



Tislelizumab Fact Sheet

<p>Description</p>	<p>Tislelizumab is an anti-programmed cell death protein-1 (PD-1) antibody to help aid the body's immune cells to detect and fight tumors.ⁱ</p> <p>Tislelizumab is the first product from BeiGene's immuno-oncology biologics program and is being developed globally as a monotherapy and in combination with other therapies for the treatment of a broad array of both solid tumor and hematologic cancers.</p> <p>Tislelizumab is approved by the China National Medical Products Administration (NMPA) as a treatment for nine indications, including multiple approvals in non-small cell lung cancer (NSCLC).ⁱⁱ Additional regulatory submissions are under review for tislelizumab as a potential second-line treatment for NSCLC in Europe, Great Britain and Australia.ⁱⁱ</p> <p>Tislelizumab is also under review as a second-line treatment for unresectable recurrent locally advanced or metastatic esophageal squamous cell carcinoma (ESCC) after prior systemic therapy in the U.S., Europe, Great Britain and Australia.</p> <p>In addition, tislelizumab has been accepted for regulatory review as a first-line treatment for patients with advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 in China.</p> <p>In January 2021, BeiGene partnered with Novartis to accelerate the clinical development and marketing of tislelizumab in the U.S., Europe and Japan.ⁱⁱ</p>
<p>Mechanism of Action</p>	<p>Tislelizumab, a humanized monoclonal antibody, is specifically designed to minimize binding to FcγR on macrophages.ⁱ</p> <p>In pre-clinical studies, binding to FcγR on macrophages has been shown to compromise the anti-tumor activity of anti-PD-1 antibodies through activation of antibody-dependent macrophage-mediated killing of T effector cells.ⁱⁱⁱ</p>
<p>Tislelizumab Clinical Development Program</p>	<p>The global tislelizumab clinical development program includes more than 11,000 subjects enrolled to-date in 30 countries and regions. BeiGene has initiated or completed more than 20 potentially registration-enabling clinical trials, including 17 Phase 3 trials and four pivotal Phase 2 trials.ⁱⁱ</p> <p>BeiGene is committed to clinical trials and the use of data from trials spanning numerous geographies and patient populations. Utilizing new technologies and opening operations in strategic markets, BeiGene is able to further increase access to areas and communities that have not been able to participate in clinical trials while meeting global quality standards for medical practice and data collection.</p>

<p>RATIONALE-309^{iv} in R/M NPC</p>	<p>RATIONALE-309 (NCT03924986) is an ongoing multicenter, randomized, double-blind, placebo-controlled Phase 3 clinical trial designed to evaluate the efficacy and safety of tislelizumab combined with gemcitabine and cisplatin (Arm A) versus placebo combined with gemcitabine and cisplatin (Arm B) as a first-line treatment for patients with R/M NPC.^{iv}</p> <ul style="list-style-type: none"> • A total of 263 patients were enrolled in the trial, with 131 and 132 randomized to Arm A and Arm B, respectively, with balanced baseline characteristics between both arms.^{iv} • Interim results from the trial were presented at the 2021 European Society for Medical Oncology Immuno-Oncology (ESMO I-O) Congress^v. The study met its primary endpoint of PFS, after a median follow up of 10.0 months.^v • Updated efficacy analyses presented at the 2022 Annual ASCO meeting^{vi} showed that, at a median follow-up of 15.5 months, tislelizumab in combination with chemotherapy continued to demonstrate a clinically significant progression-free survival (PFS) benefit over chemotherapy alone for patients with R/M NPC. • Patients administered a 200 mg intravenous dose of tislelizumab (every 3 weeks) in combination with chemotherapy achieved a median PFS of 9.6 months (stratified hazard ratio (HR)=0.50 [CI: 0.37, 0.68]) compared to 7.4 months for patients dosed with placebo control and chemotherapy, as assessed by an independent review committee.^{vi} • A positive overall survival (OS) trend was also observed with median OS not yet reached in the tislelizumab combination arm and 23 months for the chemotherapy plus placebo arm (HR=0.60 [95% CI: 0.35, 1.01]).^{vi} • The safety profile of the tislelizumab and chemotherapy combination was generally manageable and consistent with known risks of each treatment agent.^{vi}
<p>RATIONALE-306 in 1L ESCC</p>	<p>RATIONALE-306 (NCT03783442) is a global Phase 3 trial of tislelizumab in combination with chemotherapy in patients with previously untreated advanced or metastatic ESCC.</p> <p>The trial enrolled 649 patients at research centers across Asia-Pacific, Europe, and North America.</p> <p>In April 2022, BeiGene disclosed that the trial met the study's primary endpoint of OS at an interim analysis.^{vii} The study's safety profile was consistent with previous trials with no new safety signals per PR.^{vii}</p>
<p>RATIONALE-302^{viii} in 2L ESCC</p>	<p>RATIONALE-302 (NCT03430843) is a Phase 3 trial comparing tislelizumab with chemotherapy as second-line treatment for patients with advanced ESCC.^{viii}</p>

	<p>This global phase 3 study enrolled 512 patients from 132 sites in 11 countries in Asia, Europe, and North America.^{viii}</p> <ul style="list-style-type: none"> • The study met its primary endpoint with a clinically and statistically improvement in OS compared with chemotherapy in the ITT population (median OS: 8.6 vs 6.3 m; HR=0.70, 95% CI: 0.57-0.85, p=0.0001)^{viii} • Treatment with tislelizumab was associated with a higher overall response rate (ORR) (20.3% vs 9.8%) and more durable response (median DoR: 7.1 vs 4.0 months; HR 0.42, 95% CI: 0.23-0.75) than chemotherapy^{viii} • Fewer patients in the tislelizumab arm reported ≥Grade 3 (46% vs 68%) treatment-emergent adverse events than in the chemotherapy arm^{viii} • Patients experienced at least one treatment-emergent adverse event at around the same rate, with 96% reporting in the tislelizumab arm vs 98% in the chemotherapy arm.^{viii}
<p>RATIONALE-301 1L in HCC</p>	<p>RATIONALE-301 (NCT03412773) is a global, open-label randomized Phase 3 trial comparing tislelizumab with sorafenib as first-line treatment for patients with unresectable hepatocellular carcinoma (HCC).</p> <p>The primary endpoint of the study is OS. Secondary endpoints include ORR, PFS, DoR, health-related quality of life measures and safety.</p> <p>The trial enrolled 674 participants in Asia, Europe, and North America.</p>
<p>Other Pivotal Clinical Trials of Tislelizumab as a Monotherapy^{ix}</p>	<ul style="list-style-type: none"> ▪ RATIONALE-208: Phase 2 trial in patients with previously treated unresectable hepatocellular carcinoma (NCT03419897) ▪ Phase 2 trial in patients with locally advanced or metastatic urothelial bladder cancer (NCT04004221) ▪ Phase 2 trial of tislelizumab in patients with relapsed or refractory classical Hodgkin Lymphoma (NCT03209973) ▪ RATIONALE-209: Phase 2 trial in patients with microsatellite instability-high/mismatch repair deficient solid tumors (NCT03736889) ▪ RATIONALE-303: Phase 3 trial comparing tislelizumab with docetaxel in the second- or third line setting in patients with non-small cell lung cancer (NCT03358875) ▪ BGB-A317-314: Phase 3 trial comparing tislelizumab to salvage chemotherapy in patients with relapsed or refractory classical Hodgkin Lymphoma (NCT04486391)
<p>Other Pivotal Clinical Trials of Tislelizumab as a Combination</p>	<ul style="list-style-type: none"> ▪ RATIONALE-304: Phase 3 trial of tislelizumab in combination with chemotherapy versus chemotherapy as first-line treatment for patients with advanced non-squamous non-small cell lung cancer (NCT03663205)

<p>Therapy with Chemotherapy^{ix}</p>	<ul style="list-style-type: none"> ▪ RATIONALE-305: Phase 3 trial of tislelizumab combined with chemotherapy versus placebo combined with chemotherapy as first-line treatment for patients with gastric cancer (NCT03777657) ▪ RATIONALE-307 Phase 3 trial of tislelizumab in combination with chemotherapy versus chemotherapy as first-line treatment for patients with advanced squamous non-small cell lung cancer (NCT03594747) ▪ RATIONALE-310: Phase 3 trial in patients with locally advanced or metastatic urothelial carcinoma (NCT03967977) ▪ RATIONALE-311: Phase 3 trial of tislelizumab versus placebo in combination with chemoradiotherapy in patients with localized esophageal squamous cell carcinoma (NCT03957590) ▪ RATIONALE-312: Phase 3 trial of tislelizumab combined with platinum and etoposide versus placebo combined with platinum and etoposide in patients with extensive-stage small cell lung cancer (NCT04005716) ▪ RATIONALE-315: Phase 3 trial of tislelizumab in combination with platinum-based doublet chemotherapy as neoadjuvant treatment for patients with non-small cell lung cancer (NCT04379635)
<p>Clinical Trials of Tislelizumab as a Combination Therapy with Ociperlimab^{ix}</p>	<ul style="list-style-type: none"> ▪ AdvanTIG-105: Tislelizumab in combination with ociperlimab in advanced solid tumors ▪ AdvanTIG-202: Phase 2 trial of tislelizumab in combination with ociperlimab in metastatic cervical cancer (NCT04693234) ▪ AdvanTIG-203: Phase 2 trial of tislelizumab in combination with ociperlimab in advanced esophageal squamous cell carcinoma (NCT04732494) ▪ AdvanTIG-204: Phase 2 trial of tislelizumab in combination with ociperlimab with concurrent chemoradiotherapy in patients with untreated limited-stage small cell lung cancer (NCT04952597) ▪ AdvanTIG-205: Tislelizumab with ociperlimab and chemotherapy in patients with untreated metastatic non-small cell lung cancer ▪ AdvanTIG-206: A study investigating the efficacy and safety of tislelizumab and ociperlimab and BAT1706 combinations in patients with advanced hepatocellular carcinoma ▪ AdvanTIG-301: Phase 3 trial of tislelizumab in combination with ociperlimab in locally advanced, unresectable non-small cell lung cancer (NCT04866017) ▪ AdvanTIG-302: Phase 2 trial of tislelizumab in combination with ociperlimab in untreated non-small cell lung cancer (NCT04746924)

ⁱ Zhang, L., Yang, Y., Pan, J-J., et. al. RATIONALE-309: Updated progression-free survival (PFS), PFS after next line of treatment, and overall survival from a phase 3 double-blind trial of tislelizumab versus placebo, plus chemotherapy, as first-line treatment for recurrent/metastatic nasopharyngeal cancer. *Journal of Clinical Oncology* 40, no. 36_suppl (April 20, 2022) 384950-384950.

ⁱⁱ BeiGene Press Release. BeiGene Reports Second Quarter 2022 Financial Results. Accessed: <https://ir.beigene.com/news/beigene-reports-second-quarter-2022-financial-results/ac313a7f-ec4a-40db-9475-9759b3804dca/>

ⁱⁱⁱ Zhang T, 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

^{iv} Zhang, L., Yang, Y., Pan, J-J., et. al. RATIONALE-309: Updated progression-free survival (PFS), PFS after next line of treatment, and overall survival from a phase 3 double-blind trial of tislelizumab versus placebo, plus chemotherapy, as first-line treatment for recurrent/metastatic nasopharyngeal cancer. *Journal of Clinical Oncology* 40, no. 36_suppl (April 20, 2022) 384950-384950.

^v Yang, Y., Pan, J., Wang, H., RATIONALE 309: A randomized, global, double-blind, phase III trial of tislelizumab (TIS) vs placebo, plus gemcitabine + cisplatin (GP), as first-line treatment for recurrent/metastatic nasopharyngeal cancer (RM-NPC). *Annals Of Oncology* Vol 32_suppl 7, (December 1, 2021) S1430

^{vi} BeiGene Corporate Announcement April 27, 2022. Available here: <https://ir.beigene.com/news/global-phase-3-trial-of-beigene-s-pd-1-inhibitor-tislelizumab-in-combination-with-chemotherapy-meets-primary/c094ebdc-5bfb-4f42-a6f9-5b214ade9b16/>

^{vii} BeiGene Press Release. Global Phase 3 Trial of BeiGene's PD-1 Inhibitor, Tislelizumab, in Combination with Chemotherapy Meets Primary Endpoint in First-Line Advanced Esophageal Squamous Cell Carcinoma – NASDAQ (US) Website Accessed: <https://ir.beigene.com/news/global-phase-3-trial-of-beigene-s-pd-1-inhibitor-tislelizumab-in-combination-with-chemotherapy-meets-primary/c094ebdc-5bfb-4f42-a6f9-5b214ade9b16/>

^{viii} Shen, L. et. al., RATIONALE 302: Randomized, phase 3 study of tislelizumab versus chemotherapy as second-line treatment for advanced unresectable/metastatic esophageal squamous cell carcinoma. *Journal of Clinical Oncology* 2021 39:15_suppl, 4012-4012

^{ix} BeiGene (2022). Pipeline. *Our Science and Medicines*. Accessed: <https://www.beigene.com/our-science-and-medicines/pipeline/>