FLORIDA CANCER SPECIALISTS & Research Institute

TOP ARTICLES OF THE MONTH

MAY 2021 | Lucio N. Gordan, MD

1. Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non–Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50%

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PURPOSE

We report the first 5-year follow-up of any first-line phase III immunotherapy trial for non–small-cell lung cancer (NSCLC). KEYNOTE-024 (ClinicalTrials.gov identifier: NCT02142738) is an open-label, randomized controlled trial of pembrolizumab compared with platinum-based chemotherapy in patients with previously untreated NSCLC with a programmed death ligand-1 (PD-L1) tumor proportion score of at least 50% and no sensitizing EGFR or ALK alterations. Previous analyses showed pembrolizumab significantly improved progression-free survival and overall survival (OS).

METHODS

Eligible patients were randomly assigned (1:1) to pembrolizumab (200 mg once every 3 weeks for up to 35 cycles) or platinum-based chemotherapy. Patients in the chemotherapy group with progressive disease could cross over to pembrolizumab. The primary end point was progression-free survival; OS was a secondary end point.

RESULTS

Three hundred five patients were randomly assigned: 154 to pembrolizumab and 151 to chemotherapy. Median (range) time from randomization to data cutoff (June 1, 2020) was 59.9 (55.1-68.4) months. Among patients initially assigned to chemotherapy, 99 received subsequent anti–PD-1 or PD-L1 therapy, representing a 66.0% effective crossover rate. Median OS was 26.3 months (95% CI, 18.3 to 40.4) for pembrolizumab and 13.4 months (9.4-18.3) for chemotherapy (hazard ratio, 0.62; 95% CI, 0.48 to 0.81). Kaplan-Meier estimates of the 5-year OS rate were 31.9% for the pembrolizumab group and 16.3% for the chemotherapy group. Thirty-nine patients received 35 cycles (ie, approximately 2 years) of pembrolizumab, 82.1% of whom were still alive at data cutoff (approximately 5 years). Toxicity did not increase with longer treatment exposure.

CONCLUSION

Pembrolizumab provides a durable, clinically meaningful long-term OS benefit versus chemotherapy as first-line therapy for metastatic NSCLC with PD-L1 tumor proportion score of at least 50%.

2. Phase III, Randomized, Placebo-Controlled Trial of CC-486 (Oral Azacitidine) in Patients With Lower-Risk Myelodysplastic Syndromes

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PURPOSE

Treatment options are limited for patients with lower-risk myelodysplastic syndromes (LR-MDS). This phase III, placebo-controlled trial evaluated CC-486 (oral azacitidine), a hypomethylating agent, in patients with International Prognostic Scoring System LR-MDS and RBC transfusion–dependent anemia and thrombocytopenia.

METHODS

Patients were randomly assigned 1:1 to CC-486 300-mg or placebo for 21 days/28-day cycle. The primary end point was RBC transfusion independence (TI).

RESULTS

Two hundred sixteen patients received CC-486 (n = 107) or placebo (n = 109). The median age was 74 years, median platelet count was 25 × 10^9/L, and absolute neutrophil count was 1.3 × 109/L. In the CC-486 and placebo arms, 31% and 11% of patients, respectively, achieved RBC-TI (P = .0002), with median durations of 11.1 and 5.0 months. Reductions of ≥ 4 RBC units were attained by 42.1% and 30.6% of patients, respectively, with median durations of 10.0 and 2.3 months, and more CC-486 patients had ≥ 1.5 g/dL hemoglobin increases from baseline (23.4% v 4.6%). Platelet hematologic improvement rate was higher with CC-486 (24.3% v 6.5%). Underpowered interim overall survival analysis showed no difference between CC-486 and placebo (median, 17.3 v 16.2 months; P = .96). Low-grade GI events were the most common adverse events in both arms. In the CC-486 and placebo arms, 90% and 73% of patients experienced a grade 3-4 adverse event. Overall death rate was similar between arms, but there was an imbalance in deaths during the first 56 days (CC-486, n = 16; placebo, n = 6), most related to infections; the median pretreatment absolute neutrophil count for the 16 CC-486 patients was 0.57 × 10^9/L.

CONCLUSION

CC-486 significantly improved RBC-TI rate and induced durable bilineage improvements in patients with LR-MDS and high-risk disease features. More early deaths occurred in the CC-486 arm, most related to infections in patients with significant pretreatment neutropenia. Further evaluation of CC-486 in MDS is needed.

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3. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer in the APHINITY Trial: 6 Years' Follow-Up

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PURPOSE

APHINITY, at 45 months median follow-up, showed that pertuzumab added to adjuvant trastuzumab and chemotherapy significantly improved invasive disease–free survival (IDFS) (hazard ratio 0.81 [95% CI, 0.66 to 1.00], P = .045) for patients with early human epidermal growth factor receptor 2 (HER2)–positive breast cancer (BC), specifically those with node-positive or hormone receptor (HR)–negative disease. We now report the preplanned second interim overall survival (OS) and descriptive updated IDFS analysis with 74 months median follow-up.

METHODS

After surgery and central HER2-positive confirmation, 4,805 patients with node-positive or high-risk node-negative BC were randomly assigned (1:1) to either 1-year pertuzumab or placebo added to standard adjuvant chemotherapy and 1-year trastuzumab.

RESULTS

This interim OS analysis comparing pertuzumab versus placebo did not reach the P = .0012 level required for statistical significance (P = .17, hazard ratio 0.85). Six-year OS were 95% versus 94% with 125 deaths (5.2%) versus 147 (6.1%), respectively. IDFS analysis based on 508 events (intent-to-treat population) showed a hazard ratio of 0.76 (95% CI, 0.64 to 0.91) and 6-year IDFS of 91% and 88% for pertuzumab and placebo groups, respectively. The node-positive cohort continues to derive clear IDFS benefit from pertuzumab (hazard ratio 0.72 [95% CI, 0.59 to 0.87]), 6-year IDFS being 88% and 83%, respectively. Benefit was not seen in the node-negative cohort. In a subset analysis, IDFS benefit from pertuzumab showed a hazard ratio of 0.73 (95% CI, 0.59 to 0.92) for HR-positive disease and a hazard ratio of 0.83 (95% CI, 0.63 to 1.10) for HR-negative disease. Primary cardiac events remain < 1% in both the treatment groups. No new safety signals were seen.

CONCLUSION

This analysis confirms the IDFS benefit from adding pertuzumab to standard adjuvant therapy for patients with node-positive HER2-positive early BC. Longer follow-up is needed to fully assess OS benefit.

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4. Safety and Efficacy of Vadadustat for Anemia in Patients Undergoing Dialysis

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BACKGROUND

Vadadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor, a class of compounds that stimulate endogenous erythropoietin production.

METHODS

We conducted two randomized, open-label, noninferiority phase 3 trials to evaluate the safety and efficacy of vadadustat, as compared with darbepoetin alfa, in patients with anemia and incident or prevalent dialysis-dependent chronic kidney disease (DD-CKD). The primary safety end point, assessed in a time-to-event analysis, was the first occurrence of a major adverse cardiovascular event (MACE, a composite of death from any cause, a nonfatal myocardial infarction, or a nonfatal stroke), pooled across the trials (noninferiority margin, 1.25). A key secondary safety end point was the first occurrence of a MACE plus hospitalization for either heart failure or a

thromboembolic event. The primary and key secondary efficacy end points were the mean change in hemoglobin from baseline to weeks 24 to 36 and from baseline to weeks 40 to 52, respectively, in each trial (noninferiority margin, −0.75 g per deciliter).

RESULTS

A total of 3923 patients were randomly assigned in a 1:1 ratio to receive vadadustat or darbepoetin alfa: 369 in the incident DD-CKD trial and 3554 in the prevalent DD-CKD trial. In the pooled analysis, a first MACE occurred in 355 patients (18.2%) in the vadadustat group and in 377 patients (19.3%) in the darbepoetin alfa group (hazard ratio, 0.96; 95% confidence interval [CI], 0.83 to 1.11). The mean differences between the groups in the change in hemoglobin concentration were −0.31 g per deciliter (95% CI, −0.53 to −0.10) at weeks 24 to 36 and −0.07 g per deciliter (95% CI, −0.34 to 0.19) at weeks 40 to 52 in the incident DD-CKD trial and −0.17 g per deciliter (95% CI, −0.23 to −0.10) and −0.18 g per deciliter (95% CI, −0.25 to −0.12), respectively, in the prevalent DD-CKD trial. The incidence of serious adverse events in the vadadustat group was 49.7% in the incident DD-CKD trial and 55.0% in the prevalent DD-CKD trial, and the incidences in the darbepoetin alfa group were 56.5% and 58.3%, respectively.

CONCLUSION

Among patients with anemia and CKD who were undergoing dialysis, vadadustat was noninferior to darbepoetin alfa with respect to cardiovascular safety and correction and maintenance of hemoglobin concentrations. (Funded by Akebia Therapeutics and Otsuka Pharmaceutical; INNO2VATE ClinicalTrials.gov numbers, NCT02865850. opens in new tab and NCT02892149.)

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5. Vadadustat in Patients with Anemia and Non–Dialysis-Dependent CKD (NEJM)

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BACKGROUND

Vadadustat is an oral hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitor, a class of drugs that stabilize HIF and stimulate erythropoietin and red-cell production.

METHODS

In two phase 3, randomized, open-label, active-controlled, noninferiority trials, we compared vadadustat with the erythropoiesis-stimulating agent (ESA) darbepoetin alfa in patients with non–dialysis-dependent chronic kidney disease (NDD-CKD) not previously treated with an ESA who had a hemoglobin concentration of less than 10 g per deciliter and in patients with ESA-treated NDD-CKD and a hemoglobin concentration of 8 to 11 g per deciliter (in the United States) or 9 to 12 g per deciliter (in other countries). The primary safety end point, assessed in a time-to-event analysis, was the first major adverse cardiovascular event (MACE; a composite of death from any cause, nonfatal myocardial infarction, or nonfatal stroke), pooled across the two trials. Secondary safety end points included expanded MACE (MACE plus hospitalization for either heart failure or a thromboembolic event). The primary and key secondary efficacy end points in each trial were the mean change in hemoglobin concentration from baseline during two evaluation periods: weeks 24 through 36 and weeks 40 through 52.

RESULTS

A total of 1751 patients with ESA-untreated NDD-CKD and 1725 with ESA-treated NDD-CKD underwent randomization in the two trials. In the pooled analysis, in which 1739 patients received vadadustat and 1732 received darbepoetin alfa, the hazard ratio for MACE was 1.17 (95% confidence interval [CI], 1.01 to 1.36), which did not meet the prespecified noninferiority margin of 1.25. The mean between-group differences in the change in the hemoglobin concentration at weeks 24 through 36 were 0.05 g per deciliter (95% CI, −0.04 to 0.15) in the trial involving ESA-untreated patients and −0.01 g per deciliter (95% CI, −0.09 to 0.07) in the trial involving ESA-treated patients, which met the prespecified noninferiority margin of −0.75 g per deciliter.

CONCLUSION

Vadadustat, as compared with darbepoetin alfa, met the prespecified noninferiority criterion for hematologic efficacy but not the prespecified noninferiority criterion for cardiovascular safety in patients with NDD-CKD. (Funded by Akebia Therapeutics and Otsuka Pharmaceutical; PRO2TECT ClinicalTrials.gov numbers, NCT02648347. opens in new tab and NCT02680574.)

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6. High tumor mutation burden fails to predict immune checkpoint blockade response across all cancer types (Annals of Oncology)

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BACKGROUND

High tumor mutation burden (TMB-H) has been proposed as a predictive biomarker for response to immune checkpoint blockade (ICB), largely due to the potential for tumor mutations to generate immunogenic neoantigens. Despite recent pan-cancer approval of ICB treatment for any TMB-H tumor, as assessed by the targeted FoundationOne CDx assay in nine tumor types, the utility of this biomarker has not been fully demonstrated across all cancers.

PATIENTS AND METHODS

Data from over 10 000 patient tumors included in The Cancer Genome Atlas were used to compare approaches to determine TMB and identify the correlation between predicted neoantigen load and CD8 T cells. Association of TMB with ICB treatment outcomes was analyzed by both objective response rates (ORRs, $N = 1551$) and overall survival (OS, $N = 1936$).

RESULTS

In cancer types where CD8 T-cell levels positively correlated with neoantigen load, such as melanoma, lung, and bladder cancers, TMB-H tumors exhibited a 39.8% ORR to ICB [95% confidence interval (CI) 34.9-44.8], which was significantly higher than that observed in low TMB (TMB-L) tumors [odds ratio (OR) = 4.1, 95% CI 2.9-5.8, $P < 2 \times 10^{-16}$]. In cancer types that showed no relationship between CD8 T-cell levels and neoantigen load, such as breast cancer, prostate cancer, and glioma, TMB-H tumors failed to achieve a 20% ORR (ORR = 15.3%, 95% CI 9.2-23.4, P = 0.95), and exhibited a significantly lower ORR relative to TMB-L tumors (OR = 0.46, 95% CI 0.24-0.88, P = 0.02). Bulk ORRs were not significantly different between the two categories of tumors (P = 0.10) for patient cohorts assessed. Equivalent results were obtained by analyzing OS and by treating TMB as a continuous variable.

CONCLUSIONS

Our analysis failed to support application of TMB-H as a biomarker for treatment with ICB in all solid cancer types. Further tumor type-specific studies are warranted.

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7. Palbociclib In Combination With Endocrine Therapy Versus Capecitabine In Hormonal Receptor-Positive, Human Epidermal Growth Factor 2-Negative, Aromatase Inhibitor-Resistant Metastatic Breast Cancer: A Phase III Randomised Controlled Trial-Pearl

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BACKGROUND

Palbociclib plus endocrine therapy (ET) is the standard treatment of hormone receptor-positive and human epidermal growth factor receptor 2-negative, metastatic breast cancer (MBC). However, its efficacy has not been compared with that of chemotherapy in a phase III trial.

PATIENTS AND METHODS

PEARL is a multicentre, phase III randomised study in which patients with aromatase inhibitor (AI)-resistant MBC were included in two consecutive cohorts. In cohort 1, patients were randomised 1 : 1 to palbociclib plus exemestane or capecitabine. On discovering new evidence about estrogen receptor-1 *(ESR1)* mutations inducing resistance to AIs, the trial was amended to include cohort 2, in which patients were randomised 1 : 1 between palbociclib plus fulvestrant and capecitabine. The stratification criteria were disease site, prior sensitivity to ET, prior chemotherapy for MBC, and country of origin. Co-primary endpoints were progression-free survival (PFS) in cohort 2 and in wild-type *ESR1* patients (cohort 1 + cohort 2). *ESR1* hotspot mutations were analysed in baseline circulating tumour DNA.

RESULTS

From March 2014 to July 2018, 296 and 305 patients were included in cohort 1 and cohort 2, respectively. Palbociclib plus ET was not superior to capecitabine in both cohort 2 [median PFS: 7.5 versus 10.0 months; adjusted hazard ratio (aHR): 1.13; 95% confidence interval (CI): 0.85-1.50] and wild-type *ESR1* patients (median PFS: 8.0 versus 10.6 months; aHR: 1.11; 95% CI: 0.87-1.41). The most frequent grade 3-4 toxicities with palbociclib plus exemestane, palbociclib plus fulvestrant and capecitabine, respectively, were neutropenia (57.4%, 55.7% and 5.5%), hand/foot syndrome (0%, 0% and 23.5%), and diarrhoea (1.3%, 1.3% and 7.6%). Palbociclib plus ET offered better quality of life (aHR for time to deterioration of global health status: 0.67; 95% CI: 0.53-0.85).

CONCLUSIONS

There was no statistical superiority of palbociclib plus ET over capecitabine with respect to PFS in MBC patients resistant to AIs. Palbociclib plus ET showed a better safety profile and improved quality of life.

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8. Appropriate Systemic Therapy Dosing for Obese Adult Patients With Cancer: ASCO Guideline Update

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PURPOSE

To provide recommendations for appropriate dosing of systemic antineoplastic agents in obese adults with cancer.

METHODS

A systematic review of the literature collected evidence regarding dosing of chemotherapy, immunotherapy, and targeted therapies in obese adults with cancer. PubMed and the Cochrane Library were searched for randomized controlled trials, meta-analyses, or cohort studies published from November 1, 2010, through March 27, 2020. ASCO convened an Expert Panel to review the evidence and formulate recommendations.

RESULTS

Sixty studies, primarily retrospective, were included in the review. Overall, the evidence supported previous findings that obese adult patients tolerate full, body-size–based dosing of chemotherapy as well as nonobese patients. Fewer studies have addressed the dosing of targeted therapies and immunotherapies in relation to safety and efficacy in obese patients.

RECOMMENDATIONS

The Panel continues to recommend that full, weight-based cytotoxic chemotherapy doses be used to treat obese adults with cancer. New to this version of the guideline, the Panel also recommends that full, approved doses of immunotherapy and targeted therapies be offered to obese adults with cancer. In the event of toxicity, the consensus of the Panel is that dose modifications of systemic antineoplastic therapies should be handled similarly for obese and nonobese patients. Important areas for future research include the impact of sarcopenia and other measures of body composition on optimal antineoplastic dosing, and more customized dosing based on pharmacokinetic or pharmacogenetic factors.

9. Pembrolizumab Plus Ipilimumab Following Anti-PD-1/L1 Failure in Melanoma

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PURPOSE

Combination of antiprogrammed cell death protein-1 (PD-1) plus anti–cytotoxic T-cell lymphocyte-4 (anti-CTLA-4) immunotherapy shows greater response rates (RRs) than anti-PD-1 antibody alone in melanoma, but RR after initial anti-PD-1 and programmed death ligand-1 (PD-L1) antibody progression awaits robust investigation. Anti-CTLA-4 antibody alone after anti-PD-1/L1 antibody progression has a historical RR of 13%. We report the results of the first prospective clinical trial evaluating ipilimumab 1 mg/kg plus pembrolizumab following progression on anti-PD-1 immunotherapy.

METHODS

Patients with advanced melanoma who had progressed on anti-PD-1/L1 antibody as immediate prior therapy (including non–anti-CTLA-4 antibody combinations) were eligible. Patients received pembrolizumab 200 mg plus ipilimumab 1 mg/kg once every 3 weeks for four doses, followed by pembrolizumab monotherapy. The primary end point was RR by irRECIST. After 35 patients, the trial met the primary end point and was expanded to enroll a total of 70 patients to better estimate the RR.

RESULTS

Prior treatments included 60 on anti-PD-1 antibody alone and 10 on anti-PD-1/L1 antibody–based combinations. Thirteen patients had progressed in the adjuvant setting. The median length of prior treatment with anti-PD-1/L1 antibody was 4.8 months. Response assessments included five complete and 15 partial responses, making the irRECIST RR 29% among the entire trial population. The median progression-free survival was 5.0 months, and the median overall survival was 24.7 months. The median duration of response was 16.6 months. There was no difference in median time on prior anti-PD1/L1 or time to PD1 + CTLA4 initiation between responders and nonresponders. Grade 3-4 drug-related adverse events occurred in 27% of patients. Responses occurred in PD-L1–negative, non-T-cell–inflamed, and intermediate tumor phenotypes.

CONCLUSION

To our knowledge, this is the first prospective study in melanoma of pembrolizumab plus low-dose ipilimumab after anti-PD-1/L1 immunotherapy failure, demonstrating significant antitumor activity and tolerability.