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Review Comments

This is a well-written summary and commentary of the treatment and biologic landscape of this disease, relevant to the new phase 2 trial testing eribulin and ICI.

My only comment is a confusing statement that the treatment paradigm consists of FP/platinum plus ICI for pts with CPS 1+. This should be adjusted to CPS 5+. The best available data suggest minimal or questionable benefit in CPS 1-4 (Zhao et al, JCO 2021). Cat 2A/1 approval in NCCN is limited to CPS 5+. EMA approval is limited to CPS 5+. The discussion here could be more balanced and should reflect these data and consensus guidelines.

Reply: We thank the reviewer for the comments. We acknowledge the need to better clarify the statement regarding the treatment paradigm of FP/platinum plus nivolumab based on PD-L1 CPS score. We have modified the text to note that frontline treatment with FP/platinum plus nivolumab for HER2-negative disease is best supported in patients whose tumors have PD-L1 CPS $\geq$5. We have also added additional text to note that CheckMate 649 evaluated both the FOLFOX and CAPOX chemotherapy regimens.

Changes in text:
Page 2, Paragraph 2:
First-line strategies are presently informed by upfront molecular characterization of tumor tissue, including testing for microsatellite instability (MSI), programmed death ligand 1 (PD-L1), and human epidermal growth factor receptor 2 (HER2). For patients whose tumors are MSI-high or PD-L1 combined positive score (CPS) positive ($\geq$5) and HER2 negative, the treatment paradigm consists of a doublet of cytotoxic chemotherapy, including a fluoropyrimidine (5-fluorouracil [5-FU] or capecitabine) plus platinum (oxalipatin typically preferred over cisplatin due to more favorable toxicity profile) combined with an anti-programmed death 1 (PD-1) monoclonal antibody (mAb).

Page 2-3:
The CheckMate 649 study demonstrated that in previously untreated patients with advanced unresectable or metastatic esophageal, gastroesophageal junction (GEJ) and gastric adenocarcinoma, the addition of nivolumab to FOLFOX (5-FU plus oxaliplatin) or CAPOX (capecitabine plus oxaliplatin) chemotherapy compared with FOLFOX or CAPOX alone improved OS (13.8 vs 11.6 months, hazard ratio (HR) 0.80, 95% CI 0.68-0.94), progression free survival (PFS) [HR 0.77, 95% CI 0.68-0.87], and overall response rate (ORR) [60% vs 45%] in all randomized patients, with a larger magnitude of OS benefit (14.4 vs 11.1 months, HR 0.71, 95% CI 0.59-0.86) observed in patients with higher PD-L1, CPS $\geq$ 5 (4). Although the combination of fluoropyrimidine and platinum chemotherapy plus nivolumab received FDA approval for all patients with advanced HER2-negative gastroesophageal adenocarcinoma in the frontline setting regardless of PD-L1 CPS score, additional analyses have have called into question its benefit in patients with low PD-L1 expression (CPS <5) (5). Consequently, given the clearer benefit observed in patients with higher PD-L1 CPS score, current expert society

guidelines recommend the addition of nivolumab to chemotherapy for patients with PD-L1 CPS ≥5 (6).