Population Pharmacokinetic and Exposure-Response Evaluation of Nivolumab in Combination with Chemotherapy as First Line Treatment in Patients with Advanced or Metastatic Gastric or Gastroesophageal Junction or Esophageal Adenocarcinoma (CheckMate-649:CM649)

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[• REC] Please note: this presentation, including questions from the audience, is being recorded and may be made available.

Background

- Nivolumab (nivo) is a programmed death-1 (PD-1) receptor blocking monoclonal antibody; binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2.
- CM649, a randomized, open-label, Phase 3 study, demonstrated a favorable benefit-risk profile of nivo plus chemotherapy (chemo) over chemo alone in patients with non-HER2+ unresectable advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma (GC/GEJC/EAC) who have not received prior systemic therapy.
- Pharmacometric analyses supported the benefit-risk characterization of the two nivo plus chemo regimens in CM649: nivo 360 mg every 3 weeks (Q3W) plus XELOX or nivo 240 mg every 2 weeks (Q2W) plus FOLFOX. Both regimens have been approved in US/EU.

Methods

- A nivo PPK model was developed based on a previously developed model using 9,071 serum concentration values from 1,825 subjects from 7 nivo clinical studies to characterize nivo PK in GC/GEJC/EAC subjects, and to assess the impact of the baseline covariates on PK parameters.
- Using empirical Bayes estimates of PK parameters, measures of exposures (Cavg, Cmax, and Cmin) following the first dose and at steady-state were simulated and summarized.

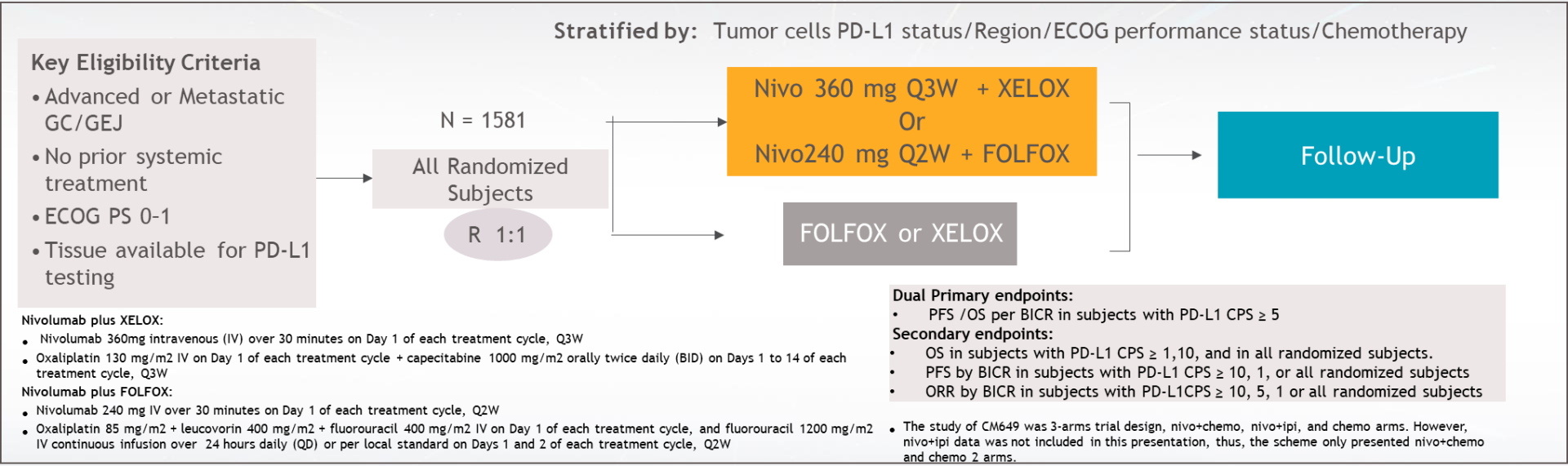
Methods (Cont'd)

- The exposure-response (ER) analysis included data from 1581 subjects from Study CM649, who had serum concentration and received either nivo + chemo (n=392 for Nivo 240 mg + FOLFOX and n=333 for Nivo 360 mg + XELOX) or chemo alone (n=791).
- Chemotherapy regimens were FOLFOX (folinic acid, fluorouracil, and oxaliplatin), and XELOX (capecitabine plus oxaliplatin).
- ER relationships for efficacy were characterized by evaluating the relationship between nivo exposure and progression-free survival (PFS) with CPS and overall survival (OS) for efficacy.

Methods (Cont'd)

- Grade 2+ immune-mediated adverse events (Gr2+ IMAEs) were evaluated in the ER analysis for safety using a Cox Proportional-Hazards (CPH) model.
- Significant covariates were assessed based on 95% CI without adjustments for multiplicity.
- ER efficacy and safety analyses were performed in 3 steps: identify the appropriate exposure matrix, select the functional form (linear or log-linear) of the ER relationship, and assess interaction between nivolumab and chemotherapy.
- Model comparisons were performed using BIC values.

CM649 Study Design Schematic and Endpoints



Nivolumab plus XELOX:

- Nivolumab 360mg intravenous (IV) over 30 minutes on Day 1 of each treatment cycle, Q3W
- Oxaliplatin 130 mg/m2 IV on Day 1 of each treatment cycle + capecitabine 1000 mg/m2 orally twice daily (BID) on Days 1 to 14 of each treatment cycle, Q3W

Nivolumab plus FOLFOX:

- Nivolumab 240 mg IV over 30 minutes on Day 1 of each treatment cycle, Q2W
- Oxaliplatin 85 mg/m2 + leucovorin 400 mg/m2 + fluorouracil 400 mg/m2 IV on Day 1 of each treatment cycle, and fluorouracil 1200 mg/m2 IV continuous infusion over 24 hours daily (QD) or per local standard on Days 1 and 2 of each treatment cycle, Q2W

Dual Primary endpoints:

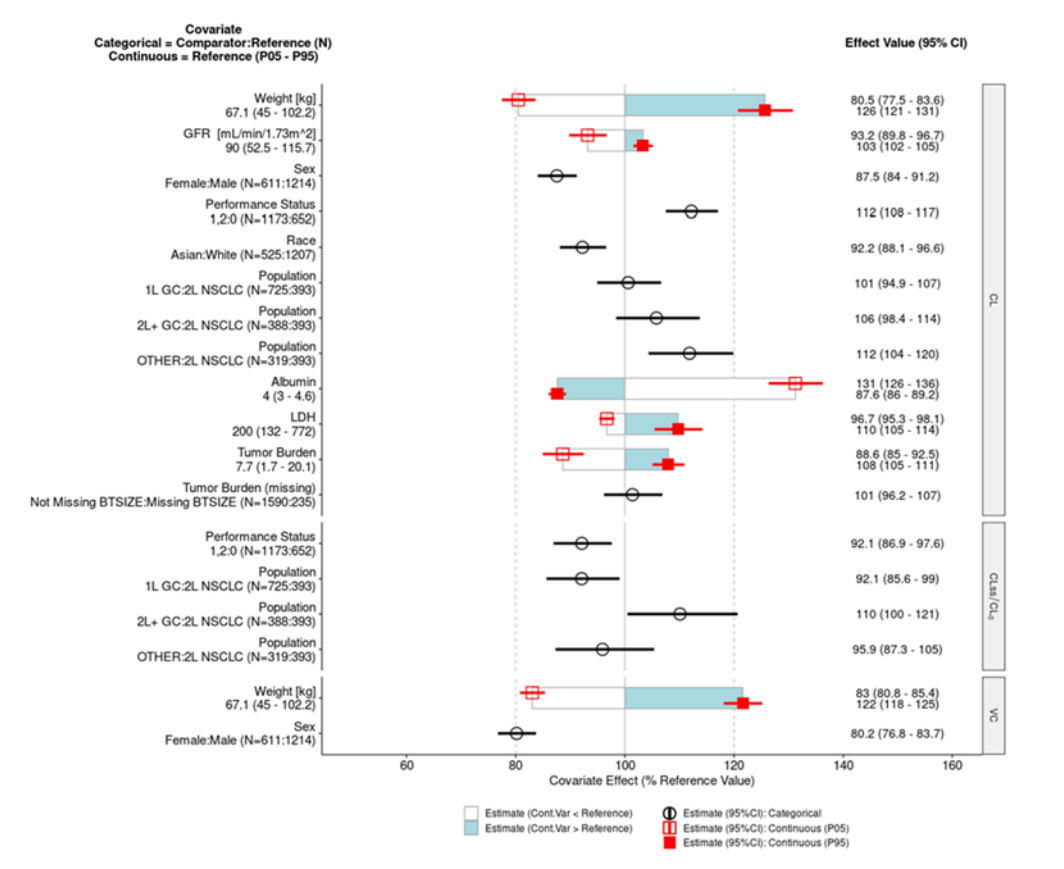
- PFS /OS per BICR in subjects with PD-L1 CPS ≥ 5

Secondary endpoints:

- OS in subjects with PD-L1 CPS ≥ 1,10, and in all randomized subjects.
- PFS by BICR in subjects with PD-L1 CPS ≥ 10, 1, or all randomized subjects
- ORR by BICR in subjects with PD-L1CPS ≥ 10, 5, 1 or all randomized subjects

- The study of CM649 was 3-arms trial design, nivo+chemo, nivo+ipi, and chemo arms. However, nivo+ipi data was not included in this presentation, thus, the scheme only presented nivo+chemo and chemo 2 arms.

Covariate Effects on Full Nivolumab PPK Model

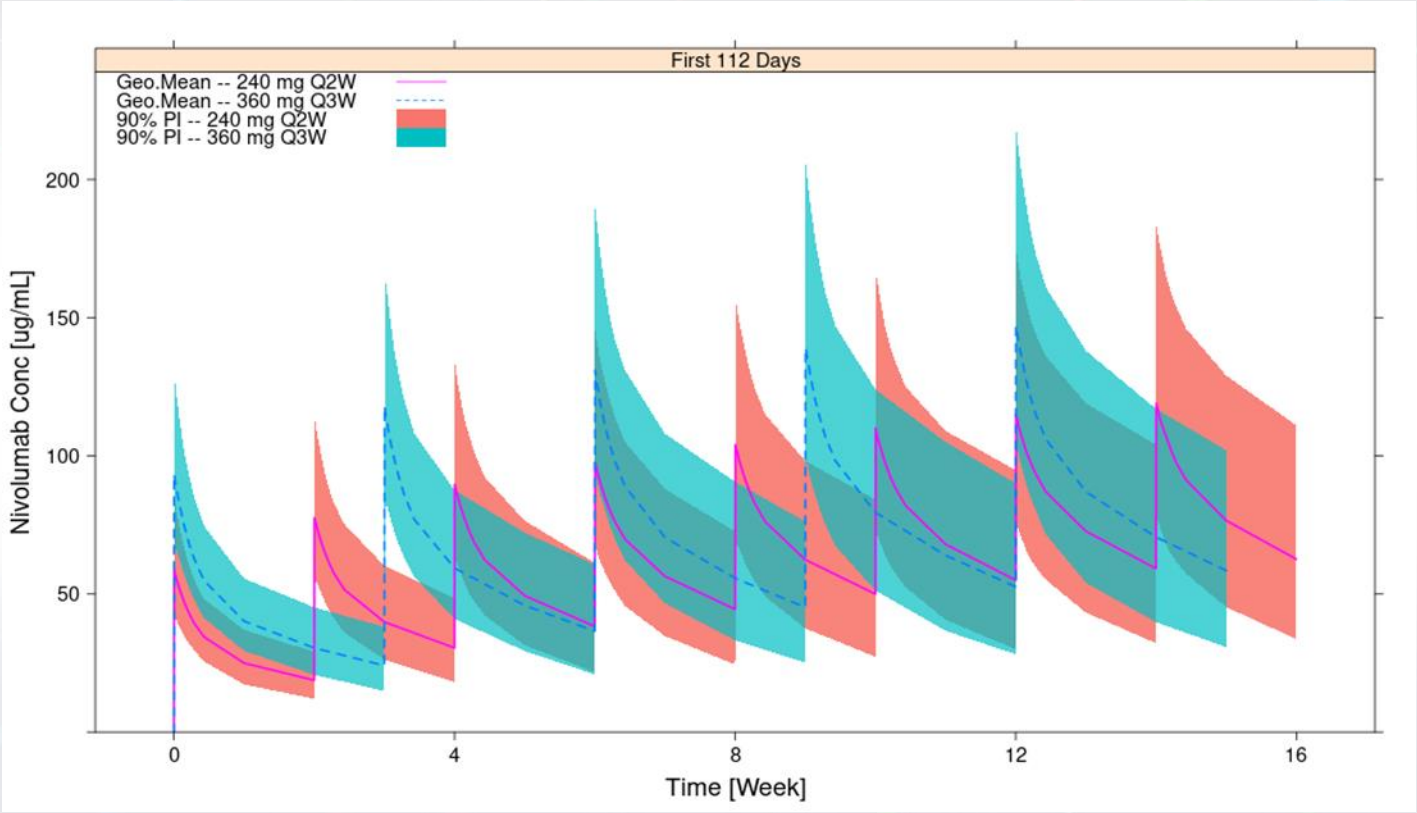


Summary Statistics of Exposures for Nivolumab 240 MG + FOLFOX Q2W and 360 MG + XELOX Q3W 1L GC/GEJC/EAC

	Geometric Mean (%CV)		Median (Min, Max)	
Summary Exposure	Nivo 240 mg + FOLFOX Q2W [µg/mL] (n=392)	Nivo 360 mg + XELOX Q3W [µg/mL] (n=333)	Nivo 240 mg + FOLFOX Q2W [µg/mL] (n=392)	Nivo 360 mg + XELOX Q3W [µg/mL] (n=333)
Cavg1	28.5 (21.7)	39.5 (21.2)	27.8 (17.1,61.8)	38.6 (20.4,68.7)
Cavgss	93.2 (33.6)	98.7 (33.3)	92.6 (36.2,243)	96.6 (32.4,217)
Cmax1	58.7 (22.5)	93.3 (20.9)	56.3 (29.6,118)	90.4 (53.1,155)
Cmaxss	134 (28.4)	166 (26.6)	134 (72.9,323)	163 (71.5,327)
Cmin1	18.8 (26.3)	24.1 (27.3)	18.8 (6.16,47.8)	24.5 (8.96,47.1)
Cminss	73.4 (38.5)	70.5 (40.1)	73.8 (18.3,212)	71.3 (15.1,176)

Abbreviations: 1L = first-line; Cavg1 = time-averaged serum concentration over the first dosing interval; Cavgss = time-averaged serum concentration at steady state; Cmax1 = post dose 1 peak serum concentration; Cmaxss = peak serum concentration at steady state; Cmin1 = trough serum concentration after the first nivolumab dose; Cminss = trough serum concentration at steady state; %CV = coefficient of variation expressed as a percent; EAC = esophageal adenocarcinoma cancer; FOLFOX = chemotherapy regimen of folinic acid, fluorouracil, and oxaliplatin; GC = gastric cancer; GEJC = gastroesophageal junction cancer; Max = maximum; Min = minimum; n = number of subjects; Q2W = every 2 weeks; Q3W = every 3 weeks; XELOX = chemotherapy regimen of capecitabine plus oxaliplatin.

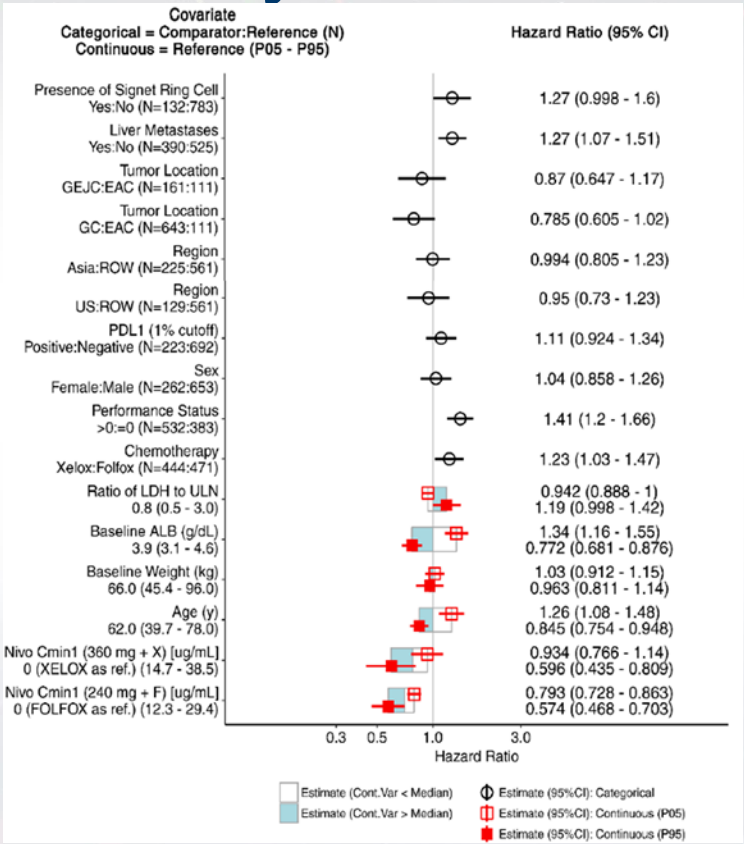
Predicted Geometric Mean (90% PI) Nivolumab Concentration-time Profiles (First 16 Weeks, Linear Scale) by Dosing Regimen (Nivolumab 240 mg Q2W + FOLFOX and Nivolumab 360 mg Q3W + XELOX), in Subjects with 1L GC/GEJC/EAC



Results – Population PK

- Nivo PK, including data in 1L GC/GEJC/EAC, was well described by a linear 2-compartment model with time-varying clearance (CL).
- Nivo PK properties in subjects with 1L GC/GEJC/EAC treated with nivo + chemo were similar to those in subjects with 2L NSCLC and 2L+ GC treated with nivo monotherapy.
- None of the covariates explored were found to have a clinically meaningful impact on nivo PK.
- The steady state exposure measures in 1L GC/GEJC/EAC were comparable between nivo 240 mg + FOLFOX Q2W and nivo 360 mg + XELOX Q3W.

Covariate Effects of the ER of PFS - All Randomized Subjects with PD-L1 CPS≥5



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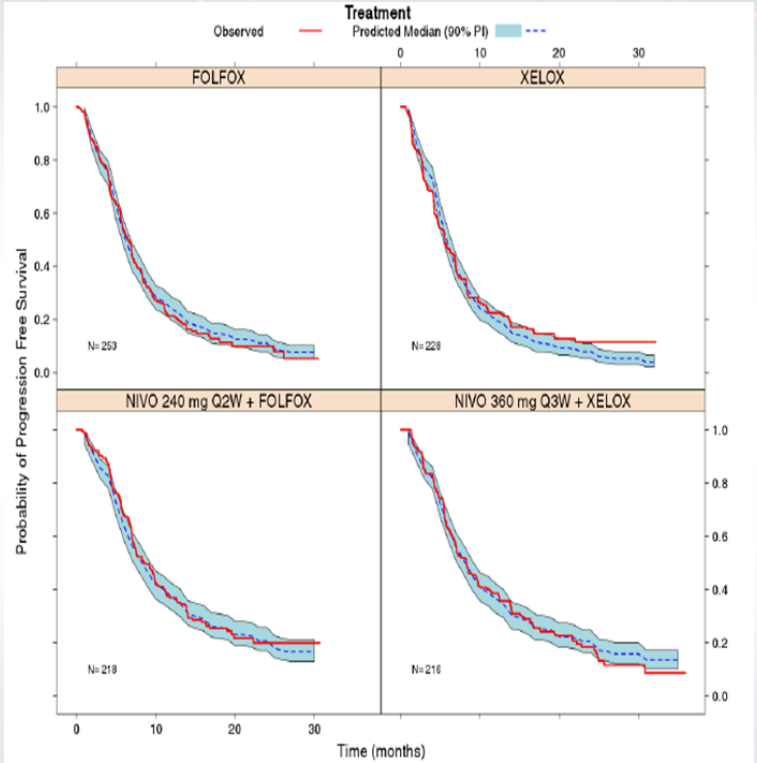
VPC Plot of Observed and Predicted Median (90% PI) of PFS, by Treatment - All Randomized Subjects with Tumor Cells PD-L1 CPS ≥5



Abbreviations: FOLFOX = chemotherapy regimen of folinic acid, fluorouracil, and oxaliplatin; N = number of subjects; NIVO = nivolumab; PI = prediction interval; PFS = progression-free survival; Q2W = every 2 weeks; Q3W = every 3 weeks; XELOX = chemotherapy regimen of capecitabine plus oxaliplatin.

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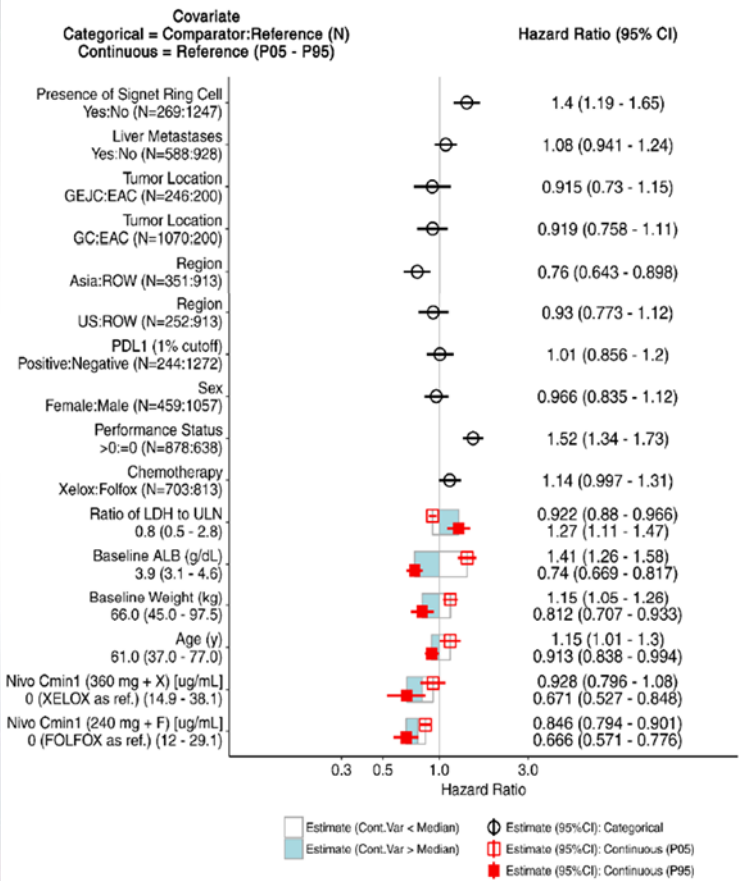
Covariate Effects of the ER of OS - All Randomized Subjects



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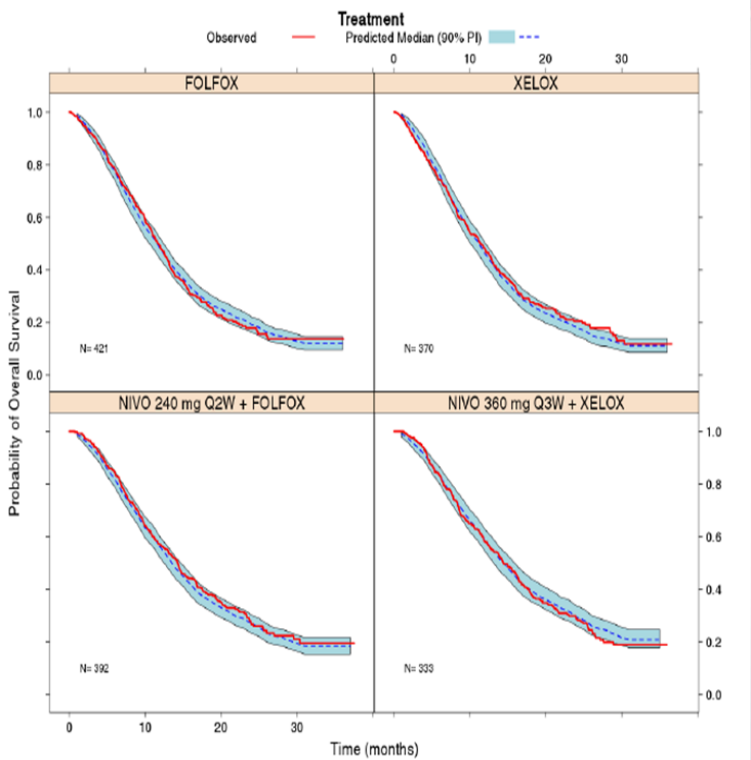
VPC Plot of Observed and Predicted Median (90% PI) of OS, by Treatment - All Randomized Subjects



Abbreviations: FOLFOX = chemotherapy regimen of folinic acid, fluorouracil, and oxaliplatin; N = number of subjects; NIVO = nivolumab; OS = overall survival; PI = prediction interval; Q2W = every 2 weeks; Q3W = every 3 weeks; XELOX = chemotherapy regimen of capecitabine plus oxaliplatin.

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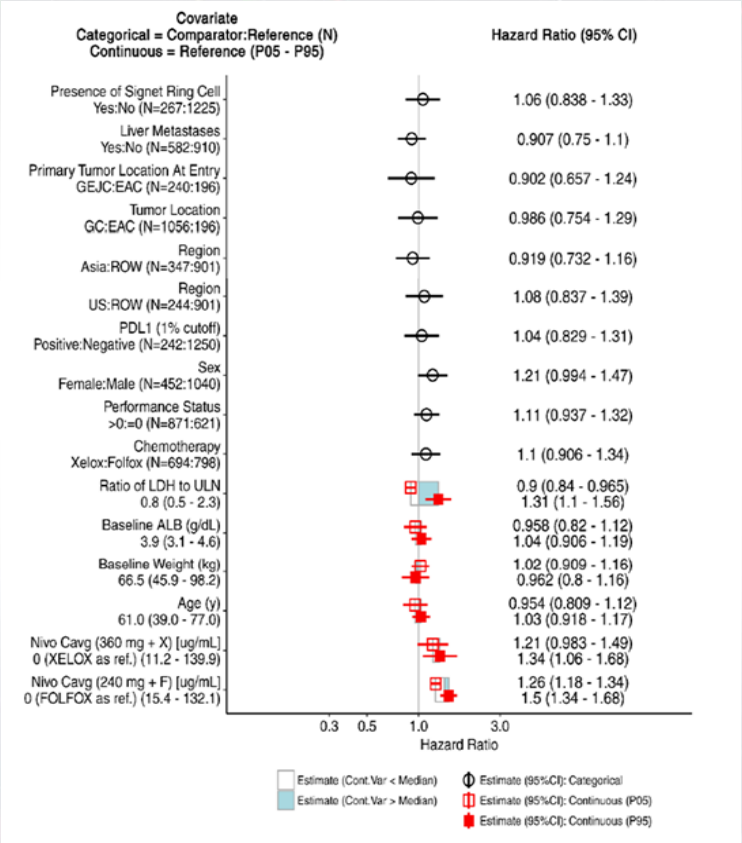
Results – ER Efficacy (PFS & OS)

- Nivo + chemo improved PFS and OS relative to chemo alone within the nivo exposure range produced by the 2 dosing regimens. Apparent ER relationships were determined for PFS and OS, but these two apparent relationships are likely steeper than the true ER relationship due to potential confounding effects of PK-disease interaction.
- The significant covariates associated with PFS were: age, liver metastases, ECOG PS, and baseline ALB. The risk of disease progression was higher in subjects with younger age, liver metastases, ECOG PS (> 0), and lower baseline ALB.

Results – ER Efficacy (PFS & OS) (Cont'd)

- The significant covariates associated with OS were: ECOG PS, Asia region, histological presence of signet ring cell, baseline weight, baseline ALB, and log ratio of baseline LDH to ULN.
- The risk of death was higher in subjects with the presence of signet ring cell, ECOG PS (> 0), higher log ratio of baseline LDH to ULN, lower baseline weight, and lower baseline ALB. OS was longer in the Asia region compared to other regions.

Covariate Effects of the Safety- Gr2+ IMAEs - All Treated Subjects



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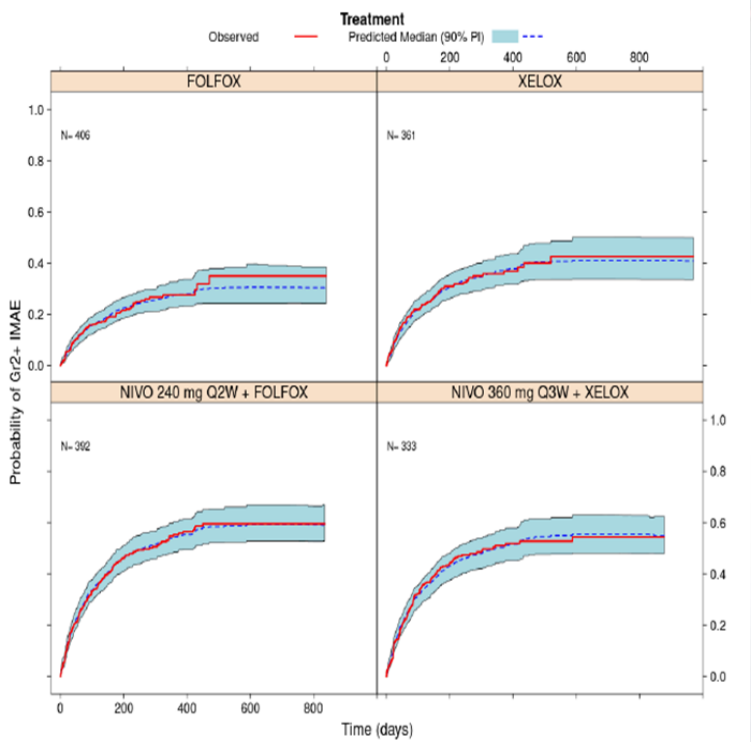
VPC Plot of Observed and Predicted Median (90% PI) of Gr2+ IMAE by Treatment - All Treated Subjects



Abbreviations: FOLFOX = chemotherapy regimen of folinic acid, fluorouracil, and oxaliplatin; Gr2+ IMAEs = Grade ≥ 2 immune-mediated adverse events; N = number of subjects; NIVO = nivolumab; PI = prediction interval; Q2W = every 2 weeks; Q3W = every 3 weeks; XELOX = chemotherapy regimen of capecitabine plus oxaliplatin.

Results – ER Safety

- The nivo + chemo arm had higher risk of Gr2+ IMAEs relative to chemo alone arm within the nivo exposure range produced by the 2 dosing regimens. The magnitude of Gr2+ IMAEs risk was similar between the 2 regimens, but the risk was higher with higher nivo exposure.
- The log ratio of baseline LDH to ULN was a significant covariate associated with Gr2+IMAEs, and the risk of Gr2+IMAEs was higher with a higher log ratio of baseline LDH to ULN.

Conclusions

- The PPK and ER analyses demonstrated that the 2 nivo + chemo regimens have similar nivo exposure at steady state, and improved benefit over chemo alone in 1L GC/GEJC/EAC subjects, resulting in similar benefit-risk profiles.

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Q&A

Questions & Answers