Novartis investigational checkpoint inhibitor tislelizumab met primary endpoint of overall survival in pivotal Phase III trial of esophageal cancer after systemic therapy

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- Tislelizumab demonstrated a 30% reduction in the risk of death and extended median overall survival by 2.3 months compared to chemotherapy in advanced or metastatic esophageal squamous cell carcinoma after prior systemic therapy[1]
- Additional Phase II data presented at ASCO showed tislelizumab demonstrated durable anti-tumor activity in patients with microsatellite instability-high, or mismatch-repair-deficient, solid tumors[2]

EAST HANOVER, N.J., June 4, 2021 - Novartis announced today results from the pivotal Phase III RATIONALE 302 trial showing the investigational anti-PD-1 immune checkpoint inhibitor tislelizumab improved overall survival (OS) versus chemotherapy (median 8.6 months vs. 6.3 months, p=0.0001).[1] The study evaluated tislelizumab in patients with unresectable recurrent locally advanced or metastatic esophageal squamous cell carcinoma (ESCC) who had received prior systemic therapy. Results were presented at the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting.

Results from RATIONALE 302 in ESCC showed tislelizumab extended median OS by 2.3 months compared to chemotherapy with a 30% reduction in the risk of death (HR=0.70, 95% CI: 0.57-0.85, p=0.0001).[1] In PD-L1 positive patients, tislelizumab extended median OS by 3.5 months with a 46% reduction in the risk of death (HR=0.54, 95% CI: 0.36-0.79, p=0.0006).[1]

"These data show that tislelizumab has the potential to help patients with esophageal squamous cell carcinoma – one of the deadliest types of cancers – live longer," said Jeff Legos, Ph.D., MBA, Senior Vice President and Head of Oncology Drug Development. "We are excited about these results from the newest asset in our portfolio of transformational medicines and look forward to sharing these data with regulatory authorities, as we continue to explore the full potential of this uniquely designed anti-PD-1 antibody."

Treatment with tislelizumab demonstrated median progression-free survival (PFS) of 1.6 months compared to 2.1 months (HR=0.83, 95% CI: 0.67–1.01). Tislelizumab demonstrated a higher and more durable anti-tumor activity than chemotherapy (objective response rate [ORR], 20.3% vs. 9.8%; median duration of response [DoR], 7.1 months vs. 4.0 months).[1]

The discontinuation rate due to treatment-related adverse events (TRAEs) was lower in patients who received tislelizumab (6.7%) compared to chemotherapy (13.8%). The most common all-grade TRAEs (≥10%) with tislelizumab were increased aspartate aminotransferase (11.4%), anemia (11%) and hypothyroidism (10.2%). No new safety signals were identified.[1]

"Most patients with this type of esophageal cancer are diagnosed with advanced disease, resulting in a poor prognosis for this difficult-to-treat cancer," said Jaffer Ajani, M.D., professor of Gastrointestinal Medical

Oncology at The University of Texas MD Anderson Cancer Center. "The impact tislelizumab had on survival compared to chemotherapy in this study is highly meaningful and encouraging news for patients, caregivers and treating oncologists."

Esophageal squamous cell carcinoma is the most common type of esophageal cancer globally and the sixth leading cause of cancer-related death worldwide.[3] Each year, esophageal cancer claims nearly as many lives as colon cancer across the globe.[3] More than two-thirds of patients with ESCC have advanced or metastatic disease at the time of diagnosis.[4] The average five-year survival rate is only five percent.[5]

RATIONALE 302 is a randomized, global Phase III study assessing tislelizumab versus chemotherapy in patients with advanced unresectable/metastatic ESCC after prior systemic therapy. The primary endpoint is OS in the intent-to-treat (ITT) population. The key secondary endpoint is OS in PD-L1 positive patients (vCPS ≥10%). Additional secondary endpoints included PFS, ORR, DoR and safety endpoints.[1]

Data on tislelizumab in MSI-H cancers presented

The RATIONALE 209 study reported that tislelizumab showed durable anti-tumor activity in patients with previously treated, locally advanced, unresectable or metastatic microsatellite instability-high (MSI-H) and mismatch repair deficient (dMMR) cancers, which are known to be more responsive to immune checkpoint modulation. Treatment with tislelizumab demonstrated an ORR of 45.9% among all tumor types, including four complete responses (CR) and 30 partial responses (PR). No disease progression was reported in the 34 responders (CR + PR), with a 12-month DoR rate of 100%.[2]

Five percent of patients treated with tislelizumab discontinued treatment due to TRAEs, and no new safety signals were identified. Grade ≥3 TRAEs occurred in 42.5% of patients.[2]

MSI-H cancer cells have a defect in the ability to correct mistakes that occur when DNA is copied, leading to mutations that contribute to cancerous growth. Many types of cancer may have a high level of microsatellite instability, but it is seen most often in CRC, gastric cancer and endometrial cancer.[6]

RATIONALE 209 is a single-arm, open-label Phase II study evaluating the efficacy and safety of tislelizumab monotherapy in adult patients with previously treated, locally advanced, unresectable or metastatic histologically confirmed MSI-H/dMMR solid tumors. Radiological imaging was performed at nine weeks, then every six weeks for the first year of therapy and every 12 weeks thereafter. The primary endpoint was IRC-assessed ORR. Secondary endpoints included time to response, DoR, disease control rate, PFS, OS and safety.[2]

Visit https://www.hcp.novartis.com/virtual-congress/a-2021/ for the latest information from Novartis, including our commitment to the Oncology community, and access to our ASCO21 Virtual Scientific Program data presentations (for registered participants).

About tislelizumab

Tislelizumab was specifically engineered to minimize binding to macrophage Fcγ receptors, a potential mechanism of anti–PD-1 resistance.[7] Tislelizumab is an important component of Novartis's immuno-oncology strategy – one of four bold approaches to reimagining cancer and transforming patients' lives.

In an agreement finalized earlier this year, BeiGene granted Novartis rights to develop, manufacture, and commercialize tislelizumab in North America, Europe, and Japan through a collaboration and license agreement.

About Novartis

Located in East Hanover, NJ Novartis Pharmaceuticals Corporation – an affiliate of Novartis – is reimagining medicine to improve and extend people's lives. As a leading global medicines company, we use innovative science and digital technologies to create transformative treatments in areas of great medical need. In our quest to find new medicines, we consistently rank among the world's top companies investing in research and development. Novartis employs nearly 16,000 people in the United States. For more information, please visit https://www.novartis.us.

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References

1. Shen L, Kato K, Kim S-B, et al. RATIONALE 302: Randomized, Phase 3 study of tislelizumab vs chemotherapy as second-line treatment for advanced or metastatic esophageal squamous cell carcinoma. ePoster presentation at American Society of Clinical Oncology Annual Meeting (ASCO); June 2021
2. Li J, Xu Y, Zang A, et al. A Phase 2 study of tislelizumab monotherapy in patients with previously treated, locally advanced unresectable or metastatic microsatellite instability-high/mismatch repair deficient solid tumors. ePoster presentation at American Society of Clinical Oncology Annual Meeting (ASCO); June 2021
3. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2018;68(6):394-

424.
4. Chen Z, Ren Y, Du XL, et al. Incidence and survival differences in esophageal cancer among ethnic groups in the United States. Oncotarget. 2017;8(29):47037-47051.
5. Howlader N, et al. SEER Cancer Statistics Review, 1975–2017. National Cancer Institute, MD, USA (2020). https://seer.cancer.gov /csr/1975_2017/
6. National Cancer Institute. Microsite instability-high cancer. Accessed May 5, 2021. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/microsatellite-instability-high-cancer
7. Zhang T, Song X, Xu L, et al. The binding of an anti-PD-1 antibody to FcγRI has a profound impact on its biological functions. Cancer Immunol Immunother. 2018;67(7):1079-1090.

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1. https://qa1.novartis.us/news/media-releases/novartis-investigational-checkpoint-inhibitor-tislelizumab-met-primary-endpoint-overall-survival-pivotal-phase-iii-trial-esophageal-cancer-after-systemic-therapy
2. https://www.hcp.novartis.com/virtual-congress/a-2021/
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