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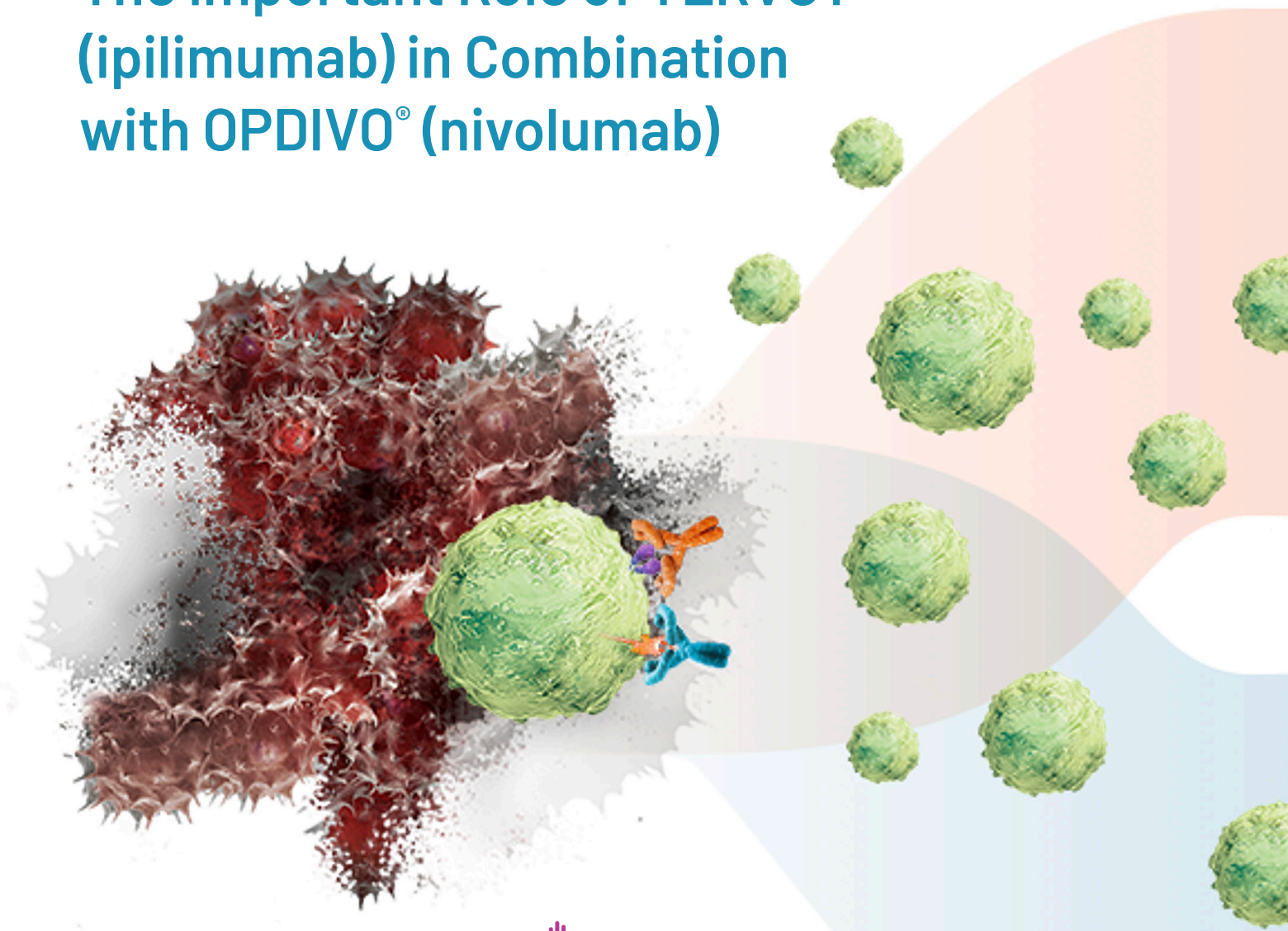
The Important Role of YERVOY® (ipilimumab) in Combination with OPDIVO® (nivolumab)



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JONS JOURNAL OF ONCOLOGY NAVIGATION & SURVIVORSHIP

ITO IMMUNOTHERAPY IN ONCOLOGY

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The Important Role of YERVOY® (ipilimumab) in Combination with OPDIVO® (nivolumab)

INTRODUCTION AND THE HISTORY OF IMMUNO-ONCOLOGY

The idea that it could be possible to harness the human body's own immune system against cancer has its origins as far back as the mid-nineteenth century. Then, the German pathologist Rudolf Virchow reported immune infiltration in human tumors.[1] Years later, American surgeon Dr William Coley, who has been called the "father of immunotherapy," attempted to induce a therapeutic immune response in patients by injecting a bacterial broth (later known as "Coley's toxins") into soft-tissue tumors that could not be surgically resected.[2] Coley observed inflammatory responses in treated patients and, in some patients, clearance of the cancer.[2]

In Coley's day, the scientific understanding of immune mechanisms had not been developed, and progress in cancer treatment stalled for decades. However, beginning in the 1970s, scientific and methodological innovations such as the engineering of antibodies as tools to harness immune mechanisms, coupled with our increased understanding of pathways and targets of the immune system, began to enable the development of new treatments.[3]

In their Nobel Prize–winning research, Dr James P. Allison and colleagues demonstrated that in vivo administration of monoclonal antibodies targeting the cytotoxic T-lymphocyte antigen 4; (CTLA-4) pathway resulted in the destruction of tumor cells and played a role in the activation of memory T-cells. CTLA-4 is an immune checkpoint receptor that inhibits cytotoxic T-cell activation, suppresses T-regulatory (Treg)-driven effector cells, and reduces proliferation of memory T-cells. Results from Dr Allison's research showed that blocking the inhibitory effect of CTLA-4 may allow for immune responses against tumor cells.[4]

The discovery of the CTLA-4 immune checkpoint pathway opened the door for other immune modulatory pathways to be investigated, including agents that target PD-1/PD-L1, such as OPDIVO® (nivolumab), which are now also approved. Thus, YERVOY® (ipilimumab), the first FDA-approved immune checkpoint inhibitor, served as the pioneer for the immune checkpoint inhibitor approach to the therapy of a variety of cancers. (See **Figure 1**.)

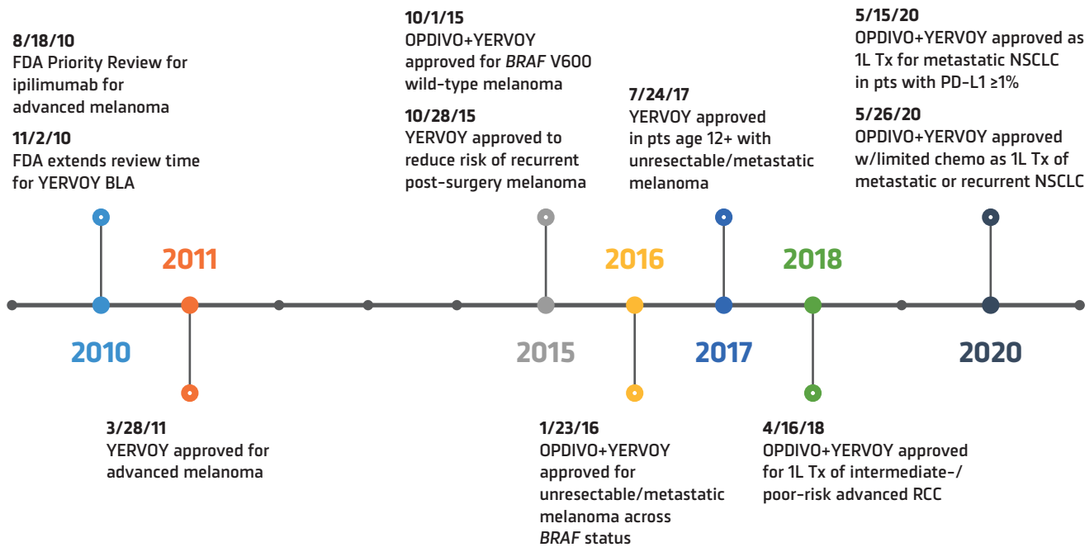
Summary of Warnings and Precautions

OPDIVO (nivolumab) and YERVOY (ipilimumab) are associated with the following Warnings and Precautions: severe and fatal immune-mediated adverse reactions (IMARs), including pneumonitis, colitis, hepatitis and hepatotoxicity, endocrinopathies, nephritis with renal dysfunction, dermatologic adverse reactions, other IMARs; infusion-related reactions; complications of allogeneic hematopoietic stem-cell transplantation; embryo-fetal toxicity; and increased mortality in patients with multiple myeloma when OPDIVO is added to a thalidomide analogue and dexamethasone, which is not recommended outside of controlled clinical trials.

Please see Important Safety Information for OPDIVO and YERVOY on pages 25-31.

Please also see full Prescribing Information for OPDIVO and YERVOY.

Figure 1 Development of YERVOY



Source: Yervoy FDA Approval History. www.drugs.com/history/yervoy.html. Accessed July 1, 2021.
BLA indicates biologics license application; 1L, first line; NSCLC, non-small cell lung cancer; RCC, renal-cell carcinoma; Tx, treatment.

MECHANISM OF ACTION (MOA) OF YERVOY AND OPDIVO AND THE COMBINATION OF THE TWO AGENTS

YERVOY MOA

CTLA-4 is a negative regulator of T-cell activation. YERVOY is a humanized monoclonal antibody that binds to CTLA-4 and helps overcome the downregulation of T-cell activation pathways. T-cell activation requires 2 signals, between the major histocompatibility complex and T-cell receptor and between B7 molecules on the antigen-presenting cell (APC) and CD28 on the T-cell. Activation leads to CTLA-4 upregulation and translocation to the cell surface. CTLA-4 on the T-cell competitively binds to B7 on the APC leading to downregulation and T-cell inactivation. YERVOY blocks interaction of CTLA-4 with CD80/CD86, which may allow for activation of T-cells and anti-tumor response.[5] (See **Figure 2**.)

Signaling through CTLA-4, an immune checkpoint receptor, leads to inhibition of cytotoxic T-cell activation, Treg-driven effector cell suppression, and may lead to a reduced proliferation of memory T-cells.

Antibody blockade of CTLA-4 by YERVOY has been shown to augment T-cell activation. Blockade of CTLA-4 may help restore T-cell responsiveness. According to preclinical data, CTLA-4–specific antibodies can help restore an immune response by increasing the activation and proliferation of T-cells and by reducing Tregs in the tumor microenvironment. Some of these T-cells may become memory cells. Immuno-oncology therapy may activate the immune response to counter tumor survival and growth strategies, and may lead to adverse reactions.

Select Important Safety Information
Summary of Warnings and Precautions

OPDIVO and YERVOY are associated with the following Warnings and Precautions: severe and fatal immune-mediated adverse reactions including pneumonitis, colitis, hepatitis and hepatotoxicity, endocrinopathies, nephritis with renal dysfunction, dermatologic adverse reactions, other immune-mediated adverse reactions; infusion-related reactions; complications of allogeneic hematopoietic stem-cell transplantation (HSCT); embryo-fetal toxicity; and increased mortality in patients with multiple myeloma when OPDIVO is added to a thalidomide analog and dexamethasone, which is not recommended outside of controlled clinical trials.

Please see Important Safety Information for OPDIVO and YERVOY on pages 25-31.
Please also see full Prescribing Information for OPDIVO and YERVOY.

CTLA-4 inhibition may allow for immune attack on tumor cells and healthy cells.[5]

YERVOY has several FDA-approved indications, including[6]:

Melanoma
- Treatment of unresectable or metastatic melanoma in adults and pediatric patients ≥12 years old.
- Treatment of adult patients with unresectable or metastatic melanoma, in combination with OPDIVO.
- Adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy.

Renal-Cell Carcinoma
- Treatment of patients with intermediate or poor risk, previously untreated advanced renal-cell carcinoma (RCC), in combination with OPDIVO.

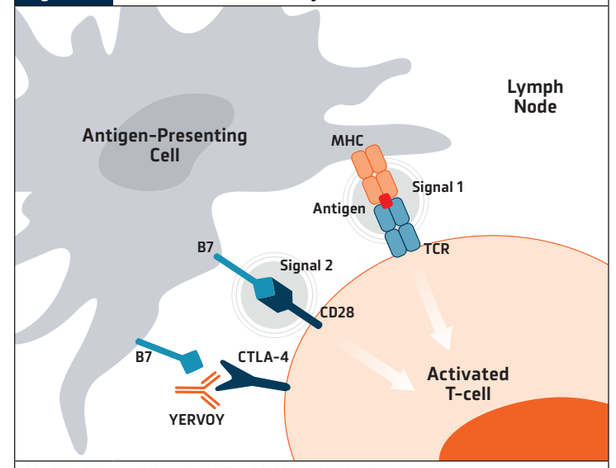
Non-Small Cell Lung Cancer
- Treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) expressing PD-L1 (≥1%) as determined by an FDA-approved test, with no *EGFR* or *ALK* genomic tumor aberrations, as first-line treatment in combination with OPDIVO.
- Treatment of adult patients with metastatic or recurrent NSCLC with no *EGFR* or *ALK* genomic tumor aberrations as first-line treatment, in combination with OPDIVO and 2 cycles of platinum-doublet chemotherapy.

OPDIVO MOA

OPDIVO is a humanized monoclonal antibody that targets and blocks PD-1 receptors. Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T-cells, inhibits T-cell proliferation and cytokine production. Blockade of PD-1 can release the PD-1 pathway-mediated inhibition of the immune response, helping restore anti-tumor immune function. (See **Figure 3**.)

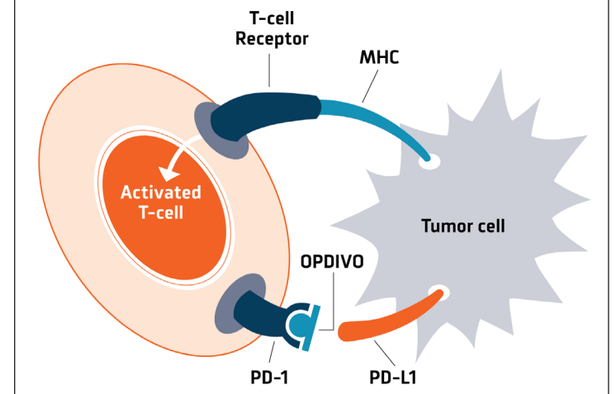
Additionally, preclinical studies suggest that complete inhibition of PD-1 signaling through both PD-L1 and PD-L2 may be more effective at reversing T-cell exhaustion than through the inhibition of PD-L1 alone.

Figure 2 Activation of T-Cell by CTLA-4 Blockade



Modified from: Ribas A. *N Engl J Med*. 2015;373:16.
MHC indicates major histocompatibility complex; TCR, T-cell receptor.

Figure 3 Identification of a Tumor Cell by PD-1 Signaling Blockade



During repeated antigen exposure, the programmed death receptor-1 (PD-1) inhibitor receptor is expressed by T-cells. Binding of PD-L1 to PD-1 suppresses the TCR signaling on T-cell activation. Blockade of PD-1 by OPDIVO derepresses TCR signaling, thereby permitting T-cell activation.
Modified from: Ribas A. *N Engl J Med*. 2015;373:16.
MHC indicates major histocompatibility complex.

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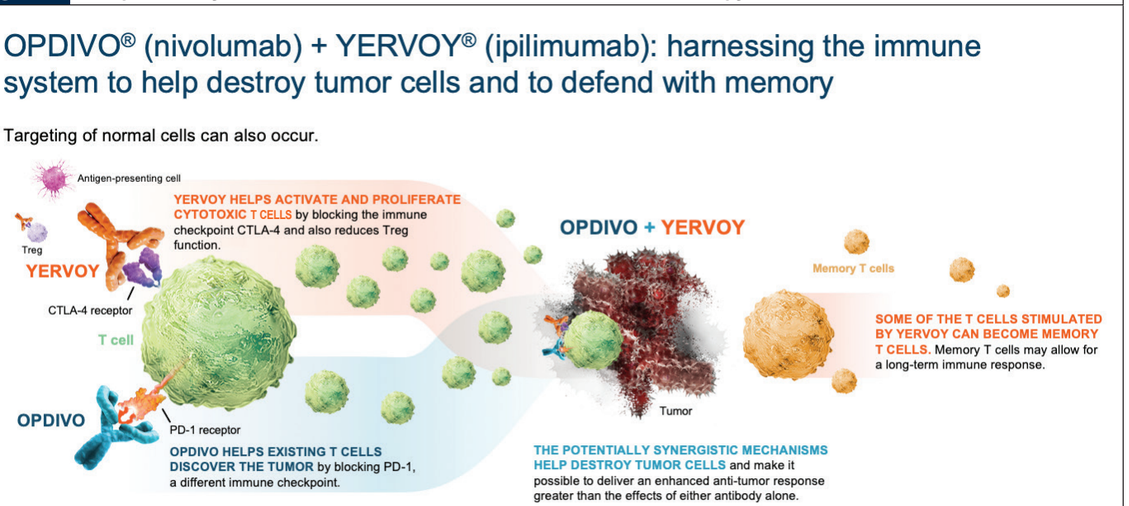
Please also see full Prescribing Information for OPDIVO and YERVOY.

Figure 4 Complementary Mechanisms of OPDIVO and YERVOY Combination Therapy



CTLA-4 indicates cytotoxic T-lymphocyte antigen 4; PD-1, programmed death receptor-1, T-cell, cytotoxic T-cell; Treg, regulatory T-cell.

OPDIVO has a number of FDA-approved indications, including[7]:

Melanoma

- Patients with unresectable or metastatic melanoma, as a single agent or in combination with YERVOY.
- Patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting.

Renal-Cell Carcinoma

- Patients with intermediate or poor risk advanced RCC, as a first-line treatment in combination with YERVOY.
- Patients with advanced RCC, as a first-line treatment in combination with cabozantinib.
- Patients with advanced RCC who have received prior anti-angiogenic therapy.

Non-Small Cell Lung Cancer

- Adult patients with metastatic NSCLC expressing PD-L1 (≥1%) as determined by an FDA-approved test, with no *EGFR* or *ALK* genomic tumor aberrations, as first-line treatment in combination with YERVOY.
- Adult patients with metastatic or recurrent NSCLC with no *EGFR* or *ALK* genomic tumor aberrations as first-line treatment, in combination with YERVOY and 2 cycles of platinum-doublet chemotherapy.
- Patients with metastatic NSCLC and progression on or after platinum-based chemotherapy. Patients with *EGFR* or *ALK* genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO.

Complementary Mechanisms of OPDIVO + YERVOY

YERVOY helps activate and proliferate cytotoxic cells by blocking the immune checkpoint CTLA-4 and also reduces Treg function. OPDIVO helps existing T-cells discover the tumor by blocking PD-1, a different immune checkpoint. The combination helps T-cells attack tumor cells and makes it possible to deliver an enhanced anti-tumor response greater than the effects of either antibody alone in metastatic melanoma, advanced RCC, and metastatic NSCLC. Some of the T-cells stimulated by YERVOY can become memory T-cells. Memory T-cells may allow for a long-term immune response. (See **Figure 4**.[6-17])

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Please also see full Prescribing Information for OPDIVO and YERVOY.

REVIEW OF THE CLINICAL DATA THAT LED TO THE APPROVAL OF YERVOY (IPILIMUMAB) ALONE AND IN COMBINATION WITH OPDIVO (NIVOLUMAB)

Clinical Data with YERVOY Monotherapy

MDX010-20 Trial: Metastatic Melanoma

In this study, patients with previously unresectable or metastatic melanoma (stage III or IV) were randomized to receive 1 of 3 treatment regimens detailed below. (See **Figure 5**.)

Patients were eligible for inclusion in the study if they had a diagnosis of unresectable stage III or IV melanoma and had received prior treatment containing ≥1 of dacarbazine, temozolomide, fotemustine, carboplatin, or interleukin-2. Additional inclusion criteria were age ≥18 years; life expectancy of ≥4 months; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; positive status for HLA-A*0201; normal hematologic, hepatic, and renal function; and no systemic treatment in the previous 28 days.

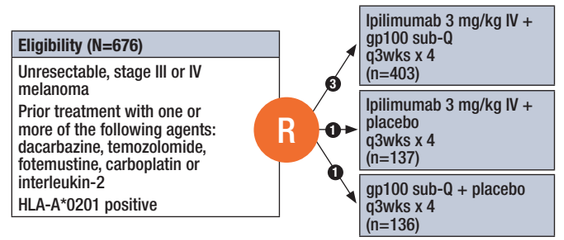
Exclusion criteria were any other cancer from which the patient had been disease-free for <5 years (except treated and cured basal-cell or squamous-cell skin cancer, superficial bladder cancer, or treated carcinoma in situ of the cervix, breast, or bladder); primary ocular melanoma; previous receipt of anti–CTLA-4 antibody or cancer vaccine; autoimmune disease; active, untreated metastases in the central nervous system (CNS); pregnancy or lactation; concomitant treatment with any nonstudy anti-cancer therapy or immunosuppressive agent; or long-term use of systemic corticosteroids.

The primary end point was overall survival (OS). Secondary end points included overall response rate, duration of response (DOR), and progression-free survival (PFS).

YERVOY, with or without a gp100 peptide vaccine, improved OS in patients with previously treated metastatic melanoma compared with patients who were treated with gp100 alone. A total of 403 patients received YERVOY plus the gp100 peptide vaccine, 137 patients received YERVOY alone, and 136 patients received gp100 alone.[18]

The median OS was 10 months among patients who received YERVOY plus gp100, compared with 6 months among patients who received gp100 alone (hazard ratio [HR] for death, 0.68; P = .0004). The median OS with YERVOY alone was 10 months (HR for death in the comparison with gp100 alone, 0.66; P = .0026.)[6] (See **Figure 6**.)[18]

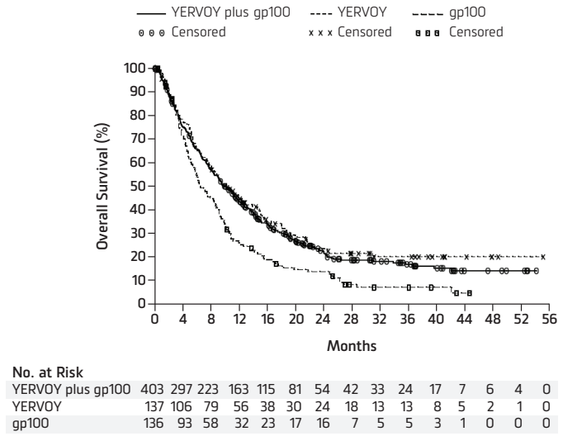
Figure 5 MDX010-20 Study Design



Patients with stable disease for 3 months after week 12, or a confirmed partial or complete response were offered reinduction with assigned treatment regimen upon disease progression.

O'Day S, et al. Proc ASCO 2010; Abstract 4; Hodi FS, et al. Proc ASCO 2010; Abstract 8509; Hodi FS, et al. *N Engl J Med.* 2010; [Epub ahead of print].

Figure 6 MDX010-20: Overall Survival



Source: Hodi FS, et al. *N Engl J Med.* 2010;363:711–723.

Among the most common adverse reactions (all grades) among patients in the YERVOY, YERVOY + gp100, and gp100 arms were fatigue (41%, 34%, and 31%, respectively), diarrhea (32%, 37%, and 20%, respectively), pruritus (31%, 21%, and 11%, respectively), and rash (29%, 25%, and 8%, respectively).[6] The researchers reported 14 study drug-related deaths (2.1%), 7 of which were associated with immune-related adverse events. Grade 3 or 4 immune-related adverse events were

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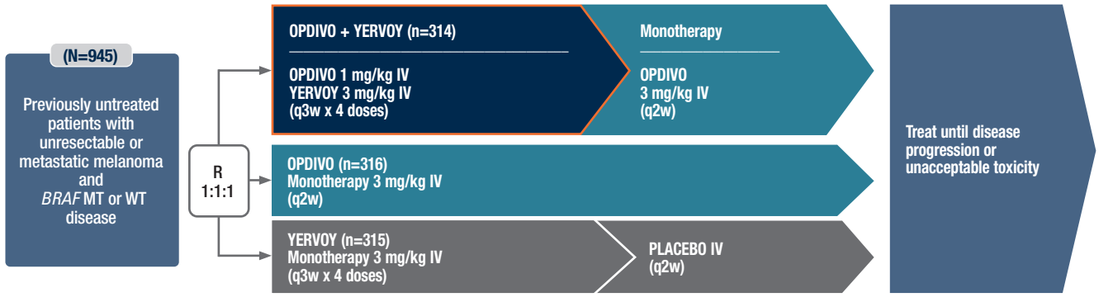
Figure 7 Checkmate 067 Trial[6,21]

Checkmate 067 study design: OPDIVO® (nivolumab) + YERVOY (ipilimumab) or OPDIVO monotherapy vs YERVOY



IV indicates intravenous; MT, mutant; q2w, every 2 weeks; q3w, every 3 weeks; q4w, every 4 weeks; R, randomization; WT, wild type.

reported in 10% to 15% of the patients in the YERVOY groups and in 3.0% of patients in the gp100-alone group. All immune-related adverse events occurred during the induction and reinduction periods.

The immune-related adverse events most often affected the skin and gastrointestinal tract. The most common immune-related adverse event was diarrhea, which occurred at any grade in 27% to 31% of the patients in the YERVOY groups. The median time to the resolution of immune-related adverse events of grade 2, 3, or 4 was 6.3 weeks (95% confidence interval [CI], 4.3-8.4) in the YERVOY + gp100 group, 4.9 weeks (95% CI, 3.1-6.4) in the YERVOY-alone group, and 3.1 weeks (95% CI, 1.1-not reached [NR]) in the gp100-alone group.[18]

This was the first immune checkpoint inhibitor treatment approved by the FDA based on the significance of the efficacy data in comparison to the current standard-of-care treatment at that time.

Clinical Data with the Combination of OPDIVO + YERVOY

Checkmate 067 Trial: Metastatic Melanoma[6,19-21]

In this study, patients with previously untreated, unresectable or metastatic melanoma (stage III or IV) were randomized to receive 1 of 3 treatment regimens detailed below. (See **Figure 7**.)

To be eligible for the study, patients were required to have histologically confirmed stage III (unresectable) or stage IV melanoma, with no history of prior systemic treatment for unresectable or metastatic melanoma.

Additional eligibility criteria included age ≥18 years, an ECOG performance status score of 0 or 1, measurable disease by computed tomography or magnetic resonance imaging per Response Evaluation Criteria in Solid Tumors (RECIST) (version 1.1), availability of tissue collected from metastatic or unresectable tumors for the assessment of PD-L1 status, and known *BRAF* V600 mutation status (or consent to *BRAF* V600 mutation testing per local standards).

Key exclusion criteria were presence of active brain metastases, ocular melanoma, or autoimmune disease, and any prior treatment with an anti–PD-1, anti–PD-L1, anti–PD-L2, or anti–CTLA-4 antibody. Patients who required systemic corticosteroid treatment or other immunosuppressive medications within 14 days of study drug administration were excluded.

In the primary analysis of Checkmate 067, OPDIVO + YERVOY and OPDIVO alone were compared to YERVOY alone in patients with metastatic melanoma.

The 2 primary end points were PFS and OS in the OPDIVO + YERVOY group and in the OPDIVO group, as compared with the YERVOY group. Secondary end points included a comparison of the objective response rate (ORR) between the OPDIVO-containing groups versus the YERVOY group and descriptive efficacy evaluations between the OPDIVO + YERVOY group and the OPDIVO group.

Serious adverse reactions occurred in 74% of patients receiving OPDIVO + YERVOY, and in 44% of patients receiving OPDIVO. Study therapy was discontinued for adverse reactions in 47% of OPDIVO + YERVOY patients, and in 18% of OPDIVO patients. Fifty-eight percent of OPDIVO + YERVOY patients had a dosing delay due to an adverse reaction, compared with 36% of

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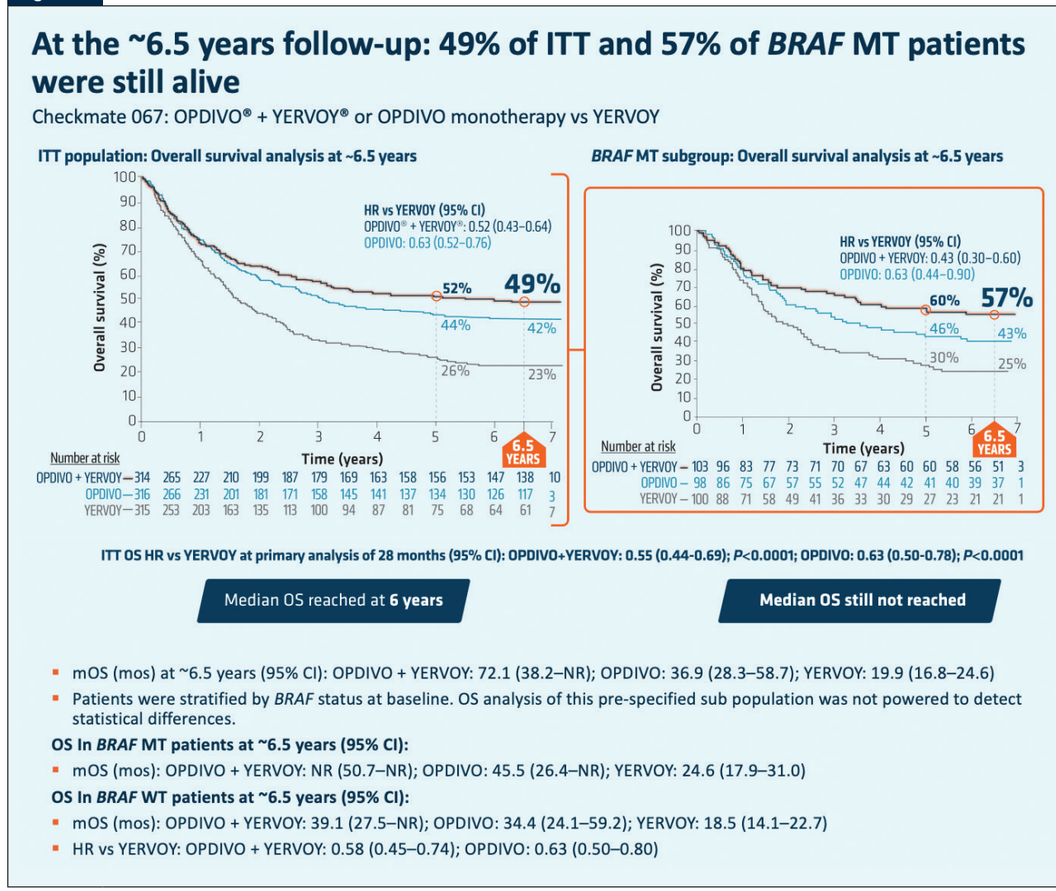
Figure 8 Checkmate 067: Overall Survival



OPDIVO patients. Grade 3 or 4 adverse reactions occurred in 72% of OPDIVO + YERVOY patients and in 51% of OPDIVO patients.

The most frequent serious adverse reactions in the OPDIVO + YERVOY and OPDIVO groups, respectively, were diarrhea (13% and 2.2%), colitis (10% and 1.9%), and pyrexia (10% and 1.0%).

The most common (≥20%) adverse reactions in OPDIVO + YERVOY patients were fatigue, diarrhea, rash, nausea, pyrexia, pruritus, musculoskeletal pain, vomiting, decreased appetite, cough, headache, dyspnea, upper respiratory tract infection, arthralgia, and increased transaminases. The most common (≥20%) adverse reactions in OPDIVO patients were fatigue, rash, musculoskeletal pain, diarrhea, nausea, cough, pruritus, upper respiratory tract infection, decreased appetite, headache, constipation, arthralgia, and vomiting.[7]

In the primary analysis of Checkmate 067, OPDIVO + YERVOY and OPDIVO alone were compared to YERVOY alone in patients with metastatic melanoma.[20] The median PFS was 11.5 months (95% CI, 8.9-16.7) with OPDIVO + YERVOY, compared with 2.9 months (95% CI, 2.8-3.4) with YERVOY (HR for death or disease progression, 0.42; 95% CI, 0.34-0.51; *P* <.0001 at 9 months). PFS was 6.9 months (95% CI, 4.3-9.5) with OPDIVO (HR for the comparison with YERVOY, 0.57; 95% CI, 0.47-0.69; *P* <.0001 at 9 months).

In patients with PD-L1–positive tumors, the median PFS was 14.0 months in the OPDIVO + YERVOY group and in the OPDIVO group, and 3.9 months in the

Please see Important Safety Information for OPDIVO and YERVOY on pages 25-31.
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YERVOY group. In patients with PD-L1–negative tumors, PFS was 11.2 months (95% CI, 8.0-NR) with combination therapy, 5.3 months (95% CI, 2.8-7.1) with OPDIVO, and 2.8 months (95% CI, 2.8-3.1) with YERVOY.

These results showed that among previously untreated patients with metastatic melanoma, OPDIVO alone or combined with YERVOY resulted in significantly longer PFS than YERVOY alone. In patients with PD-L1–negative tumors, the combination of PD-1 and CTLA-4 blockade was more effective than either agent alone.

At the American Society of Clinical Oncology (ASCO) 2021 Annual Meeting, researchers presented 6.5-year extended follow-up data from the Checkmate 067 trial.[21] (See **Figure 8**.)

Intent to treat (ITT) OS HR versus YERVOY at primary analysis of 28 months was 0.55 for OPDIVO + YERVOY (95% CI, 0.44-0.69; *P* <.0001) and 0.63 for OPDIVO (95% CI, 0.50-0.78; *P* <.0001). The results from the extended follow-up were as follows:
median OS (mOS; months) at ~6.5 years (95% CI): OPDIVO + YERVOY: 72.1 (38.2-NR); OPDIVO: 36.9 (28.3-58.7); YERVOY: 19.9 (16.8-24.6).

Patients were stratified by *BRAF* status at baseline. OS analysis of this prespecified sub-population was not powered to detect statistical differences.

OS in *BRAF* mutant (MT) patients at ~6.5 years (95% CI):
mOS (months): OPDIVO + YERVOY: NR (50.7-NR); OPDIVO: 45.5 (26.4-NR); YERVOY: 24.6 (17.9-31.0). (See **Figure 9**.)
OS in *BRAF* wild type (WT) patients at ~6.5 years (95% CI):
mOS (months): OPDIVO + YERVOY: 39.1 (27.5-NR); OPDIVO: 34.4 (24.1-59.2): YERVOY: 18.5 (14.1-22.7)
HR versus YERVOY: OPDIVO + YERVOY: 0.58 (0.45-0.74); OPDIVO: 0.63 (0.50-0.80).

In the OPDIVO arm:
- ORR: 42% (36-47); complete response: 17%; partial response: 25%
- 92% (71-98) of complete responders were alive at 6.5 years
- 76% (66-83) of partial responders were alive at 6.5 years

At a median follow-up of 80.8 months, in the OPDIVO + YERVOY ITT population (N=145), 77% (N=112) were off study treatment and never received subsequent therapy, 18% (N=26) received subsequent therapy, and 5% (N=7) were still on study therapy. Similarly, at a median follow-up of 81.0 months, in the *BRAF* MT patients (N=59), 70% (N=41) were off study treatment and never received subsequent therapy, 24% (N=14) received subsequent systemic therapy, and 7% (N=4) were still on study therapy.

See **Table 1** for information on safety data and adverse reactions in Checkmate 067.

See **Figure 9** for additional summary of Checkmate 067 data.

Figure 9 Checkmate 067 Summary

At ~6.5 years: Over half of *BRAF* MT patients with advanced melanoma were alive

Of *BRAF* MT patients who received OPDIVO® + YERVOY®:

57%	37%	88%
of patients were still *alive*	of patients were *progression free*	of patients who achieved a *partial response* were still alive
At ~6.5 years of follow-up: OPDIVO + YERVOY: • mOS: NR (50.7–NR) • HR vs YERVOY: 0.43 (0.30-0.60) YERVOY at 6.5 years: • OS rate: 25% • mOS: 24.6 (17.9–31.0)	At ~6.5 years of follow-up: OPDIVO + YERVOY: • mPFS: 16.8 (8.3–32.0) • HR vs YERVOY: 0.44 (0.31–0.62) YERVOY at 6.5 years: • PFS rate: 9% • mPFS: 3.4 (2.8–5.2)	At ~6.5 years of follow-up: OPDIVO + YERVOY: • ORR: 58% (48-68) CR: 21% PR: 37% • 75% (41-91) of complete responders were alive • 88% (74-95) of partial responders were alive YERVOY at 6.5 years: • ORR: 15% (9-24); CR: 5%; PR: 10% • 50% (1-91) of complete responders were alive • 81% (42-95) of partial responders were alive

OPDIVO + YERVOY: Median overall survival *not yet reached*

OS HR vs YERVOY in the ITT population (95% CI)
In the primary analysis at 28 months (95% CI):
- OPDIVO + YERVOY: 0.55 (0.44–0.69); *P*<0.0001
- OPDIVO: 0.63 (0.50–0.78); *P*<0.0001

At the ~6.5-year extended follow-up analysis:
- OPDIVO + YERVOY: 0.52 (0.43–0.64)
- OPDIVO: 0.63 (0.52–0.76)

OS at ~6.5-year follow-up in *BRAF* MT patients with OPDIVO:
- 43% of *BRAF* MT patients (n=98) were alive at 78 months
- HR vs YERVOY (95% CI): 0.63 (0.44–0.90)

PFS HR vs YERVOY in the ITT population (95% CI)
In the primary analysis at 9 months (95% CI):
- OPDIVO + YERVOY: 0.42 (0.34–0.51); *P*<0.0001
- OPDIVO: 0.57 (0.47–0.69); *P*<0.0001

At the ~6.5-year extended follow-up analysis:
- OPDIVO + YERVOY: 0.42 (0.35–0.51)
- OPDIVO: 0.53 (0.44–0.64)

At the ~6.5-year extended follow-up analysis in *BRAF* MT patients:
- OPDIVO: 23% of *BRAF* MT patients (n=98) were progression free at 78 months
- HR vs YERVOY (95% CI): 0.71 (0.51-0.98)

ORR in the ITT population (95% CI)
In the primary analysis at 9 months (95% CI):
- OPDIVO + YERVOY: 50% (44–55); *P*<0.0001; CR: 9% PR: 41%
- OPDIVO: 40% (34–46); *P*<0.0001; CR: 9% PR: 31%
- YERVOY: 14% (10–18); CR: 2% PR: 12%

At the ~6.5-year extended follow-up analysis:
- OPDIVO ORR: 42% (36–47); CR: 17% PR: 25%
- 92% (71–98) of complete responders were alive
- 76% (66–83) of partial responders were alive

At the ~6.5-year extended follow-up analysis in *BRAF* MT patients:
- OPDIVO ORR: 37% (27–47); CR: 12% PR: 25%
- 100% (100–100) of complete responders were alive
- 65% (44–79) of partial responders were alive

ITT indicates intent to treat; MT, mutant; NR, not reached.

Table 1 Checkmate 067: Safety Data

Adverse reactions*	OPDIVO + YERVOY (n=313) All grades	OPDIVO + YERVOY (n=313) Grades 3–4	OPDIVO (n=313) All grades	OPDIVO (n=313) Grades 3–4	YERVOY (n=311) All grades	YERVOY (n=311) Grades 3–4
General disorders and administration site conditions, %						
Fatigue†	62	7	59	1.6	51	4.2
Pyrexia	40	1.6	16	0	18	0.6
Gastrointestinal disorders, %						
Diarrhea	54	11	36	5	47	7
Nausea	44	3.8	30	0.6	31	1.9
Vomiting	31	3.8	20	1.0	17	1.6
Skin and subcutaneous tissue disorder, %						
Rash‡	53	6	40	1.9	42	3.5
Vitiligo	9	0	10	0.3	15	0
Musculoskeletal and connective tissue disorders, %						
Musculoskeletal pain§	32	2.6	42	3.8	36	1.9
Arthralgia	21	0.3	21	1.0	16	0.3
Metabolism and nutrition disorders, %						
Decreased appetite	29	1.9	22	0	24	1.3
Respiratory, thoracic, and mediastinal disorders, %						
Cough/productive cough	27	0.3	28	0.6	22	0
Dyspnea/exertional dyspnea	24	2.9	18	1.3	17	0.6
Infections, %						
Upper respiratory tract infection‖	23	0	22	0.3	17	0
Endocrine disorders, %						
Hypothyroidism	19	0.6	11	0	5	0
Hyperthyroidism	11	1.3	6	0	1	0
Investigations, %						
Decreased weight	12	0	7	0	7	0.3
Vascular disorders, %						
Hypertension¶	7	2.2	11	5	9	2.3

Toxicity was graded per NCI CTCAE v4.
*ARs occurring at a higher incidence than in the YERVOY arm (between-arm difference of ≥5% [all grades] or ≥2% [Grades 3–4]).
†Includes asthenia and fatigue.
‡Includes pustular rash, dermatitis, acneiform dermatitis, allergic dermatitis, atopic dermatitis, bullous dermatitis, exfoliative dermatitis, psoriasiform dermatitis, drug eruption, exfoliative rash, erythematous rash, generalized rash, macular rash, maculopapular rash, morbilliform rash, papular rash, papulosquamous rash, and pruritic rash.
§Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, and spinal pain.
‖Includes upper respiratory tract infection, nasopharyngitis, pharyngitis, and rhinitis.
¶Includes hypertension and blood pressure increased.
AR indicates adverse reaction; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

Please see Important Safety Information for OPDIVO and YERVOY on pages 25-31.
Please also see full Prescribing Information for OPDIVO and YERVOY.

Checkmate 214 Trial: Renal-Cell Carcinoma in Select Patients[7,22-25]

In this study, patients with treatment-naïve, advanced RCC with a clear-cell component were stratified by International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk and randomized to receive 1 of 2 treatment regimens detailed in **Figure 10**.

The coprimary end points were ORR, PFS, and OS among intermediate- and poor-risk patients.

Eligible patients were ≥18 years, with previously untreated advanced RCC with a clear-cell component. Additional key inclusion criteria were measurable disease according to the RECIST version 1.1, and a Karnofsky performance status score of ≥70 (on a scale from 0 to 100, with lower scores indicating greater disability).

Key exclusion criteria were CNS metastases or autoimmune disease and glucocorticoid or immunosuppressant use. Patients were characterized according to IMDC risk (favorable [score of 0], intermediate [score of 1 or 2], or poor [score of 3 to 6]).

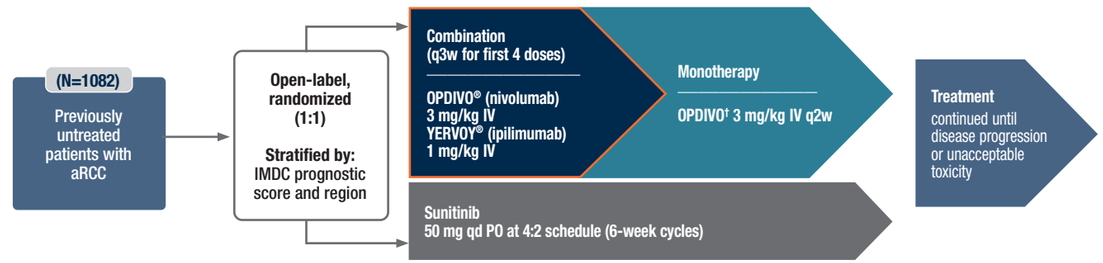
In the primary analysis of Checkmate 214 (minimum follow-up of 17.5 months, median follow-up time of 25.2 months), mOS was not yet reached (95% CI, 28.2-NE) with OPDIVO + YERVOY and 25.9 months (95% CI, 22.1-NE) with sunitinib (HR, 0.63; 99.8% CI, 0.44-0.89; *P* <.0001). ORR at primary analysis was 41.6% (95% CI, 36.9-46.5) with OPDIVO + YERVOY and 26.5% (95% CI, 22.4-31.0) with sunitinib. For the coprimary end point of PFS, the median PFS (mPFS) was 11.6 months (95% CI, 8.7-15.5) with OPDIVO + YERVOY and 8.4 months (95% CI, 7.0-10.8) with sunitinib. The between-group difference did not meet the prespecified threshold (*P* = .009) for statistical significance (HR for disease progression or death, 0.82; 99.1% CI, 0.64-1.05; *P* = .03). Median DOR at primary analysis was not yet reached (95% CI, 21.8-NE) with OPDIVO + YERVOY and 18.2 months (95% CI, 14.8-NE) for sunitinib.

Serious adverse reactions occurred in 59% of patients receiving OPDIVO + YERVOY, and in 43% of patients receiving sunitinib. Study therapy was discontinued for adverse reactions in 31% of OPDIVO + YERVOY patients, and in 21% of patients receiving sunitinib. Fifty-four percent of patients receiving OPDIVO + YERVOY had a dose interruption for an adverse reaction, as did 43% of patients receiving sunitinib.

The most frequent serious adverse reactions reported in ≥2% of patients treated with OPDIVO + YERVOY were diarrhea, pyrexia, pneumonia, pneumonitis, hypophysitis, acute kidney injury, dyspnea, adrenal insufficiency, and colitis; in patients treated with sunitinib, they were pneumonia, pleural effusion, and dyspnea.

The most common adverse reactions (reported in ≥20% of patients) were fatigue, rash, diarrhea, musculoskeletal pain, pruritus, nausea, cough, pyrexia, arthral-

Figure 10 Checkmate 214 Trial[22-24]



The co-primary end points were ORR, PFS, and OS among intermediate- and poor-risk patients. PFS and ORR were IRRC-assessed per RECIST v1.1.

- Short-term induction dosing with OPDIVO + YERVOY during the combination phase followed by OPDIVO monotherapy during the maintenance phase
- Similar to trials reflective of the real-world population, 77% of patients in Checkmate 214 were intermediate/poor risk as measured by IMDC
- Patients were included regardless of their PD-L1 status. Patients were excluded due to any history of – or concurrent – brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression
- Median follow up for the primary analysis was 25.2 months
- The safety analysis included 1082 patients. The efficacy analysis of the coprimary end points included 425 patients in the OPDIVO + YERVOY arm and 422 patients in the sunitinib arm

†After completing 4 doses of the combination, the recommended dose of OPDIVO in the single-agent phase is either 240 mg every 2 weeks or 480 mg every 4 weeks administered as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.
aRCC indicates advanced renal-cell carcinoma; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IV, intravenous; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, orally; q2w, every 2 weeks; q3w, every 3 weeks; qd, every day.

Please see Important Safety Information for OPDIVO and YERVOY on pages 25-31.
Please also see full Prescribing Information for OPDIVO and YERVOY.

Table 2 Checkmate 214: Safety Data

Adverse reactions	OPDIVO + YERVOY (n=547)		Sunitinib (n=535)	
	Grades 1–4	Grades 3–4	Grades 1–4	Grades 3–4
Adverse reactions, %				
All causes	99	65	99	76
General disorders and administration site conditions, %				
Fatigue*	58	8	69	13
Pyrexia	25	0.7	17	0.6
Edema†	16	0.5	17	0.6
Respiratory, thoracic, and mediastinal disorders, %				
Cough/productive cough	28	0.2	25	0.4
Dyspnea/exertional dyspnea	20	2.4	21	2.1
Gastrointestinal disorders, %				
Diarrhea	38	4.6	58	6
Nausea	30	2.0	43	1.5
Vomiting	20	0.9	28	2.1
Abdominal pain	19	1.6	24	1.9
Constipation	17	0.4	18	0
Skin and subcutaneous tissue disorder, %				
Rash‡	39	3.7	25	1.1
Pruritus/generalized pruritus	33	0.5	11	0
Endocrine disorders, %				
Hypothyroidism	18	0.4	27	0.2
Nervous system disorders, %				
Heachache	19	0.9	23	0.9
Metabolism and nutrition disorders, %				
Decreased appetite	21	1.8	29	0.9
Musculoskeletal and connective tissue disorders, %				
Musculoskeletal pain§	37	4.0	40	2.6
Arthralgia	23	1.3	16	0

- In the 48-month follow-up analysis, all-cause adverse events occurring in >15% of patients receiving OPDIVO + YERVOY and not previously included in the primary analysis include: upper respiratory tract infection (OPDIVO + YERVOY: 21.4% Grades 1-4, 0.4% Grades 3-4; sunitinib: 14.8% Grades 1-4)[26]

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0.
*Includes asthenia.
†Includes peripheral edema, peripheral swelling.
‡Includes dermatitis described as acneiform, bullous, and exfoliative, drug eruption, rash described as exfoliative, erythematous, follicular, generalized, macular, maculopapular, papular, pruritic, and pustular, fixed-drug eruption.
§Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, and spinal pain.

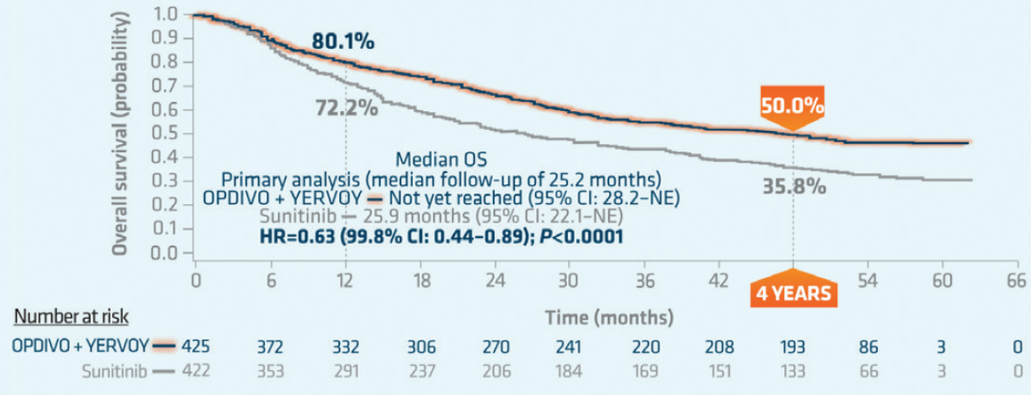
Please see Important Safety Information for OPDIVO and YERVOY on pages 25-31.
Please also see full Prescribing Information for OPDIVO and YERVOY.

Figure 11 Checkmate 214: Overall Survival

In an extended follow-up analysis at 48 months in 1L int-/poor-risk aRCC

OPDIVO® + YERVOY®: A chance for durable survival at 4 years

Checkmate 214: Overall survival in intermediate- or poor-risk patients†



The 48-month overall survival rate analysis was not pre-specified within the study protocol.

In the primary analysis, the pre-specified 12-month overall survival rate was 80% (95% CI: 76–84) with OPDIVO + YERVOY vs 72% (95% CI: 67–76) with sunitinib. The median follow-up time was 25.2 months.

†Performance status is based on IMDC prognostic score (0=favorable, 1–2=intermediate, 3+=poor).

mOS at primary analysis (median follow-up time of 25.2 months)
- OPDIVO + YERVOY: Not yet reached (95% CI: 28.2-NE)
- Sunitinib: 25.9 months (95% CI: 22.1-NE)
- HR=0.63 (99.8% CI: 0.44-0.89); *P*<0.0001

mOS at extended follow-up (minimum follow-up time of 48 months)
- OPDIVO + YERVOY: 48.1 months (95% CI: 35.6-NE)
- Sunitinib: 26.6 months (95% CI: 22.1-33.5)
- HR=0.65 (95% CI: 0.54-0.78)

1L indicates first line; aRCC, advanced renal-cell carcinoma; I-O, immuno-oncology; NE, not estimable; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium.

gia, decreased appetite, dyspnea, and vomiting. The most common laboratory abnormalities which have worsened compared to baseline in ≥30% of OPDIVO + YERVOY–treated patients include increased lipase, anemia, increased creatinine, increased alanine transaminase (ALT), increased aspartate transaminase (AST), hyponatremia, increased amylase, and lymphopenia.[7] (See **Table 2**.)[26]

Extended 5-year data for Checkmate 214 was presented in September at the European Society for Medical Oncology Congress 2021.

After 4 years' minimum follow-up, OS HR was 0.65 (95% CI, 0.54-0.78) with OPDIVO + YERVOY (mOS 48.1 months; 95% CI, 35.6-NE [not estimable]) versus sunitinib (mOS 26.6 months; 95% CI, 22.1-33.5). After 4 years, 50% of patients in the OPDIVO + YERVOY arm were alive and 35.8% were alive in the sunitinib arm.[22] (See **Figure 11**.)

Four-year PFS rates were 32.7% versus 12.3% (I/P), with OPDIVO + YERVOY versus sunitinib. (See **Figure 12**.)

At 4 years, OPDIVO + YERVOY has a chance for long-term survival and long-term response. mOS at primary analysis was not yet reached (95% CI, 28.2-NE) with OPDIVO + YERVOY, ORR at primary analysis was 41.6% (95% CI, 36.9-46.5), and mPFS was 11.6 months (95% CI, 8.7-15.5). ORR at extended

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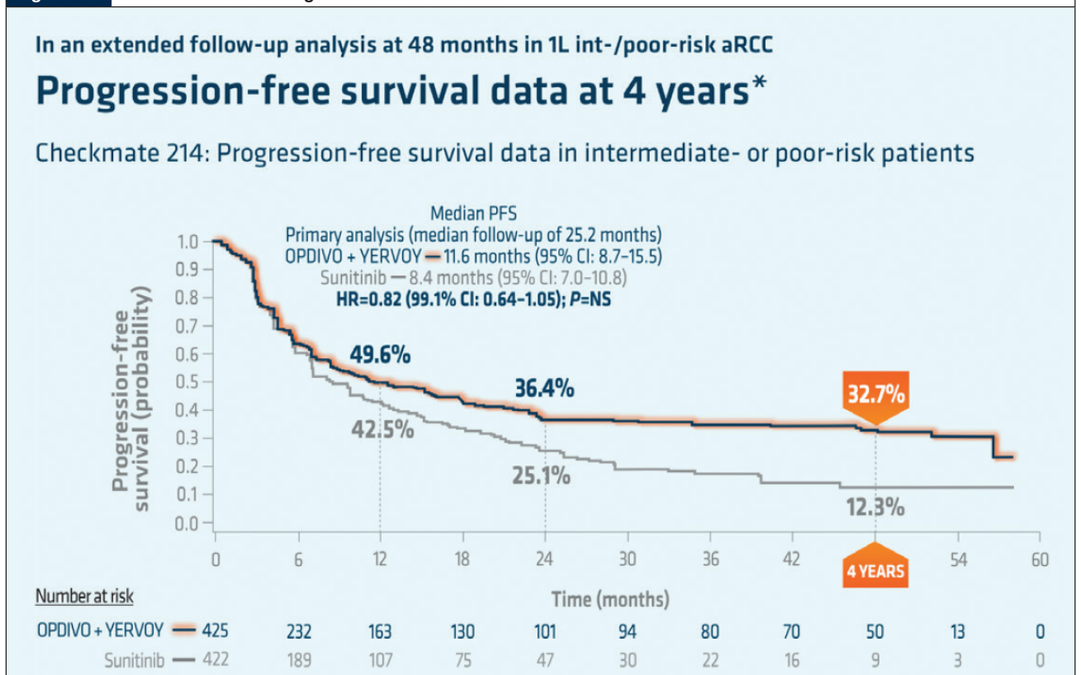
Figure 12 Checkmate 214: Progression-Free Survival



mPFS* at primary analysis (median follow-up time of 25.2 months)
- OPDIVO + YERVOY: 11.6 months (95% CI: 8.7–15.5)
- Sunitinib: 8.4 months (95% CI: 7.0–10.8)
- HR=0.82 (99.1% CI: 0.64–1.05)
- Per a prespecified analysis, PFS did not meet statistical significance

mPFS* at extended follow-up analysis (minimum follow-up time of 48 months)
- OPDIVO + YERVOY: 11.2 months (95% CI: 8.4–16.1)
- Sunitinib: 8.3 months (95% CI: 7.0–10.8)
- HR=0.74 (95% CI: 0.62–0.88)

1L indicates first line; aRCC, advanced renal-cell carcinoma; HR, hazard ratio; RECIST, Response Evaluation Criteria in Solid Tumors.

Figure 13 Checkmate 227 Part 1a Study Design[7,27,28]

DOR indicates duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small cell lung cancer; NSQ, pemetrexed + carboplatin or cisplatin; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; q2w, every 2 weeks; q6w, every 6 weeks; SQ, gemcitabine + carboplatin or cisplatin.

follow up (minimum follow-up time of 48 months) was 41.9% (n=178/425; 95% CI, 37-47) with OPDIVO + YERVOY. This included 10.4% among complete responders (n=44/425) and 31.5% among partial responders (n=134/425). For the sunitinib group, ORR was 26.8% (n=113/422; 95% CI, 23-31), including 1.4% among complete responders (n=6/422) and 25.4% among partial responders (n=107/422).

Among responders, median DOR (minimum follow-up time of 48 months) was not reached for OPDIVO + YERVOY (95% CI, 45.8-NE) compared with 19.7 months for sunitinib (95% CI, 15.4-25.0); HR, 0.45 (95% CI, 0.31-0.65).

Checkmate 227 Trial Part 1a: Metastatic Non-Small Cell Lung Cancer in Select Patients[7,27,28]

This study was an open-label, phase 3 trial that evaluated OPDIVO + YERVOY (N=396) compared to platinum-based chemotherapy (N=397) as first-line therapy in patients with stage IV or recurrent NSCLC, regardless of histology, no known sensitizing *EGFR* or *ALK* alterations, and PD-L1 expression ≥1%. In Checkmate 227, randomization was stratified by histology and 29% of patients enrolled had squamous disease and 71% had non-squamous disease. (See **Figure 13**.)

Key inclusion criteria for this trial included age ≥18 years, pathologically confirmed locally advanced or metastatic NSCLC ECOG performance status 0 or 1, and PD-L1 expression of ≥1% as determined by PD-L1 IHC 28-8 pharmDx assay at a central laboratory.

Key exclusion criteria included prior systemic anticancer treatment with locally advanced/metastatic disease, sensitizing *EGFR* or *ALK* alterations, untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression.

In Checkmate 227, patients in the comparator arm received up to 4 cycles of platinum-doublet chemotherapy every 3 weeks. Patients with non-squamous NSCLC received pemetrexed plus carboplatin or cisplatin, with optional pemetrexed maintenance following chemotherapy. Patients with squamous NSCLC received gemcitabine plus carboplatin or cisplatin.

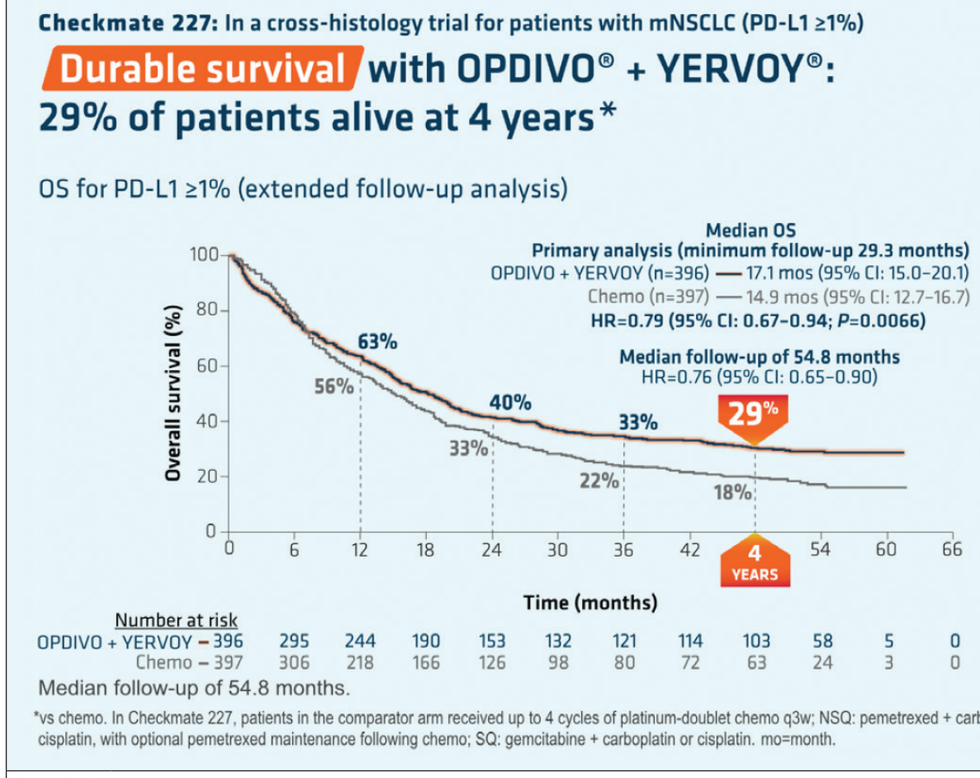
The primary end point in this trial was OS, with prespecified descriptive efficacy outcome measures that included PFS, ORR, and DOR.[29]

In the primary analysis with a minimum follow-up of 29.3 months, among the patients with PD-L1 expression ≥1%, the median OS was 17.1 months (95% CI, 15.0-20.1) with OPDIVO + YERVOY and 14.9 months (95% CI, 12.7-16.7) with chemotherapy (P = .0066). Median PFS was 5.1 months (95% CI, 4.1-6.3) with OPDIVO + YERVOY and 5.6 months (95% CI, 4.6-5.8) with chemotherapy alone (HR, 0.82; 95% CI, 0.69-0.97).[27,28]

In Checkmate 227, serious adverse reactions occurred in 58% of patients (N=576). The most frequent (≥2%) serious adverse reactions were pneumonia, diarrhea/colitis, pneumonitis, hepatitis, pulmonary embolism, adrenal insufficiency, and hypophysitis. Fatal adverse reactions occurred in 1.7% of patients; these included events of pneumonitis (4 patients), myocarditis, acute kidney injury, shock, hyperglycemia, multi-system organ failure, and renal failure.[7]

The most common (≥20%) adverse reactions were fatigue (44%), rash (34%), decreased appetite (31%), musculoskeletal pain (27%), diarrhea/colitis (26%), dyspnea (26%), cough (23%), hepatitis (21%), nausea (21%), and pruritus (21%).[7]

Figure 14 Checkmate 227: 4-Year Overall Survival in Patients with PD-L1 ≥1%



*vs chemo. In Checkmate 227, patients in the comparator arm received up to 4 cycles of platinum-doublet chemo q3w; NSQ: pemetrexed + carboplatin or cisplatin, with optional pemetrexed maintenance following chemo; SQ: gemcitabine + carboplatin or cisplatin. mo=month.

Study Design

- Checkmate 227 was a randomized, open-label phase 3 trial in patients with metastatic or recurrent NSCLC. Key eligibility criteria included patients 18 years or older, stage IV or recurrent NSCLC, ECOG PS 0/1, and no prior systemic anti-cancer therapy. Patients with known *EGFR* or *ALK* translocations sensitive to available targeted inhibitor therapy, untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Treatment continued until disease progression, unacceptable toxicity, or for up to 24 months. Tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory. In Part 1a (n=793), patients with PD-L1 ≥1% were randomized to either OPDIVO 3 mg/kg q2w + YERVOY 1 mg/kg q6w (n=396) or platinum-doublet chemo† (n=397). The primary end point in Part 1a was OS in patients with PD-L1 ≥1%. Pre-specified descriptive efficacy measures included PFS, ORR, and DOR.

†In Checkmate 227, patients in the comparator arm received up to 4 cycles of platinum-doublet chemo q3w; NSQ: pemetrexed + carboplatin or cisplatin, with optional pemetrexed maintenance following chemo; SQ: gemcitabine + carboplatin or cisplatin.

At the ASCO 2021 annual meeting, researchers presented 4-year extended follow-up data for the Checkmate 227 trial.[30] (See **Figure 14**.)

After a median follow-up of 54.8 months (database lock, February 18, 2021), patients with PD-L1 ≥1% treated with OPDIVO + YERVOY showed a long-term OS compared with chemotherapy (HR, 0.76; 95% CI, 0.65-0.90). Four-year OS rates were 29% for the OPDIVO + YERVOY group and 18% for the chemotherapy group.[30]

Among patients (PD-L1 ≥1%) who progressed on OPDIVO + YERVOY versus chemotherapy, 7% versus 40% received subsequent immunotherapy.

With a minimum follow-up of 4 years, all patients had completed the maximum 2 years of treatment or discontinued. Safety was consistent with prior reports and no new safety signals were identified.[27-29] (See **Table 3**.)

Please see Important Safety Information for OPDIVO and YERVOY on pages 25-31.
Please also see full Prescribing Information for OPDIVO and YERVOY.

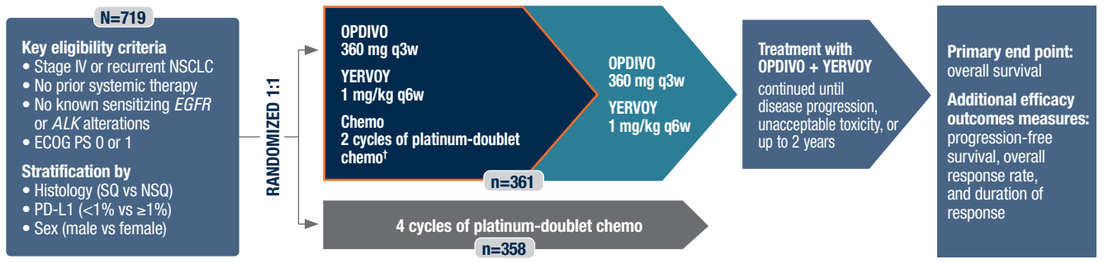
Table 3 Checkmate 227: Adverse Reactions in ≥10% of Patients Receiving OPDIVO + YERVOY

	OPDIVO + YERVOY (n=576)		Chemo (n=570)	
Adverse reactions	All grades (%)	Grades 3-4 (%)	All grades (%)	Grades 3-4 (%)
General				
Fatigue*	44	6	42	4.4
Pyrexia	18	0.5	11	0.4
Edema†	14	0.2	12	0.5
Skin and subcutaneous tissue				
Rash‡	34	4.7	10	0.4
Pruritus§	21	0.5	3.3	0
Metabolism and nutrition				
Decreased appetite	31	2.3	26	1.4
Musculoskeletal and connective tissue				
Musculoskeletal pain‖	27	1.9	16	0.7
Arthralgia	13	0.9	2.5	0.2
Gastrointestinal				
Diarrhea/colitis¶	26	3.6	16	0.9
Nausea	21	1.0	42	2.5
Constipation	18	0.3	27	0.5
Vomiting	13	1.0	18	2.3
Abdominal pain#	10	0.2	9	0.7
Respiratory, thoracic, and mediastinal				
Dyspnea**	26	4.3	16	2.1
Cough††	23	0.2	13	0
Hepatobiliary				
Hepatitis‡‡	21	9	10	1.2
Endocrine				
Hypothyroidism§§	16	0.5	1.2	0
Hyperthyroidism‖‖	10	0	0.5	0
Infections and infestations				
Pneumonia¶¶	13	7	8	4.0
Nervous system				
Headache	11	0.5	6	0

Safety was assessed in the overall population in Checkmate 227 Part 1. Efficacy analysis was conducted in the Part 1a population.
*Includes fatigue and asthenia.
†Includes eyelid edema, face edema, generalized edema, localized edema, edema, edema peripheral, and periorbital edema.
‡Includes autoimmune dermatitis, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis contact, dermatitis exfoliative, dermatitis psoriasiform, granulomatous dermatitis, rash generalized, drug eruption, dyshidrotic eczema, eczema, exfoliative rash, nodular rash, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, toxic skin eruption.
§Includes pruritus and pruritus generalized.
‖Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, and pain in extremity.
¶Includes colitis, colitis microscopic, colitis ulcerative, diarrhea, enteritis infectious, enterocolitis, enterocolitis infectious, and enterocolitis viral.
#Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and abdominal tenderness.
**Includes dyspnea and dyspnea exertional.
††Includes cough and productive cough.
‡‡Includes alanine aminotransferase increased, aspartate aminotransferase increased, autoimmune hepatitis, blood bilirubin increased, hepatic enzyme increased, hepatic failure, hepatic function abnormal, hepatitis, hepatitis E, hepatocellular injury, hepatotoxicity, hyperbilirubinemia, immune-mediated hepatitis, liver function test abnormal, liver function test increased, transaminases increased.
§§Includes autoimmune thyroiditis, blood thyroid stimulating hormone increased, hypothyroidism, primary hypothyroidism, thyroiditis, and tri-iodothyronine free decreased.
‖‖Contains blood thyroid stimulating hormone decreased, hyperthyroidism, and tri-iodothyronine free increased.
¶¶Includes lower respiratory tract infection, lower respiratory tract infection bacterial, lung infection, pneumonia, pneumonia adenoviral, pneumonia aspiration, pneumonia bacterial, pneumonia klebsiella, pneumonia influenzal, pneumonia viral, atypical pneumonia, organizing pneumonia.

Please see Important Safety Information for OPDIVO and YERVOY on pages 25-31.
Please also see full Prescribing Information for OPDIVO and YERVOY.

Figure 15 Checkmate 9LA Trial[7,31]



ALK indicates anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; NSQ, non-squamous; PD-L1, programmed death-ligand 1; q3w, every 3 weeks; q6w, every 6 weeks; SQ, squamous.
†In Checkmate 9LA, patients received 2 cycles of platinum-doublet chemo q3w in the experimental arm, and 4 cycles in the comparator arm; NSQ: pemetrexed + carboplatin or cisplatin (optional pemetrexed maintenance therapy in the comparator arm only); SQ: paclitaxel + carboplatin.

Researchers concluded that after 4 years' minimum follow-up, first-line OPDIVO + YERVOY continued to provide long-term OS compared with chemotherapy in patients with advanced NSCLC.

Checkmate 9LA Trial: Recurrent or Metastatic Non-Small Cell Lung Cancer in Select Patients[7,31]

Checkmate 9LA was a randomized, phase 3, open-label study that evaluated OPDIVO + YERVOY plus 2 cycles of platinum-based chemotherapy (N=361) compared to 4 cycles of platinum-based chemotherapy alone (N=358) as first-line therapy in patients with stage IV or recurrent NSCLC.[7] (See **Figure 15**.)

Eligible patients were aged at least 18 years with histologically confirmed squamous or non-squamous stage IV or recurrent NSCLC, an ECOG performance status of 0 to 1, and no previous systemic anticancer therapy as the primary treatment for advanced or metastatic disease.

Exclusion criteria included known *EGFR* mutations and *ALK* translocations that were sensitive to targeted therapy, unknown or undetermined *EGFR* status in patients with non-squamous histology, and autoimmune disease. Patients were also excluded if they had untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression.

In Checkmate 9LA, patients received 2 cycles of platinum-doublet chemotherapy every 3 weeks in the experimental arm, and 4 cycles in the comparator arm. Patients with non-squamous NSCLC received pemetrexed + carboplatin or cisplatin (optional pemetrexed maintenance therapy in the comparator arm only). Patients with squamous NSCLC received paclitaxel + carboplatin.[7]

The primary end point was OS. Additional efficacy outcome measures were PFS, ORR, and DOR.

Checkmate 9LA Overall Survival

At the initial prespecified interim analysis for the primary end point of OS at a minimum follow-up of 8.1 months, median OS was 14.1 months (95% CI, 13.2-16.2) for patients treated with OPDIVO + YERVOY combined with 2 cycles of chemotherapy and 10.7 months (95% CI, 9.5-12.5) for patients treated with chemotherapy alone (HR, 0.69; 96.71% CI, 0.55-0.87; P = .0006).[7,29]

Median PFS at the 6.5-month minimum follow-up was 6.8 months (95% CI, 5.6-7.7) with OPDIVO + YERVOY with chemotherapy versus 5.0 months (95% CI, 4.3-5.6) with chemotherapy alone (HR, 0.70; 97.48% CI, 0.57-0.86; P = .0001).[7,29]

Please see Important Safety Information for OPDIVO and YERVOY on pages 25-31.
Please also see full Prescribing Information for OPDIVO and YERVOY.

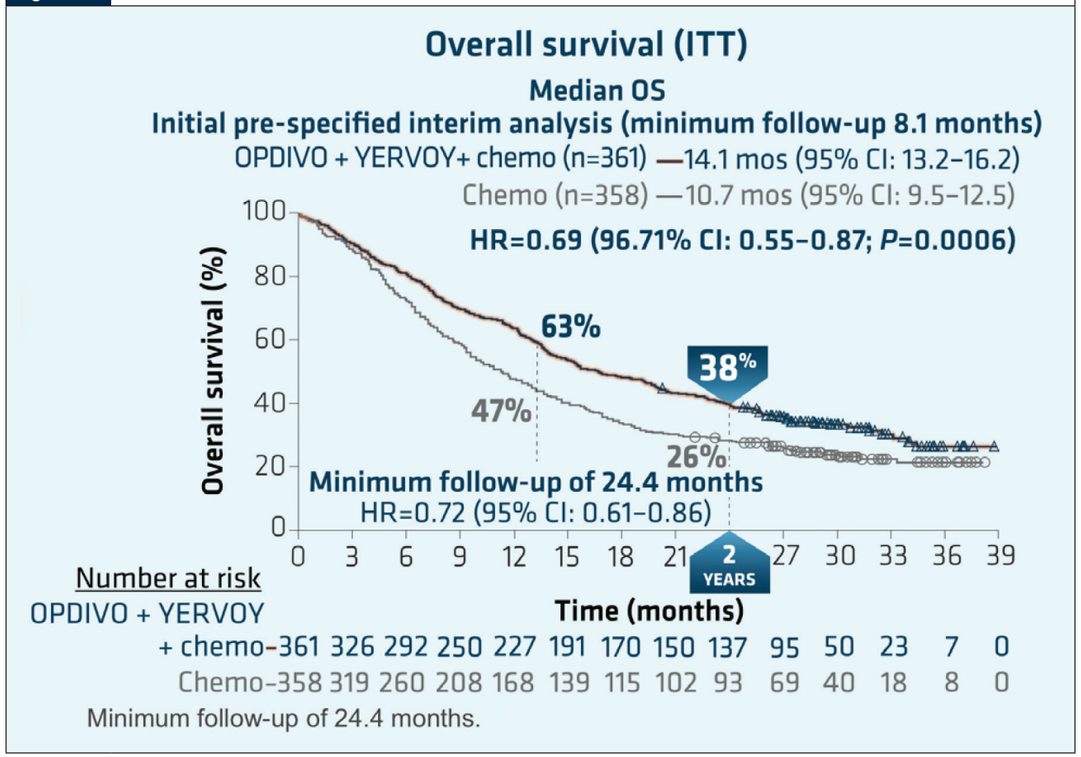
Table 4 Checkmate 9LA: Adverse Reactions in ≥10% of Patients Receiving OPDIVO + YERVOY + Chemotherapy

	OPDIVO + YERVOY + chemo* (n=358)		Chemo (n=349)	
Adverse reactions	All grades (%)	Grades 3-4 (%)	All grades (%)	Grades 3-4 (%)
General				
Fatigue†	49	5	40	4.9
Pyrexia	14	0.6	10	0.6
Musculoskeletal and connective tissue				
Musculoskeletal pain‡	39	4.5	27	2.0
Gastrointestinal				
Nausea	32	1.7	41	0.9
Diarrhea§	31	6	18	1.7
Constipation	21	0.6	23	0.6
Vomiting	18	2.0	17	1.4
Abdominal pain‖	12	0.6	11	0.9
Skin and subcutaneous tissue				
Rash¶	30	4.7	10	0.3
Pruritus#	21	0.8	2.9	0
Alopecia	11	0.8	10	0.6
Metabolism and nutrition				
Decreased appetite	28	2.0	22	1.7
Respiratory, thoracic, and mediastinal				
Cough**	19	0.6	15	0.9
Dyspnea††	18	4.7	14	3.2
Endocrine				
Hypothyroidism‡‡	19	0.3	3.4	0
Nervous system				
Headache	11	0.6	7	0
Dizziness§§	11	0.6	6	0

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events v4.
*Two cycles of platinum-doublet chemo.
†Includes fatigue and asthenia.
‡Includes myalgia, back pain, pain in extremity, musculoskeletal pain, bone pain, flank pain, muscle spasms, musculoskeletal chest pain, musculoskeletal disorder, osteitis, musculoskeletal stiffness, non-cardiac chest pain, arthralgia, arthritis, arthropathy, joint effusion, psoriatic arthropathy, synovitis.
§Includes colitis, ulcerative colitis, diarrhea, and enterocolitis.
‖Includes abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, and gastrointestinal pain.
¶Includes acne, dermatitis, acneiform dermatitis, allergic dermatitis, atopic dermatitis, bullous dermatitis, generalized exfoliative dermatitis, eczema, keratodema, blennorrhagica, palmar-plantar erythrodysesthesia syndrome, rash, erythematous rash, generalized rash, macular rash, maculo-papular rash, morbilliform rash, papular rash, pruritic rash, skin exfoliation, skin reaction, skin toxicity, Stevens-Johnson syndrome, and urticaria.
#Includes pruritus and generalized pruritus.
**Includes cough, productive cough, and upper-airway cough syndrome.
††Includes dyspnea, dyspnea at rest, and exertional dyspnea.
‡‡Includes autoimmune thyroiditis, increased blood thyroid stimulating hormone, hypothyroidism, thyroiditis, and decreased free triiodothyronine.
§§Includes dizziness, vertigo, and positional vertigo.

Please see Important Safety Information for OPDIVO and YERVOY on pages 25-31.
Please also see full Prescribing Information for OPDIVO and YERVOY.

Figure 16 Checkmate 9LA: 2-Year Overall Survival



Serious adverse reactions occurred in 57% of patients receiving OPDIVO + YERVOY with chemotherapy. The most frequent (>2%) serious adverse reactions were diarrhea (6%), fatigue (5%), rash (4.7%), dyspnea (4.7%), and musculoskeletal pain (4.5%). (See **Table 4**.)

At the ASCO 2021 annual meeting, researchers presented 2-year follow-up data for the Checkmate 9LA trial.[32] (See **Figure 16**.)

After minimum follow-up of 24.4 months for OS, the median OS for each arm was 15.8 months and 11.0 months, respectively (HR, 0.72; 95% CI, 0.61-0.86). Two-year OS rates were 38% for the OPDIVO + YERVOY + limited chemotherapy group versus 26% for the chemotherapy-alone group.[32] The OS benefit for OPDIVO + YERVOY + limited chemotherapy in this exploratory analysis was consistent across PD-L1 expression at 2 years, with OS of 37% (HR, 0.67; 95% CI, 0.51-0.88) in patients with PD-L1 expression <1%, and OS of 41% (HR, 0.70; 95% CI, 0.56-0.89) for those with PD-L1 expression ≥1%.

Median PFS (minimum follow-up of 23.3 months) with OPDIVO + YERVOY + chemotherapy versus chemotherapy alone was 6.7 months compared with 5.3 months for chemotherapy alone (HR, 0.67; 95% CI, 0.56-0.79).[32]

Checkmate 9LA Overall Survival in Patients Expressing PD-L1 <1%

In patients with PD-L1 expression <1%, 37% of patients treated with OPDIVO + YERVOY with limited chemotherapy were alive at 2 years, and 22% of those treated with chemotherapy alone. In patients with PD-L1 ≥1%, 41% of patients treated with OPDIVO + YERVOY with limited chemotherapy were alive at 2 years and 28% of those treated with chemotherapy alone were alive at 2 years.

A limitation of these data is that Checkmate 9LA was not powered to detect differences in the treatment effect in PD-L1 subgroups; therefore, results from this exploratory analysis should be interpreted with caution because of the limited patient numbers and potential imbalances in baseline characteristics within the subgroup.

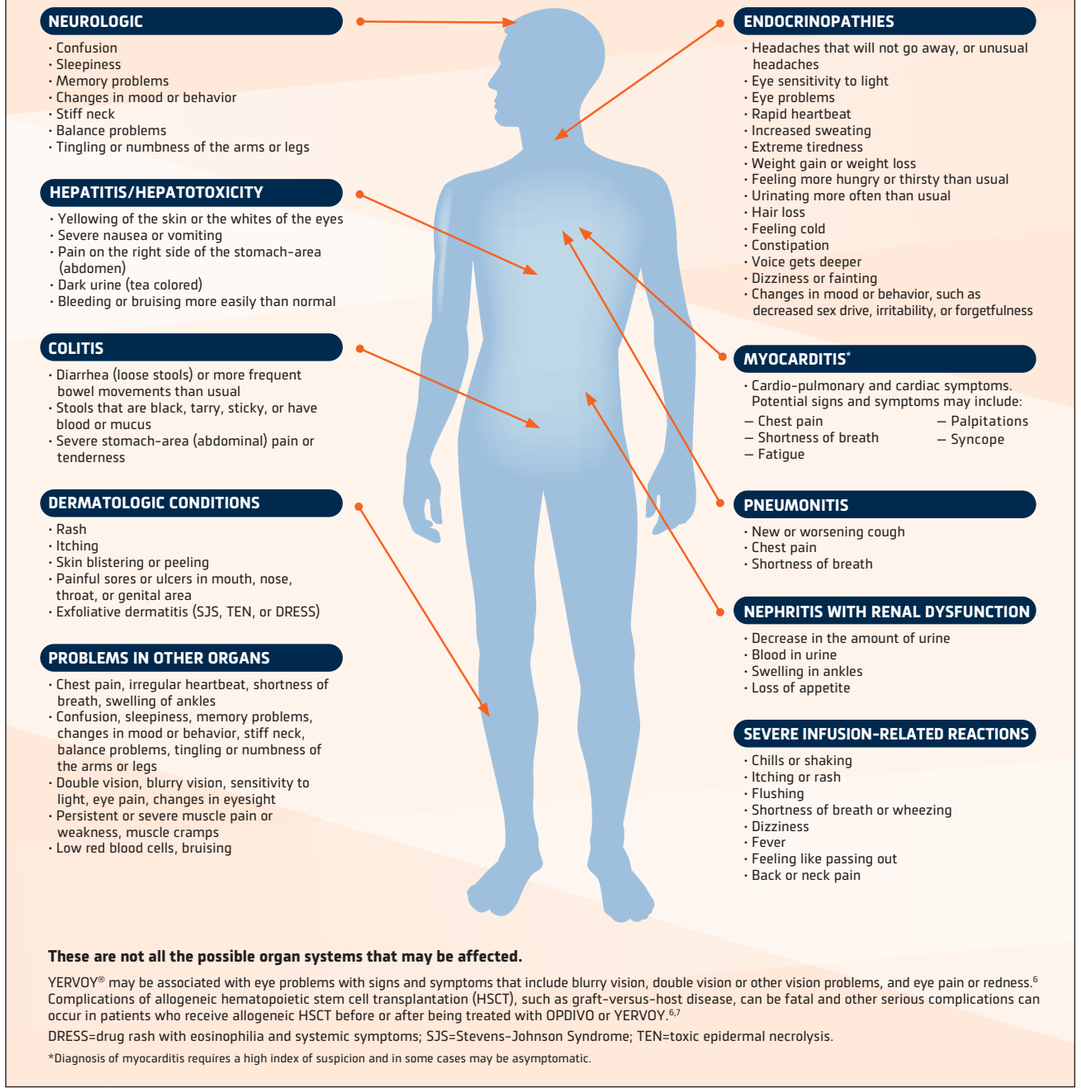
Please see Important Safety Information for OPDIVO and YERVOY on pages 25-31.
Please also see full Prescribing Information for OPDIVO and YERVOY.

IMMUNE-MEDIATED ADVERSE REACTIONS (IMARS) ASSOCIATED WITH THE USE OF CTLA-4 INHIBITORS ALONE AND IN COMBINATION WITH PD-1 INHIBITORS – CLASS EFFECTS OF IMMUNOMODULATING AGENTS

Inhibition of CTLA-4 and PD-1/PD-L1, alone and in combination, is associated with a range of side effects that resemble autoimmune reactions.[7,33-35] (See **Figure 17**.)

Education of patients, clinical staff, and ancillary providers and the building of multidisciplinary teams to manage immunotherapy side effects are crucial to achieve

Figure 17 Potential IMARs: Signs and Symptoms[7,33,34]



These are not all the possible organ systems that may be affected.

YERVOY® may be associated with eye problems with signs and symptoms that include blurry vision, double vision or other vision problems, and eye pain or redness.[6] Complications of allogeneic hematopoietic stem cell transplantation (HSCT), such as graft-versus-host disease, can be fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with OPDIVO or YERVOY.[6,7]

DRESS=drug rash with eosinophilia and systemic symptoms; SJS=Stevens-Johnson Syndrome; TEN=toxic epidermal necrolysis.

*Diagnosis of myocarditis requires a high index of suspicion and in some cases may be asymptomatic.

Please see Important Safety Information for OPDIVO and YERVOY on pages 25-31.
Please also see full Prescribing Information for OPDIVO and YERVOY.

the best individual outcomes. It is important for healthcare providers to remain vigilant in screening for adverse events, ask the right probing questions, and educate their patients on communicating with them right away if they experience any evidence of side effects.[35-37]

Instruct patients to contact you or your staff if they begin to experience any of these symptoms. Identifying IMARs early and starting management of IMARs right away may help control the impact IMARs have on your patients' treatment journey. (See **Figure 18**.)

Figure 18 Routine Monitoring Tests for Potential IMARs

Monitoring and consultation considerations for potential and suspected immune-mediated adverse reactions (IMARs)

Considerations when managing IMARs

Early recognition of potential IMARs

Close monitoring of signs/symptoms

Withholding or discontinuing therapy, use/taper of corticosteroids

- While some side effects of immunotherapy may appear similar to other treatments, they may need to be managed differently
- **IMARs, which may be severe or fatal, can occur in any organ system or tissue. IMARs listed herein may not include all possible IMARs**
- Prompt patient reporting of side effects may help lead to identification of IMARs
- While some patients may have to discontinue treatment, others may need to withhold treatment and may be able to resume after appropriate intervention and IMAR resolution

Routine monitoring for potential IMARs

- Patients treated with OPDIVO® (nivolumab) should be monitored at baseline and periodically during treatment
- Patients treated with OPDIVO + YERVOY® (ipilimumab) should be monitored at baseline and before each dose
- In patients treated with OPDIVO in combination with CABOMETYX® (cabozantinib), consider more frequent monitoring of liver enzymes than when the drugs are administered as single agents
- Patients should also be monitored for signs and symptoms of other adverse reactions, including infusion-related reactions and complications of allogeneic hematopoietic stem cell transplantation
- IMARs can occur at any time during treatment and after discontinuation of therapy
- Monitor closely for symptoms and signs of underlying IMARs
- This is not an exhaustive list of clinical tests and exams

IMAR	Recommended monitoring for OPDIVO, OPDIVO + YERVOY, and their approved combinations
Hepatitis	Liver enzymes
Endocrinopathies	Adrenocorticotropic hormone levels (for OPDIVO + YERVOY only) Thyroid function Hyperglycemia
Nephritis and renal dysfunction	Serum creatinine

Monitoring and consultation for suspected IMARs

- In cases of suspected IMARs, initiate appropriate workup to exclude alternative etiologies, including infection
- Institute medical management promptly, including specialty consultation as appropriate

Source: www.opdivohcp.com/assets/commercial/us/opdivo-hcp-pan-tumor/en/pdf/Immune_Mediated_Adverse_Management_Guide.pdf

Please see Important Safety Information for OPDIVO and YERVOY on pages 25-31.
Please also see full Prescribing Information for OPDIVO and YERVOY.

Questions that a healthcare provider may ask their patients to identify IMARs early include[7]:

- Have you experienced any fatigue, fever, or swelling in your extremities?
- Have you noticed a rash or itching of your skin?
- Has your appetite increased or decreased recently?
- Have you experienced recent joint pain or pain or cramping in your muscles?
- Are you having new gastrointestinal problems such as diarrhea, nausea, vomiting, constipation, or abdominal pain?
- Have you developed shortness of breath or a cough that was not present previously?
- Have you noted any unintentional weight changes, either an increase or decrease?
- Have you experienced nervousness, anxiety and irritability, or frequent headaches?

Recommended Dose Modifications for Adverse Reactions[6,7]

- No dose reduction for OPDIVO or YERVOY monotherapy is recommended.
- In general, withhold YERVOY for severe (grade 3) IMARs. Permanently discontinue YERVOY for life-threatening (grade 4) IMARs, recurrent severe (grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, persistent moderate (grade 2) or severe (grade 3) reactions lasting 12 weeks or longer after last YERVOY dose (excluding endocrinopathy), or an inability to reduce corticosteroid dose to ≤10 mg of prednisone or equivalent per day within 12 weeks of initiating steroids.
- Recommendations for OPDIVO and YERVOY dose modifications are provided in the Prescribing Information (in Tables 3 and 4). When OPDIVO is administered in combination with YERVOY, if OPDIVO is withheld or discontinued, YERVOY should also be withheld or discontinued.
- In general, withhold OPDIVO for severe (grade 3) IMARs. Permanently discontinue OPDIVO for life-threatening (grade 4) IMARs, recurrent severe (grade 3) IMARs that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to ≤10 mg of prednisone or equivalent per day within 12 weeks of initiating steroids.

IMPORTANT SAFETY INFORMATION FOR YERVOY

Severe and Fatal Immune-Mediated Adverse Reactions

Immune-mediated adverse reactions listed herein may not be inclusive of all possible severe and fatal immune-mediated adverse reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. While immune-mediated adverse reactions usually manifest during treatment, they can also occur at any time after starting or discontinuing YERVOY. Early identification and management are essential to ensure safe use of YERVOY. Monitor for signs and symptoms that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone (ACTH) level, and thyroid function at baseline and before each dose. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). In general, if YERVOY interruption or discontinuation is required, administer systemic corticosteroid therapy (1 or 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy. Toxicity management guidelines for adverse events that do not necessarily require systemic corticosteroids (e.g., endocrinopathies) are discussed below.

Please see Important Safety Information for OPDIVO and YERVOY on pages 25-31.
Please also see full Prescribing Information for OPDIVO and YERVOY.

Immune-Mediated Colitis

YERVOY can cause immune-mediated colitis, which may be fatal. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Immune-mediated diarrhea/colitis occurred in 12% (62/511) of patients who received YERVOY 3 mg/kg as a single agent, including Grade 3-5 (7%) and Grade 2 (5%).

Immune-Mediated Hepatitis

Immune-mediated hepatitis occurred in 4.1% (21/511) of patients who received YERVOY 3 mg/kg as a single agent, including Grade 3-5 (1.6%) and Grade 2 (2.5%).

Immune-Mediated Dermatologic Adverse Reactions

YERVOY can cause immune-mediated rash or dermatitis, including bullous and exfoliative dermatitis, Stevens-Johnson Syndrome, toxic epidermal necrolysis (TEN), and DRESS (drug rash with eosinophilia and systemic symptoms). Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous/exfoliative rashes. Immune-mediated rash occurred in 15% (76/511) of patients who received YERVOY 3 mg/kg as a single agent, including Grade 3-5 (2.5%) and Grade 2 (12%).

Immune-Mediated Endocrinopathies

Grade 2-5 immune-mediated endocrinopathies occurred in 4% (21/511) of patients who received YERVOY 3 mg/kg as a single agent. Severe to life-threatening (Grade 3-4) endocrinopathies occurred in 9 patients (1.8%). All 9 of these patients had hypopituitarism with some patients having additional concomitant endocrinopathies, such as adrenal insufficiency, hypogonadism, and hypothyroidism. Six of the 9 patients were hospitalized for severe endocrinopathies. Moderate (Grade 2) endocrinopathy occurred in 12 patients (2.3%), including hypothyroidism, adrenal insufficiency, hypopituitarism, hyperthyroidism and Cushing's syndrome. YERVOY can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field cuts. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated.

Other Immune-Mediated Adverse Reactions

Across clinical trials of YERVOY administered as a single agent or in combination with nivolumab, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1% of patients unless otherwise specified, as shown below:

Nervous System: Autoimmune neuropathy (2%), meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, nerve paresis, motor dysfunction

Cardiovascular: Angiopathy, myocarditis, pericarditis, temporal arteritis, vasculitis

Ocular: Blepharitis, episcleritis, iritis, orbital myositis, scleritis, uveitis. Some cases can be associated with retinal detachment. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada–like syndrome, which has been observed in patients receiving YERVOY and may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss.

Gastrointestinal: Duodenitis, gastritis, pancreatitis (1.3%)

Musculoskeletal and Connective Tissue: Arthritis, myositis, polymyalgia rheumatica, polymyositis, rhabdomyolysis

Other (hematologic/immune): Aplastic anemia, conjunctivitis, cytopenias (2.5%), eosinophilia (2.1%), erythema multiforme, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), hypersensitivity vasculitis, meningitis, neurosensory hypoacusis, psoriasis, sarcoidosis, systemic inflammatory response syndrome, and solid organ transplant rejection.

Infusion-Related Reactions

Severe infusion-related reactions can occur with YERVOY. Discontinue YERVOY in patients with severe or life-threatening (Grade 3 or 4) infusion reactions. Interrupt or slow the rate of infusion in patients with mild or moderate (Grade 1 or 2) infusion reactions. Infusion-related reactions occurred in 2.9% (28/982) of patients who received single-agent YERVOY 3 mg/kg or 10 mg/kg for the treatment of melanoma.

Complications of Allogeneic Hematopoietic Stem Cell Transplant after YERVOY

Fatal or serious graft-versus-host disease (GVHD) can occur in patients who receive YERVOY either before or after allogeneic hematopoietic stem cell transplantation (HSCT). These complications may occur despite intervening therapy between CTLA-4 receptor blocking antibody and allogeneic HSCT. Follow patients closely for evidence of GVHD and intervene promptly. Consider the benefit versus risks of treatment with YERVOY after allogeneic HSCT.

Embryo-Fetal Toxicity

Based on its mechanism of action, YERVOY can cause fetal harm when administered to a pregnant woman. The effects of YERVOY are likely to be greater during the second and third trimesters of pregnancy. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with YERVOY and for 3 months after the last dose.

Lactation

There are no data on the presence of YERVOY in human milk or its effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with YERVOY and for 3 months following the last dose.

Common Adverse Reactions

The most common adverse reactions (≥5%) in patients who received YERVOY at 3 mg/kg were fatigue (41%), diarrhea (32%), pruritus (31%), rash (29%), and colitis (8%).

Please see US Full Prescribing Information [insert location].

Please see Important Safety Information for OPDIVO and YERVOY on pages 25-31.
Please also see full Prescribing Information for OPDIVO and YERVOY.

IMPORTANT SAFETY INFORMATION FOR OPDIVO + YERVOY

Severe and Fatal Immune-Mediated Adverse Reactions

Immune-mediated adverse reactions listed herein may not include all possible severe and fatal immune-mediated adverse reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. While immune-mediated adverse reactions usually manifest during treatment, they can also occur after discontinuation of OPDIVO or YERVOY. Early identification and management are essential to ensure safe use of OPDIVO and YERVOY. Monitor for signs and symptoms that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone (ACTH) level, and thyroid function at baseline and periodically during treatment with OPDIVO and before each dose of YERVOY. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). In general, if OPDIVO or YERVOY interruption or discontinuation is required, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy. Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

OPDIVO and YERVOY can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation. In patients receiving OPDIVO monotherapy, immune-mediated pneumonitis occurred in 3.1% (61/1994) of patients, including Grade 4 (<0.1%), Grade 3 (0.9%), and Grade 2 (2.1%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, immune-mediated pneumonitis occurred in 7% (31/456) of patients, including Grade 4 (0.2%), Grade 3 (2.0%), and Grade 2 (4.4%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, immune-mediated pneumonitis occurred in 3.9% (26/666) of patients, including Grade 3 (1.4%) and Grade 2 (2.6%). In NSCLC patients receiving OPDIVO 3 mg/kg every 2 weeks with YERVOY 1 mg/kg every 6 weeks, immune-mediated pneumonitis occurred in 9% (50/576) of patients, including Grade 4 (0.5%), Grade 3 (3.5%), and Grade 2 (4.0%). Four patients (0.7%) died due to pneumonitis.

Immune-Mediated Colitis

OPDIVO and YERVOY can cause immune-mediated colitis, which may be fatal. A common symptom included in the definition of colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has

Please see Important Safety Information for OPDIVO and YERVOY on pages 25-31.
Please also see full Prescribing Information for OPDIVO and YERVOY.

been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. In patients receiving OPDIVO monotherapy, immune-mediated colitis occurred in 2.9% (58/1994) of patients, including Grade 3 (1.7%) and Grade 2 (1%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, immune-mediated colitis occurred in 25% (115/456) of patients, including Grade 4 (0.4%), Grade 3 (14%), and Grade 2 (8%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, immune-mediated colitis occurred in 9% (60/666) of patients, including Grade 3 (4.4%) and Grade 2 (3.7%).

Immune-Mediated Hepatitis and Hepatotoxicity

OPDIVO and YERVOY can cause immune-mediated hepatitis. In patients receiving OPDIVO monotherapy, immune-mediated hepatitis occurred in 1.8% (35/1994) of patients, including Grade 4 (0.2%), Grade 3 (1.3%), and Grade 2 (0.4%). In patients receiving OPDIVO 1 mg/ kg with YERVOY 3 mg/kg every 3 weeks, immune-mediated hepatitis occurred in 15% (70/456) of patients, including Grade 4 (2.4%), Grade 3 (11%), and Grade 2 (1.8%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, immune-mediated hepatitis occurred in 7% (48/666) of patients, including Grade 4 (1.2%), Grade 3 (4.9%), and Grade 2 (0.4%).

Immune-Mediated Endocrinopathies

OPDIVO and YERVOY can cause primary or secondary adrenal insufficiency, immune-mediated hypophysitis, immune-mediated thyroid disorders, and Type 1 diabetes mellitus, which can present with diabetic ketoacidosis. Withhold OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism; initiate hormone replacement as clinically indicated. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism; initiate hormone replacement or medical management as clinically indicated. Monitor patients for hyperglycemia or other signs and symptoms of diabetes; initiate treatment with insulin as clinically indicated.

In patients receiving OPDIVO monotherapy, adrenal insufficiency occurred in 1% (20/1994), including Grade 3 (0.4%) and Grade 2 (0.6%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, adrenal insufficiency occurred in 8% (35/456), including Grade 4 (0.2%), Grade 3 (2.4%), and Grade 2 (4.2%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, adrenal insufficiency occurred in 7% (48/666) of patients, including Grade 4 (0.3%), Grade 3 (2.5%), and Grade 2 (4.1%).

In patients receiving OPDIVO monotherapy, hypophysitis occurred in 0.6% (12/1994) of patients, including Grade 3 (0.2%) and Grade 2 (0.3%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, hypophysitis occurred in 9% (42/456), including Grade 3 (2.4%) and Grade 2 (6%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, hypophysitis occurred in 4.4% (29/666) of patients, including Grade 4 (0.3%), Grade 3 (2.4%), and Grade 2 (0.9%).

In patients receiving OPDIVO monotherapy, thyroiditis occurred in 0.6% (12/1994) of patients, including Grade 2 (0.2%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, thyroiditis occurred in 2.7% (22/666) of patients, including Grade 3 (4.5%) and Grade 2 (2.2%).

In patients receiving OPDIVO monotherapy, hyperthyroidism occurred in 2.7% (54/1994) of patients, including Grade 3 (<0.1%) and Grade 2 (1.2%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, hyperthyroidism occurred in 9% (42/456) of patients, including Grade 3 (0.9%) and Grade 2 (4.2%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, hyperthyroidism occurred in 12% (80/666) of patients, including Grade 3 (0.6%) and Grade 2 (4.5%).

In patients receiving OPDIVO monotherapy, hypothyroidism occurred in 8% (163/1994) of patients, including Grade 3 (0.2%) and Grade 2 (4.8%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, hypothyroidism occurred in 20% (91/456) of patients, including Grade 3 (0.4%) and Grade 2 (11%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, hypothyroidism occurred in 18% (122/666) of patients, including Grade 3 (0.6%) and Grade 2 (11%).

In patients receiving OPDIVO monotherapy, diabetes occurred in 0.9% (17/1994) of patients, including Grade 3 (0.4%) and Grade 2 (0.3%), and 2 cases of diabetic ketoacidosis. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, diabetes occurred in 2.7% (15/666) of patients, including Grade 4 (0.6%), Grade 3 (0.3%), and Grade 2 (0.9%).

Please see Important Safety Information for OPDIVO and YERVOY on pages 25-31.
Please also see full Prescribing Information for OPDIVO and YERVOY.

Immune-Mediated Nephritis with Renal Dysfunction

OPDIVO and YERVOY can cause immune-mediated nephritis. In patients receiving OPDIVO monotherapy, immune-mediated nephritis and renal dysfunction occurred in 1.2% (23/1994) of patients, including Grade 4 (<0.1%), Grade 3 (0.5%), and Grade 2 (0.6%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, immune-mediated nephritis with renal dysfunction occurred in 4.1% (27/666) of patients, including Grade 4 (0.6%), Grade 3 (1.1%), and Grade 2 (2.2%).

Immune-Mediated Dermatologic Adverse Reactions

OPDIVO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate nonexfoliative rashes.

YERVOY can cause immune-mediated rash or dermatitis, including bullous and exfoliative dermatitis, SJS, TEN, and DRESS. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous/exfoliative rashes.

Withhold or permanently discontinue OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information).

In patients receiving OPDIVO monotherapy, immune-mediated rash occurred in 9% (171/1994) of patients, including Grade 3 (1.1%) and Grade 2 (2.2%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, immune-mediated rash occurred in 28% (127/456) of patients, including Grade 3 (4.8%) and Grade 2 (10%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, immune-mediated rash occurred in 16% (108/666) of patients, including Grade 3 (3.5%) and Grade 2 (4.2%).

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received OPDIVO monotherapy or OPDIVO in combination with YERVOY or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions: *cardiac/vascular*: myocarditis, pericarditis, vasculitis; *nervous system*: meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy; *ocular*: uveitis, iritis, and other ocular inflammatory toxicities can occur; *gastrointestinal*: pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis; *musculoskeletal and connective tissue*: myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, polymyalgia rheumatica; *endocrine*: hypoparathyroidism; *other (hematologic/immune)*: hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis (HLH), systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection.

In addition to the immune-mediated adverse reactions listed above, across clinical trials of YERVOY monotherapy or in combination with OPDIVO, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1% of patients unless otherwise specified: *nervous system*: autoimmune neuropathy (2%), myasthenic syndrome/myasthenia gravis, motor dysfunction; *cardiovascular*: angiopathy, temporal arteritis; *ocular*: blepharitis, episcleritis, orbital myositis, scleritis; *gastrointestinal*: pancreatitis (1.3%); *other (hematologic/immune)*: conjunctivitis, cytopenias (2.5%), eosinophilia (2.1%), erythema multiforme, hypersensitivity vasculitis, neurosensory hypoacusis, psoriasis.

Some ocular IMAR cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada–like syndrome, which has been observed in patients receiving OPDIVO and YERVOY, as this may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss.

Infusion-Related Reactions

OPDIVO and YERVOY can cause severe infusion-related reactions. Discontinue OPDIVO and YERVOY in patients with severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild (Grade 1) or moderate (Grade 2) infusion-related reactions. In patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate trial in which patients received OPDIVO monotherapy as a 60-minute infusion or a 30-minute infusion, infusion-related

Please see Important Safety Information for OPDIVO and YERVOY on pages 25-31.
Please also see full Prescribing Information for OPDIVO and YERVOY.

reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO. In melanoma patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, infusion-related reactions occurred in 2.5% (10/407) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, infusion-related reactions occurred in 5.1% (28/547) of patients.

Complications of Allogeneic Hematopoietic Stem Cell Transplantation

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with OPDIVO or YERVOY. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between OPDIVO or YERVOY and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with OPDIVO and YERVOY prior to or after an allogeneic HSCT.

Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal studies, OPDIVO and YERVOY can cause fetal harm when administered to a pregnant woman. The effects of YERVOY are likely to be greater during the second and third trimesters of pregnancy. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and YERVOY and for at least 5 months after the last dose.

Increased Mortality in Patients with Multiple Myeloma when OPDIVO is Added to a Thalidomide Analogue and Dexamethasone

In randomized clinical trials in patients with multiple myeloma, the addition of OPDIVO to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

Lactation

There are no data on the presence of OPDIVO or YERVOY in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for 5 months after the last dose.

Serious Adverse Reactions

In Checkmate 037, serious adverse reactions occurred in 41% of patients receiving OPDIVO (n=268). Grade 3 and 4 adverse reactions occurred in 42% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse drug reactions reported in 2% to <5% of patients receiving OPDIVO were abdominal pain, hyponatremia, increased aspartate aminotransferase, and increased lipase. In Checkmate 066, serious adverse reactions occurred in 36% of patients receiving OPDIVO (n=206). Grade 3 and 4 adverse reactions occurred in 41% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse reactions reported in ≥2% of patients receiving OPDIVO were gamma-glutamyltransferase increase (3.9%) and diarrhea (3.4%). In Checkmate 067, serious adverse reactions (74% and 44%), adverse reactions leading to permanent discontinuation (47% and 18%) or to dosing delays (58% and 36%), and Grade 3 or 4 adverse reactions (72% and 51%) all occurred more frequently in the OPDIVO plus YERVOY arm (n=313) relative to the OPDIVO arm (n=313). The most frequent (≥10%) serious adverse reactions in the OPDIVO plus YERVOY arm and the OPDIVO arm, respectively, were diarrhea (13% and 2.2%), colitis (10% and 1.9%), and pyrexia (10% and 1.0%). In Checkmate 227, serious adverse reactions occurred in 58% of patients (n=576). The most frequent (≥2%) serious adverse reactions were pneumonia, diarrhea/colitis, pneumonitis, hepatitis, pulmonary embolism, adrenal insufficiency, and hypophysitis. Fatal adverse reactions occurred in 1.7% of patients; these included events of pneumonitis (4 patients), myocarditis, acute kidney injury, shock, hyperglycemia, multi-system organ failure, and renal failure. In Checkmate 9LA, serious adverse reactions occurred in 57% of patients (n=358). The most frequent (>2%) serious adverse reactions were pneumonia, diarrhea, febrile neutropenia, anemia, acute kidney injury, musculoskeletal pain, dyspnea, pneumonitis, and respiratory failure. Fatal adverse reactions occurred in 7 (2%) patients, and included hepatic toxicity, acute renal failure, sepsis, pneumonitis, diarrhea with hypokalemia, and massive hemoptysis in the setting of thrombocytopenia. In Checkmate 214, serious adverse reactions occurred in 59% of patients receiving OPDIVO plus YERVOY (n=547). The most frequent serious adverse reactions reported in ≥2% of patients were diarrhea, pyrexia, pneumonia, pneumonitis, hypophysitis, acute kidney injury, dyspnea, adrenal insufficiency, and colitis.

Common Adverse Reactions

In Checkmate 037, the most common adverse reaction (≥20%) reported with OPDIVO (n=268) was rash (21%). In Checkmate 066, the most common adverse reactions (≥20%) reported with OPDIVO (n=206) vs dacarbazine (n=205) were fatigue (49% vs 39%), musculoskeletal pain (32% vs 25%), rash (28% vs 12%), and pruritus (23% vs 12%). In Checkmate 067, the most common (≥20%) adverse reactions in the OPDIVO plus YERVOY arm (n=313) were fatigue (62%), diarrhea (54%), rash (53%), nausea (44%), pyrexia (40%), pruritus (39%), musculoskeletal pain (32%), vomiting (31%), decreased appetite (29%), cough (27%), headache (26%), dyspnea (24%), upper respiratory tract infection (23%), arthralgia (21%), and increased transaminases (25%). In Checkmate 067, the most common (≥20%) adverse reactions in the OPDIVO arm (n=313) were fatigue (59%), rash (40%), musculoskeletal pain (42%), diarrhea (36%), nausea (30%), cough (28%), pruritus (27%), upper respiratory tract infection (22%), decreased appetite (22%), headache (22%), constipation (21%), arthralgia (21%), and vomiting (20%). In Checkmate 227, the most common (≥20%) adverse reactions were fatigue (44%), rash (34%), decreased appetite (31%), musculoskeletal pain (27%), diarrhea/colitis (26%), dyspnea (26%), cough (23%), hepatitis (21%), nausea (21%), and pruritus (21%). In Checkmate 9LA, the most common (>20%) adverse reactions were fatigue (49%), musculoskeletal pain (39%), nausea (32%), diarrhea (31%), rash (30%), decreased appetite (28%), constipation (21%), and pruritus (21%). In Checkmate 214, the most common adverse reactions (≥20%) reported in patients treated with OPDIVO plus YERVOY (n=547) were fatigue (58%), rash (39%), diarrhea (38%), musculoskeletal pain (37%), pruritus (33%), nausea (30%), cough (28%), pyrexia (25%), arthralgia (23%), decreased appetite (21%), dyspnea (20%), and vomiting (20%).

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Clinical Trials and Patient Populations

Checkmate 037–previously treated metastatic melanoma; Checkmate 066–previously untreated metastatic melanoma; Checkmate 067–previously untreated metastatic melanoma, as a single agent or in combination with YERVOY; Checkmate 227–previously untreated metastatic non-small cell lung cancer, in combination with YERVOY; Checkmate 9LA–previously untreated recurrent or metastatic non-small cell lung cancer in combination with YERVOY and 2 cycles of platinum-doublet chemotherapy by histology; Checkmate 214–previously untreated renal cell carcinoma, in combination with YERVOY.

SUMMARY

YERVOY is a CTLA-4–specific monoclonal antibody that served as a pioneer as the first approved immune checkpoint inhibitor for treating a variety of cancers. YERVOY's blockade of CTLA-4 may help restore an immune response by increasing the activation and proliferation of T-cells (which some can become memory T-cells) and by reducing Tregs in the tumor microenvironment.[5,6] Complementing the mechanism of YERVOY is the action of OPDIVO, an anti–PD-1 monoclonal antibody, that works to release PD-1 pathway-mediated inhibition of the immune response and help reverse T-cell exhaustion.

Clinical studies with YERVOY monotherapy have shown efficacy in patients with metastatic melanoma. In addition, combination therapy with YERVOY + OPDIVO has demonstrated improved long-term OS over comparator arms as first-line therapy in patients with unresectable or metastatic melanoma (the Checkmate 067 trial),[19,21] over sunitinib in those with treatment-naïve, intermediate/poor risk, advanced RCC (the Checkmate 214 trial),[22-24] and in comparison with platinum-based chemotherapy as first-line therapy in patients with stage IV NSCLC over a 4-year follow-up period (the Checkmate 227 trial).[30] Moreover, data from Checkmate 9LA of OPDIVO + YERVOY plus 2 cycles of platinum-based chemotherapy as first-line therapy in patients with stage IV or recurrent NSCLC, no known sensitizing *EGFR* or *ALK* aberrations, and regardless of histology or PD-L1 expression, showed an OS benefit compared to 4 cycles of platinum-based chemotherapy alone over a 2-year follow-up period.[31,32]

Inhibition of CTLA-4 and PD-1, alone and in combination, is associated with a range of side effects (IMARs) that resemble autoimmune reactions.[7,35] Healthcare providers should monitor patients closely during and after treatment and educate patients on detecting IMARs.[37]

REFERENCES

1. Korniluk Koper O, Kemona H, Dymicka-Piekarska V. From inflammation to cancer. *Ir J Med Sci*. 2017;186:57-62.
2. Coley WB. Contribution to the knowledge of sarcoma. *Ann Surg*. 1891;14:199-220.
3. Hoos A. Development of immuno-oncology drugs–from CTLA4 to PD1 to the next generations. *Nat Rev Drug Discov*. 2015;15:235-247.
4. Leach DR, Krummel MF, Allison JP. Enhancement of antitumor immunity by CTLA-4 blockade. *Science*. 1996;271:1734-1736.
5. Letendre P, Monga V, Milhelp M, Zakharia Y. Ipilimumab: from preclinical development to future clinical perspectives in melanoma. *Future Oncol*. 2017;13:625-636.
6. YERVOY® (ipilimumab) [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2020.
7. OPDIVO® (nivolumab) [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2021.
8. Farber DL, Yudanin NA, Restifo NP. Human memory T cells: generation, compartmentalization and homeostasis. *Nat Rev Immunol*. 2014;14(1):24-35.
9. Ansell SM, Hurvitz SA, Koenig PA, et al. Phase I study of ipilimumab, an anti–CTLA-4 monoclonal antibody, in patients with relapsed and refractory B-cell non–Hodgkin lymphoma. *Clin Cancer Res*. 2009;15(20):6446-6453.
10. Felix J, Lambert J, Roelens M, et al. Ipilimumab reshapes T cell memory subsets in melanoma patients with clinical response. *Oncoimmunology*. 2016;5(7):e1136045.
11. Pedicord VA, Montalvo W, Leiner IM, Allison JP. Single dose of anti–CTLA-4 enhances CD8+ T-cell memory formation, function, and maintenance. *Proc Natl Acad Sci U S A*. 2011;108(1):266-271.
12. de Coaña YP, Wolodarski M, Poschke I, et al. Ipilimumab treatment decreases monocytic MDSCs and increases CD8 effector memory T cells in long-term survivors with advanced melanoma. *Oncotarget*. 2017;8(13):21539-21553.
13. Weber JS, Hamid O, Chasalow SD, et al. Ipilimumab increases activated T cells and enhances humoral immunity in patients with advanced melanoma. *J Immunother*. 2012;35:89-97.
14. Buchbinder EI, Desai A. CTLA-4 and PD-1 pathways: similarities, differences, and implications of their inhibition. *Am J Clin Oncol*. 2016;39:98-106.
15. Selby M, Engelhardt J, Lu L-S, et al. Antitumor activity of concurrent blockade of immune checkpoint molecules CTLA-4 and PD-1 in preclinical models. Presented at: 2013 American Society of Clinical Oncology (ASCO) Annual Meeting. Abstract 3061.
16. Metro G, Ricciuti B, Brambilla M, et al. The safety of nivolumab for the treatment of advanced non-small cell lung cancer. *Expert Opin Drug Saf*. 2017;16(1):101-109.
17. Byrne EH, Fisher DE. Immune and molecular correlates in melanoma treated with immune checkpoint blockade. *Cancer*. 2017;123(S11):2143-2153.
18. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363:711-723.
19. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med*. 2019;381:1535-1546.
20. Larkin J, Chiarion Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med*. 2015;373:23-34.
21. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. CheckMate 067: 6.5-year outcomes in patients (pts) with advanced melanoma. Presented at: 2021 American Society of Clinical Oncology (ASCO) Annual Meeting; June 4-8, 2021. Abstract 9506. https://meetinglibrary.asco.org/record/195983/abstract. Accessed June 8, 2021.
22. Albiges L, Tannir NM, Burotto M, et al. Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 4-year follow-up of the phase III CheckMate 214 trial. *ESMO Open*. 2020;5:e001079.
23. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med*. 2018;378:1277-1290.
24. Motzer RJ, Rini BI, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2019;20:1370-1385.
25. Data on file. NIVO 158. Princeton, NJ: Bristol-Myers Squibb Company; 2018.
26. Data on file. NIVO 593. Princeton, NJ: Bristol-Myers Squibb Company; 2020.
27. Ramalingam SS, Ciuleanu T-E, Pluzanski A, et al. Nivolumab + ipilimumab versus platinum doublet chemotherapy as first-line treatment for advanced non-small cell lung cancer: three-year update from CheckMate 227 Part 1. Presented at: 2020 American Society of Clinical Oncology (ASCO) Annual Meeting; May 29-31, 2020. Abstract 9500.
28. Hellmann MD, Paz-Ares L, Caro RB, et al. Nivolumab plus ipilimumab in advanced non–small-cell lung cancer. *N Engl J Med*. 2019;381:2020-2031.
29. Hellmann MD, Paz-Ares L, Caro RB, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer [supplementary appendix]. *N Engl J Med*. 2019;381:2020-2031.
30. Paz-Ares LG, Ciuleanu T-E, Lee J-S, et al. Nivolumab (NIVO) plus ipilimumab (IPI) versus chemotherapy (chemo) as first-line (1L) treatment for advanced non-small cell lung cancer (NSCLC): 4-year update from CheckMate 227. Presented at: 2021 American Society of Clinical Oncology (ASCO) Annual Meeting; June 4-8, 2021. Abstract 9016.
31. Reck M, Ciuleanu T-E, Cobo M, et al. Nivolumab + ipilimumab + 2 cycles of platinum doublet chemotherapy vs. 4 cycles chemotherapy as first-line treatment for stage IV/recurrent NSCLC: CheckMate 9LA. Presented at American Society of Clinical Oncology (ASCO) 2020; May 29-31, 2020. Abstract 9501.
32. Reck M, Ciuleanu T-E, Cobo M, et al. First-line nivolumab (NIVO) plus ipilimumab (IPI) plus two cycles of chemotherapy (chemo) versus chemo alone (4 cycles) in patients with advanced non-small cell lung cancer (NSCLC): two-year update from CheckMate 9LA. Presented at: 2021 American Society of Clinical Oncology (ASCO) Annual Meeting; June 4-8, 2021. Abstract 9000.
33. Public Disclosure. 00053330. Princeton, NJ: Bristol-Myers Squibb Company; 2019.
34. Zhang L, Jones-O'Connor M, Awadalla M, et al. Cardiotoxicity of immune checkpoint inhibitors. *Curr Treat Options Cardiovasc Med*. 2019;21:32.
35. Palmieri DJ, Carlino MS. Immune checkpoint inhibitor toxicity. *Curr Oncol Rep*. 2018;20:72.
36. Naing A, Hajjar J, Gulley JL, et al. Strategies for improving the management of immune-related adverse events. *J Immunother Cancer*. 2020;8:e001754.
37. Myers G. Immune-related adverse events of immune checkpoint inhibitors: a brief review. *Curr Oncol*. 2018;25:342-347.

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