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ORIGINAL RESEARCH

A phase II study of retifanlimab, a humanized anti-PD-1 monoclonal antibody, in patients with solid tumors (POD1UM-203)

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Background: POD1UM-203, an open-label, multicenter, phase II study, evaluated retifanlimab, a humanized monoclonal antibody targeting programmed cell death protein-1 (PD-1) in patients with selected solid tumors where immune checkpoint inhibitor therapies have previously shown efficacy.

Patients and methods: Eligible patients (≥18 years) had measurable disease and included unresectable or metastatic melanoma, treatment-naive metastatic non-small-cell lung cancer (NSCLC) with high programmed death-ligand 1 (PD-L1) expression (tumor proportion score ≥50%), cisplatin-ineligible locally advanced/metastatic urothelial carcinoma (UC) with PD-L1 expression (combined positive score ≥10%), or treatment-naive locally advanced/metastatic clear-cell renal cell carcinoma (RCC). Retifanlimab 500 mg was administered intravenously every 4 weeks as a 30-min infusion. The primary endpoint was investigator-assessed overall response rate.

Results: Overall, 121 patients (35 melanoma, 23 NSCLC, 29 UC, 34 RCC) were enrolled and treated. The overall response rate [95% confidence interval (CI)] was 40.0% (23.9-57.9) in the melanoma cohort, 34.8% (16.4-57.3) in the NSCLC cohort, 37.9% (20.7-57.7) in the UC cohort, and 23.5% (10.7-41.2) in the RCC cohort. Median duration of response was 11.5 months (95% CI 2.2-not reached) in the UC cohort, and was not reached in the other cohorts. Retifanlimab safety was consistent with previous experience for PD-(L)1 inhibitors.

Conclusions: Retifanlimab demonstrated durable antitumor activity in patients with melanoma, NSCLC, UC, or RCC. The efficacy and safety of retifanlimab were as expected for a PD-(L)1 inhibitor. These data support further study of retifanlimab in solid tumors.

Key words: checkpoint inhibitor, PD-1 inhibitor, phase II, retifanlimab, solid tumor

INTRODUCTION

The development of checkpoint inhibitors, including monoclonal antibodies against cytotoxic T-lymphocyte-associated protein 4, programmed cell death protein-1 (PD-1), and programmed death-ligand 1 (PD-L1), has revolutionized the treatment of a wide range of cancers.[1,2] Immune checkpoint inhibitors, including PD-(L)1 inhibitors, either as monotherapy or in combination with other anticancer therapies, have shown high levels of efficacy and become standard of care for a number of solid tumor types, including melanoma,[3] non-small-cell lung cancer (NSCLC),[4] urothelial carcinoma,[5] and renal cell carcinoma (RCC).[6]

Retifanlimab is a humanized, hinge-stabilized immunoglobulin G4 kappa (IgG4κ) monoclonal antibody against human PD-1.[7] It contains a human IgG4 Fc domain to limit effector function while retaining neonatal Fc receptor binding to extend the circulating half-life. Preclinical studies demonstrated that retifanlimab blocks PD-(L)1 interactions, interrupts PD-1 signaling, and enhances antigen-induced interferon-gamma release with a similar potency to replicas of the PD-1 inhibitors nivolumab and pembrolizumab.[7] Early clinical studies demonstrated that retifanlimab is biologically active and leads to an increase in circulating T-cell activation,[8] and that a simple, flat-dosing regimen of 500 mg by intravenous infusion every 4 weeks (Q4W) provided sufficient target engagement with the highest probability of efficacy.[9]

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A phase I study (POD1UM-101) of retifanlimab in patients with advanced solid tumors demonstrated that retifanlimab was generally well tolerated with a safety profile characteristic of the PD-1 inhibitor class, and had early signs of clinical activity.[10,11] Another phase II study (POD1UM-202) demonstrated that retifanlimab had encouraging efficacy and an expected safety profile in patients with previously treated, advanced or metastatic squamous carcinoma of the anal canal.[12] In this paper, we report results from POD1UM-203, a phase II study investigating retifanlimab treatment in patients with melanoma, NSCLC, urothelial carcinoma, and RCC.

PATIENTS AND METHODS

Study design

POD1UM-203 is an open-label, multicenter, phase II study designed to assess the efficacy and safety of retifanlimab in patients with select advanced solid tumors (NCT03679767; EudraCT 2018-002941-12). The study was conducted across 34 study centers in Europe and the United States. The study protocol and amendments were reviewed and approved by the institutional review board and/or independent ethics committee at each center before enrollment of patients. The study was conducted in accordance with the International Council for Harmonisation Guideline E6 for Good Clinical Practice, the principles of the Declaration of Helsinki, and other applicable local ethical and legal requirements. Each patient provided informed consent before screening assessments were carried out.

All patients received retifanlimab 500 mg Q4W via intravenous infusion over 30 min on day 1 of each 28-day cycle. Treatment could be delayed because of toxicity for up to 12 weeks. Patients who were unable to restart retifanlimab treatment within 12 weeks from the start of treatment delay due to toxicity discontinued the study. Treatment continued for up to 2 years in the absence of disease progression, intolerable toxicity, death, withdrawal of consent, loss to follow-up, or premature discontinuation for any other reason.

Patients who discontinued study treatment for reasons other than disease progression [i.e. adverse events (AEs)] had tumor assessments until disease progression, the start of a new anticancer treatment, withdrawal of consent, loss to follow-up, end of the study, or death.

Patient eligibility

Eligible patients were 18 years of age or older, with measurable disease/lesions according to RECIST v1.1, Eastern Cooperative Oncology Group performance status score of 0 or 1, and willingness to avoid pregnancy or fathering children. Patients with the following tumor types were enrolled in one of the four disease-specific cohorts: unresectable or metastatic melanoma; treatment-naive metastatic NSCLC with high PD-L1 expression (tumor proportion score $\geq$50%) and no *EGFR*−, *ALK*−, or *ROS*-activating genomic tumor aberrations; cisplatin-ineligible (as determined by the investigator) locally advanced or metastatic urothelial carcinoma with tumors expressing PD-L1 with a combined positive score of $\geq$10; or treatment-naive locally advanced or metastatic RCC with a clear-cell component (with or without sarcomatoid features).

Key exclusion criteria included previous treatment with any anti-PD-(L)1 therapy; active autoimmune disease requiring systemic immunosuppression in excess of physiologic maintenance doses of corticosteroids (defined as $>$10 mg of prednisone or equivalent); evidence of interstitial lung disease or active noninfectious pneumonitis; known active brain metastases and/or leptomeningeal disease; clinically significant cardiovascular or pulmonary conditions; known active hepatitis A, B, or C or human immunodeficiency virus (HIV) infection; and active infections requiring systemic therapy. Patients with a history of HIV infection were eligible to enroll in the study if they had CD4+ cell counts $\geq$300/μl, undetectable viral load, and were receiving antiretroviral therapy. HIV testing was only required for patients known to be HIV-positive.

Outcomes and assessments

The primary endpoint was the overall response rate (ORR), defined as the percentage of patients having a complete response (CR) or partial response according to RECIST v1.1 as determined by the investigator. Secondary endpoints included duration of response (DOR; defined as the time from initial objective response until disease progression, as determined by the investigator, or death from any cause), disease control rate (defined as the proportion of patients with CR, partial response, or stable disease according to RECIST v1.1), progression-free survival (PFS; defined as the time from the start of therapy until disease progression, as determined by the investigator, or death from any cause), overall survival (OS; defined as the time from the start of therapy until death due to any cause), safety, and pharmacokinetics (PK). Assessment of immunogenicity of retifanlimab was an exploratory endpoint.

Tumor imaging and response assessments were evaluated at the screening visit and every 8 weeks ($\pm$7 days) during treatment. Safety was assessed by the frequency, duration, and severity of AEs, laboratory tests, vital signs, and electrocardiograms. AEs (graded according to Common Terminology Criteria for Adverse Events v5.0) were monitored throughout the study and for at least 28 days ($\pm$7 days) after the last dose of retifanlimab. Immune-related adverse events (irAEs) were sponsor-defined irAEs using predefined preferred terms and were monitored until 90 days after the last dose of retifanlimab.

The PK of retifanlimab when administered as a 30-min infusion was assessed by measuring serum concentrations of retifanlimab pre-infusion and 10 min after infusion on day 1 of cycles 1, 2, 4, and 6. Additional samples were collected 4 h after infusion on day 1 of cycle 1 and on the day of end-of-treatment visit. The following parameters were assessed: maximum plasma drug concentration, minimum plasma drug concentration, area under the plasma concentration—time curve from time 0 to the last

measurable time point, and time to maximum plasma drug concentration. Antidrug antibodies (ADAs) were also measured in serum samples collected on day 1 of cycles 1, 2, and every two cycles thereafter and on the day of end-of-treatment visit.

Statistical methods

There was no formal hypothesis testing in this study; response rates and associated 95% confidence intervals (CIs) were calculated. The study planned to enroll ∼30 patients into each disease-specific cohort to provide a preliminary assessment of efficacy, safety, and PK. Summary of patient demographics, baseline characteristics, as well as efficacy and safety analyses were conducted on the full analysis set, which included all patients who received at least one dose of retifanlimab. The PK-evaluable population included patients who received at least one dose of retifanlimab and provided a baseline sample and at least one post-dose PK sample.

Efficacy analyses were carried out independently for each disease cohort. The primary analysis of ORR was carried out once all patients had been followed for at least 6 months from the start of retifanlimab or prematurely discontinued retifanlimab. Kaplan—Meier estimates with 95% CIs were used to estimate median DOR, PFS, and OS. AEs were tabulated by preferred term and system organ class for all events, related events, and events of grade 3 or higher. PK parameters were analyzed using standard non-compartmental analysis (WinNonlin v8.2, Certara USA Inc., Princeton, NJ). The proportion of patients who were negative for ADAs to retifanlimab at baseline and became positive during the study, the proportion who remained negative during the study, and the proportion who were positive at baseline and had increases or decreases in ADA titer over the course of the study were summarized.

RESULTS

Patients

Between 9 January 2019 and 8 April 2020, 121 patients were enrolled and treated with retifanlimab 500 mg Q4W at 34 study sites. Of the 121 patients, 35 had melanoma, 23 had NSCLC, 29 had urothelial carcinoma, and 34 had RCC; baseline patient characteristics are summarized in Table 1. Across all cohorts, the median age was 70 years (range 38-92) and most patients (63.6%) were at least 65 years of age. Most patients were male (66.1%) and White (90.9%). In the melanoma cohort, 31.4% of patients had received at least one prior systemic anticancer therapy, which may have included BRAF/MEK-targeted therapy. In the urothelial carcinoma cohort, 82.8% of patients had received at least one prior systemic anticancer therapy, with any previous systemic therapy [excluding PD-(L)1-directed therapy] permitted. In the urothelial carcinoma cohort, patients were cisplatin ineligible because of renal dysfunction (34.5%), performance status (6.9%), or other investigator-determined reasons (58.6%; health/fitness concerns, poor response to previous platinum-based chemotherapy, neuropathy, or hearing loss). In the RCC cohort, the Memorial Sloan Kettering Cancer Center prognostic criteria[13] at initial diagnosis were favorable in 17.6%, intermediate in 32.4%, poor in 11.8%, and not provided in 38.2% of patients. In accordance with the protocol, none of the patients in the RCC and NSCLC cohorts had received prior therapy, except for one patient in the NSCLC cohort (which was a protocol deviation).

As of the 15 April 2021 data cut-off, 37 patients (30.6%) were ongoing treatment and 84 (69.4%) had discontinued treatment (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.102387). The most common reason for treatment discontinuation was progressive disease (55 patients, 45.5%) followed by AEs (17 patients, 14.0%). Median duration of retifanlimab exposure was 5.7 months (range 1 day to 22.1 months). Eighty patients (66.1%) were treated for over 3 months, 60 (49.6%) for over 6 months, 51 (42.1%) for over 9 months, and 39 (32.2%) for over 12 months. The median number of infusions was 7 (range 1-24).

Efficacy

ORR was 40.0% (95% CI 23.9 to 57.9) in the melanoma cohort, 34.8% (95% CI 16.4 to 57.3) in the NSCLC cohort, 37.9% (95% CI 20.7 to 57.7) in the urothelial carcinoma cohort, and 23.5% (95% CI 10.7 to 41.2) in the RCC cohort (Table 2). Except for the NSCLC cohort, CRs were observed in each cohort, with six CRs (17.1%) in the melanoma cohort. Disease control rate was 54.3% (95% CI 36.6 to 71.2) in the melanoma cohort, 65.2% (95% CI 42.7 to 83.6) in the NSCLC cohort, 55.2% (95% CI 35.7 to 73.6) in the urothelial carcinoma cohort, and 64.7% (95% CI 46.5 to 80.3) in the RCC cohort. After median follow-up times of 9.2-12.9 months (Figure 1A), the median DOR was not reached in the melanoma, NSCLC, and RCC cohorts; median DOR was 11.5 months (95% CI 2.2-not estimable) in the urothelial carcinoma cohort. Best percentage changes from baseline in target lesions for each patient are shown in Figure 2.

After median follow-up times of 3.5-5.3 months, median PFS ranged from 3.6 months (95% CI 1.8-not estimable) in the melanoma cohort to 5.7 months (95% CI 1.8-13.6) in the urothelial carcinoma cohort (Figure 1B). Median OS was 14.7 months (95% CI 8.7-not estimable) in the melanoma cohort, 15.2 months (95% CI 7.7-not estimable) in the urothelial carcinoma cohort, and not reached in the NSCLC (95% CI 5.2-not estimable) and RCC (95% CI not estimable-not estimable) cohorts (Figure 1C) after median follow-up times of 13.0, 11.9, 12.9, and 15.1 months, respectively.

Safety

A total of 110 patients (90.9%) had at least one treatment-emergent adverse event (TEAE) and 53 (43.8%) had grade ≥3 TEAEs (Table 3). The most frequently reported TEAEs were asthenia (19.8%), arthralgia (18.2%), pruritus (16.5%), and decreased appetite (15.7%). The most frequently reported grade ≥3 TEAEs were anemia (5.0%), pneumonia (4.1%), and alanine aminotransferase

Table 1. Baseline demographics and disease characteristics

Characteristic	Melanoma ($n = 35$)	NSCLC ($n = 23$)	UC ($n = 29$)	RCC ($n = 34$)	Total ($N = 121$)[a]
Age, median (range), years	69 (38-92)	69 (50-87)	72 (54-88)	66.5 (48-87)	70 (38-92)
≥65	21 (60.0)	14 (60.9)	23 (79.3)	19 (55.9)	77 (63.6)
≥75	15 (42.9)	4 (17.4)	11 (37.9)	7 (20.6)	37 (30.6)
Sex, *n* (%)					
Men	15 (42.9)	16 (69.6)	25 (86.2)	24 (70.6)	80 (66.1)
Women	20 (57.1)	7 (30.4)	4 (13.8)	10 (29.4)	41 (33.9)
Race, *n* (%)					
White	35 (100.0)	22 (95.7)	20 (69.0)	33 (97.1)	110 (90.9)
Asian	0	1 (4.3)	0	0	1 (0.8)
Other[b]	0	0	6 (20.7)	0	6 (5.0)
Missing	0	0	3 (10.3)	1 (2.9)	4 (3.3)
ECOG PS, *n* (%)					
0	14 (40.0)	3 (13.0)	11 (37.9)	17 (50.0)	—
1	21 (60.0)	20 (87.0)	18 (62.1)	17 (50.0)	—
Median time since initial diagnosis (range), months	22.1 (1.0-240.8)	2.5 (0.7-6.4)	14.2 (4.8-92.7)	8.6 (1.0-266.6)	—
Median time since unresectable/metastatic diagnosis (range), months	1.94 (0.5-138.8)	1.8 (0.2-4.9)	3.9 (0.5-46.5)	2.6 (0.5-40.0)	—
Prior systemic therapy, *n* (%)	11 (31.4)	1 (4.3)	24 (82.8)	0	36 (29.8)
1 line	7 (20.0)	0	15 (51.7)	0	22 (18.2)
2 lines	2 (5.7)	1 (4.3)	9 (31.0)	0	12 (9.9)
≥2 lines	2 (5.7)	0	0	0	2 (1.7)
Prior radiotherapy, *n* (%)[c]	4 (11.4)	6 (26.1)	4 (13.8)	4 (11.8)	18 (14.9)
Prior surgery, *n* (%)	29 (82.9)	5 (21.7)	26 (89.7)	26 (76.5)	86 (71.1)
Histology at baseline, *n* (%)					
Cutaneous	30 (85.7)	—	—	—	30 (24.8)
Acral	1 (2.9)	—	—	—	1 (0.8)
Adenocarcinoma	—	15 (65.2)	12 (41.4)	—	27 (22.3)
Large cell carcinoma	—	1 (4.3)	—	—	1 (0.8)
Squamous	—	7 (30.4)	1 (3.4)	—	8 (6.6)
Transitional cell	—	—	12 (41.4)	—	12 (9.9)
Clear cell	—	—	—	31 (91.2)	31 (25.6)
Clear cell with other component	—	—	—	3 (8.8)	3 (2.5)
Other	4 (11.4)[d]	0	4 (13.8)[e]	0	8 (6.6)
Stage at baseline, *n* (%)					
Stage 2A	1 (2.9)	—	—	—	—
Stage 3	—	—	—	3 (8.8)	—
Stage 3A	1 (2.9)	—	—	—	—
Stage 3B	1 (2.9)	—	—	—	—
Stage 3C	3 (8.6)	—	—	—	—
Stage 4	29 (82.9)	—	23 (79.3)	31 (91.2)	—
Stage 4A	—	16 (69.6)	1 (3.4)	—	—
Stage 4B	—	7 (30.4)	5 (17.2)	—	—

Data cut-off date: 15 April 2021.

ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small-cell lung cancer; RCC, renal cell carcinoma; UC, urothelial carcinoma.

[a]Enrolled at 34 study sites: 24 in Romania, 23 in France, 19 in Italy, 17 in the United States, 11 in Spain, 10 in Hungary, 9 in Poland, and 8 in Austria.

[b]Other includes not applicable/not available/not specified/not reported for patients in France.

[c]Includes patients who received neoadjuvant, adjuvant, or palliative radiotherapy.

[d]Two patients had mucosal, one had nodular, and one had superficial spreading melanoma.

[e]Two patients had UC (not otherwise specified), one had epidermoid, and one had papillary UC.

increased, hypertension, and sepsis (each 3.3%). Seventy-two patients (59.5%) had treatment-related adverse events (TRAEs) and 14 (11.6%) had grade ≥3 TRAEs. The most frequently reported TRAEs were asthenia and pruritus (each 12.4%), and arthralgia and rash (each 9.1%) (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.102387). TEAEs led to treatment discontinuation in 16 patients (13.2%) owing to sepsis [$n = 2$ (1.7%)], and right ventricular failure, general physical health deterioration, hepatic failure, hepatocellular injury, coronavirus disease (COVID-19) pneumonia, pneumonia, alanine aminotransferase increased, blood creatinine increased, myelodysplastic syndrome, acute kidney injury, azotemia, chronic obstructive pulmonary disease, dry skin, and hemorrhage [each $n = 1$ (0.8%)]. TEAEs led to infusion interruption in none of the patients and dose delay in 28 patients (23.1%).

Thirty-six patients (29.8%) had serious adverse events (SAEs), with the most frequently reported being pneumonia (5.0%), chronic obstructive pulmonary disease (3.3%), sepsis (2.5%), hepatocellular injury (1.7%), and pulmonary embolism (1.7%); all other SAEs occurred in one patient each. Five patients (4.1%) had SAEs considered related to retifanlimab (hepatocellular injury in two patients; hypophysitis, infusion-related reaction, and acute kidney injury reported in one patient each). Seven patients

Table 2. Summary of best overall response according to RECIST v1.1 (full analysis set)

Variable	Melanoma ($n = 35$)	NSCLC ($n = 23$)	UC ($n = 29$)	RCC ($n = 34$)
ORR,[a] *n* (%)	14 (40.0)	8 (34.8)	11 (37.9)	8 (23.5)
95% CI[b]	23.9-57.9	16.4-57.3	20.7-57.7	10.7-41.2
Best overall response,[c] *n* (%)				
CR	6 (17.1)	0	1 (3.4)	2 (5.9)
PR	8 (22.9)	8 (34.8)	10 (34.5)	6 (17.6)
SD	5 (14.3)	7 (30.4)	5 (17.2)	14 (41.2)
PD	12 (34.3)	6 (26.1)	11 (37.9)	8 (23.5)
NE[d]	1 (2.9)	0	0	0
Missing[e]	3 (8.6)	2 (8.7)	2 (6.9)	4 (11.8)

Data cut-off date: 15 April 2021.
CI, confidence interval; CR, complete response; NE, not evaluable; NSCLC, non-small-cell lung cancer; ORR, overall response rate; PD, progressive disease; PR, partial response; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; UC, urothelial carcinoma.
[a]A patient was considered an objective responder if the patient had an overall response of CR or PR at any post-baseline visit until the first PD or start of new anticancer therapy.
[b]CIs were calculated based on the exact method for binomial distributions.
[c]The best response recorded from the start of the treatment until the first PD or new anticancer therapy, in the order of CR, PR, SD, PD, and NE.
[d]Patient had no measurable disease at baseline.
[e]All patients with missing best overall response discontinued treatment before the first on-study response assessment.

(5.8%) had fatal TEAEs (right ventricular failure, death, general physical health deterioration, COVID-19 pneumonia, sepsis, cerebrovascular accident, and hemorrhage, which were reported in one patient each). None of the deaths were considered treatment related by the investigator or the sponsor.

Out of 29 patients (24.0%) who had irAEs (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2024.102387), three (2.5%) were grade ≥3 (acute kidney injury, pancreatitis, and macular rash) and two (1.7%) were SAEs (acute kidney injury and hypophysitis). irAEs led to dose delay in six patients (rash, $n = 3$ and myositis, macular rash, and popular rash, each $n = 1$) and treatment discontinuation in one patient (acute kidney injury); there were no infusion interruptions owing to irAEs. Eight patients (6.6%) had 10 treatment-emergent infusion reactions [most commonly, pruritus ($n = 4$)], all of which were grade 1 or 2 in severity, and none were fatal or led to retifanlimab infusion interruption, dose delay, or treatment discontinuation.

Pharmacokinetics

At the PK data cut-off of 15 April 2021, first-dose PK parameters had been analyzed in all 121 patients after a 30-min retifanlimab infusion. After a single dose, serum retifanlimab time to maximum plasma drug concentration was ∼0.6 h. Geometric mean maximum plasma drug concentration was 139 mg/l after a single dose of retifanlimab and 177 mg/l at steady state. Geometric mean area under the plasma concentration—time curve from time 0 to the last measurable time point was 1530 day•mg/l after a single dose and 1960 day•mg/l at steady state (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2024.102387).

Immunogenicity

As of 15 April 2021, 113 patients had been assessed for ADAs. One patient was ADA positive at baseline and two patients had treatment-emergent ADAs, neither of which was clinically significant.

DISCUSSION

In this multicenter, phase II study, retifanlimab demonstrated promising antitumor activity in patients with unresectable or metastatic melanoma, treatment-naive metastatic NSCLC (PD-L1 ≥50%), cisplatin-ineligible locally advanced or metastatic urothelial carcinoma, and treatment-naive locally advanced or metastatic clear-cell RCC. Retifanlimab was generally well tolerated, with no unexpected safety signals reported. The flat-dose regimen of 500 mg Q4W administered in our study is based on clinical data from the first-in-human study of retifanlimab monotherapy (POD1UM-101). Favorable PK properties and parameters of retifanlimab dosing of 500 mg Q4W allowed once-monthly visits for scheduled infusions.

Responses with retifanlimab were durable in all tumor cohorts. Importantly, the median OS was not reached in the NSCLC and RCC cohorts and was over 1 year in the melanoma and urothelial carcinoma cohorts. Efficacy data in our study are consistent with previous experience with established PD-(L)1 inhibitors in the same tumor types. For example, the ORRs in our study cohorts are similar to those reported with PD-(L)1 inhibitors in melanoma (21.0%-40.0%),[14-16] NSCLC (20.7%-39.0%),[17-20] urothelial carcinoma (21.1%-38.0%),[21-23] and RCC (20.0%-36.4%),[24-26] with a high level of disease control. Additionally, the median PFS and median OS reported in the current study across all tumor cohorts were in a similar range to what would be expected for the PD-(L)1 class.[14-29]

The safety profile was also consistent with previous trials of retifanlimab and PD-(L)1 inhibitors. The most common TEAEs were asthenia, arthralgia, pruritus, decreased appetite, and diarrhea with an acceptable incidence of grade ≥3 TRAEs. Indeed, the overall safety profile of retifanlimab was very similar to that of PD-1 inhibitors in a systematic review of NSCLC studies.[15,22,25,30,31] The irAE profile with retifanlimab was also consistent with that reported with other PD-1 inhibitors,[32] with hypothyroidism and rash being the most commonly reported.[30,33] There were no unexpected irAEs, and the majority of irAEs reported were grade 1 or 2 in severity and manageable with standard-of-care measures. Retifanlimab was not associated with a high rate of infusion-related reactions, confirming the utility of the 30-min infusion schedule that was used in this study.

Limitations of our study include having no comparator arm(s), making interpretation of the antitumor activity of retifanlimab against best supportive care limited. However, RECIST ORR is a well-established surrogate endpoint in trials

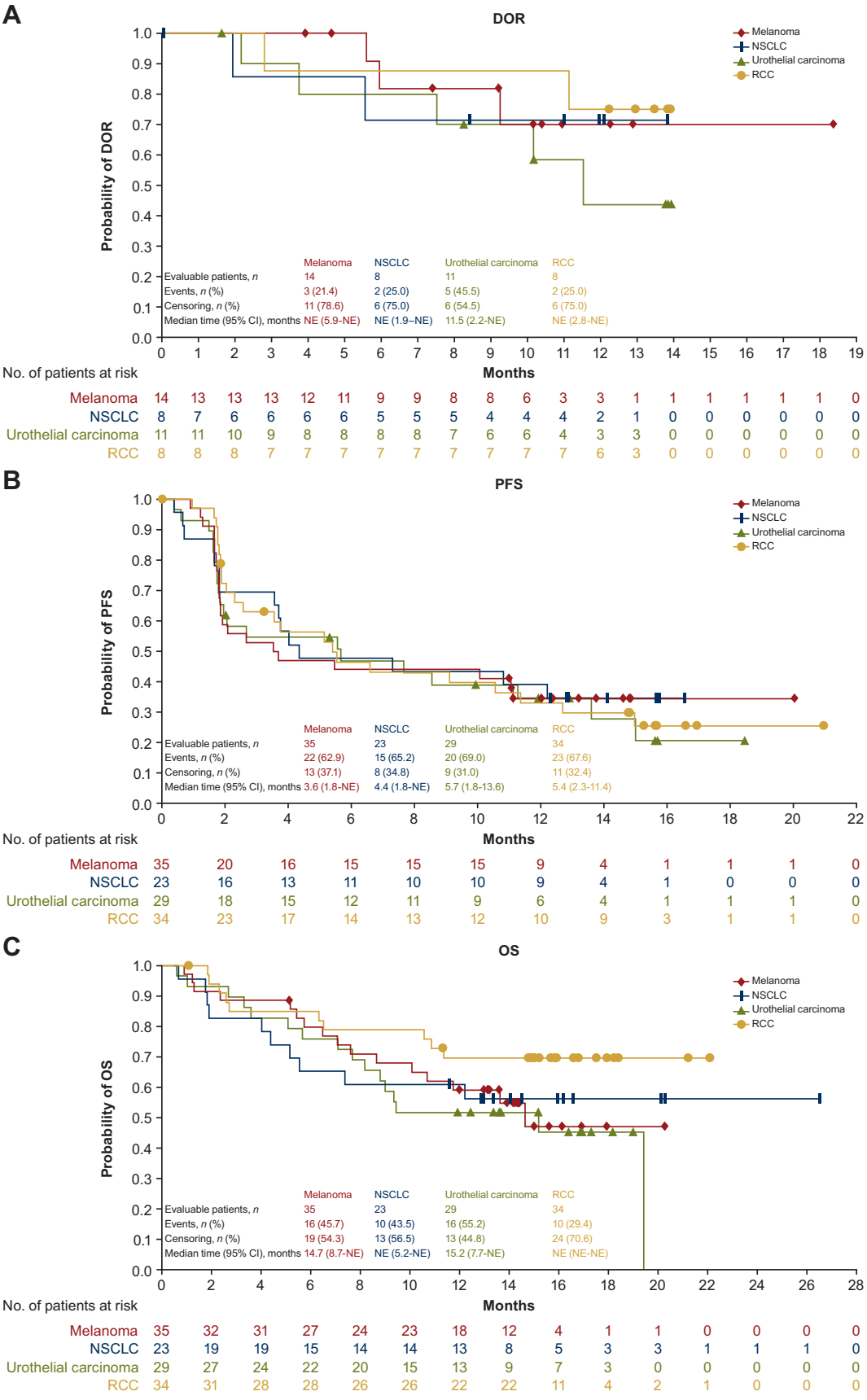

Figure 1. DOR, PFS and OS in patients with solid tumors treated with retifanlimab. Kaplan–Meier estimates of (A) DOR according to RECIST v1.1, (B) PFS according to RECIST v1.1, and (C) OS (full analysis set). Data cut-off date: 15 April 2021.
CI, confidence interval; DOR, duration of response; NE, not estimable; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma.

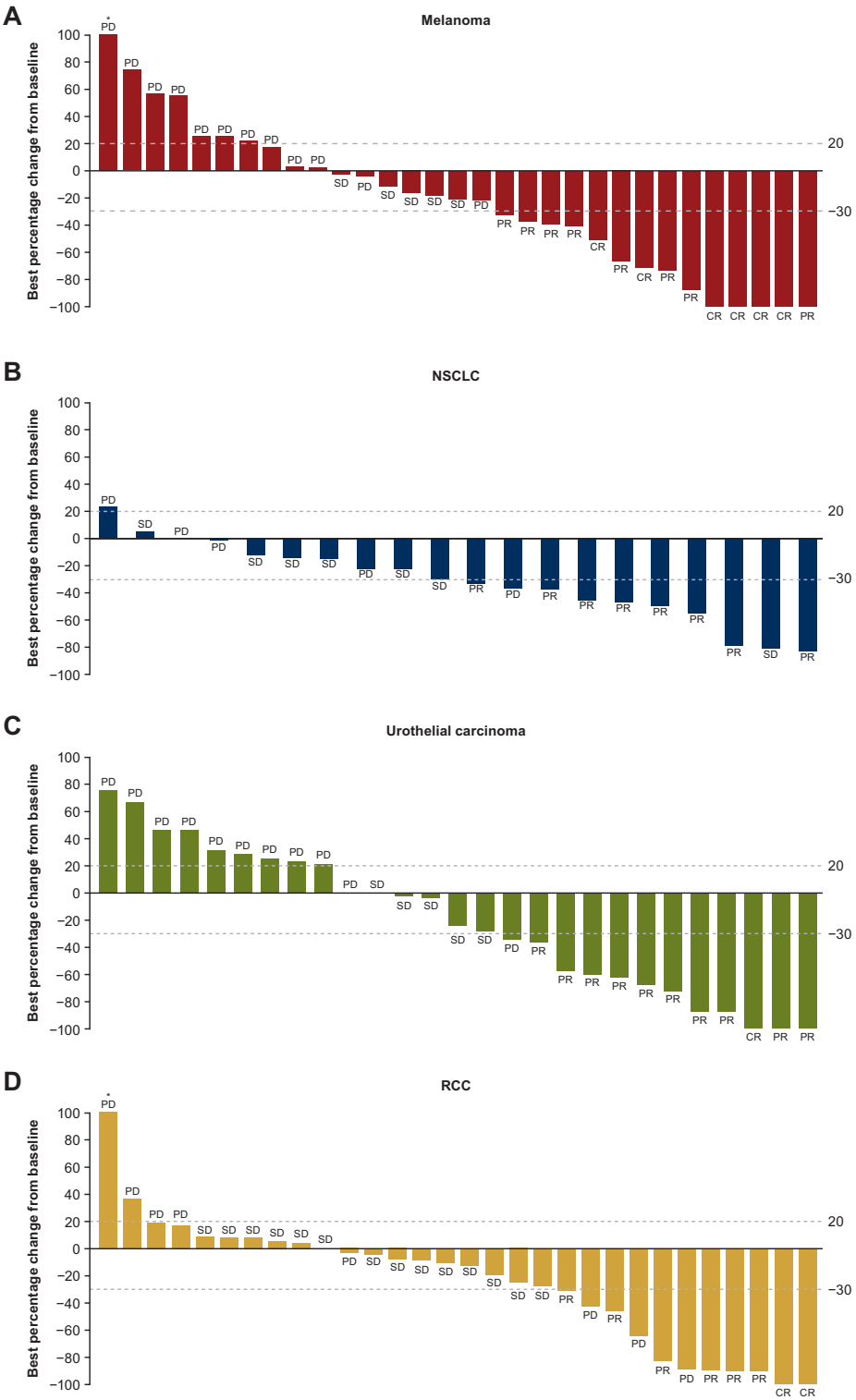

Figure 2. Change in tumor size in patients with solid tumors treatment with retifanlimab. Watefall plots of best percentage change from baseline in target lesion size for individual patients in the (A) melanoma, (B) NSCLC, (C) urothelial carcinoma, and (D) RCC cohorts (full analysis set). Out of 121 patients enrolled in the study, 13 were not assessable because of missing baseline target lesions ($n = 1$), missing post-baseline disease assessment ($n = 11$), or not evaluable disease assessment ($n = 1$). Best overall response is provided for each patient in the figure. The upper-limit dotted line indicates a criterion for PD ($\geq$20% increase in sum of target lesion diameters) and the lower-limit dotted line indicates a criterion for PR ($\geq$30% decrease in sum of target lesion diameters). An asterisk (*) indicates patient with >100% change in target lesion size. The best percentage change in sum of target lesions was before new anticancer therapy. Data cut-off date: 15 April 2021.
CR, complete response; NSCLC, non-small-cell lung cancer; PD, progressive disease; PR, partial response; RCC, renal cell carcinoma; SD, stable disease.

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Table 3. TEAEs reported in ≥5% of patients by MedDRA preferred term (safety assessable population)

Preferred term, *n* (%)	Melanoma (*n* = 35)		NSCLC (*n* = 23)		UC (*n* = 29)		RCC (*n* = 34)		Total (*N* = 121)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Any TEAE	31 (88.6)	13 (37.1)	19 (82.6)	12 (52.2)	28 (96.6)	15 (51.7)	32 (94.1)	13 (38.2)	110 (90.9)	53 (43.8)
Asthenia	7 (20.0)	0	3 (13.0)	1 (4.3)	8 (27.6)	0	6 (17.6)	1 (2.9)	24 (19.8)	2 (1.7)
Arthralgia	8 (22.9)	0	0	0	8 (27.6)	0	6 (17.6)	2 (5.9)	22 (18.2)	2 (1.7)
Pruritus	8 (22.9)	0	3 (13.0)	0	4 (13.8)	0	5 (14.7)	0	20 (16.5)	0
Decreased appetite	4 (11.4)	0	5 (21.7)	1 (4.3)	7 (24.1)	0	3 (8.8)	0	19 (15.7)	1 (0.8)
Diarrhea	6 (17.1)	0	3 (13.0)	1 (4.3)	4 (13.8)	0	3 (8.8)	0	16 (13.2)	1 (0.8)
Anemia	1 (2.9)	1 (2.9)	0	0	9 (31.0)	2 (6.9)	5 (14.7)	3 (8.8)	15 (12.4)	6 (5.0)
Urinary tract infection	3 (8.6)	0	3 (13.0)	0	4 (13.8)	0	5 (14.7)	0	15 (12.4)	0
Pyrexia	3 (8.6)	0	3 (13.0)	0	4 (13.8)	0	4 (11.8)	0	14 (11.6)	0
Rash	4 (11.4)	0	2 (8.7)	0	3 (10.3)	0	5 (14.7)	0	14 (11.6)	0
Constipation	1 (2.9)	0	2 (8.7)	0	6 (20.7)	0	4 (11.8)	0	13 (10.7)	0
Pneumonia	1 (2.9)	0	5 (21.7)	3 (13.0)	0	0	7 (20.6)	2 (5.9)	13 (10.7)	5 (4.1)
Dyspnea	2 (5.7)	0	3 (13.0)	1 (4.3)	1 (3.4)	0	6 (17.6)	0	12 (9.9)	1 (0.8)
Fatigue	5 (14.3)	0	2 (8.7)	0	2 (6.9)	0	2 (5.9)	0	11 (9.1)	0
Hypothyroidism	5 (14.3)	0	1 (4.3)	0	2 (6.9)	0	3 (8.8)	0	11 (9.1)	0
Nausea	4 (11.4)	0	0	0	4 (13.8)	0	3 (8.8)	0	11 (9.1)	0
Blood creatinine increased	1 (2.9)	0	1 (4.3)	0	5 (17.2)	1 (3.4)	2 (5.9)	0	9 (7.4)	1 (0.8)
Cough	4 (11.4)	0	0	0	1 (3.4)	0	4 (11.8)	0	9 (7.4)	0
Headache	7 (20.0)	1 (2.9)	1 (4.3)	0	1 (3.4)	0	0	0	9 (7.4)	1 (0.8)
Peripheral edema	1 (2.9)	0	1 (4.3)	0	4 (13.8)	0	3 (8.8)	1 (2.9)	9 (7.4)	1 (0.8)
Back pain	2 (5.7)	0	1 (4.3)	1 (4.3)	3 (10.3)	0	2 (5.9)	0	8 (6.6)	1 (0.8)
Pain in extremity	2 (5.7)	0	1 (4.3)	0	3 (10.3)	0	2 (5.9)	0	8 (6.6)	0
Dry skin	2 (5.7)	0	1 (4.3)	1 (4.3)	1 (3.4)	0	3 (8.8)	0	7 (5.8)	1 (0.8)
Paresthesia	3 (8.6)	0	0	0	1 (3.4)	0	3 (8.8)	0	7 (5.8)	0
ALT increased	1 (2.9)	1 (2.9)	2 (8.7)	2 (8.7)	1 (3.4)	0	2 (5.9)	1 (2.9)	6 (5.0)	4 (3.3)
Hypertension	0	0	1 (4.3)	0	3 (10.3)	2 (6.9)	2 (5.9)	2 (5.9)	6 (5.0)	4 (3.3)
Myalgia	2 (5.7)	0	1 (4.3)	0	2 (6.9)	0	1 (2.9)	0	6 (5.0)	0

Data cut-off date: 15 April 2021.

ALT, alanine aminotransferase; MedDRA, Medical Dictionary for Regulatory Activities; NSCLC, non-small-cell lung cancer; RCC, renal cell carcinoma; TEAE, treatment-emergent adverse event; UC, urothelial carcinoma.

of advanced cancer that can be used to guide further development decisions.[34] The sample size of ∼30 per cohort is sufficient to conclude that retifanlimab has meaningful clinical activity in melanoma, NSCLC, urothelial carcinoma, and RCC, and to provide a reasonable assessment of safety at the dose and schedule used in this trial. Over 40% of patients in the urothelial carcinoma cohort had adenocarcinoma histology; however, there are no data on how many tumors were of mixed histology, which prevents generalization of results in this rare cancer type.

In summary, this phase II study has demonstrated that retifanlimab has antitumor activity in a variety of solid tumors and was generally well tolerated. Both the antitumor activity and safety of retifanlimab were consistent with the known activity and safety profiles of established PD-1 inhibitors in these same diseases. Furthermore, clinical and PK data showed that the more convenient 30-min infusion schedule of retifanlimab is acceptable for administration. These findings support further clinical development of retifanlimab as monotherapy or in combination with other anticancer therapies in patients with solid tumors. Recently, retifanlimab was granted accelerated approval by the Food and Drug Administration for adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma.[35]

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DISCLOSURE

AMDG reports being an advisor/board member for Bristol Myers Squibb, GlaxoSmithKline, Incyte Corporation, Merck Sharp & Dohme, Novartis, Pierre Fabre, and Sanofi; and honoraria for Bristol Myers Squibb, GlaxoSmithKline, Merck Sharp & Dohme, Pierre Fabre, Roche, Sanofi, and Vyvamed. MS reports research funding from AbbVie, Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Clovis Oncology, Daiichi Sankyo, Eli Lilly & Company, Gilead Sciences, GlaxoSmithKline, Incyte Corporation, Merck Serono, Merck Sharp & Dohme, Mylan, Pfizer, PharmaMar, Regeneron, Roche, and Tesaro. JM reports a consulting/advisory role with AstraZeneca, Boehringer Ingelheim, and Daiichi Sankyo; and travel expenses from Merck Sharp & Dohme, Pfizer, and Roche. MM reports being an advisor/board member for Amgen, AstraZeneca, Bristol Myers Squibb, Janssen, Merck

Sharp & Dohme, Roche, and Sanofi; honoraria from Bristol Myers Squibb, Eli Lilly & Company, Merck Sharp & Dohme, and Pierre Fabre; and travel accommodations from Eli Lilly & Company and Merck Sharp & Dohme. GG reports a consulting/advisory role for AstraZeneca, Bayer, Bristol Myers Squibb, Ipsen, Janssen, MSD Oncology, Pfizer, and Sanofi/Aventis; part of a speakers' bureau with Amgen, Astellas Pharma, Bristol Myers Squibb, Ipsen, Janssen Oncology, MSD Oncology, and Sanofi/Aventis; and travel accommodations from Astellas Pharma, AstraZeneca, Bristol Myers Squibb, Ipsen, Janssen Oncology, Pfizer, and Sanofi. MC and SL are employees of and have stock ownership in Incyte Corporation. SR is a former employee and has stock ownership in Incyte Corporation. TC reports a consulting/advisory role for Novartis; part of a speakers' bureau with Ipsen and Janssen-Cilag; and travel accommodations from Pfizer and Sanofi. SM has declared no conflicts of interest.

DATA SHARING

Data are available upon reasonable request. Incyte Corporation (Wilmington, DE) is committed to data sharing that advances science and medicine while protecting patient privacy. Qualified external scientific researchers may request anonymized datasets owned by Incyte Corporation for the purpose of conducting legitimate scientific research. Researchers may request anonymized datasets from any interventional study (except phase I studies) for which the product and indication have been approved on or after 1 January 2020 in at least one major market (e.g. US, EU, JPN). Data will be available for request after the primary publication or 2 years after the study has ended. Information on Incyte Corporation's clinical trial data-sharing policy and instructions for submitting clinical trial data requests are available at: https://www.incyte.com/Portals/0/Assets/Compliance%20and%20Transparency/clinical-trial-data-sharing.pdf?ver=2020-05-21-132838-960.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by institutional review boards or independent ethics committees in Austria (Ethikkommission der Medizinischen Universität Graz; Ethikkommission des Landes Oberosterreich, Linz; Ethikkommission des Landes Niederösterreich Abt. Sanitätsrecht u. Krankenanstalten, St.Pölten); France (CPP Ouest IV, Nantes); Hungary (Borsod-Abaúj-Zemplén Megyei Kórház és Egyetemi Oktató Kórház Regionális, Intézményi Tudományos Kutatásetikai Bizottsága, Miskolc; Heténi Géza Kórház Etikai Bizottság, Szolnok); Italy (Comitato Etico Regionale Marche, Torrette di Ancona; Comitato Etico Area Vasta Sud Est (CEAVSE), Siena; Comitato Etico Val Padana, Cremona; Comitato Etico Della Romagna—Cerom, Meldola; Comitato Etico Centrale IRCCS Sezione IFO—Bietti, Roma); Poland (Komisja Bioetyczna przy Uniwersytecie Medycznym w Lublinie, Lublin; Komisja Bioetyczna przy Narodowym Instytucie Onkologii im. Marii Skłodowskiej—Curie, Państwowy Instytut Badawczy, Warszawa); Romania (National Bioethics Commission for Medicines and Medical Devices, Bucharest); Spain (Secretaría Técnica CEIm Fundación para la Investigación Biomédica, Hospital Gregorio Marañón, Madrid); United States (Christiana Care Institutional Review Board, Newark, DE; Copernicus Group IRB, Cary, NC; US Oncology, Inc. IRB, The Woodlands, TX). All patients provided written informed consent before enrolling in the study.

REFERENCES

1. Robert C. A decade of immune-checkpoint inhibitors in cancer therapy. *Nat Commun*. 2020;11:3801.
2. Sharma P, Siddiqui BA, Anandhan S, et al. The next decade of immune checkpoint therapy. *Cancer Discov*. 2021;11:838-857.
3. Carlino MS, Larkin J, Long GV. Immune checkpoint inhibitors in melanoma. *Lancet*. 2021;398:1002-1014.
4. Reck M, Remon J, Hellmann MD. First-line immunotherapy for non—small-cell lung cancer. *J Clin Oncol*. 2022;40:586-597.
5. Houssiau H, Seront E. The evolution of immune checkpoint inhibitors in advanced urothelial carcinoma. *Cancers*. 2022;14:1640.
6. Lavacchi D, Pellegrini E, Palmieri VE, et al. Immune checkpoint inhibitors in the treatment of renal cancer: current state and future perspective. *Int J Mol Sci*. 2020;21:4691.
7. La Motte-Mohs R, Shah K, Brown JG, et al. Preclinical characterization of MGA012, a novel clinical-stage PD-1 monoclonal antibody. *J ImmunoTher Cancer*. 2017;5:Abstract P336.
8. Condamine T, Owens S, Feldman P, et al. Pharmacodynamic correlates in a phase I study of INCMGA00012, a PD-1 antagonistic monoclonal antibody. *Cancer Res*. 2019;79(suppl 13):Abstract CT085.
9. Chen X, Wang P, Kaul S, et al. Assessment of flat dosing strategy for INCMGA00012 in patients with advanced tumors. *Cancer Res*. 2019;79(suppl 13):Abstract LB-268.
10. Mehnert JM, Joshua A, Lakhani N, et al. First-in-human phase 1 study of INCMGA00012 in patients with advanced solid tumors: interim results of the cohort expansion phase. *J ImmunoTher Cancer*. 2018;6:Abstract P669.
11. Mehnert JM, Paz-Ares L, Pikiel J, et al. A phase 1 study of INCMGA00012, a PD-1 inhibitor, in patients with advanced solid tumors: preliminary results for patients with advanced cervical cancer (POD1UM-101). *J ImmunoTher Cancer*. 2019;7(suppl 1):282:Abstract P394.
12. Rao S, Anandappa G, Capdevila J, et al. A phase II study of retifanlimab (INCMGA00012) in patients with squamous carcinoma of the anal canal who have progressed following platinum-based chemotherapy (POD1UM-202). *ESMO Open*. 2022;7:100529.
13. Motzer RJ, Bacik J, Murphy BA, et al. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. *J Clin Oncol*. 2002;20:289-296.
14. Ribas A, Puzanov I, Dummer R, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. *Lancet Oncol*. 2015;16:908-918.
15. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without *BRAF* mutation. *N Engl J Med*. 2015;372:320-330.
16. Weber J, Gibney G, Kudchadkar R, et al. Phase I/II study of metastatic melanoma patients treated with nivolumab who had progressed after ipilimumab. *Cancer Immunol Res*. 2016;4:345-353.
17. Herbst RS, Giaccone G, de Marinis F, et al. Atezolizumab for first-line treatment of PD-L1—selected patients with NSCLC. *N Engl J Med*. 2020;383:1328-1339.
18. Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet*. 2019;393:1819-1830.
19. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Updated analysis of KEYNOTE-024: pembrolizumab versus platinum-based chemotherapy for advanced non—small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater. *J Clin Oncol*. 2019;37:537-546.
20. Sezer A, Kilickap S, Gümüş M, et al. Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at

least 50%: a multicentre, open-label, global, phase 3, randomised, controlled trial. *Lancet*. 2021;397:592-604.
21. Balar AV, Castellano D, O'Donnell PH, et al. First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. *Lancet Oncol*. 2017;18:1483-1492.
22. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med*. 2017;376:1015-1026.
23. Sharma P, Callahan MK, Bono P, et al. Nivolumab monotherapy in recurrent metastatic urothelial carcinoma (CheckMate 032): a multicentre, open-label, two-stage, multi-arm, phase 1/2 trial. *Lancet Oncol*. 2016;17:1590-1598.
24. McDermott DF, Lee JL, Bjarnason GA, et al. Open-label, single-arm phase II study of pembrolizumab monotherapy as first-line therapy in patients with advanced clear cell renal cell carcinoma. *J Clin Oncol*. 2021;39:1020-1028.
25. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med*. 2015;373:1803-1813.
26. Motzer RJ, Rini BI, McDermott DF, et al. Nivolumab for metastatic renal cell carcinoma: results of a randomized phase II trial. *J Clin Oncol*. 2015;33:1430-1437.
27. Ascierto PA, Long GV, Robert C, et al. Survival outcomes in patients with previously untreated *BRAF* wild-type advanced melanoma treated with nivolumab therapy: three-year follow-up of a randomized phase 3 trial. *JAMA Oncol*. 2019;5:187-194.
28. Hamid O, Puzanov I, Dummer R, et al. Final analysis of a randomised trial comparing pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory advanced melanoma. *Eur J Cancer*. 2017;86:37-45.
29. Vuky J, Balar AV, Castellano D, et al. Long-term outcomes in KEYNOTE-052: phase II study investigating first-line pembrolizumab in cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer. *J Clin Oncol*. 2020;38:2658-2666.
30. Pillai RN, Behera M, Owonikoko TK, et al. Comparison of the toxicity profile of PD-1 versus PD-L1 inhibitors in non—small cell lung cancer: a systematic analysis of the literature. *Cancer*. 2018;124:271-277.
31. Carbone DP, Reck M, Paz-Ares L, et al. First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. *N Engl J Med*. 2017;376:2415-2426.
32. Baraibar I, Melero I, Ponz-Sarvise M, Castanon E. Safety and tolerability of immune checkpoint inhibitors (PD-1 and PD-L1) in cancer. *Drug Saf*. 2019;42:281-294.
33. Wang PF, Chen Y, Song SY, et al. Immune-related adverse events associated with anti-PD-1/PD-L1 treatment for malignancies: a meta-analysis. *Front Pharmacol*. 2017;8:730.
34. Food and Drug Administration. Guidance for industry: clinical trial endpoints for the approval of cancer drugs and biologics. 2016. Available at https://www.fda.gov/media/71195/download. Accessed September 5, 2022.
35. US FDA. ZYNYZ™ (retifanlimab-dlwr) injection, for intravenous use. U. S. Wilmington, DE: Incyte Corporation. 2023. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761334Orig1s000correctedlbl.pdf. Accessed May 12, 2023.