FLORIDA CANCER SPECIALISTS & Research Institute

TOP ARTICLES OF THE MONTH

NOVEMBER - DECEMBER 2021 | Lucio N. Gordan, MD

1. 21-Gene Assay to Inform Chemotherapy Benefit in Node-Positive Breast Cancer

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ABSTRACT

Background

The recurrence score based on the 21-gene breast-cancer assay has been clinically useful in predicting a chemotherapy benefit in hormone-receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative, axillary lymph-node–negative breast cancer. In women with positive lymph-node disease, the role of the recurrence score with respect to predicting a benefit of adjuvant chemotherapy is unclear.

Methods

In a prospective trial, we randomly assigned women with hormone-receptor–positive, HER2-negative breast cancer, one to three positive axillary lymph nodes, and a recurrence score of 25 or lower (scores range from 0 to 100, with higher scores indicating a worse prognosis) to endocrine therapy only or to chemotherapy plus endocrine (chemoendocrine) therapy. The primary objective was to determine the effect of chemotherapy on invasive disease–free survival and whether the effect was influenced by the recurrence score. Secondary end points included distant relapse–free survival.

Results

A total of 5083 women (33.2% premenopausal and 66.8% postmenopausal) underwent randomization, and 5018 participated in the trial. At the prespecified third interim analysis, the chemotherapy benefit with respect to increasing invasive disease–free survival differed according to menopausal status (P=0.008 for the comparison of chemotherapy benefit in premenopausal and postmenopausal participants), and separate prespecified analyses were conducted. Among postmenopausal women, invasive disease–free survival at 5 years was 91.9% in the endocrine-only group and 91.3% in the chemoendocrine group, with no chemotherapy benefit (hazard ratio for invasive disease recurrence, new primary cancer [breast cancer or another type], or death, 1.02; 95% confidence interval [CI], 0.82 to 1.26; P=0.89). Among premenopausal women, invasive disease–free survival at 5 years was 89.0% with endocrine-only therapy and 93.9% with chemoendocrine therapy (hazard ratio, 0.60; 95% CI, 0.43 to 0.83; P=0.002), with a similar increase in distant relapse–free survival (hazard ratio, 0.58; 95% CI, 0.39 to 0.87; P=0.009). The relative chemotherapy benefit did not increase as the recurrence score increased.

Conclusions

Among premenopausal women with one to three positive lymph nodes and a recurrence score of 25 or lower, those who received chemoendocrine therapy had longer invasive disease–free survival and distant relapse–free survival than those who received endocrine-only therapy, whereas postmenopausal women with similar characteristics did not benefit from adjuvant chemotherapy.

2. Randomized Trial of Cytoreductive Surgery for Relapsed Ovarian Cancer

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ABSTRACT

Background

Treatment for patients with recurrent ovarian cancer has been mainly based on systemic therapy. The role of secondary cytoreductive surgery is unclear.

Methods

We randomly assigned patients with recurrent ovarian cancer who had a first relapse after a platinum-free interval (an interval during which no platinum-based chemotherapy was used) of 6 months or more to undergo secondary cytoreductive surgery and then receive platinum-based chemotherapy or to receive platinum-based chemotherapy alone. Patients were eligible if they presented with a positive Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) score, defined as an Eastern Cooperative Oncology Group performance-status score of 0 (on a 5-point scale, with higher scores indicating greater disability), ascites of less than 500 ml, and complete resection at initial surgery. A positive AGO score is used to identify patients in whom a complete resection might be achieved. The primary end point was overall survival. We also assessed quality of life and prognostic factors for survival.

Results

A total of 407 patients underwent randomization: 206 were assigned to cytoreductive surgery and chemotherapy, and 201 to chemotherapy alone. A complete resection was achieved in 75.5% of the patients in the surgery group who underwent the procedure. The median overall survival was 53.7 months in the surgery group and 46.0 months in the no-surgery group (hazard ratio for death, 0.75; 95% confidence interval, 0.59 to 0.96; P=0.02). Patients with a complete resection had the most favorable outcome, with a median overall survival of 61.9 months. A benefit from surgery was seen in all analyses in subgroups according to prognostic factors. Quality-of-life measures through 1 year of follow-up did not differ between the two groups, and we observed no perioperative mortality within 30 days after surgery.

Conclusions

In women with recurrent ovarian cancer, cytoreductive surgery followed by chemotherapy resulted in longer overall survival than chemotherapy alone. (Funded by the AGO Study Group and others; DESKTOP III ClinicalTrials.gov number, NCT01166737.)

3. Belzutifan for Renal Cell Carcinoma in von Hippel–Lindau Disease

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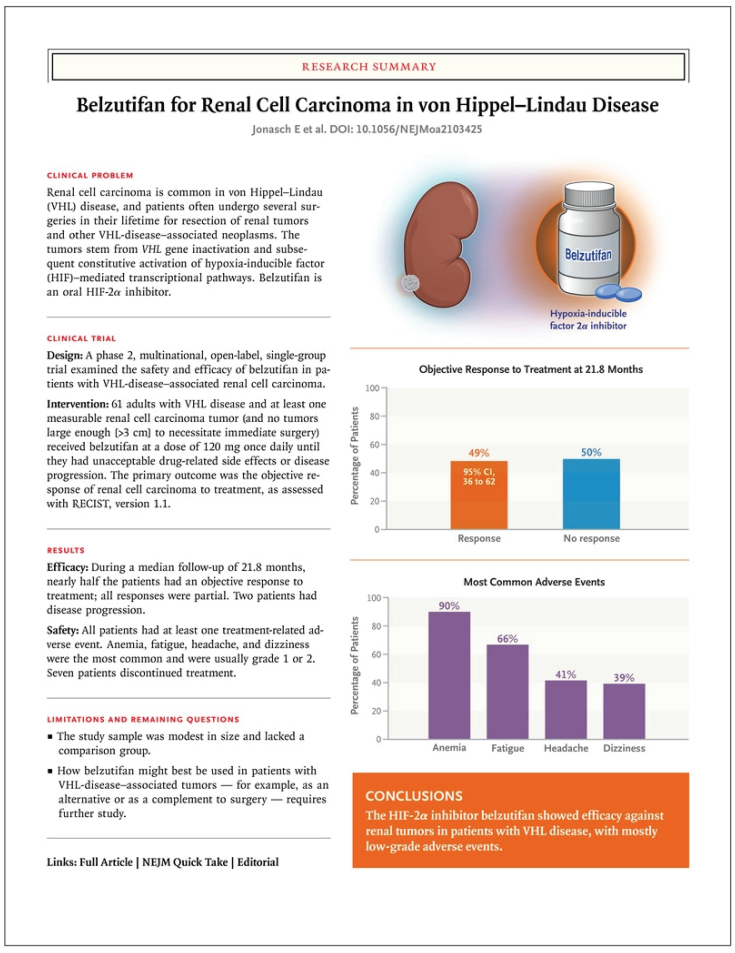

RESEARCH SUMMARY

Belzutifan for Renal Cell Carcinoma in von Hippel–Lindau Disease

Jonasch E et al. DOI: 10.1056/NEJMoa2103425

CLINICAL PROBLEM

Renal cell carcinoma is common in von Hippel–Lindau (VHL) disease, and patients often undergo several surgeries in their lifetime for resection of renal tumors and other VHL-disease–associated neoplasms. The tumors stem from *VHL* gene inactivation and subsequent constitutive activation of hypoxia-inducible factor (HIF)–mediated transcriptional pathways. Belzutifan is an oral HIF-2α inhibitor.

CLINICAL TRIAL

Design: A phase 2, multinational, open-label, single-group trial examined the safety and efficacy of belzutifan in patients with VHL-disease–associated renal cell carcinoma.

Intervention: 61 adults with VHL disease and at least one measurable renal cell carcinoma tumor (and no tumors large enough [>3 cm] to necessitate immediate surgery) received belzutifan at a dose of 120 mg once daily until they had unacceptable drug-related side effects or disease progression. The primary outcome was the objective response of renal cell carcinoma to treatment, as assessed with RECIST, version 1.1.

RESULTS

Efficacy: During a median follow-up of 21.8 months, nearly half the patients had an objective response to treatment; all responses were partial. Two patients had disease progression.

Safety: All patients had at least one treatment-related adverse event. Anemia, fatigue, headache, and dizziness were the most common and were usually grade 1 or 2. Seven patients discontinued treatment.

LIMITATIONS AND REMAINING QUESTIONS

- The study sample was modest in size and lacked a comparison group.
- How belzutifan might best be used in patients with VHL-disease–associated tumors — for example, as an alternative or as a complement to surgery — requires further study.

Links: Full Article | NEJM Quick Take | Editorial

ABSTRACT

Background

Patients with von Hippel–Lindau (VHL) disease have a high incidence of renal cell carcinoma owing to VHL gene inactivation and constitutive activation of the transcription factor hypoxia-inducible factor 2α (HIF-2α).

Methods

In this phase 2, open-label, single-group trial, we investigated the efficacy and safety of the HIF-2α inhibitor belzutifan (MK-6482, previously called PT2977), administered orally at a dose of 120 mg daily, in patients with renal cell carcinoma associated with VHL disease. The primary end point was objective response (complete or partial response) as measured according to the Response Evaluation Criteria in Solid Tumors, version 1.1, by an independent central radiology review committee. We also assessed responses to belzutifan in patients with non–renal cell carcinoma neoplasms and the safety of belzutifan.

Results

After a median follow-up of 21.8 months (range, 20.2 to 30.1), the percentage of patients with renal cell carcinoma who had an objective response was 49% (95% confidence interval, 36 to 62). Responses were also observed in patients with pancreatic lesions (47 of 61 patients [77%]) and central nervous system hemangioblastomas (15 of 50 patients [30%]). Among the 16 eyes that could be evaluated in 12 patients with retinal hemangioblastomas at baseline, all (100%) were graded as showing improvement. The most common adverse events were anemia (in 90% of the patients) and fatigue (in 66%). Seven patients discontinued treatment: four patients voluntarily discontinued, one discontinued owing to a treatment-related adverse event (grade 1 dizziness), one discontinued because of disease progression as assessed by the investigator, and one patient died (of acute toxic effects of fentanyl).

Conclusion

In women with recurrent ovarian cancer, cytoreductive surgery followed by chemotherapy resulted in longer overall survival than chemotherapy alone. (Funded by the AGO Study Group and others; DESKTOP III ClinicalTrials.gov number, NCT01166737.)

4. Daratumumab, Carfilzomib, Lenalidomide, and Dexamethasone With Minimal Residual Disease Response-Adapted Therapy in Newly Diagnosed Multiple Myeloma

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ABSTRACT

Purpose

The MASTER trial combined daratumumab, carfilzomib, lenalidomide, and dexamethasone (Dara-KRd) in newly diagnosed multiple myeloma (NDMM), using minimal residual disease (MRD) by next-generation sequencing (NGS) to inform the use and duration of Dara-KRd post-autologous hematopoietic cell transplantation (AHCT) and treatment cessation in patients with two consecutive MRD-negative assessments.

Methods

This multicenter, single-arm, phase II trial enrolled patients with NDMM with planed enrichment for high-risk cytogenetic abnormalities (HRCAs). Patients received Dara-KRd induction, AHCT, and Dara-KRd consolidation, according to MRD status. MRD was evaluated by NGS at the end of induction, post-AHCT, and every four cycles (maximum of eight cycles) of consolidation. Primary end point was achievement of MRD negativity (< 10–5). Patients with two consecutive MRD-negative assessments entered treatment-free MRD surveillance.

Results

Among 123 participants, 43% had none, 37% had 1, and 20% had 2+ HRCA. Median age was 60 years (range, 36-79 years), and 96% had MRD trackable by NGS. Median follow-up was 25.1 months. Overall, 80% of patients reached MRD negativity (78%, 82%, and 79% for patients with 0, 1, and 2+ HRCA, respectively), 66% reached MRD < 10–6, and 71% reached two consecutive MRD-negative assessments during therapy, entering treatment-free surveillance. Two-year progression-free survival was 87% (91%, 97%, and 58% for patients with 0, 1, and 2+ HRCA, respectively). Cumulative incidence of MRD resurgence or progression 12 months after cessation of therapy was 4%, 0%, and 27% for patients with 0, 1, or 2+ HRCA, respectively. Most common serious adverse events were pneumonia (6%) and venous thromboembolism (3%).

Conclusion

Dara-KRd, AHCT, and MRD response-adapted consolidation leads to high rate of MRD negativity in NDMM. For patients with 0 or 1 HRCA, this strategy creates the opportunity of MRD surveillance as an alternative to indefinite maintenance.

5. Long-Term Outcomes With Nivolumab Plus Ipilimumab or Nivolumab Alone Versus Ipilimumab in Patients With Advanced Melanoma

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**J.L. and F.S.H. contributed equally to this work.*

ABSTRACT

Purpose

In the phase III CheckMate 067 trial, durable clinical benefit was demonstrated previously with nivolumab plus ipilimumab and nivolumab alone versus ipilimumab. Here, we report 6.5-year efficacy and safety outcomes.

Patients and Methods

Patients with previously untreated unresectable stage III or stage IV melanoma were randomly assigned 1:1:1 to receive nivolumab 1 mg/kg plus ipilimumab 3 mg/kg once every 3 weeks (four doses) followed by nivolumab 3 mg/kg once every 2 weeks (n = 314), nivolumab 3 mg/kg once every 2 weeks (n = 316), or ipilimumab 3 mg/kg once every 3 weeks (four doses; n = 315). Coprimary end points were progression-free survival and overall survival (OS) with nivolumab plus ipilimumab or nivolumab versus ipilimumab. Secondary end points included objective response rate, descriptive efficacy assessments of nivolumab plus ipilimumab versus nivolumab alone, and safety. Melanoma-specific survival (MSS; descriptive analysis), which excludes deaths unrelated to melanoma, was also evaluated.

Results

Median OS (minimum follow-up, 6.5 years) was 72.1, 36.9, and 19.9 months in the combination, nivolumab, and ipilimumab groups, respectively. Median MSS was not reached, 58.7, and 21.9 months, respectively; 6.5-year OS rates were 57%, 43%, and 25% in patients with BRAF-mutant tumors and 46%, 42%, and 22% in those with BRAF–wild-type tumors, respectively. In patients who discontinued treatment, the median treatment-free interval was 27.6, 2.3, and 1.9 months, respectively. Since the 5-year analysis, no new safety signals were observed.

Conclusion

These 6.5-year CheckMate 067 results, which include the longest median OS in a phase III melanoma trial reported to date and the first report of MSS, showed durable, improved clinical outcomes with nivolumab plus ipilimumab or nivolumab versus ipilimumab in patients with advanced melanoma and, in descriptive analyses, with the combination over nivolumab monotherapy.

6. Abiraterone Acetate in Patients With Castration-Resistant, Androgen Receptor–Expressing Salivary Gland Cancer: A Phase II Trial

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ABSTRACT

Purpose

The activity of androgen-deprivation therapy (ADT) in androgen receptor–positive (AR+) salivary gland carcinomas (SGCs) has been established in the past few years. Second-line treatment in castration-resistant patients is still unknown. We investigated the activity of abiraterone acetate as second-line treatment in ADT-resistant, AR+ patients with SGC.

Patients and Methods

This was a single-institution phase II trial. A two-stage Simon's design was applied. The primary end point was confirmed objective response rate. Secondary end points were disease control rate, safety, progression-free survival, and overall survival. Patients were eligible when the following criteria were met: histologic diagnosis of AR-overexpressing SGC, measurable disease according to RECIST 1.1, clinical and/or radiologic progression on ADT, suppressed serum testosterone, and no limits for the number of previous chemotherapy lines. All patients received abiraterone 1 g daily plus prednisone 10 mg and luteinizing hormone-releasing hormone agonist until progression or unacceptable toxicities.

Results

From 2015 to 2019, 24 AR+ patients with SGC (23 men; median age 65.8 years) were treated within the study. The overall response rate was 21% (5 partial responses), with a disease control rate of 62.5%. The median duration of response was 5.82 months. Median progression-free survival was 3.65 months (95% CI, 1.94 to 5.89), and median overall survival was 22.47 months (95% CI, 6.74 to not reached). Objective response to previous ADT did not correlate with the activity of abiraterone. Adverse events (AEs) were recorded in 22 cases (92%) with grade 3 AEs in six patients (25%): fatigue (two), flushing (one), supraventricular tachycardia (one), and two non–drug-related AEs. No drug-related grade 4 or 5 AEs were recorded.

Conclusion

Abiraterone plus luteinizing hormone-releasing hormone agonist is active and safe as a second-line option in AR-expressing, castration-resistant SGC.

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7. Hepatectomy Followed by mFOLFOX6 Versus Hepatectomy Alone for Liver-Only Metastatic Colorectal Cancer (JCOG0603): A Phase II or III Randomized Controlled Trial

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ABSTRACT

Purpose

Adjuvant chemotherapy after hepatectomy is controversial in liver-only metastatic colorectal cancer (CRC). We conducted a randomized controlled trial to examine if adjuvant modified infusional fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) is superior to hepatectomy alone for liver-only metastasis from CRC.

Patients and Methods

In this phase II or III trial (JCOG0603), patients age 20-75 years with confirmed CRC and an unlimited number of liver metastatic lesions were randomly assigned to hepatectomy alone or 12 courses of adjuvant mFOLFOX6 after hepatectomy. The primary end point of phase III was disease-free survival (DFS) in intention-to-treat analysis.

Results

Between March 2007 and January 2019, 300 patients were randomly assigned to hepatectomy alone (149 patients) or hepatectomy followed by chemotherapy (151 patients). At the third interim analysis of phase III with median follow-up of 53.6 months, the trial was terminated early according to the protocol because DFS was significantly longer in patients treated with hepatectomy followed by chemotherapy. With median follow-up of 59.2 months, the updated 5-year DFS was 38.7% (95% CI, 30.4 to 46.8) for hepatectomy alone compared with 49.8% (95% CI, 41.0 to 58.0) for chemotherapy (hazard ratio, 0.67; 95% CI, 0.50 to 0.92; one-sided P = .006). However, the updated 5-year overall survival (OS) was 83.1% (95% CI, 74.9 to 88.9) with hepatectomy alone and 71.2% (95% CI, 61.7 to 78.8) with hepatectomy followed by chemotherapy. In the chemotherapy arm, the most common grade 3 or higher severe adverse event was neutropenia (50% of patients), followed by sensory neuropathy (10%) and allergic reaction (4%). One patient died of unknown cause after three courses of mFOLFOX6 administration.

Conclusion

DFS did not correlate with OS for liver-only metastatic CRC. Adjuvant chemotherapy with mFOLFOX6 improves DFS among patients treated with hepatectomy for CRC liver metastasis. It remains unclear whether chemotherapy improves OS.

8. Capecitabine Versus Active Monitoring in Stable or Responding Metastatic Colorectal Cancer After 16 Weeks of First-Line Therapy: Results of the Randomized FOCUS4-N Trial

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**R.A.A. and D.F. are joint first authors, L.C.B. and T.S.M. are joint last authors.*

ABSTRACT

Purpose

Despite extensive randomized evidence supporting the use of treatment breaks in metastatic colorectal cancer (mCRC), they are not universally offered to patients despite improvements in quality of life without detriment to overall survival (OS). FOCUS4-N was set up to explore the impact of oral maintenance therapy in patients who are responding to first-line therapy.

Methods

FOCUS4 was a molecularly stratified trial program that registered patients with newly diagnosed mCRC. The FOCUS4-N trial was offered to patients in whom a targeted subtrial was unavailable or biomarker tests failed. Patients were randomly assigned using a 1:1 ratio between maintenance capecitabine and active monitoring (AM). The primary outcome was progression-free survival (PFS) with secondary outcomes including OS toxicity and tolerability.

Results

Between March 2014 and March 2020, 254 patients were randomly assigned (127 to capecitabine and 127 to AM) across 88 UK sites. Baseline characteristics were balanced. There was strong evidence of efficacy for PFS (hazard ratio = 0.40; 95% CI, 0.21 to 0.75; P < .0001), but no significant improvement in OS (hazard ratio, 0.93; 95% CI, 0.69 to 1.27; P = .66) was observed. Compliance with treatment was good, and toxicity from capecitabine versus AM was as expected with grade ≥ 2 fatigue (25% v 12%), diarrhea (23% v 13%), and hand-foot syndrome (26% v 3%). Quality of life showed little difference between the groups.

Conclusion

Despite strong evidence of disease control with maintenance therapy, OS remains unaffected and FOCUS4-N provides additional evidence to support the use of treatment breaks as safe management alternatives for patients who are stable or responding to first-line treatment for mCRC. Capecitabine without bevacizumab may be used to extend PFS in the interval after 16 weeks of first-line therapy.

9. Nivolumab Versus Gemcitabine or Pegylated Liposomal Doxorubicin for Patients With Platinum-Resistant Ovarian Cancer: Open-Label, Randomized Trial in Japan (NINJA)

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ABSTRACT

Purpose

This phase III, multicenter, randomized, open-label study investigated the efficacy and safety of nivolumab versus chemotherapy (gemcitabine [GEM] or pegylated liposomal doxorubicin [PLD]) in patients with platinum-resistant ovarian cancer.

Materials and Methods

Eligible patients had platinum-resistant epithelial ovarian cancer, received ≤ 1 regimen after diagnosis of resistance, and had an Eastern Cooperative Oncology Group performance score of ≤ 1. Patients were randomly assigned 1:1 to nivolumab (240 mg once every 2 weeks [as one cycle]) or chemotherapy (GEM 1000 mg/m^2 for 30 minutes [once on days 1, 8, and 15] followed by a week's rest [as one cycle], or PLD 50 mg/m^2 once every 4 weeks [as one cycle]). The primary outcome was overall survival (OS). Secondary outcomes included progression-free survival (PFS), overall response rate, duration of response, and safety.

Results

Patients (n = 316) were randomly assigned to nivolumab (n = 157) or GEM or PLD (n = 159) between October 2015 and December 2017. Median OS was 10.1 (95% CI, 8.3 to 14.1) and 12.1 (95% CI, 9.3 to 15.3) months with nivolumab and GEM or PLD, respectively (hazard ratio, 1.0; 95% CI, 0.8 to 1.3; *P* = .808). Median PFS was 2.0 (95% CI, 1.9 to 2.2) and 3.8 (95% CI, 3.6 to 4.2) months with nivolumab and GEM or PLD, respectively (hazard ratio, 1.5; 95% CI, 1.2 to 1.9; *P* = .002). There was no statistical difference in overall response rate between groups (7.6% *v* 13.2%; odds ratio, 0.6; 95% CI, 0.2 to 1.3; *P* = .191). Median duration of response was numerically longer with nivolumab than GEM or PLD (18.7 *v* 7.4 months). Fewer treatment-related adverse events were observed with nivolumab versus GEM or PLD (61.5% *v* 98.1%), with no additional or new safety risks.

Conclusion

Although well-tolerated, nivolumab did not improve OS and showed worse PFS compared with GEM or PLD in patients with platinum-resistant ovarian cancer.

10. Daprodustat for the Treatment of Anemia in Patients Undergoing Dialysis

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ABSTRACT

Background

Among patients with chronic kidney disease (CKD), the use of recombinant human erythropoietin and its derivatives for the treatment of anemia has been linked to a possibly increased risk of stroke, myocardial infarction, and other adverse events. Several trials have suggested that hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitors (PHIs) are as effective as erythropoiesis-stimulating agents (ESAs) in increasing hemoglobin levels.

Methods

In this randomized, open-label, phase 3 trial, we assigned patients with CKD who were undergoing dialysis and who had a hemoglobin level of 8.0 to 11.5 g per deciliter to receive an oral HIF-PHI (daprodustat) or an injectable ESA (epoetin alfa if they were receiving hemodialysis or darbepoetin alfa if they were receiving peritoneal dialysis). The two primary outcomes were the mean change in the hemoglobin level from baseline to weeks 28 through 52 (noninferiority margin, −0.75 g per deciliter) and the first occurrence of a major adverse cardiovascular event (a composite of death from any cause, nonfatal myocardial infarction, or nonfatal stroke), with a noninferiority margin of 1.25.

Results

A total of 2964 patients underwent randomization. The mean (±SD) baseline hemoglobin level was 10.4±1.0 g per deciliter overall. The mean (±SE) change in the hemoglobin level from baseline to weeks 28 through 52 was 0.28±0.02 g per deciliter in the daprodustat group and 0.10±0.02 g per deciliter in the ESA group (difference, 0.18 g per deciliter; 95% confidence interval [CI], 0.12 to 0.24), which met the prespecified noninferiority margin of −0.75 g per deciliter. During a median follow-up of 2.5 years, a major adverse cardiovascular event occurred in 374 of 1487 patients (25.2%) in the daprodustat group and in 394 of 1477 (26.7%) in the ESA group (hazard ratio, 0.93; 95% CI, 0.81 to 1.07), which also met the prespecified noninferiority margin for daprodustat. The percentages of patients with other adverse events were similar in the two groups.

Conclusions

Among patients with CKD undergoing dialysis, daprodustat was noninferior to ESAs regarding the change in the hemoglobin level from baseline and cardiovascular outcomes. (Funded by GlaxoSmithKline; ASCEND-D ClinicalTrials.gov number, NCT02879305.)