Clinical Development of BeiGene TIGIT and OX40 Targeted Therapies

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Senior Vice President, Global Medical Affairs & New Market Development
Disclosure information

Todd Yancey
I am an employee of BeiGene, Ltd.

Editorial acknowledgment
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BeiGene is committed to discovering and developing innovative products that will bring meaningful value to people with cancer around the world.

Our mission is to build the first next-generation biopharmaceutical company — one that expands the highest quality therapies to billions more people — through courage, persistent innovation, and challenging the status quo.

Build an exceptional research organization with broad capabilities and scope.

Fight for a life without cancer, striving for exceptional science, quality, and impact, by driving affordability through operational excellence and efficiency.

Strive to bring together more affordable medicines to more patients.
BeiGene’s internal pipeline consists of a wide range of monotherapies and combination therapies (1/2)

These therapies include novel oral small molecules and monoclonal antibodies for cancer

<table>
<thead>
<tr>
<th>Assets</th>
<th>Programs</th>
<th>Dose escalation</th>
<th>Dose expansion</th>
<th>PIVOTAL</th>
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<tbody>
<tr>
<td>Zanubrutinib</td>
<td>monotherapy</td>
<td>R/R MCL, (approved in multiple geographies), 1L and R/R WM (filings accepted in multiple geographies; approved in Canada)</td>
<td>R/R MCL, R/R CLL/SLL (conditionally approved by NMPA in China 06.03.20)</td>
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<td>B-cell malignancies</td>
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<td>combination</td>
<td>1L CLL/SLL, R/R CLL/SLL, R/R MZL, lupus nephritis, previously treated CLL/SLL (ibrutinib/acalbrutinib intolerant)</td>
<td>+ obinutuzumab B-cell malignancies</td>
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<td>1L CLL/SLL</td>
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<td>Previously treated advanced MSI-high or dMMR solid tumors</td>
<td>Solid tumors</td>
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<td>1L NPC, 1L GC, 1L ESCC</td>
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<td>1L SCLC and NSCLC</td>
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<tr>
<td></td>
<td>+ pamiparib (PARP) or + zanubrutinib (BTK)</td>
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1L, first-line; 2L, second-line; 3L, third-line; BTK, Bruton’s tyrosine kinase; cHL, classical Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; ESCC, esophageal squamous cell carcinoma; FL, follicular lymphoma; GC, gastric cancer; HCC, hepatocellular carcinoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NK, natural killer; NMPA, National Medicinal Products Administration; NPC, nasopharyngeal carcinoma; NSCLC, non-small cell lung cancer; non-sq, non-squamous; PARP, poly-ADP ribose polymerase; PD-1, programmed cell death protein-1; PH, phase; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; SCLC, small cell lung cancer; sNDA, supplemental new drug application; sq, squamous; UC, urothelial carcinoma; WM, Waldenstrom macroglobulinemia
BeiGene’s internal pipeline consists of a wide range of monotherapies and combination therapies (2/2)

These therapies include novel oral small molecules and monoclonal antibodies for cancer

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<tr>
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<tr>
<td>Pamiparib (PARP)</td>
<td>monotherapy</td>
<td>3L gBRCA + OC, Advanced OC and TNBC (approved for OC)</td>
<td>2L/3L platinum-sensitive OC maintenance</td>
<td>1L platinum-sensitive GC maintenance</td>
<td>TNBC or HR+HER2 BRCA mutated breast cancer</td>
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<td>Ociperlimab (BGB-A1217, TIGIT)</td>
<td>+ tislelizumab</td>
<td>1L Stage III unresectable NSCLC, 1L PD-L1 high advanced NSCLC</td>
<td>Solid tumors</td>
<td>1L PD-L1 high ESCC, 2L CC, 1L LS-SCLC, 1L HCC</td>
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<td>Lirafenib (RAF dimer)</td>
<td>+ mirdametinib</td>
<td>B-Raf- or K-RAS/N-RAS-mutated solid tumors</td>
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<tr>
<td>BGB-A445 (OX40)</td>
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<td>BGB-10188 (PI3-K5)</td>
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<td>B-cell malignancies: solid tumors</td>
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<td>BGB-15025 (HPK1)</td>
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1L, first-line; 2L, second-line; 3L, third-line; BCL-2, B cell lymphoma 2; BRCA, breast cancer gene; CC, cervical cancer; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; gBRCA, germline breast cancer gene; HCC, hepatocellular carcinoma; HER2, human epidermal growth factor receptor 2; HPK1, hematopoietic progenitor kinase 1; KRAS, kirsten rat sarcoma viral oncogene homolog; NRAS, neuroblastoma RAS viral oncogene homolog; NSCLC, non-small cell lung cancer; OC, ovarian cancer; PD-L1, programmed death-ligand 1; PH, phase; R/M, recurrent/metastatic; PI3-K5, phosphoinositide 3-kinase 5; RT, radiotherapy; TIGIT, T-cell immunoreceptor with immunoglobulin and tyrosine-based inhibitory motif domain; TIM-3, T-cell immunoglobulin and mucin domain-3; TMZ, temozolomide; TNBC, triple negative breast cancer
Our global clinical studies enroll participants from over 35 countries

BeiGene has products marketed in the US, Canada, and China

Over 370 participants from more than 20 clinical studies are from South Korea
BeiGene has over 20 clinical studies with sites in South Korea

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<td>+ chemotherapy</td>
<td>1L GC</td>
<td>1L ESSC</td>
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<td>1L ESCC</td>
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<td>B-cell malignancies</td>
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<td>1L MBC/GC</td>
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<tr>
<td>Ociperlimab</td>
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<td>Solid tumors</td>
<td>2L+ CC</td>
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<td>2L PD-L1 high ESCC</td>
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<td>1L Stage III unresectable NSCLC</td>
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<td>1L PD-L1 high advanced NSCLC</td>
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<td>Solid tumors</td>
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<td>+ zanidatamab</td>
<td>Solid tumors</td>
<td>2L+ BTC</td>
<td>PH2</td>
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1L, first-line; 2L, second-line; BTC, biliary tract carcinoma; CC, cervical cancer; ESCC, esophageal squamous cell carcinoma; FL, follicular lymphoma; GEA, gastroesophageal carcinoma; GC, gastric cancer; HER2, human epidermal growth factor receptor 2; LS-SCLC, limited stage small cell lung cancer; MBC, metastatic breast cancer; MZL, marginal zone lymphoma; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; PH, phase; R/R, relapsed/refractory; UCB, urothelial carcinoma of the bladder
Given the high unmet medical need among patients with solid tumors, novel targets are required.

Targeting more than one part of the cancer immunity cycle may enhance antitumor activity.

CTLA4, cytotoxic T-lymphocyte associated protein 4; MDSC, myeloid-derived suppressor cells; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TIM-3, T-cell immunoglobulin and mucin domain-3; TIGIT, T-cell immunoreceptor with immunoglobulin and tyrosine-based inhibitory motif domains; Treg, regulatory T cell; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.
Tislelizumab is a globally developed next-generation monoclonal antibody against PD-1

Tislelizumab is the first drug candidate produced from BeiGene’s immuno-oncology biologic program

**Mechanism of action**

Tislelizumab was designed to minimize FcγR binding on macrophages in order to abrogate antibody-dependent cellular phagocytosis, a potential mechanism of resistance to anti-PD-1 therapy

**Clinical program**

- China NMPA approval of tislelizumab in 1L Sq NSCLC (Jan 2021)
- China NMPA approval of tislelizumab in R/R cHL (Dec 2019); in R/R PD-L1+ UC (04.2020)
- NMPA accepted sNDAs for 1L non-Sq NSCLC (Jun 2020); 2L/3L HCC (Jul 2020); 2L/3L NSCLC (Mar 2021)

**Select Phase 3 data**

FcyR, Fcγ receptors; mAb, monoclonal antibody; PD-1, programmed cell death protein

Tislelizumab is a globally developed next-generation monoclonal antibody against PD-1

Tislelizumab is under investigation in clinical studies for the treatment of a broad range of tumors

- Approximately **7,700 participants** enrolled in tislelizumab clinical studies
- Over **25 clinical trials** in multiple indications
  - Classical Hodgkin lymphoma
  - Urothelial carcinoma
  - NSCLC
  - HCC
  - ESCC
  - GC
  - Nasopharyngeal cancer
  - Extensive-stage SCLC
  - NK/T-cell lymphomas
  - MSI-H or dMMR solid tumors

**Mechanism of action**

**Clinical program**

**Select Phase 3 data**

dMMR, deficient mismatch repair; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; HCC, hepatocellular carcinoma; MSI-high, microsatellite instability high; NK cell, natural killer cell; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; SCLC, small-cell lung cancer
Tislelizumab is a globally developed next-generation monoclonal antibody against PD-1

Tislelizumab has demonstrated clinical efficacy and tolerability compared with chemotherapy

1L squamous NSCLC (N=360)\(^1\)
- **Arm A**: Tislelizumab + paclitaxel + carboplatin: mPFS 7.6 months; HR 0.52\(^a\)
- **Arm B**: Tislelizumab + nab-paclitaxel + carboplatin: mPFS 7.6 months; HR 0.48\(^a\)
- **Arm C**: Paclitaxel + carboplatin: mPFS 5.5 months
- Grade ≥3 TEAE (n=355): 88.3%, 86.4%, and 83.8% of patients in arm A, B, and C, respectively

1L non-squamous NSCLC (N=334)\(^2\)
- **Arm A**: Tislelizumab + pemetrexed-platinum: mPFS 9.7 months; HR 0.65\(^b\)
- **Arm B**: Pemetrexed-platinum mPFS 7.6 months
- Grade ≥3 TEAE (n=332): 67.6% and 53.6% of patients in arm A and B, respectively

2L/3L NSCLC (N=805)\(^3\)
- **Arm A**: Tislelizumab monotherapy: mOS 17.2 months; HR 0.64\(^c\)
- **Arm B**: Docetaxel: mOS 11.9 months
- Grade ≥3 TEAE (n=792): 38.6% and 74.8% of patients in arm A and B, respectively

2L ESCC (N=512)\(^4\)
- **Arm A**: Tislelizumab monotherapy: mOS 8.6 months; HR 0.70\(^d\)
- **Arm B**: Chemotherapy: mOS 6.3 months
- Grade ≥3 TEAE (n=495): 46.3% and 67.9% of patients in arm A and B, respectively

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\(^a\)P<0.001, \(^b\)P=0.004; \(^c\)P<0.0001; \(^d\)P =0.0001.

Immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway have improved clinical outcomes compared with conventional therapy; however, resistance can occur over time\textsuperscript{1–3}

<table>
<thead>
<tr>
<th>Tislelizumab</th>
<th>Ociperlimab</th>
<th>BGB-A445</th>
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<tbody>
<tr>
<td>A next-generation mAb antibody against PD-1</td>
<td>A humanized IgG1 mAb designed to bind to TIGIT with high specificity and affinity</td>
<td>A humanized IgG1 agonist mAb designed to bind to OX40 with high specificity and affinity</td>
</tr>
</tbody>
</table>

Ociperlimab and BGB-A445 have unique mechanisms of action.

Dual targeting of signaling pathways may produce synergistic immune cell activation and enhance antitumor activity\textsuperscript{4,5}

IgG1, immunoglobin G1; mAb, monoclonal antibody; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TIGIT, T-cell immunoreceptor with immunoglobulin and tyrosine-based inhibitory motif domains

Immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway have improved clinical outcomes compared with conventional therapy; however, resistance can occur over time\textsuperscript{1–3}.

Dual targeting of signaling pathways may produce synergistic immune cell activation and enhance antitumor activity\textsuperscript{4,5}.

Tislelizumab

- A next-generation mAb antibody against PD-1

Ociperlimab

- A humanized IgG1 mAb designed to bind to TIGIT with high specificity and affinity

BGB-A445

- A humanized IgG1 agonist mAb designed to bind to OX40 with high specificity and affinity

Ociperlimab and BGB-A445 have unique mechanisms of action.

---

IgG1, immunoglobulin G1; mAb, monoclonal antibody; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TIGIT, T-cell immunoreceptor with immunoglobulin and tyrosine-based inhibitory motif domains

TIGIT is a co-inhibitory immune checkpoint receptor expressed on immune cells, including T and NK cells\(^1\)

**TIGIT is upregulated on CD8+ T cells, Tregs, and NK cells across multiple solid tumor malignancies\(^2\)**

Expression of TIGIT may suppress immune responses, and promote T-cell exhaustion, and inhibit NK cell cytotoxicity\(^1\)–\(^4\)

CD155 (PVR) is the main ligand to which TIGIT binds. CD155 is expressed on tumor cells and antigen-presenting cells\(^2\)

TIGIT binds to CD112 (nectin-2). CD112 is over-expressed on tumor cells of many human malignancies\(^2\)

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Solid tumor cells exploit the TIGIT pathway to inhibit anti-cancer immune responses

Engagement of TIGIT to its ligands leads to inhibitory signaling in T cells and NK cells, disruption of CD226 co-stimulatory signaling, and inhibition of a wide range of immune cells by promoting the suppressive function of Tregs\(^1\)–\(^3\)

The suppressive effect of TIGIT is counterbalanced by CD226, an immune-activating receptor which competes with TIGIT to bind to CD155 and CD112\(^1\)

CD226 is expressed on NK and cytotoxic T cells\(^1\)

Preclinical data: Ociperlimab is a humanized IgG1 monoclonal antibody designed to bind to TIGIT with high specificity and affinity

Ociperlimab suppresses TIGIT-mediated inhibitory signaling. This results in reactivation of T cell and NK cell function, T cell expansion, and reduction of Tregs

CD, cluster of differentiation; HLA, human leukocyte antigen; Ig, immunoglobulin; IFN, interferon; NK, natural killer; pp65, major human cytomegalovirus structural protein; PVR, poliovirus receptor; TIGIT, T cell immunoreceptor with immunoglobulin (Ig) and tyrosine-based inhibitory motif (ITIM) domains.


Ociperlimab blocks the interaction between TIGIT, and CD155 (PVR) and CD112 (nectin-2) on tumor cells, resulting in re-activation of T cell-mediated and NK cell antitumor immune responses

Ociperlimab increases ligand availability for the CD226 co-stimulatory receptor, which leads to re-activation of T cells and NK cells
Anti-TIGIT antibodies were incubated overnight with human PMBCs from a lung cancer donor, and NK cells from a healthy donor.

FACS was used to assess:

A) Treg levels
B) CD8\(^+\) T cells
C) CD4\(^+\) T cells
D) TIGIT expression on T cells

*\(p<0.05\), **\(p<0.01\), ***\(p<0.001\). Ociperlimab MF = variant with “silent Fc” mutations. Ab, antibody; CD, cluster of differentiation; FACS, fluorescence-activated cell sorting; iso, isolated; NK, natural killer; PMBC, peripheral blood mononuclear cells; TIGIT, T-cell immunoreceptor with immunoglobulin and tyrosine-based inhibitory motif domains; Tregs, regulatory T cells

1. Chen X et al. Presented at AACR 2021
Preclinical data: Ociperlimab removes TIGIT from T-cell surfaces in an Fc function-dependent manner

Ociperlimab induced trogocytosis on CD4+ and CD8+ T cells

T cells were incubated with ociperlimab and FcγR-blocking antibodies. Lower MFI observed when FcγR were blocked, suggesting that FcγR are essential for ociperlimab-TIGIT binding.

*\(p<0.05\), ****\(p<0.0001\). T cells and monocytes from the same healthy donor were incubated with CF633-labeled ociperlimab or CF633-labeled ociperlimab MF overnight. T cells and monocytes were incubated with ociperlimab and treated with FcγR blocking antibodies, to determine dependence on FcγR. Changes in TIGIT MFI on T cells were measured by FACS. Ociperlimab MF = variant with "silent Fc" mutations. CD, cluster of differentiation; FACS, fluorescence-activated cell sorting; Fc, fragment crystallizable; MFI, mean fluorescence intensity; R, receptor; TIGIT, T-cell immunoreceptor with immunoglobulin and tyrosine-based inhibitory motif domains. 1. Chen X et al. Presented at AACR 2021

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<th>CD8+ T cells</th>
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<td>-100</td>
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<tr>
<td>Ociperlimab MF</td>
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<td>+</td>
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<td>FcγRI blockade -</td>
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<td>FcγRII blockade -</td>
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<td>FcγRIII blockade -</td>
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<th>TIGIT MFI change (%) on human CD4+ T cells</th>
<th>TIGIT MFI change (%) on human CD8+ T cells</th>
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<td>FcγRII blockade</td>
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<td>FcγRIII blockade</td>
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**TIGIT MFI change (%)**

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<td>FcγRIII blockade</td>
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**TIGIT MFI change (%)**
Preclinical data: The Fc effector function is critical for the antitumor activity of ociperlimab

Ociperlimab reduced Tregs (A), down-regulated TIGIT (B), and up-regulated CD226 (C) on T cells in a Fc effector function-dependent manner in vivo.

Ociperlimab also induced significant tumor growth inhibition (approx. 70%) on Day 19 of treatment, relative to the vehicle group (P<0.05) (data not shown).

\*p<0.05, \*\*p<0.01, \*\*\*p<0.001, \*\*\*\*p<0.0001. CT26WT tumor-bearing humanized TIGIT knock-in mice were treated ociperlimab or ociperlimab MF. Data shown as mean ± SEM. Ociperlimab MF = variant with "silent Fc" mutations. CD, cluster of differentiation; Fc, fragment crystallizable; Q5D, every 5 days; MFI, mean fluorescence intensity; SEM, standard error of the mean; TIGIT, T cell immunoreceptor with immunoglobulin and tyrosine-based inhibitory motif domains; Treg, regulatory T cell. 1. Chen X et al. Presented at AACR 2021.
Rationale for combining ociperlimab with tislelizumab

Targeting of immunomodulatory pathways by combining ociperlimab with tislelizumab may lead to synergistic immune activation

CD, cluster of differentiation; IFN, interferon; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; PVR, poliovirus receptor; TCR, T cell receptor; TIGIT, T cell immunoreceptor with immunoglobulin and tyrosine-based inhibitory motif domains; TNF, tumor necrosis factor

1. Chen X et al. Presented at AACR 2021

Preclinical data: Ociperlimab in combination with tislelizumab significantly enhanced T cell functions

Ociperlimab augmented T cell responses in combination with tislelizumab

IFN\(\gamma\) secretion was higher with ociperlimab plus tislelizumab, compared with ociperlimab alone

Conc., concentration; IFN, interferon
1. Chen X et al. Presented at AACR 2021
AdvanTIG-105 (Phase 1) dose-escalation study

This was the first in-human trial of ociperlimab

Phase 1a, dose-escalation, first-in-human study

**Primary endpoints**
- AEs and serious AEs
- MTD or MAD

**Secondary endpoints**
- ORR, DoR, and DCR, as assessed using RECIST v1.1
- Serum concentrations at specified timepoints and PK parameters of ociperlimab and tislelizumab
- Immunogenic responses to ociperlimab and tislelizumab, evaluated through the detection of ADAs

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Key eligibility criteria:
- Adults (≥ 18 years)
- Histologically or cytologically confirmed advanced or metastatic solid tumor that has been previously treated with standard systemic therapy
- ≥ 1 evaluable lesion per RECIST v1.1
- ECOG PS ≤ 1

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**Phase 1 study: dose escalation**
(28 days for first cycle, 21 days for cycles thereafter)

- **Ociperlimab 900 mg IV C1D1** → tislelizumab 200 mg IV C1D8 → ociperlimab 900 mg IV + tislelizumab 200 mg IV C2D1, then Q3W (n≥3)
- **Ociperlimab 450 mg IV C1D1** → tislelizumab 200 mg IV C1D8 → ociperlimab 450 mg IV + tislelizumab 200 mg IV C2D1, then Q3W (n≥3)
- **Ociperlimab 150 mg IV C1D1** → tislelizumab 200 mg IV C1D8 → ociperlimab 150 mg IV + tislelizumab 200 mg IV C2D1, then Q3W (n=1)
- **Ociperlimab 50 mg IV C1D1** → tislelizumab 200 mg IV C1D8 → ociperlimab 50 mg IV + tislelizumab 200 mg IV C2D1, then Q3W (n=1)

**Phase 1b dose-expansion study (following on from this Phase 1 dose-escalation study)**

All patients treated until disease progression, intolerable toxicity, or withdrawal

Dose expansion in cohorts by tumor type

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ADA, anti-drug antibody; AE, adverse event; C, cycle; D, day; DCR, disease control rate; DLT, dose-limiting toxicity; DoR, duration of response; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IV, intravenous; MAD, maximum administered dose; MTD, maximum tolerated dose; ORR, objective response rate; PK, pharmacokinetic; Q3W, every three weeks; RECIST, Response Evaluation Criteria In Solid Tumours; RP2D, recommended Phase 2 dose; SAE, serious adverse event; v, version

1. Frentzas et al. Presented at ASCO 2021
As of February 2021, a total of 26 patients were enrolled

A range of solid tumor types were included in the study

- Median age of patients was 55.5 years, and 11 (42.3%) patients were male; majority of patients were white (n=18, [69.2%])
- Tumor types included squamous and non-squamous NSCLC, head and neck cancer, gastric/gastroesophageal junction cancer, esophageal cancer, pancreatic cancer, colorectal cancer, uterine cancer, and melanoma

<table>
<thead>
<tr>
<th></th>
<th>OCI 50 mg plus TIS 200 mg (n=1)</th>
<th>OCI 150 mg plus TIS 200 mg (n=3)</th>
<th>OCI 450 mg plus TIS 200 mg (n=6)</th>
<th>OCI 900 mg plus TIS 200 mg (n=16)</th>
<th>Total (N=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients treated with any study drug, n (%)</td>
<td>1 (100.0)</td>
<td>3 (100.0)</td>
<td>6 (100.0)</td>
<td>16 (100.0)</td>
<td>26 (100.0)</td>
</tr>
<tr>
<td>Patients discontinued from ociperlimab, n (%)</td>
<td>1 (100.0)</td>
<td>2 (66.7)</td>
<td>5 (83.3)</td>
<td>14 (87.5)</td>
<td>22 (84.6)</td>
</tr>
<tr>
<td>Patients discontinued from tislelizumab, n (%)</td>
<td>1 (100.0)</td>
<td>2 (66.7)</td>
<td>5 (83.3)</td>
<td>14 (87.5)</td>
<td>22 (84.6)</td>
</tr>
<tr>
<td>Reasons for discontinuation from study drugs, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse event</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (6.3)</td>
<td>1 (3.8)</td>
</tr>
<tr>
<td>Withdrawal by patient</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (12.5)</td>
<td>2 (7.7)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>1 (100.0)</td>
<td>2 (66.7)</td>
<td>5 (83.3)</td>
<td>11 (68.8)</td>
<td>19 (73.1)</td>
</tr>
<tr>
<td>Patients discontinued from study, n (%)</td>
<td>1 (100.0)</td>
<td>2 (66.7)</td>
<td>3 (50.0)</td>
<td>8 (50.0)</td>
<td>14 (53.8)</td>
</tr>
</tbody>
</table>

Data cut-off: February 21, 2021
NSCLC: non-small cell lung cancer; OCI, ociperlimab; TIS, tislelizumab
1. Frentzas et al. Presented at ASCO 2021
Ociperlimab was administered at a starting dose of 50 mg

Ociperlimab exposure increased approximately dose proportionally from 50–900 mg

After IV administration, serum concentration of ociperlimab decreased in a biphasic manner

Complete and sustained receptor occupancy of CD8 T cells (shown), CD4, Treg, and NK cells in peripheral blood mononuclear cells was observed at ≥50 mg doses of ociperlimab and at all timepoints

Data cut-off: February 21, 2021
Conc., concentration; C, cycle; D, day; CD, cluster of differentiation; HR, hour; IV, intravenous; PRE, pre; RO, receptor occupancy
1. Frentzas et al. Presented at ASCO 2021
Preliminary antitumor activity was observed

Partial response was observed in two patients (one patient at 450 mg and one patient at 900 mg ociperlimab). SD was observed in 9 patients (one at 150, three at 450, and five at 900 mg). The longest duration of stable disease was 54 weeks (one patient at 150 mg ociperlimab).

Three patients had a >30% reduction in target lesions.

Data cut-off: February 21, 2021
AE, adverse event; N, no; NE, not evaluable; PD-L1, programmed death-ligand 1; TC, tumor cell; Y, yes
1. Frentzas et al. Presented at ASCO 2021
Ociperlimab plus tislelizumab was well tolerated in patients with advanced solid tumors

The type and severity of adverse events observed were consistent with tislelizumab monotherapy

- Twenty-five (96.2%) out of 26 patients had ≥1 TEAE. Fifteen (57.7%) patients experienced at least one immune-related TEAE
- There were three Grade ≥3 immune-related AEs (colitis, cortisol decrease, and diabetic ketoacidosis), which occurred in the ociperlimab 900 mg group
- No DLTs were observed

<table>
<thead>
<tr>
<th>Patients with ≥1 TEAE</th>
<th>OCI 50 mg plus TIS 200 mg, n (%) (n=1)</th>
<th>OCI 150 mg plus TIS 200 mg, n (%) (n=3)</th>
<th>OCI 450 mg plus TIS 200 mg, n (%) (n=6)</th>
<th>OCI 900 mg plus TIS 200 mg, n (%) (n=16)</th>
<th>Total, n (%) (N=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any treatment-related TEAE</td>
<td>1 (100.0)</td>
<td>3 (100.0)</td>
<td>6 (100.0)</td>
<td>15 (93.8)</td>
<td>25 (96.2)</td>
</tr>
<tr>
<td>Serious TEAE</td>
<td>1 (100.0)</td>
<td>1 (33.3)</td>
<td>5 (83.3)</td>
<td>10 (62.5)</td>
<td>17 (65.4)</td>
</tr>
<tr>
<td>Serious treatment-related TEAE</td>
<td>1 (100.0)</td>
<td>1 (33.3)</td>
<td>2 (33.3)</td>
<td>9 (56.3)</td>
<td>13 (50.0)</td>
</tr>
<tr>
<td>Grade ≥3 TEAE</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>4 (25.0)</td>
<td>4 (15.4)</td>
</tr>
<tr>
<td>Grade ≥3 treatment-related TEAE</td>
<td>1 (100.0)</td>
<td>1 (33.3)</td>
<td>3 (50.0)</td>
<td>11 (68.8)</td>
<td>16 (61.5)</td>
</tr>
<tr>
<td>Immune-related TEAE</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>4 (25.0)</td>
<td>4 (15.4)</td>
</tr>
<tr>
<td>Serious immune-related TEAE</td>
<td>1 (100.0)</td>
<td>1 (33.3)</td>
<td>5 (83.3)</td>
<td>8 (50.0)</td>
<td>15 (57.7)</td>
</tr>
<tr>
<td>Grade ≥3 immune-related TEAE</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>3 (18.8)</td>
<td>3 (11.5)</td>
</tr>
</tbody>
</table>

Data cut-off: February 21, 2021

AE, adverse events; DLT, dose-limiting toxicity; OCI, ociperlimab; TEAE, treatment-emergent adverse event; TIS, tislelizumab

1. Frentzas et al. Presented at ASCO 2021
In AdvanTIG-105 Phase 1 dose-escalation, ociperlimab plus tislelizumab was well tolerated in patients with advanced solid tumors. The Phase 1b dose-expansion study is ongoing.

The type and severity of adverse events observed were consistent with tislelizumab monotherapy. No DLTs were observed. Recommended Phase 2 dose was determined: ociperlimab 900 mg IV plus tislelizumab 200 mg IV Q3W. Preliminary antitumor activity was observed.

Data cut-off: February 21, 2021
DLT, dose-limiting toxicity
1. Frentzas et al. Presented at ASCO 2021
Ociperlimab plus tislelizumab combination therapy is being investigated across a broad range of solid tumors

There are currently six ongoing Phase 2/3 studies

<table>
<thead>
<tr>
<th>Phase</th>
<th>Key objectives</th>
<th>Tumor type</th>
<th>Locations</th>
</tr>
</thead>
<tbody>
<tr>
<td>AdvanTIG-202¹</td>
<td>Antitumor efficacy and safety of tislelizumab with or without ociperlimab</td>
<td>Cervical cancer</td>
<td>18 global locations, inc. Korea</td>
</tr>
<tr>
<td>AdvanTIG-203²</td>
<td>Antitumor efficacy and safety of tislelizumab + ociperlimab vs tislelizumab + placebo</td>
<td>ESCC</td>
<td>100 global locations, inc. Korea</td>
</tr>
<tr>
<td>AdvanTIG-204³</td>
<td>Evaluate the efficacy and safety tislelizumab + ociperlimab + cCRT, followed by ociperlimab + tislelizumab vs tislelizumab vs cCRT alone</td>
<td>LS-SCLC</td>
<td>32 global locations, inc. Korea</td>
</tr>
<tr>
<td>AdvanTIG-206⁴</td>
<td>Efficacy and safety of ociperlimab in combination with tislelizumab plus BAT1706*, and tislelizumab plus BAT1706</td>
<td>HCC</td>
<td>25 global locations</td>
</tr>
<tr>
<td>AdvanTIG-301⁵</td>
<td>Efficacy and safety of tislelizumab + ociperlimab + cCRT followed by tislelizumab + ociperlimab vs tislelizumab vs cCRT followed by durvalumab</td>
<td>NSCLC</td>
<td>200 locations globally inc. Korea</td>
</tr>
<tr>
<td>AdvanTIG-302⁶</td>
<td>Efficacy and safety of tislelizumab + ociperlimab vs pembrolizumab + placebo</td>
<td>NSCLC</td>
<td>170 global locations, inc. Korea</td>
</tr>
</tbody>
</table>

¹BAT1706 is a recombinant humanized anti-VEGF monoclonal antibody injection, and a proposed biosimilar to the bevacizumab injection, Avastin®

2. NCT04693234; 3. NCT04732494; 4. NCT04952597; 5. NCT04948697; 6. NCT04866017; 7. NCT04746924
Immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway have improved clinical outcomes compared with conventional therapy; however, resistance can occur over time\textsuperscript{1–3}

Dual targeting of signaling pathways may produce synergistic immune cell activation and enhance antitumor activity\textsuperscript{4,5}

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**Tislelizumab**

A next-generation mAb antibody against PD-1

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**Ociperlimab**

A humanized IgG1 mAb designed to bind to TIGIT with high specificity and affinity

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**BGB-A445**

A humanized IgG1 agonist mAb designed to bind to OX40 with high specificity and affinity

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**Ociperlimab and BGB-A445**

Have unique mechanisms of action

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OX40 is an immune co-stimulatory receptor primarily expressed on activated T cells

- Binding of OX40 to its ligand (OX40L) promotes T cell survival, differentiation, expansion, cytokine production, and effector function
- OX40 agonist antibodies improve effector function of T cells while counteracting the immunosuppressive effects of regulatory T cells and have shown to induce tumor regression in vivo

BGB-A445 is a unique non-ligand blocking OX40 antibody

- Unlike ligand-blocking OX40 antibodies, BGB-A445 does not disrupt OX40-OX40L engagement
- BGB-A445 achieves maximal T-cell activation by keeping natural ligand (OX40L) stimulation from APCs

BGB-A445’s non-ligand blocking properties differentiates it from all other OX40 antibodies that disrupt OX40-OX40L engagement

Ab. antibody; APC, antigen-presenting cells
BGB-A445 in combination with tislelizumab is currently under investigation in participants with advanced solid tumors

This is a two-part dose-escalation and dose-expansion Phase 1 study

**Primary endpoints:** Phase 1a: AEs, SAEs, MTD or MAD, recommended Phase 2 dose; Phase 1b: ORR

Key eligibility criteria:
- Adults ≥ 18 years of age
- Phase 1a: patients with histologically or cytologically confirmed advanced or metastatic tumor who have previously received standard systemic therapy, or for whom treatment is not available or tolerated
- ≥ 1 measurable lesion per RECIST v1.1
- ECOG PS ≤ 1
- Available FFPE tumor sample

AE, adverse events; ECOG, Eastern Cooperative Oncology Group; FFPE, formalin-fixed paraffin embedded; IV, intravenous; MAD, multiple ascending dose; MTD, maximum tolerated dose; ORR, overall response rate; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event

1. NCT04215978. Available at ClinicalTrials.gov. Accessed June 2021
BeiGene is a global biopharmaceutical company with drug development capabilities across the globe


Ociperlimab and BGB-A445 are humanized monoclonal antibodies designed to bind to TIGIT and OX40, respectively, with high specificity and affinity\(^1,2\)

Dual targeting of tislelizumab with either ociperlimab or BGB-A445 may lead to synergistic immune cell activation to enhance antitumor activity\(^1–4\)

We are growing our pipeline to create combination therapies with meaningful and lasting impact on patients with cancer

We are looking to expand our portfolio with the aim of reaching a wider range of patients with different unmet medical needs
Any questions?