Patients randomly assigned received either margetuximab at a dose of 15 mg/kg intravenously weekly or trastuzumab at a dose of 8 mg/kg intravenously every 3 weeks. All patients had received prior trastuzumab; all but 1 had received prior pertuzumab and 489 (52%) had received prior ado-trastuzumab emtansine. Treatment options for third-line treatment and beyond include chemotherapy with trastuzumab, pertuzumab, or other HER2-targeted agents (Table 1). For 80% power to detect a median OS improvement from 12 to 16 months (HR, 0.75) at a 2-sided α = 0.025, 732 patients were required in each treatment group. The median follow-up of 20.2 months among all ITT patients, patients received a median of 14.1 cycles over 23.5 weeks. The median OS was 23.3 months with margetuximab versus 20.8 months with trastuzumab (HR by unstratified Cox model, 1.77 (95% CI, 1.01-3.12); median, 5.8 [95% CI, 5.5-7.0] months vs 4.9 [95% CI, 4.2-5.6] months; P = 0.033). Similarly disrupts signaling as trastuzumab but with greater affinity.

**Secondary Endpoints**

**Overall Response Rate (ORR)**

The margetuximab + chemotherapy group had a significantly higher ORR (93% (95% CI, 91-95)) vs 70% (95% CI, 62-77; P < 0.001) in patients with prior treatment with an HER2-targeted agent (Table 1, Figure 4).

**Duration of Response**

Median duration of response was 32 months in the margetuximab + chemotherapy group vs 11 months in the trastuzumab + chemotherapy group (P = 0.012). Overall survival was similar in patients with PD-L1+ and PD-L1− tumors (P = 0.59-0.98; median, 5.8 [95% CI, 5.5-7.0] months vs 4.9 [95% CI, 4.2-5.6] months; P = 0.033).

**Progression-Free Survival (PFS)**

The median PFS was 16.2 months in the margetuximab + chemotherapy group vs 5.8 months in the trastuzumab + chemotherapy group (HR by unstratified Cox model, 1.66 (95% CI, 1.04-2.65); median, 12.9 months vs 5.8 months; P = 0.04; Table 2).

**Safety**

AEs of LV dysfunction requiring dose delay or discontinuation were reported in 3 patients (1%) in the margetuximab group and 2 patients (1%) in the trastuzumab group (Table 4). AEs of LV dysfunction were generally mild and did not result in permanent LV dysfunction. There were no cardiac deaths in either treatment group. There were 72 (31.0%) AEs of grade 3 or 4 in the margetuximab group and 57 (25.7%) in the trastuzumab group. There were 7 grade 5 AEs in the margetuximab group and 4 in the trastuzumab group (all grades: margetuximab vs trastuzumab: bleeding (margetuximab group) and anemia (trastuzumab group; Table 4). Other grade 5 AEs were reported in 1 patient in each treatment group (both, pain in extremity).

**References**