 mos.			13.6 mos.		
		Nivo + ipi [$n = 62$]	5.6 mos.			NR		
Durvalumab + tremelimumab	Study 006 [129] NCT02000947	Durva + treme [n=63]	PFS NA[f]			OS NA[f]		
Anti-PD-1/PD-L1 + chemotherapy								
Pembrolizumab + chemotherapy	KEYNOTE-021 [52,53,130] NCT02039674		mPFS	1-yr. PFS	18-mo. PFS	mOS	1-yr. OS	18-mo. OS
		Pembro + carbopl/ pemetr [$n = 60$]	19.0 mos.	57%	52%	NR	77%	70%
		Carbopl/ pemetr [$n = 63$]	8.9 mos.	37%	29%	20.9 mos.	69%	56%
		P value	0.0067	NA	NA	0.03	NA	NA
Pembrolizumab + chemotherapy	KEYNOTE-059 [131] NCT02335411		mPFS	6-mo. PFS		mOS	6-mo. OS	
		Pembro (3 L+) [$n = 259$]	2.0 mos.	15%		5.5 mos.	46%	

Table 3 (continued)

Agent	Trialt name/ number	PFS and OS data (if available)						
		Pembro + cispl/5-FU or cape (1 L) [$n = 25$]	6.6 mos.	68%		13.8 mos.	76%	
		Pembro (1 L, PD-L1+) [$n = 31$]	3.3 mos.	35%		20.7 mos.	73%	
Nivolumab + chemotherapy	CheckMate 012 [132] NCT01454102			mPFS	24-wk. PFS	mOS	1-yr. OS	2-yr. OS
		Nivo 10 mg/kg + gem/cispl [$n = 12$]		5.7 mos.	51%	11.6 mos.	50%	25%
		Nivo 10 mg/kg + pemetr/cispl [$n = 15$]		6.8 mos.	71%	19.2 mos.	87%	33%
		Nivo 10 mg/kg + paclit/carbopl [$n = 15$]		4.8 mos.	38%	14.9 mos.	60%	27%
		Nivo 5 mg/kg + paclit/carbopl [$n = 14$]		7.1 mos.	51%	NR	86%	62%
		Nivo + paclit/carbopl [combined, $n = 29$]		NA	NA	NA	NA	NA
		Nivo + chemo [combined, $N = 56$]		NA	NA	NA	NA	NA
Atezolizumab + chemotherapy	NCT01633970 [133]			mPFS		mOS		
		Atezo + carbopl + pemetr [$n = 25$]		8.4 mos.		19.3 mos.		
		Atezo + carbopl + nab-paclit [$n = 26$]		5.7 mos.		14.8 mos.		
		Atezo + carbopl + paclit [$n = 25$]		7.1 mos.		12.9 mos.		
		Atezo + chemo [combined, $N = 76$]		NA		NA		
Anti-PD-1 + immunotherapy								
			mPFS	6-mo. PFS	1-yr. PFS	18-mo. PFS	OS	
Pembrolizumab + epacadostat (IDO1 inhibitor)	KEYNOTE-037 [134-137] ECHO-202 NCT02178722	Pembro + epa [n=63, advanced melonama]	12.4 mos.	65%	52%	49%	NA	
		Pembro + epa [n=38, recurrent or metastatic HNSCC (2L+)]	NA	NA	NA	NA	NA	
		Pembro + epa [n=36, advanced NSCLC (1L-3L)]	NA	NA	NA	NA	NA	
		Pembro + epa [n=30, advanced RCC]	NA	NA	NA	NA	NA	
		Pembro + epa [n=40, advanced UC (1L+)]	NA	NA	NA	NA	NA	
Anti-PD-L1 + targeted therapy								
Avelumab + axitinib (VEGFR-TKI)	JAVELIN Renal 100 [139] NCT02493751		PFS			OS		
		Avelumab + axitinib	NA			NA		

5-FU 5-Fluorouracil, *Atezo* atezolizumab, *Avel* avelumab, *BORR* best overall response rate, *Cape* capecitabine, *Carbopl* carboplatin, *Chemo* chemotherapy, *Cispl* cisplatin, *CTLA-4* cytotoxic T-lymphocyte-associated antigen-4, *DOR* duration of response, *Durva* durvalumab, *Epa* epacadostat, *FDA* U.S. Food and Drug Administration, *Gem* gemcitabine, *HNSCC* head and neck squamous cell carcinoma, *IDO1* indoleamine 2,3-dioxygenase 1, *IMT* immunotherapy, *Ipi* ipilimumab, *irBORR* immune-related best overall response rate, *irPFS* immune-related progression-free survival, *L* line of therapy, *mDOR* median duration of response, *mOS* median overall survival, *mPFS* median progression-free survival, *NA* not available, *Nab-paclit* nab-paclitaxel, *Nivo* nivolumab, *NR* not reached, *NSCLC* non-small cell lung cancer, *ORR* objective response rate, *OS* overall survival, *Paclit* paclitaxel, *PD-1* programmed cell death-1, *PD-L1* programmed death ligand-1, *Pembro* pembrolizumab, *Pemetr* pemetrexed, *PFS* progression-free survival, *q* every, *RCC* renal cell carcinoma, *SCLC* small cell lung cancer, *Sun* sunitinib, *Treme* tremelimumab, *UC* urothelial carcinoma, *VEGFR-TKI* vascular endothelial growth factor receptor tyrosine kinase inhibitor

Data for combination regimens listed in Table 4 are summarized in this table; only data available in at least 30 patients are summarized in this table

[a]As of May 2017

[b]Four doses of ipilimumab + paclitaxel/carboplatin followed by two doses of placebo + paclitaxel/carboplatin

[c]Two doses of placebo + paclitaxel/carboplatin followed by four doses of ipilimumab + paclitaxel/carboplatin

[d]*P* value refers to the comparison of phased ipilimumab vs. placebo + paclitaxel/carboplatin

[e]*P* value refers to the following comparisons: nivolumab vs. ipilimumab and nivolumab + ipilimumab vs. ipilimumab

[f]In the MYSTIC trial (see Table 4), durvalumab + tremelimumab combination did not meet a primary endpoint of progression-free survival compared to chemotherapy; the trial continues as planned to assess the additional primary endpoints of overall survival for the durvalumab + tremelimumab combination [140]

Table 4 Ongoing pharma-sponsored phase 3 trials of immunotherapy-based combination approaches for advanced malignancies

Combination Regimen	Trial Design	Trial name/number	Tumor Type	Line	Estimated Primary Completion Date
Ipilimumab-based combinations					
Ipilimumab + chemotherapy	Ipilimumab + carboplatin/paclitaxel vs. Placebo + carboplatin/paclitaxel	CA184-104 NCT01285609	Stage IV or recurrent squamous NSCLC	Any	June 2015
	Ipilimumab + carboplatin/paclitaxel vs. Placebo + carboplatin/paclitaxel	CA184-153 NCT02279732	Stage IV or recurrent squamous NSCLC	Any	September 2018
Nivolumab-based combinations					
Nivolumab + ICB	Nivolumab + ipilimumab vs. Nivolumab vs. Bevacizumab	CheckMate 143 NCT02017717	Grade 4 glioblastoma	1/2L	January 2017
	Nivolumab + ipilimumab	CheckMate 817 NCT02869789	Stage IV or recurrent NSCLC	1L	September 2018
	Nivolumab + ipilimumab vs. Nivolumab vs. Placebo	CheckMate 451 NCT02538666	Extensive-stage disease SCLC with ongoing response of stable disease or better following platinum-based 1L chemotherapy	Consolidation therapy	September 2018
Nivolumab + ICB or chemotherapy	Nivolumab + ipilimumab vs. Nivolumab + platinum doublet chemotherapy vs. Nivolumab vs. Platinum doublet chemotherapy	CheckMate 227 NCT02477826	Stage IV or recurrent NSCLC	1L	January 2018
Nivolumab + immunomodulatory therapy	Nivolumab + pomalidomide + dexamethasone vs. Nivolumab + elotuzumab + pomalidomide + dexamethasone vs. Pomalidomide + dexamethasone	CheckMate 602 NCT02726581	Refractory or relapsed and refractory multiple myeloma	3L+	November 2018
Pembrolizumab-based combinations					
Pembrolizumab + chemotherapy	Pembrolizumab + carboplatin + paclitaxel or nab-paclitaxel vs. Placebo + carboplatin + paclitaxel or nab-paclitaxel	KEYNOTE-407 NCT02775435	Stage IV squamous NSCLC	1L	March 2018
	Neoadjuvant chemotherapy + pembrolizumab vs. Neoadjuvant chemotherapy + placebo → Surgery Adjuvant pembolizumab vs adjuvant placebo	KEYNOTE-522 NCT03036488	Locally advanced non-metastatic triple-negative breast cancer (TNBC)	Neoadjuvant/ adjuvant	November 2018
Pembrolizumab + investigational ICB	Pembrolizumab + epacadostat vs. Pembrolizumab + placebo	KEYNOTE-252 ECHO-301 NCT02752074	Unresectable or metastatic melanoma	1L	May 2018
Pembrolizumab + immunomodulatory therapy	Pembrolizumab + pomalidomide + dexamethasone vs. Pomalidomide + dexamethasone	KEYNOTE-183 NCT02576977	Refractory or relapsed and refractory multiple myeloma	3L+	August 2018
Pembrolizumab + oncolytic viral immunotherapy	Pembrolizumab + T-VEC vs. Pembrolizumab + placebo	KEYNOTE-034 MASTERKEY-265 NCT02263508	Unresectable stage IIIB-IVM1c melanoma	1L (*BRAF* wt) 2L (*BRAF* mut+)	December 2018
Atezolizumab-based combinations					
Atezolizumab + chemotherapy + targeted therapy	Atezolizumab + carboplatin/paclitaxel vs. Atezolizumab + carboplatin/paclitaxel + bevacizumab vs. Carboplatin/paclitaxel + bevacizumab	IMpower 150 NCT02366143	Stage IV non-squamous NSCLC	1L	November 2017
Atezolizumab + chemotherapy	Atezolizumab + nab-paclitaxel/carboplatin vs. Nab-paclitaxel/carboplatin	IMpower 130 NCT02367781	Stage IV non-squamous NSCLC	1L	December 2017
	Atezolizumab + carboplatin/paclitaxel vs. Atezolizumab + carboplatin/nab-paclitaxel vs. Carboplatin/nab-paclitaxel	IMpower 131 NCT02367794	Stage IV squamous NSCLC	1L	January 2018
	Atezolizumab + gemcitabine + carboplatin/cisplatin vs. Placebo + gemcitabine + carboplatin/cisplatin vs. Atezolizumab	IMvigor 130 NCT02807636	Locally advanced or metastatic UC	1L	December 2018

Table 4 (continued)

Avelumab-based combinations					
Avelumab + chemotherapy	Avelumab + PLD vs. Avelumab vs. PLD	JAVELIN Ovarian 200 NCT02580058	Platinum-resistant/refractory ovarian cancer	1-4L	March 2018
Avelumab + targeted therapy	Avelumab + axitinib vs. Sunitinib	JAVELIN Renal 101 NCT02684006	Advanced or metastatic RCC	1L	December 2018
Durvalumab-based combinations					
Durvalumab + investigational ICB	Durvalumab + tremelimumab vs. Durvalumab vs. Paclitaxel/carboplatin or gemcitabine/cisplatin or gemcitabine/carboplatin or pemetrexed/cisplatin or pemetrexed/carboplatin	MYSTIC[b] NCT02453282	Stage IV NSCLC	1L	June 2017
	Sub-study A (PD-L1+): Durvalumab vs. Vinorelbine or gemcitabine or erlotinib Sub-study B (PD-L1−): Durvalumab + tremelimumab vs. Durvalumab vs. Tremelimumab vs. Vinorelbine or gemcitabine or erlotinib	ARCTIC NCT02352948	NSCLC	3L	November 2017
	Durvalumab + tremelimumab vs. Durvalumab vs. Cetuximab or docetaxel or paclitaxel or methotrexate or 5-fluorouracil or capecitabine	EAGLE NCT02369874	Recurrent or metastatic HNSCC	2L	February 2018
	Durvalumab + tremelimumab vs. Durvalumab vs. Cetuximab + carboplatin or cisplatin + 5-fluorouracil	KESTREL NCT02551159	Recurrent or metastatic HNSCC	1L	March 2018
	Durvalumab + tremelimumab vs. Durvalumab vs. Gemcitabine + carboplatin or cisplatin	DANUBE NCT02516241	Stage IV UC	1L	April 2018
	Durvalumab + tremelimumab vs. Paclitaxel/carboplatin or gemcitabine/cisplatin or gemcitabine/carboplatin or pemetrexed/cisplatin or pemetrexed/carboplatin	NEPTUNE NCT02542293	Stage IV NSCLC	1L	October 2018

HNSCC head and neck squamous cell carcinoma, *ICB* immune checkpoint blocker, *L* line of therapy, *NSCLC* non-small cell lung cancer, *PD-1* programmed cell death-1, *PD-L1* programmed cell death ligand-1, *PLD* pegylated liposomal doxorubicin, *RCC* renal cell carcinoma, *SCLC* small cell lung cancer, *T-VEC* talimogene laherparepvec, *UC* urothelial carcinoma

This table includes phase 3 pharma-sponsored studies that expect to have primary results on or before Q4 2018 (based on clinicaltrials.gov) in tumor types different from those in which the combination regimens are already approved

[a] Durvalumab + tremelimumab combination did not meet a primary endpoint of progression-free survival compared to chemotherapy; the trial continues as planned to assess the additional primary endpoints of overall survival for the durvalumab + tremelimumab combination [140]

the phase 2 KEYNOTE-002 trial, which examined global health status and functional scales (quality of life and physical, emotional, cognitive, and social functioning) as well as symptom scales (fatigue, nausea, pain, dyspnea, insomnia, appetite loss, constipation, and diarrhea), showed that pembrolizumab improved or maintained HRQoL when compared with chemotherapy in patients with ipilimumab-refractory melanoma [160]. A recent analysis of HRQoL from the phase 3 KEYNOTE-045 study showed that pembrolizumab improved HRQoL when compared with chemotherapy in patients with platinum-refractory advanced UC [161]. Several phase 3 studies comparing nivolumab with chemotherapy reported similar findings in treatment-naïve patients with melanoma (CheckMate 066) [162] and in patients with recurrent HNSCC (CheckMate 141) [31, 163]. Nivolumab was also associated with HRQoL improvement over the targeted agent, everolimus, in previously treated patients with advanced RCC (CheckMate 025) [164]. The phase 3 CheckMate 067 showed that ipilimumab/nivolumab combination therapy maintained HRQoL in treatment-naïve patients with melanoma; in this study, no clinically meaningful deterioration was observed in patients treated with

ipilimumab/nivolumab combination therapy compared with those treated with ipilimumab [165]. Taken together, these findings indicating HRQoL improvement or maintenance with immunotherapy may support the preferred use of immunotherapies over some targeted agents, such as everolimus, or chemotherapy, especially from a patient perspective.

8 Conclusions and Future Directions of Immunotherapy

Immunotherapies are an emerging treatment for many cancer types, with distinct properties that distinguish these anticancer agents from traditional chemotherapy or targeted agents. Unlike chemotherapy or targeted agents, which generally act directly on the tumor cells, cancer immunotherapies generally function by modulating the immune system, thereby indirectly affecting tumor survival. Because of this, a unique pattern of responses has been reported with immunotherapies that includes pseudoprogression or mixed tumor responses, which can result in the perception of disease progression. In randomized controlled trials, ICBs have been consistently associated with durable responses and often increased rates of response compared with standards of care. Observations of improved or maintained HRQoL versus standard of care further add to the clinical benefits of ICB therapy. In addition, treatment with ICBs is associated with a distinct set of imAEs, which have the potential to be serious. Further studies are needed to evaluate the efficacy and safety of checkpoint blockade in special, difficult-to-treat populations, such as patients with preexisting immune-related conditions, low performance status, or brain metastases. ICBs are currently being studied in the neoadjuvant and adjuvant settings as well as in combination with novel investigational agents including other classes of immunotherapy and targeted agents. As the indications for ICBs expand and cancer treatment continues to shift towards a more personalized approach, the ability to identify patients who will derive the most benefit from immunotherapy will continue to evolve.

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