CheckMate 649: a Randomized, Multicenter, Open-Label, Phase 3 Study of Nivolumab Plus Ipilimumab vs Oxaliplatin Plus Fluorouracil in Patients With Previously Untreated Advanced or Gastroesophageal Junction Cancer

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Background
Gastric/Gastroesophageal Junction Cancer
- Gastric cancer is the fifth most common cancer worldwide by incidence and the third leading cause of cancer mortality.
- Gastroesophageal junction (GEJ) cancer is often treated in a similar manner as gastric cancer due to biological similarities.
- The combination of platinum compounds (eg, oxaliplatin) and fluoropyrimidine is a standard of care for first-line metastatic gastric/GEJ cancer.
- Median overall survival (OS) with this regimen ranges from 8 to 11 months in the United States and Europe and 12 to 14 months in Asian countries.
- New treatment options are needed to improve survival in patients with metastatic gastric/GEJ cancer.

Targeting Immune Checkpoints in Gastric/Gastroesophageal Junction Cancer

- Nivolumab is a fully human IgG4 monoclonal antibody that targets PD-1.
- PD-1 is an immune checkpoint receptor that regulates T-cell activation through binding of PD-L1 and PD-L2.
- In an ongoing phase 1/2 study in patients with gastric/GEJ/esophageal cancer refractory to ≥ 2 chemotherapy regimens (oxaliplatin plus fluoropyrimidine [XELOX] or oxaliplatin plus capecitabine [FOLFOX]), combination treatment with nivolumab and ipilimumab may increase antitumor effects by enhancing T-cell function through distinct mechanisms (Figure 1).

Study Rationale

- With a median OS of 8 to 14 months, there is an unmet need for new first-line treatment options to improve survival in patients with advanced or metastatic gastric/GEJ cancer.
- Immune checkpoint inhibitors have demonstrated clinical activity in multiple advanced solid tumor types, with improved tolerability compared with standard chemotherapies.
- In an ongoing phase 1/2 study in patients with gastric/GEJ/esophageal cancer refractory to 2 chemotherapy regimens with or without PD-L1–expressing tumors (PD-L1+), nivolumab plus ipilimumab 3 mg/kg demonstrated a manageable safety profile and preliminary antitumor activity:
  - Among all patients, the ORR was 26%, median OS was 6.9 months, and OS rate at 12 months was 34%.
  - In patients with PD-L1+ tumors, an ORR of 44% was observed.
  - Based on the activity in heavily pretreated patients, we hypothesized that nivolumab plus ipilimumab would improve outcomes in patients with previously untreated advanced or metastatic gastric/GEJ cancer compared with chemotherapy standard of care.

- CheckMate 649 (NCT0287216) is a phase 3 study of nivolumab plus ipilimumab vs oxaliplatin plus fluorouracil as first-line therapy in patients with advanced or metastatic gastric/GEJ cancer.

Study Objectives

- To compare OS with nivolumab plus ipilimumab vs that with chemotherapy standard of care (oxaliplatin plus fluoropyrimidine) in patients with previously untreated advanced or metastatic gastric/GEJ cancer with PD-L1+ tumors (PD-L1+ 1% expression).

Study Design

- CheckMate 649 is a randomized, multicenter, open-label, phase 3 study (Figure 2).
- An estimated 1266 patients will be randomized to receive nivolumab plus ipilimumab or 1 of 2 chemotherapy regimens (oxaliplatin plus fluoropyrimidine [XELOX] or oxaliplatin plus capecitabine [FOLFOX]).

Study Characteristics

- Nivolumab + ipilimumab (4 doses), Randomized
- Nivolumab + FOLFOX
- Tumor microenvironment

Enrollment Criteria

- Key enrollment criteria are below (Table 1).

Table 1. Key Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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<tbody>
<tr>
<td>Men and women ≥ 18 years old</td>
<td>Presence of unknown or new primary lesion</td>
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<tr>
<td>Irreversible or metastatic gastric/GEJ cancer and histologically confirmed adenocarcinoma</td>
<td>Active known or suspected autoimmune disease</td>
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<tr>
<td>No prior systemic treatment, including HER2 inhibitors, as primary therapy for advanced or metastatic disease</td>
<td>Presence of grade ≥ 1 peripheral neuropathy</td>
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<tr>
<td>No previous treatment for chemotherapy and/or radiation within the past 6 months</td>
<td>Unknown HER2 status</td>
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<tr>
<td>ECOG performance status of 0 or 1</td>
<td>History of a positive test for HIV or known AIDS</td>
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<tr>
<td>Must agree to provide a tumor tissue sample for determination of PD-L1 status</td>
<td>Positive test for hepatitis B or C indicating acute or chronic infection</td>
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Study Endpoints and Assessments

- Study endpoints are below (Figure 3).

Figure 3. Study Endpoints

<table>
<thead>
<tr>
<th>Primary Endpoints</th>
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<tbody>
<tr>
<td>OS in patients with PD-L1+ tumors</td>
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<tr>
<th>Secondary Endpoints</th>
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<tr>
<td>OS in all randomized patients</td>
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<tr>
<td>OS in patients with PD-L1+ tumors</td>
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Study Sites

- Enrolment is planned for 95 study sites in 20 countries (Figure 4).

References

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