Novel Discoveries in Endometrial Cancer: Are we finally making progress?

Moderators: Melissa Geller, MD, and Shannon Westin, MD

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A randomized phase II/III study of paclitaxel/carboplatin/metformin versus paclitaxel/carboplatin/placebo as initial therapy for measurable stage III or IVA, stage IVB, or recurrent endometrial cancer: An NRG Oncology/GOG study

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Objective: Obesity and diabetes are associated with increased risk and worse outcomes for endometrial cancer. Paclitaxel and carboplatin is the standard initial therapy for advanced and recurrent endometrial cancer. Thus, we evaluated the efficacy and tolerability of the addition of the antidiabetic drug metformin to paclitaxel and carboplatin in endometrial cancer patients.

Method: In this randomized phase II–III trial, up to 540 patients with chemotherapy-naïve stage III–IVA (with measurable disease) and stage IVB or recurrent (with or without measurable disease) endometrial cancer were to be randomly assigned to treatment with paclitaxel and carboplatin with metformin (850 mg BID) versus paclitaxel and carboplatin with placebo. After completion of up to 10 cycles of paclitaxel and carboplatin with metformin or placebo, metformin or placebo was continued as maintenance therapy until disease progression. The primary endpoint of phase II was progression-free survival (PFS). The primary endpoint of phase III was overall survival (OS). The phase II study had 90% power with 20% alpha. The phase II–III study had 88% power with 5% alpha. Secondary endpoints were objective response, duration of response, and toxicity.

Results: From March 17, 2014, to February 1, 2018, 469 patients were randomized to the phase II and III studies. The phase II study deemed metformin worthy of further investigation in the phase III study. An interim phase III analysis stopped accrual for futility. Paclitaxel and carboplatin with metformin was well tolerated, with no unexpected serious toxicity. The addition of metformin to paclitaxel and carboplatin did not significantly improve OS (log rank one-sided P = 0.185, HR = 0.886, 95% CI 0.676–1.161) or PFS (HR = 0.885, 95% CI 0.711–1.101). At a median follow-up of 28 months and 215 deaths, median OS was 30 and 35 months, on paclitaxel and carboplatin with placebo and pPaclitaxel and carboplatin with metformin, respectively. Objective response rates were also similar between the paclitaxel and carboplatin with metformin and the paclitaxel and carboplatin with placebo arms (62% and 60%, respectively). BMI was neither prognostic nor predictive of response to paclitaxel and carboplatin with metformin. The OS HR for BMI was 0.987 per unit increase (95% CI 0.965–1.010) among patients treated with metformin.

Conclusion: PFS and OS were not significantly increased with the addition of metformin to paclitaxel and carboplatin for the treatment of advanced and recurrent endometrial cancer. Additional translational studies are underway to identify potential biomarkers of endometrial cancer patients that may have benefited from metformin treatment.

Randomized phase II trial of carboplatin-paclitaxel compared to carboplatin-paclitaxel-trastuzumab in advanced or recurrent uterine serous carcinomas that overexpress HER2/Neu (NCT01367002): Updated survival analysis

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Objective: HER2/Neu is a growth-factor receptor expressed in 30% of uterine serous carcinomas (USC). Based on the preliminary results of a multicenter, randomized phase II trial, trastuzumab (a humanized monoclonal antibody targeting

HER2/Neu) in combination with carboplatin/paclitaxel is now recognized as an alternative standard in treating advanced or recurrent HER2/Neu+ USC. Herein, we report updated survival data.

Method: Eligible patients had primary stage III–IV or recurrent, HER2/Neu+ disease. Patients were randomized to receive carboplatin/paclitaxel (control) for 6 cycles ± intravenous trastuzumab (experimental) until progression or toxicity. The primary endpoint was progression-free survival (PFS), and secondary endpoints were toxicity and overall survival (OS). Survival differences between treatment arms were assessed for significance via 1-sided log-rank tests.

Results: Forty-three progressions and 38 deaths (44 PFS events) occurred among 58 evaluable patients; median follow-up was 25.9 months (range 0.33–91 months). Among all patients, updated PFS continued to favor the trastuzumab arm, with medians of 8.0 (control) versus 12.9 (experimental) months (P = 0.005, HR = 0.46, 90% CI 0.28–0.76). Similarly, updated median PFS was 9.3 (control) versus 17.7 (experimental) months among 41 stage III–IV patients undergoing primary treatment (P = 0.015, HR = 0.44, 90% CI 0.23–0.83), and was 7.0 (control) versus 9.2 (experimental) months among 17 patients with recurrent disease (P = 0.004, HR = 0.12, 90% CI 0.03–0.48). Among all patients, OS was significantly higher in the trastuzumab arm than in the control arm, with medians of 24.4 (control) versus 29.6 (experimental) months, respectively (P = 0.046, HR = 0.58, 90% CI 0.34—0.99; **Figure 1**). This benefit was particularly striking in stage III–IV patients, who had OS medians of 25.4 months (control) versus not reached (experimental, P = 0.041, HR = 0.49, 90% CI 0.25–0.97). In a subgroup analysis, no significant OS benefit from trastuzumab was observed in patients with recurrent disease. Finally, long-term toxicity was not different between treatment arms.

Conclusion: In this updated survival analysis of a randomized phase II trial, the addition of trastuzumab to carboplatin/paclitaxel increased PFS and OS in women with advanced/recurrent, HER2/Neu+ uterine serous carcinoma. The greatest benefit was observed in women with stage III–IV disease who were treated upfront.

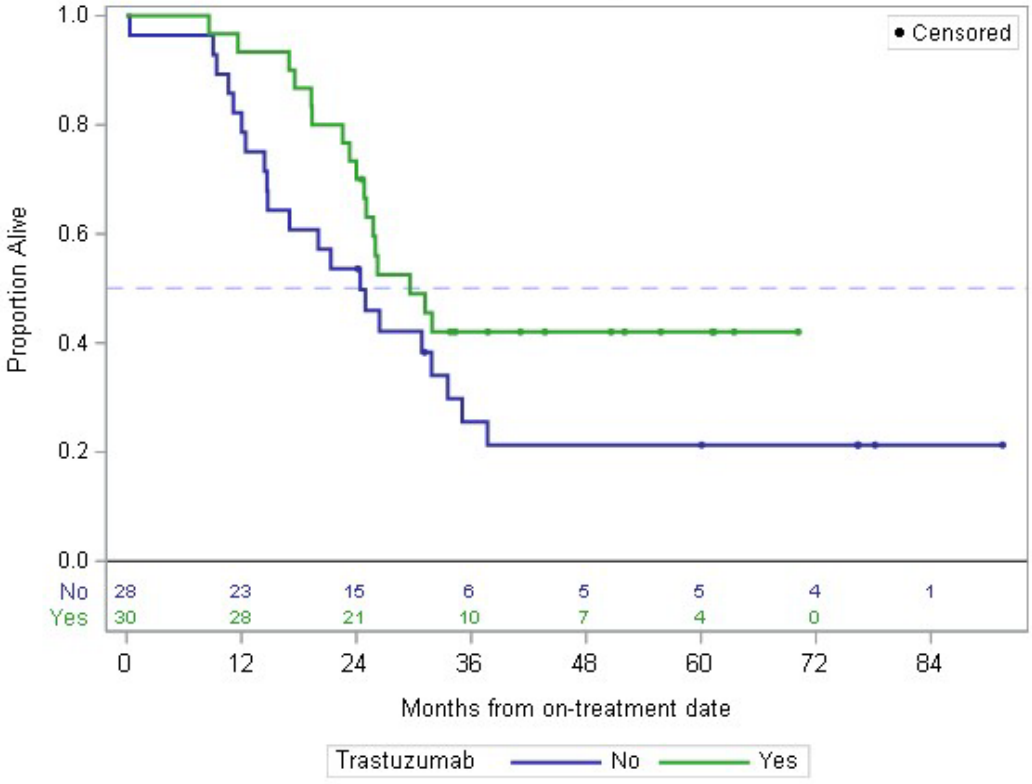

Fig. 1. Overall survival vs trastuzumab, all evaluable subjects (with number of subjects at risk).

Safety and efficacy of the anti–PD-1 monoclonal antibody dostarlimab in patients with recurrent or advanced dMMR endometrial cancer

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Objective: Dostarlimab (TSR-042) is a humanized programmed death (PD)-1 receptor monoclonal antibody that blocks interaction with PD-1 ligands, PD-L1 and PD-L2. The objective of this interim analysis is to assess the safety and efficacy of dostarlimab in patients with mismatch repair (MMR)-deficient endometrial cancer who are enrolled in the GARNET trial (NCT02715284).

Method: Patients with MMR-deficient endometrial cancer, as confirmed by immunohistochemistry, with recurrent or advanced disease that progressed on a platinum doublet regimen, were enrolled. Patients received 500 mg Q3W of dostarlimab for the first 4 cycles, then 1,000 mg Q6W until disease progression or discontinuation. The primary endpoints were objective response rate (ORR) and duration of response (DOR), as assessed against Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 by blinded independent central review.

Results: Seventy patients with MMR-deficient endometrial cancer treated with dostarlimab, with measurable disease at baseline and ≥6 months of follow-up by the data cutoff date (July 8, 2019), were included in this interim analysis. Median age was 64.5 years. ORR was 43%: 9 (13%) patients had a confirmed complete response and 21 (30%) had a confirmed partial response (**Table 1**). Of the responders, 77% remained on treatment at data cutoff. The Kaplan–Meier estimated likelihood of maintaining response was 96% at 6 months and 77% at 12 months. The disease control rate was 59%. With median follow-up of 11.2 months at data cutoff, median DOR was not reached. Fifty patients (71%) experienced ≥1 treatment-related adverse event (TRAE); the most common were fatigue, diarrhea, and nausea (each, 16%). Ten (14%) patients had a grade ≥3 TRAE; lipase increased, transaminases increased, and colitis, diarrhea, and anemia (each, 3%) were the most common. Two (3%) patients discontinued treatment due to TRAEs. Immune-related TRAEs were reported in 19 (27%) patients, and grade ≥3 immune-related TRAEs were reported in 7 (10%) patients; diarrhea (6%) was the most common immune-related TRAE. There were 4 (6%) deaths due to adverse events; none were assessed as related to dostarlimab.

Conclusion: Preliminary data for dostarlimab demonstrated clinical activity in patients with previously treated recurrent or advanced MMR-deficient endometrial cancer with an acceptable safety profile.

Table 1.

Best overall response by RECIST v1.1, *n* (%)	**dMMR EC** ***n* = 70**
CR	9 (13)
PR	21 (30)
SD	11 (16)
PD	26 (37)
NE	3 (4)
CR = complete response; dMMR = mismatch repair deficient; EC = endometrial cancer; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease	

Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer: Final analysis of a multicentre, open-label, single-arm, phase 2 trial

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A phase II trial of the Wee1 inhibitor adavosertib (AZD1775) in recurrent uterine serous carcinoma

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Objective: Uterine serous carcinoma (USC) is an aggressive subtype of endometrial carcinoma characterized by frequent TP53 mutations (>90%), often concomitantly with oncogenic mutations or amplifications that can increase replication stress. We hypothesized that USCs would therefore be uniquely sensitive to further interference of cell cycle regulation by Wee1 inhibition. This 2-stage single-arm phase 2 study was conducted to assess the activity of the oral Wee1 inhibitor adavosertib as monotherapy in recurrent USCs.

Method: Women with recurrent USC were eligible for this study; cancers with any component assessed as serous (with the exception of carcinosarcomas) were considered eligible. Patients were required to have had at least 1 prior platinum-based chemotherapy regimen; those with MSI-H/MMRd disease were required to have already received prior therapy with a PD1/PDL1 therapy or to be ineligible for such therapy. There was no upper limit on the number of prior lines patients could have received. All patients were required to have RECIST measurable disease. Patients received adavosertib 300 mg daily on days 1 through 5 and 8 through 12 of a 21-day cycle. In a planned total accrual of 35 patients, if at least 4 patients had confirmed response or 8 patients were progression-free at 6 months (PFS6), the trial would be considered positive, with an alpha of 10% and a beta of 15% to detect coprimary endpoints of an at least 20% overall response rate (ORR) or a 30% PFS6 rate.

Results: Between October 11, 2018, and August 20, 2019, 27 patients were enrolled in the study. Median follow-up was 3.5 months. The median number of prior lines was 3 (range 1–7). As of August 20, 2019, 21 patients were evaluable for response. In these patients, 6 confirmed responses were observed, for an ORR of 30% (95% CI 12%–54%), with 1 additional patient having an unconfirmed response. Data are not mature for PFS. **Figure 1** shows the waterfall plot of best responses. The most frequently observed adverse events included anemia (67%), diarrhea (67%), nausea (58%), and fatigue (50%). Frequently observed grade 3 or higher adverse effects included anemia (21%), neutropenia (21%), and syncope (21%). Updated data will be presented.

Conclusion: Adavosertib monotherapy demonstrated clinical activity in women with USC, with a preliminary response rate of 30%. Further studies in this patient population are warranted.

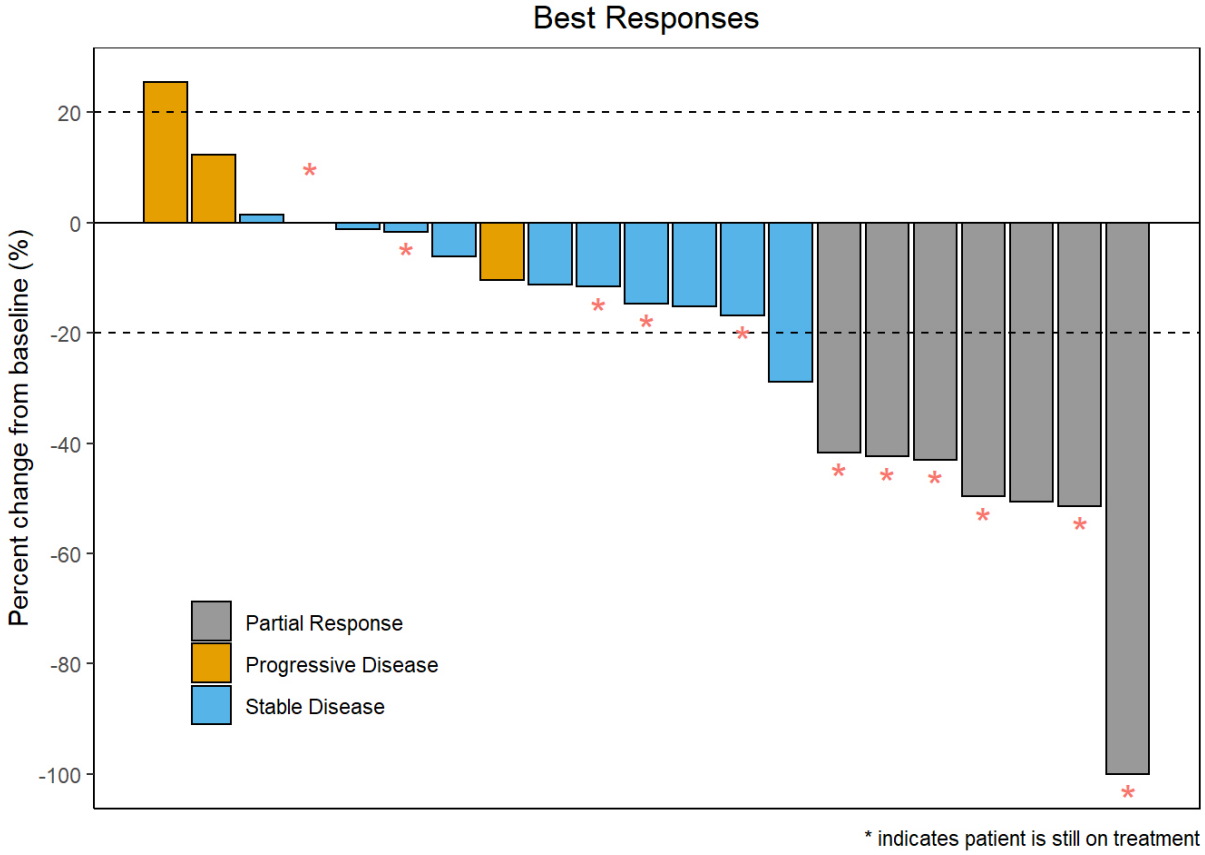

Fig. 1.