Immunotherapy Highlights

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This article will summarize the key data in the field of immunotherapy presented during the 2018 annual meeting of the American Society of Clinical Oncology (ASCO).

ANTI-PD-1 AS MONOTHERAPY OR COMBINED WITH STANDARD CHEMOTHERAPY AS FIRST-LINE TREATMENT OPTIONS IN PATIENTS WITH METASTATIC NON-SMALL-CELL LUNG CANCER (NSCLC)

The KEYNOTE-042 randomized phase III trial (comparing pembrolizumab [PEMBRO] with chemotherapy as first-line treatment of advanced NSCLC with PD-L1 expression of ≥1% and without sensitizing EGFR- or ALK-mutations) showed that PEMBRO is a more effective initial treatment than platinum-based chemotherapy for these patients, with an increase in median overall survival (OS) of 4 to 8 months (depending on PD-L1 tumor proportion score [TPS]) in the PEMBRO arm compared to chemotherapy.[1] Severe side effects occurred in fewer patients receiving PEMBRO than chemotherapy (18% *vs.* 41%). Based on findings from the previous KEYNOTE-024 trial, the U.S. Food and Drug Administration (FDA) approved PEMBRO for initial treatment of NSCLC with high PD-L1 expression (≥50%), which accounts for about one-third of these cancers.[2] These data thereby augment the potential role of PEMBRO monotherapy as standard first-line therapy for advanced NSCLC with a PD-L1 TPS of ≥1%.

Combining PEMBRO with platinum-based chemotherapy in the first-line setting significantly prolonged median OS in patients with metastatic squamous NSCLC (N=559 patients), according to data from the phase III KEYNOTE-407 trial.[3] The median OS of 11.3 months with chemotherapy increased to 15.9 months when PEMBRO was added (HR[95%CI]: 0.64[0.49-0.85]; p=0.0008); also the median progression-free survival (PFS) improved significantly with the combination (6.4 *vs.* 4.8 months; HR[95%CI]: 0.56[0.45-0.70]; p<0.0001). The OS and PFS benefit was relevant for all investigated patient subgroups, including PD-L1 TPS. The objective response rate (ORR) was also significantly increased (58.4% *vs.* 35.0%; p=0.0004) and the responses on PEMBRO also proved to be more durable (median, 7.7 *vs.* 4.8 months). The frequency of adverse events (AE) was mostly similar for overall events (98.2% *vs.* 97.9%) and grade 3-5 events (69.8% *vs.* 68.2%). KEYNOTE-407 complements the positive KEYNOTE-189 clinical trial, which demonstrated significantly improved median OS regardless of PD-L1 TPS in patients with metastatic non-squamous NSCLC.[4]

FOUR- AND FIVE-YEAR OUTCOME AFTER INITIATION OF PEMBRO TREATMENT FOR METASTATIC MELANOMA PATIENTS

Updated results from the phase III KEYNOTE-006 study, which included 834 patients and compared PEMBRO with ipilimumab (IPI) in patients with unresectable advanced melanoma were presented.[5] The majority of patients (75%) was treated in the first-line setting. After a median follow-up of 45.9 months (range 0.3-50), the median OS was 32.7 months with PEMBRO, and 15.9 months with IPI (HR[95%-CI]: 0.73[0.61–0.89]). The median PFS was also better with PEMBRO (8.3 *vs.* 3.3 months, HR[95%CI]: 0.56[0.47-0.67]). This PFS benefit was similar in treatment-naive patients with

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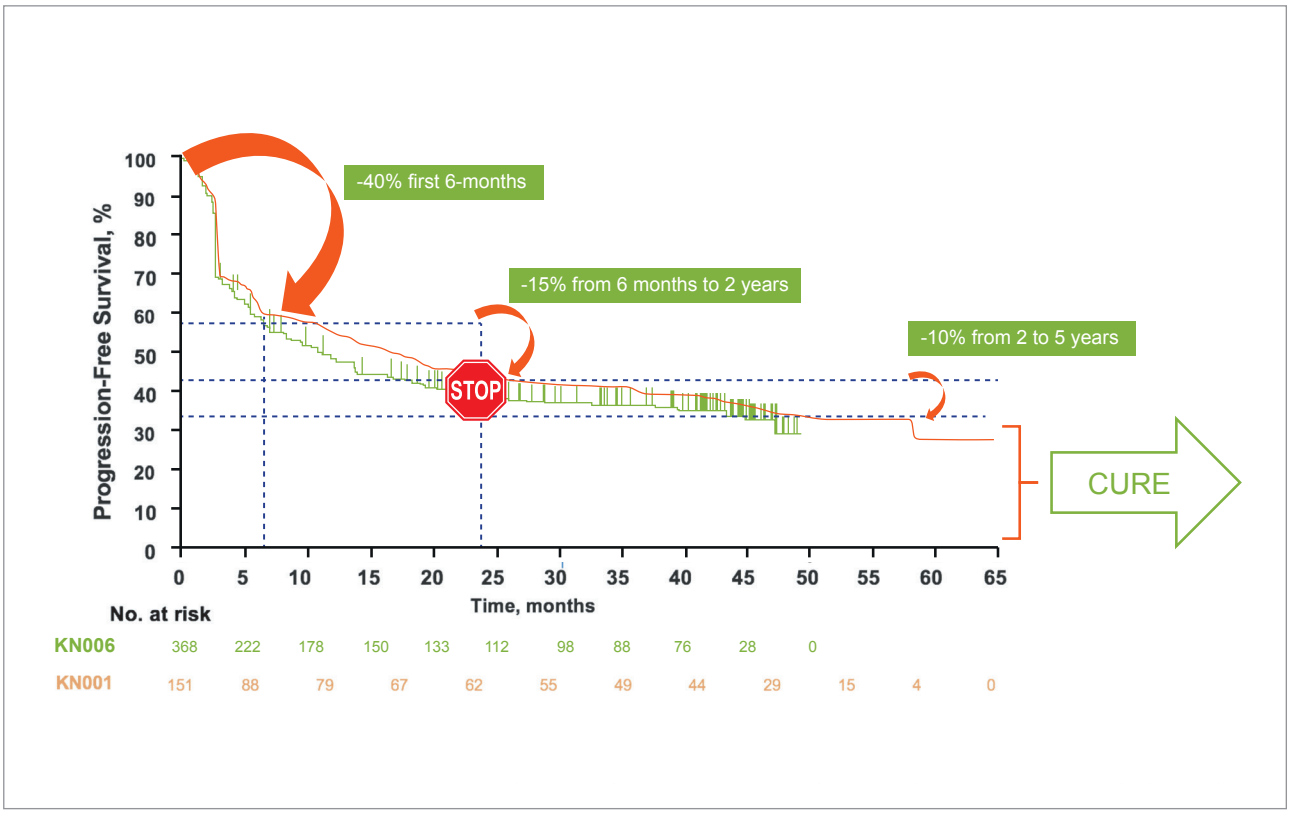

FIGURE 1. Updated analysis of progression-free survival of treatment-nave advanced melanoma patients in the KEYNOTE-001 and KEYNOTE-006 trials.[5]

a HR of 0.54 (95%CI: 0.43–0.67) (*Figure 1*). The ORR was 42% with PEMBRO (76 complete responses [CR]) and 17% with IPI (9 CR). According to the protocol, 103 patients who were free from progression stopped PEMBRO after 2 years. Eighty-six patients (86%) remained progression-free, while 14 patients were progressive after a median follow-up of 20.3 months (range: 0.03-24.8). The risk for progression seems associated with the RECIST response at the time of stopping PEMBRO (prior response 2 CR, 9 PR, 3 SD) (*Figure 2*).[5]

FDG-PET at 1 year of PEMBRO may have predictive value for estimating the risk for progression after stopping anti-PD1 therapy.[6] Responses were observed among a small number of patients (N=9) who were retreated with PEMBRO at progression. Real-world studies on the outcome of patients stopping anti-PD1 therapy in the absence of progression are in line with the data of the KEYNOTE-006 trial.[7-9]

Outcome with even longer follow-up for melanoma patients treated with PEMBRO was provided in the updated analysis of the phase I KEYNOTE-001 trial.[10] The five-year PFS- and OS-rates were 21% and 34% in all patients and 29% and 41% in treatment-naive patients, respectively. Responses were ongoing in 73% of the total population and 82% of treatment-naïve patients. An 18-gene gene expression panel score was associated with response to PEMBRO.[10]

PD1-BLOCKADE WITH NIVOLUMAB FOR THE ADJUVANT THERAPY OF PATIENTS WITH STAGE III MELANOMA

An update was presented with 2-year results from the CheckMate-238 trial, confirming the superiority of adjuvant nivolumab (NIVO) over IPI following resection of stage IIIB/C or IV melanoma. NIVO yields a higher recurrence-free survival (RFS) rate at 24 months compared with IPI (63% *vs.* 50%; p < 0.0001), regardless of disease stage, PD-L1 TPS, or *BRAF*-mutation status.[11] The median RFS reached 30.8 months with NIVO as compared to 24.1 months with IPI (HR[95%CI]: 0.66[0.54-0.81]; p<0.0001). Across all pre-specified subgroups, NIVO consistently outperformed IPI at prolonging RFS. Distant metastases represented the most common type of recurrence in both groups. Distant metastasis-free survival (DMFS) was higher with NIVO: the 2-year-DMFS rate was 71% with NIVO *vs.* 64% with IPI (HR[95%CI]: 0.76[0.59-0.98]; p=0.0340) in patients with stage III disease. At the time of the analysis, only five deaths have been recorded in the IPI arm *vs.* none in the NIVO arm. In a prior analysis conducted after a minimum follow-up of 18 months, NIVO demonstrated better tolerability compared with IPI based on the rates of treatment discontinuation (9.7% *vs.* 42.6%) and grade 3/4 immune-related AEs (14.4% *vs.* 45.9%).[11]

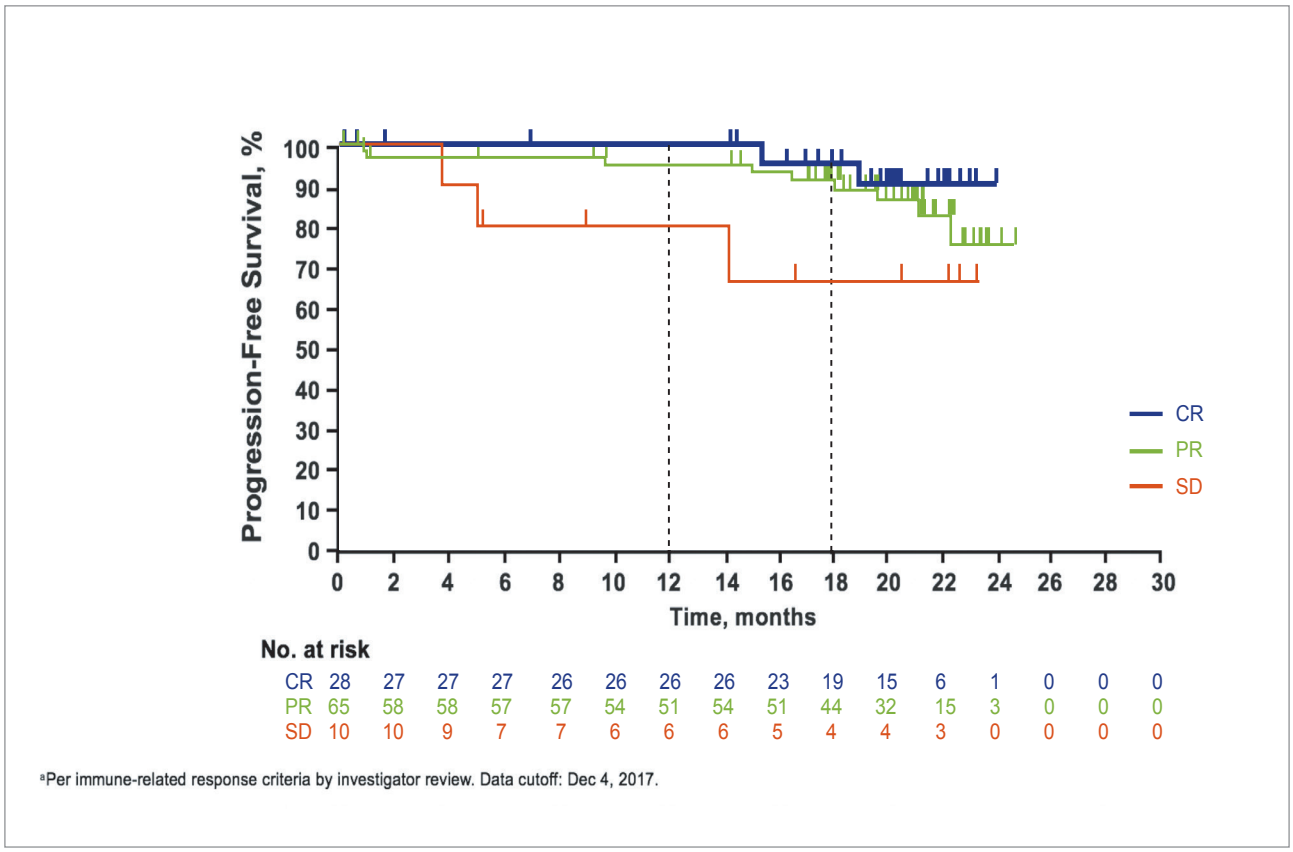

FIGURE 2. Progression-free survival in metastatic melanoma patients who completed protocol-specified time on pembrolizumab (N=103).[5]

PD-1 BLOCKADE IS THE NEW STANDARD TREATMENT FOR PATIENTS WITH ADVANCED MERKEL CELL CARCINOMA (MCC)

The PD-1/PD-L1 pathway is commonly upregulated in MCC, a rare aggressive skin cancer often associated with the Merkel cell polyomavirus (MCPyV). Results were presented that are representative for the activity of different anti-PD-(L)1 monoclonal antibody therapies in the second line-, first-line and neo-adjuvant treatment setting for MCC.

In the single-arm phase II JAVELIN Merkel 200 study, patients with metastatic MCC (mMCC) whose disease had progressed on or after chemotherapy received avelumab.[11] Eighty-eight patients were followed for a median of 29.2 months (range 24.8-38.1 months). At the 2-year follow-up update, avelumab continues to demonstrate clinically meaningful activity across all patient subgroups, irrespective of PD-L1 TPS or MCPyV status. The confirmed ORR of 33% (95%CI: 23.3%-43.8%; CR in 11.4%) remained unchanged. Responses remained ongoing in 19 of 29 patients who responded to treatment, including 12 patients whose duration of response exceeded 2 years. PFS rates were 29% at 12 months, 29% at 18 months, and 26% at 24 months. Median OS was 12.6 months (95%CI: 7.5-17.1) and the 2-year OS rate was 36% (50% at 12 months and 39% at 18 months). The safety profile for avelumab in this trial has not changed with longer follow-up: 67 patients (76.1%) had a treatment-related adverse event (TRAE), 10 patients (11.4%) had a grade 3 or more TRAE, and 20 patients (22.7%) had an immune-related AE. No treatment-related deaths occurred.[11]

An update was also presented for the NCT02267603 single-arm phase II trial investigating PEMBRO as a first-line treatment in patients with unresectable MCC.[12] Among the 42 patients with ≥21 week follow-up, the confirmed ORR was 50% (95%CI: 34.2-65.8; CR 19%, PR 31%). PEMBRO was well tolerated and achieved an ORR of 52% in virus-positive and 44% in virus-negative tumors. The median duration was not reached. Median PFS and OS were 16.8 months and not reached respectively, higher as compared to historical chemotherapy results (3.1-4.6 months and 9-10.2 months respectively) (*Figure 3*).[12]

The multicenter phase I/II CheckMate-358 trial (NCT02488759) was designed to determine the safety and tolerability of neoadjuvant NIVO in patients with advanced, virus-associated cancers. Data from NIVO as neoadjuvant therapy in patients with resectable MCC were presented.[13]

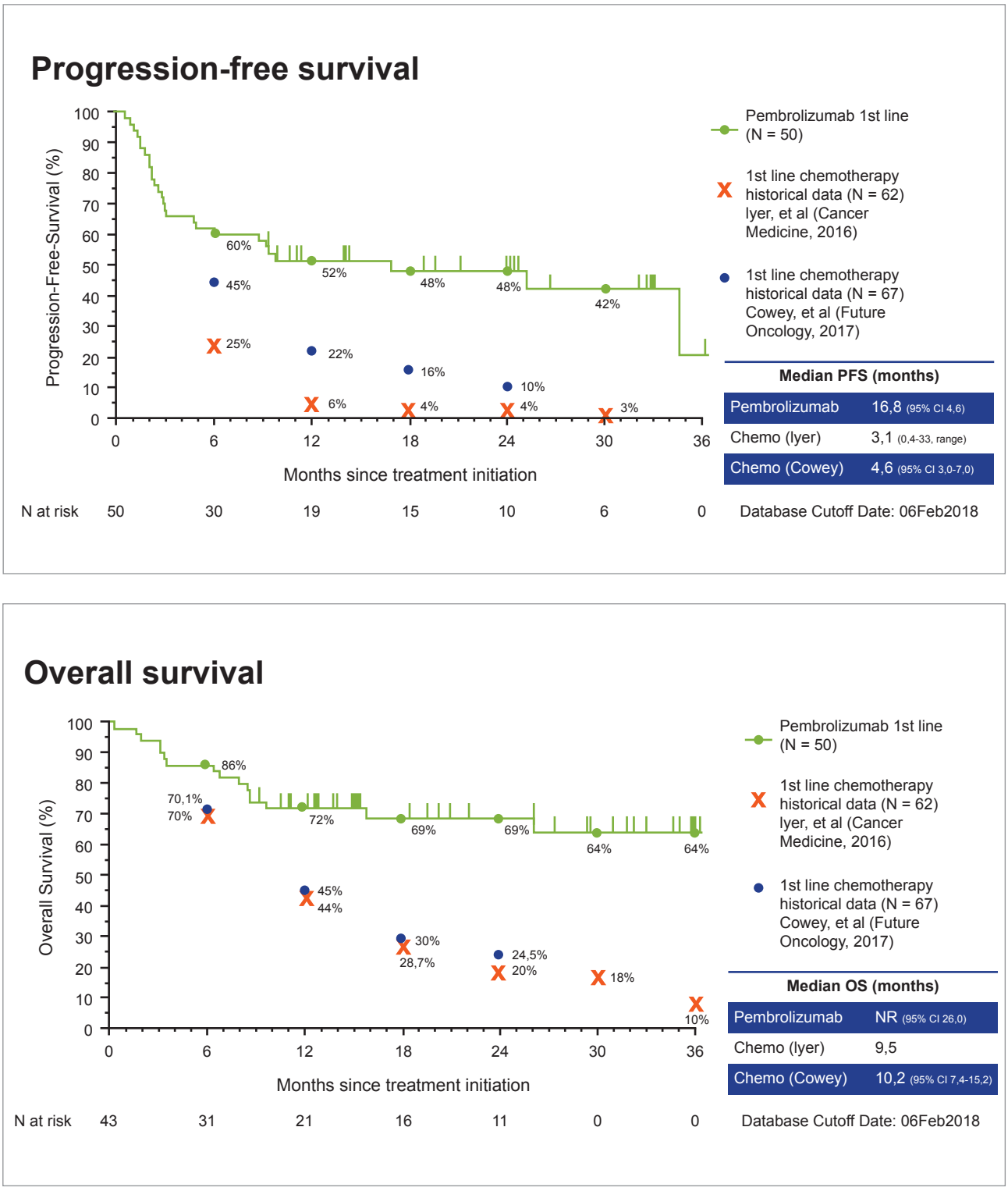

FIGURE 3. Progression-free and overall survival with pembrolizumab as first-line therapy for advanced Merkel cell carcinoma.[12]

Twenty-nine patients were enrolled. Fifteen of 21 evaluable patients (71%) were MCPyV positive and 6 of 20 evaluable patients (30%) were PD-L1 positive (≥1% cutoff). Patients received 240 mg of NIVO intravenously on days 1 and 15, with surgery planned for day 29. Twenty-six of 29 patients (90%) received both doses of NIVO. Three patients (10%) only received a single dose because of AE; two of these three patients did not have surgery and withdrew from the trial. Median follow-up after the initial dose of NIVO was 67.1 weeks (range 2.3-106.3). No new safety signals were identified. Twelve patients (41%) had a TRAE, two patients (7%) had a grade 3/4 TRAE. Among 25 evaluable patients, the median change in

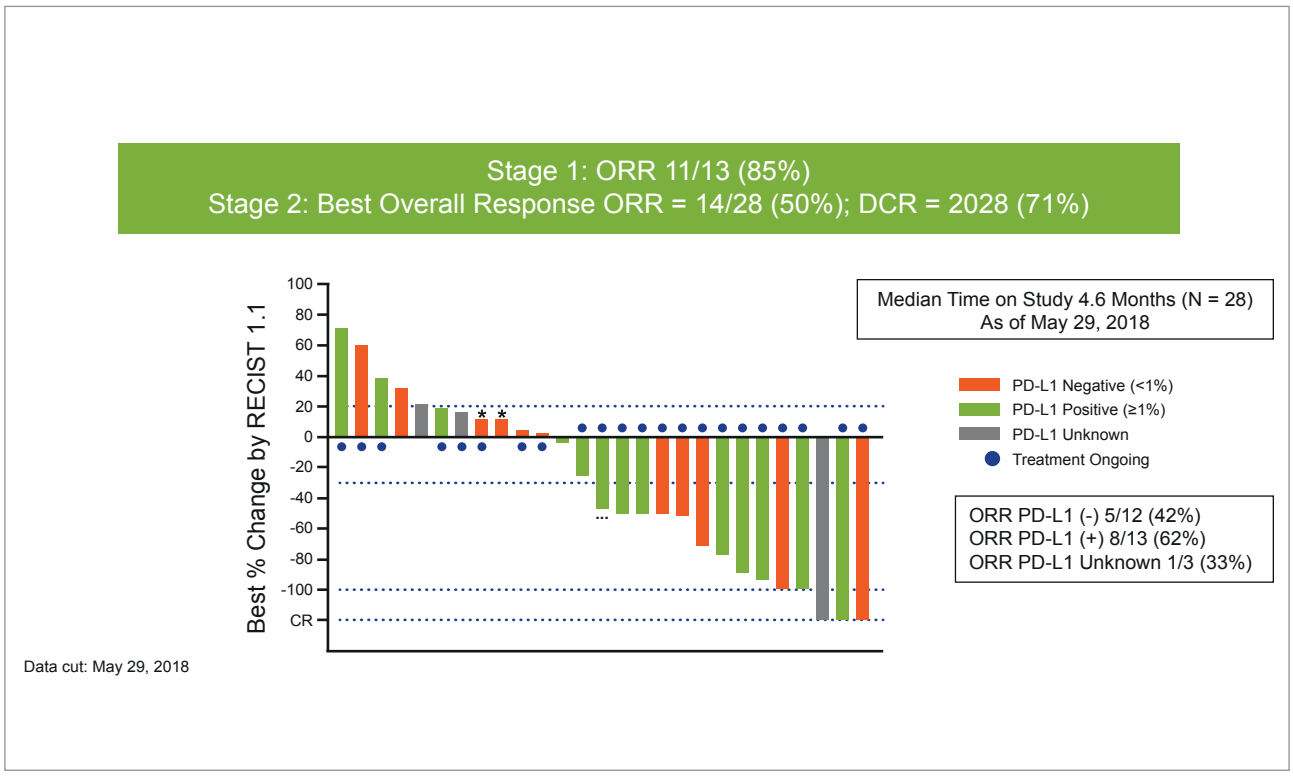

FIGURE 4. Waterfall plot depicting the best response to the combination of nivolumab and the CD122-agonist NKTR-214 in treatment-naive metastatic melanoma in the phase I/2 PIVOT study.[16]

radiographic tumor reduction was -19.2% (range, -100 to 73). Responses were observed regardless of MCPyV or PD-L1 positivity. Eight of 17 patients (47%) had a pathologic CR and 3 patients (18%) had a major pathologic response. The PFS rate 12 months after surgery was 72.6% (95% CI 48.6-86.8) and OS was 75.0% (95% CI 31.5-93.1). Of the 15 patients with pathologic CR or major pathologic response by site and/or central review, none have relapsed after surgery (median follow-up of 12 months [range 0.5-12 months]).[13]

SOBERING RESULTS FROM RANDOMIZED CLINICAL TRIALS AIMING TO IMPROVE THE RESULTS OBTAINED WITH ANTI-PD-1 MONOTHERAPY

Results from the ECHO-301/KEYNOTE-252 (NCT02752074) trial, a phase III, randomized, double-blind study evaluating the efficacy and safety of PEMBRO plus the IDO1-inhibitor epacadostat or placebo in 706 patients with untreated advanced melanoma were presented.[14] Baseline characteristics were comparable in both arms. Patients were followed-up for a median of 12.4 months. The median PFS was virtually identical between the two arms (4.7 and 4.9 months; HR 1.00, 95% CI 0.83-1.21; p=0.517; 12-month PFS rate 37% in both arms) and also the OS curves for the study arms were superimposable (12-month OS rate of 74% for both arms). No differences were seen in the subgroup analyses for both PFS and OS. The ORR was 34.2% and 31.5% in the epacadostat plus PEMBRO and PEMBRO alone arms, respectively. TRAE occurred at a similar frequency in the study arms (about 80%) as well as the frequency of serious TRAEs (about 10%). Epacadostat plus PEMBRO combination therapy will continue to be evaluated in phase III studies in NSCLC, renal cancer, head and neck cancer, and bladder cancer.[14]

In patients with recurrent glioblastoma (GBM), adding PEMBRO to the anti-vascular epithelial growth factor (VEGF) monoclonal antibody bevacizumab, led to a 6-month PFS rate of 26%, about the same as the historical rate with bevacizumab alone.[15]

NOVEL TARGETS FOR COMBINATION IMMUNE CHECKPOINT THERAPY

Early data from the ongoing PIVOT phase I/II study, evaluating the combination of NIVO with NKTR-214, were presented.[16] In (pre)clinical studies, NKTR-214, a CD122 receptor agonist, resulted in activation and expansion of effector T- and NK-cells over regulatory T-cells in the tumor microenvironment leading to increased proliferation of tumor-infiltrating lymphocytes (TILs) and PD-L1 expression. Enrollment is ongoing in the phase II of the PIVOT study in over 400 patients with advanced treatment-naive melanoma,

renal cell carcinoma (RCC), urothelial carcinoma, NSCLC and triple negative breast cancer (TNBC). Prespecified efficacy criteria were achieved in three tumor types. For melanoma patients, the prespecified efficacy criteria were met for ORR in stage 1 (ORR 11/13 [85%]). Median time on study for 28 patients in stage 2 (N1+N2) was only 4.6 months. Responses were observed in 14/28 (50%) of patients (*Figure 4*). In RCC patients, the prespecified efficacy criteria were also met for ORR in stage 1 (N1=11) with 7/11 (64%) of patients achieving a PR. Median time on study for 26 patients in stage 2 (N1+N2) is 5.6 months. Responses were observed in 12/26 (46%) patients. In patients with treatment-naive urothelial carcinoma prespecified efficacy criteria were met for ORR in stage 1 (N1=10) with 6/10 (60%) of patients achieving either a response. Median time on study for 10 patients in stage 1 is 3.9 months. As of May 7, 2018, a total of 283 patients have been treated at the recommended phase II dose. The most common TRAE were grade 1-2 flu-like symptoms, rash, fatigue and pruritus. A total of 40/283 (14.1%) of patients experienced a grade 3 or higher TRAE with 6/283 (2.1%) patients discontinuing treatment due to a TRAE. 10/283 (3.5%) of patients experienced a grade 3 or higher immune-mediated AE. There was one NIVO-related grade 5 pneumonitis.[16]

M7824 is a bifunctional fusion protein targeting PD-L1 and transforming growth factor β (TGF-β), which functions as a TGF-β 'trap'. TGF-β is a potential target for human papilloma virus (HPV)-associated cancers (HAC) as genome wide association studies in HPV-positive cancers have shown TGF-β to be significantly overexpressed. NCT02517398 is a phase I, 3+3 dose-escalation study. Safety was manageable, the only DLT was colitis (at 20 mg/kg) and no MTD was reached. An ORR of 37.5% in patients with HAC including a confirmed ORR of 45.5% in patients with known HPV-positive disease was reported.[17]

LAG525 is a monoclonal antibody which blocks binding of LAG-3 to MHC class II. NCT02460224 reported on the phase I/II study of LAG525 with or without spartalizumab (anti-PD-1 monoclonal antibody) in advanced malignancies. Primarily due to progressive disease (79% and 67%, respectively), 115/119 patients (97%) receiving LAG525 monotherapy and 99/121 patients (82%) receiving LAG525 plus spartalizumab went off study treatment. DLTs developed in 4 patients in both arms without any clear dose relationships detected. Common related AEs were fatigue for LAG525 alone and fatigue, diarrhea and nausea (12%) for the combination. Grade 3-4 AEs were reported in 10 patients (8%) in the LAG525 arm and 10 patients (8%) in the combination arm. No MTD was identified for either arm. LAG525 plus spartalizumab led to durable RECIST responses (11 PR, 1 CR) in some solid tumors, including mesothelioma (2/8) and TNBC (2/5). In tumor biopsies of TNBC, a trend in alteration of biomarker profiles from immune-cold to immune-activated was seen.[18]

ENTERING A NEW ERA OF PERSONALIZED NEO-EPITOPE THERAPEUTIC VACCINES?

The vaccine approach known as GAPVAC uses a personalized strategy for patients with newly diagnosed glioblastoma.[19] The first step of the regimen (GAPVAC1) aims to vaccinate against peptides commonly found on glioblastoma cells. GAPVAC1 was administered along with GM-CSF and poly-ICLC (both immunostimulatory compounds) at the same time as patients initiate adjuvant chemotherapy. Of the 13 patients who completed the GAPVAC1 regimen, 92% generated immune responses against MHC class I-associated peptides and 69% against class II-associated peptides. While receiving GAPVAC1 a second time, a personalized vaccine (GAPVAC2) was created matched to an individual patient's glioblastoma neo-antigens. Of the 10 patients who completed the GAPVAC2 regimen, 80% had an immune response against the target neo-antigens. The median OS of the 15 patients who received at least the first vaccine dose was 29 months; the median PFS was 14.2 months.[19]

A second presentation on a mutation-specific peptide vaccine targeting IDH1R132H in patients with newly diagnosed malignant astrocytomas (phase I trial) reported that the study met its primary endpoints by demonstrating safety and immunogenicity and that 28/30 patients (93.3%) evaluable for immunogenicity displayed IDH1R132H-specific T-cellular (24/30 patients) or humoral (26/30 patients) immune responses not detectable before vaccination.[20] Until end of study (week 32), 4/32 (12.5 %) patients had PD according to RANO criteria, all other patients (N=28, 87.5%) had stable disease. Twelve (37.5%) patients displayed pseudo-progressions.[20]

REFERENCES

1. Lopes G, Wu Y, Kudaba I, Kowalski D, et al. Pembrolizumab (pembro) versus platinum-based chemotherapy (chemo) as first-line therapy for advanced/metastatic NSCLC with a PD-L1 tumor proportion score (TPS) ≥ 1%: Open-label, phase 3 KEYNOTE-042 study. J Clin Oncol. 2018;36(suppl; abstr LBA4).

2. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016;375(19):1823-33.

3. Paz-Ares L, Luft A, Tafreshi A, Gumus M, et al. Phase 3 study of carboplatin-paclitaxel/nab-paclitaxel (Chemo) with or without pembrolizumab (Pembro) for patients (Pts) with metastatic squamous (Sq) non-small cell lung cancer (NSCLC). J Clin Oncol. 2018;36(suppl; abstr 105).

4. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, et al. Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer. N Engl J Med.

2018;378(22):2078-92.

5. Long G, Schachter J, Ribas A, Arance A, et al. 4-year survival and outcomes after cessation of pembrolizumab (pembro) after 2-years in patients (pts) with ipilimumab (ipi)-naive advanced melanoma in KEYNOTE-006. J Clin Oncol. 2018;36(suppl; abstr 9503).

6. Tan A, Emmett L, Lo S, Liu V, et al. Utility of 1-year FDG-PET (PET) to determine outcomes from anti-PD-1 (PD1) based therapy i n patients (pts) with metastatic melanoma (MM). J Clin Oncol. 2018;36(suppl; abstr 9517).

7. Nguyen K, Mason R, Ladwa R, Warburton L, et al. Relapse after cessation of PD-1 based therapy for complete responders in metastatic melanoma. J Clin Oncol. 2018;36(suppl; abstr 9536).

8. Christiansen S, Swoboda D, Gardner K, Rapisuwon S, et al. Off treatment survival (OTS) in patients (pts) with advanced melanoma after anti-PD1 therapy. J Clin Oncol. 2018;36((suppl; abstr 9554)).

9. Schwartsman G, Ma J, Bassett R, Haydu L, et al. Outcomes of metastatic melanoma (MM) patients (pts) after discontinuation of anti-Programmed-Death 1 (PD1) therapy without disease progression. J Clin Oncol. 2018;36(suppl; abstr 9549).

10. Hamid O, Robert C, Daud A, Hodi F, et al. 5-year survival outcomes in patients (pts) with advanced melanoma treated with pembrolizumab (pembro) in KEYNOTE-001. J Clin Oncol. 2018;36(suppl; abstr 9516).

11. Weber J, Mandala M, Del Vecchio M, Gogas H, et al. Adjuvant therapy with nivolumab (NIVO) versus ipilimumab (IPI) after complete resection of stage III/IV melanoma: Updated results from a phase III trial (CheckMate 238). J Clin Oncol. 2018;36(suppl; abstr 9502).

12. Nghiem P, Bhatia S, Lipson E, Sharfman W, et al. Durable tumor regression and overall survival (OS) in patients with advanced Merkel cell carcinoma (aMCC) receiving pembrolizumab as first-line therapy. J Clin Oncol. 2018;36(suppl; abstr 9506).

13. Topalian S, Bhatia S, Kudchadkar R, Amin A, et al. Nivolumab (Nivo) as neoadjuvant therapy in patients with resectable Merkel cell carcinoma (MCC) in CheckMate 358. J Clin Oncol. 2018;36(suppl; abstr 9505).

14. Long G, Dummer R, Hamid O, Gajewski T, et al. Epacadostat (E) plus pembrolizumab (P) versus pembrolizumab alone in patients (pts) with unresectable or metastatic melanoma: Results of the phase 3 ECHO-301/KEYNOTE-252 study. J Clin Oncol. 2018;36(suppl; abstr 108).

15. Reardon D, Nayak L, Peters K, Leigh Clarke J, et al. Phase II study of pembrolizumab or pembrolizumab plus bevacizumab for recurrent glioblastoma (rGBM) patients. J Clin Oncol. 2018;36(suppl; abstr 2006).

16. Diab A, Hurwitz M, Cho D, Papadimitrakopoulou V, et al. NKTR-214 (CD122-biased agonist) plus nivolumab in patients with advanced solid tumors: Preliminary phase 1/2 results of PIVOT. J Clin Oncol. 2018;36(suppl; abstr 3006).

17. Strauss J, Gatti-Mays M, Redman J, Madan R, et al. Safety and activity of M7824, a bifunctional fusion protein targeting PD-L1 and TGF-β, in patients with HPV associated cancers. J Clin Oncol. 2018;36(suppl; abstr 3007).

18. Hong D, Schoffski P, Calvo A, Sarantopoulos J, et al. Phase I/II study of LAG525 ± spartalizumab (PDR001) in patients (pts) with advanced malignancies. J Clin Oncol. 2018;36(suppl; abstr 3012).

19. Wick W, Dietrich P-Y, Kuttruff S, Hilf N, et al. GAPVAC-101: First-in-human trial of a highly personalized peptide vaccination approach for patients with newly diagnosed glioblastoma. J Clin Oncol. 2018;36(suppl; abstr 2000).

20. Platten M, Schilling D, Bunse L, Wick A, et al. A mutation-specific peptide vaccine targeting IDH1R132H in patients with newly diagnosed malignant astrocytomas: A first-in-man multicenter phase I clinical trial of the German Neurooncology Working Group (NOA-16). J Clin Oncol. 2018;36(suppl; abstr 2001).