Clinical Development of BeiGene TIGIT and OX40 Targeted Therapies

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Disclosure information

Todd Yancey

I am an employee of BeiGene, Ltd.

Editorial acknowledgment

Medical writing support for the development of this presentation, under the direction of the author, was provided by Yasmin Issop, PhD, and Tamsin Grewal, MSc, of Ashfield MedComms, an Ashfield Health company, and was funded by BeiGene, Ltd.

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

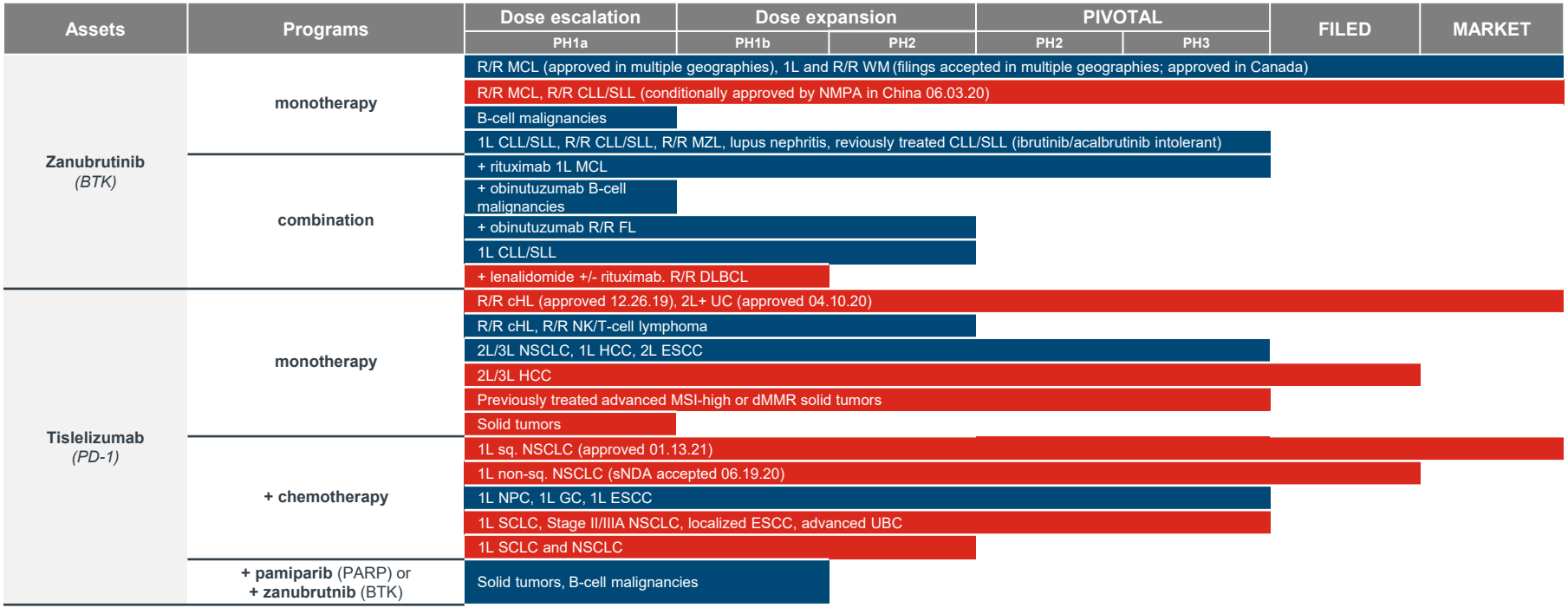
Fight for a life without cancer, striving for exceptional science, quality, and impact, by driving affordability through operational excellence and efficiency

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

Global
China



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

Global
China

Assets	Programs	Dose escalation	Dose expansion		PIVOTAL		FILED	MARKET
		PH1a	PH1b	PH2	PH2	PH3		
Pamiparib (*PARP*)	**monotherapy**	3L gBRCA + OC, Advanced OC and TNBC (approved for OC)						
		2L/3L platinum-sensitive OC maintenance						
		1L platinum-sensitive GC maintenance						
		TNBC or HR+/HER2 BRCA mutated breast cancer						
		Solid tumors						
	+ TMZ (*chemotherapy*)	Solid tumors						
	+ RT/TMZ (*RT/chemotherapy*)	Glioblastoma						
Ociperlimab (BGB-A1217, *TIGIT*)	**+ tislelizumab**	1L Stage III unresectable NSCLC, 1L PD-L1 high advanced NSCLC						
		2L PD-L1 high ESCC, 2L+ CC, 1L LS-SCLC, 1L HCC						
		Solid tumors						
Lifirafenib (*RAF dimer*)	**+ mirdametinib**	B-Raf- or K-RAS/N-RAS-mutated solid tumors						
BGB-A333 (*PD-L1*)	**monotherapy + tislelizumab**	Solid tumors						
BGB-A425 (*TIM-3*)	**monotherapy + tislelizumab**	Solid tumors						
BGB-A445 (*OX40*)	**+ tislelizumab**	Solid tumors						
BGB-11417 (*BCL-2*)	**monotherapy + zanubrutinib**	B-cell malignancies						
BGB-10188 (*PI3-K5*)	**monotherapy; + tislelizumab; + zanubrutinib**	B-cell malignancies: solid tumors						
BGB-15025 (*HPK1*)	**monotherapy + tislelizumab**	Advanced solid tumors						

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

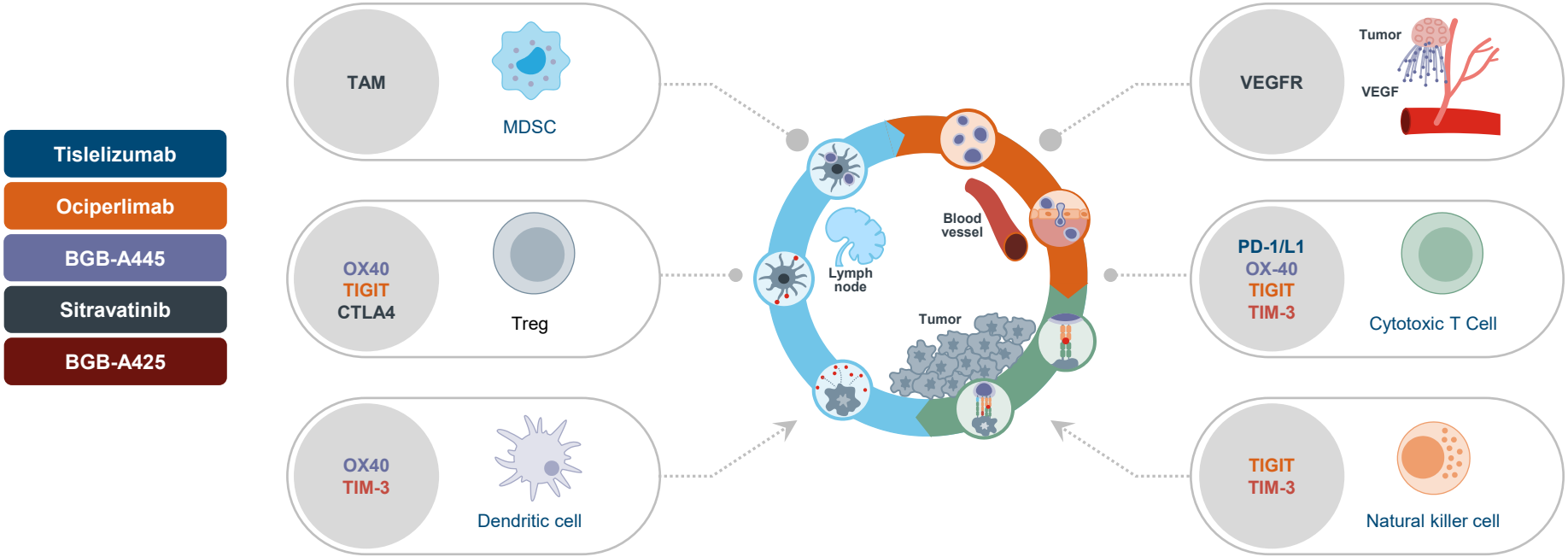
BeiGene has over 20 clinical studies with sites in South Korea

Assets	Programs	Dose Esc.	Dose expansion		PIVOTAL		FILED	MARKET
		PH1a	PH1b	PH2	PH2	PH3		
Tislelizumab	monotherapy	Solid tumors						
		2L UC						
		2L ESCC						
	+ chemotherapy	1L GC						
		1L ESCC						
Zanubrutinib	monotherapy	B-cell malignancies						
		B-cell malignancies						
		R/R MZL						
	combination	B-cell malignancies						
		R/R FL						
		1L MBC/GC						
Ociperlimab	+ tislelizumab	Solid tumors						
		2L+ CC						
		2L PD-L1 high ESCC						
		1L LS-SCLC						
		1L NSCLC						
		1L Stage III unresectable NSCLC						
		1L PD-L1 high advanced NSCLC						
BGB-A425	+ tislelizumab	Solid tumors						
Tislelizumab	+ fruquintinib-201	Solid tumors						
Tislelizumab	+ zanidatamab	2L+ BTC						

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

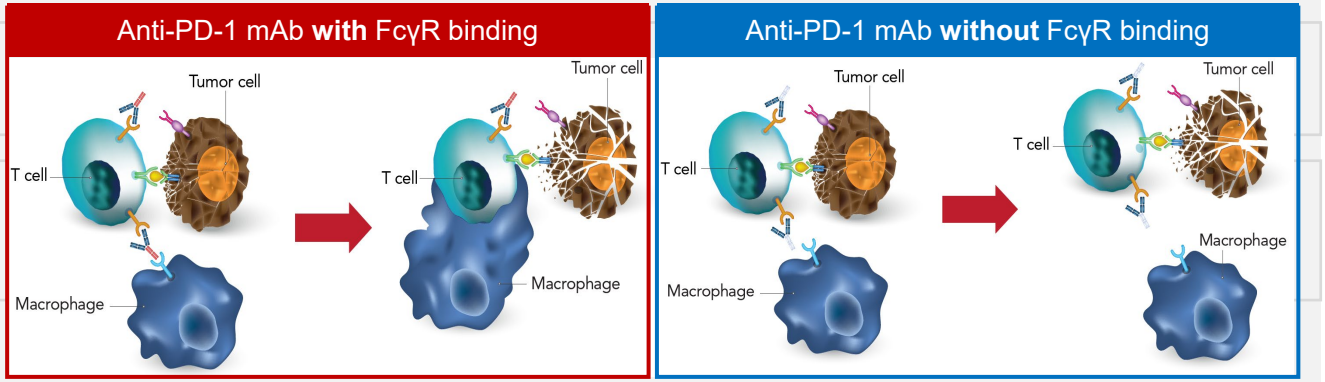
Tislelizumab is the first drug candidate produced from BeiGene's immuno-oncology biologic program

Mechanism of action

Clinical program

Select Phase 3 data

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[1]



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

1. Zhang T et al. Cancer Immunol Immunother 2018:1079–90; 6.

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

Mechanism of action

Clinical program

Select Phase 3 data

- 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**

dMMR, deficient mismatch repair; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; HCC, hepatocellular cell 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

Mechanism of action

Clinical program

Select Phase 3 data

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

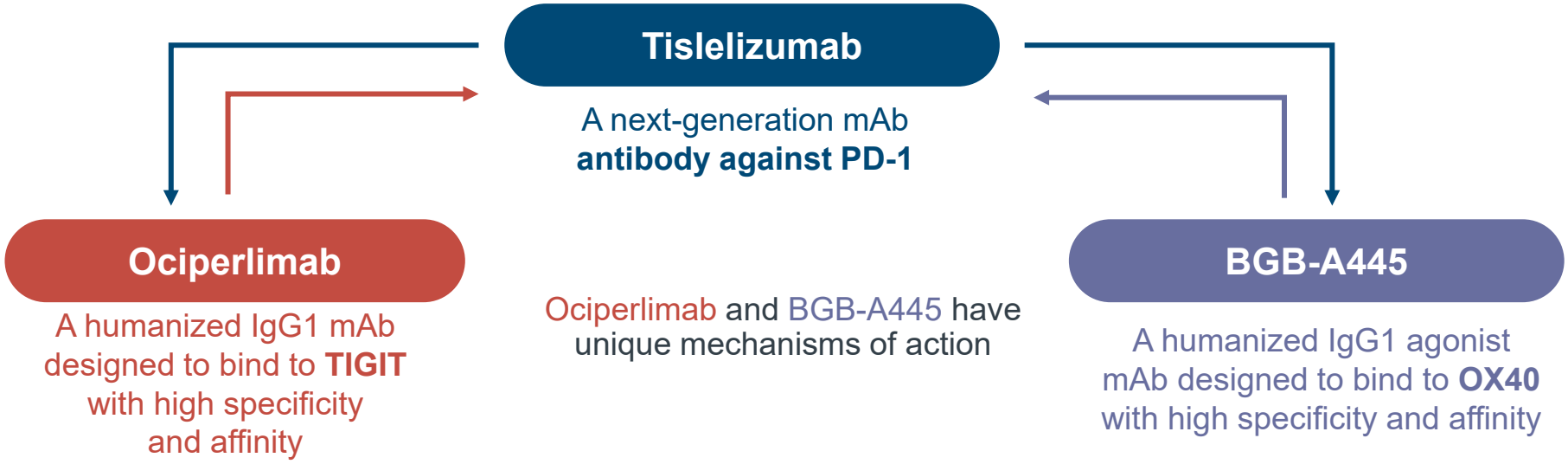
[a] $P<0.001$, [b] $P=0.004$; [c] $P<0.0001$; [d] $P=0.0001$.

1L, first-line' 2L, second line; 3L, third-line; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; mOS, median overall survival; mPFS, median progression-free survival; NSCLC, non-small cell lung cancer; PD-1, programmed death protein 1; TEAE, treatment emergent adverse event

1. Wang J et al. JAMA Oncol. 2021 May 1;7(5):709–717; 2. Lu S et al. J Thorac Oncol. 2021 May 22;S1556-0864(21):02176–6; 3. Zhou C et al. AACR 2021; 4. Shen L et al. ASCO 2021

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

Dual targeting of signaling pathways may produce synergistic immune cell activation and enhance antitumor activity[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

1. Sun L et al. Sci Rep. 2020 Feb 7;10(1):2083. doi: 10.1038/s41598-020-58674-4; 2. Haslam A et al. JAMA Netw Open. 2019;2:e192535; 3. Lei Q et al. Front Cell Dev Biol. 2020 Jul 21;8:672; 4.Chen X et al. AACR 2021; 5. Rodriguez-Abreu D et al. J Clin Oncol. 2020;38:9503

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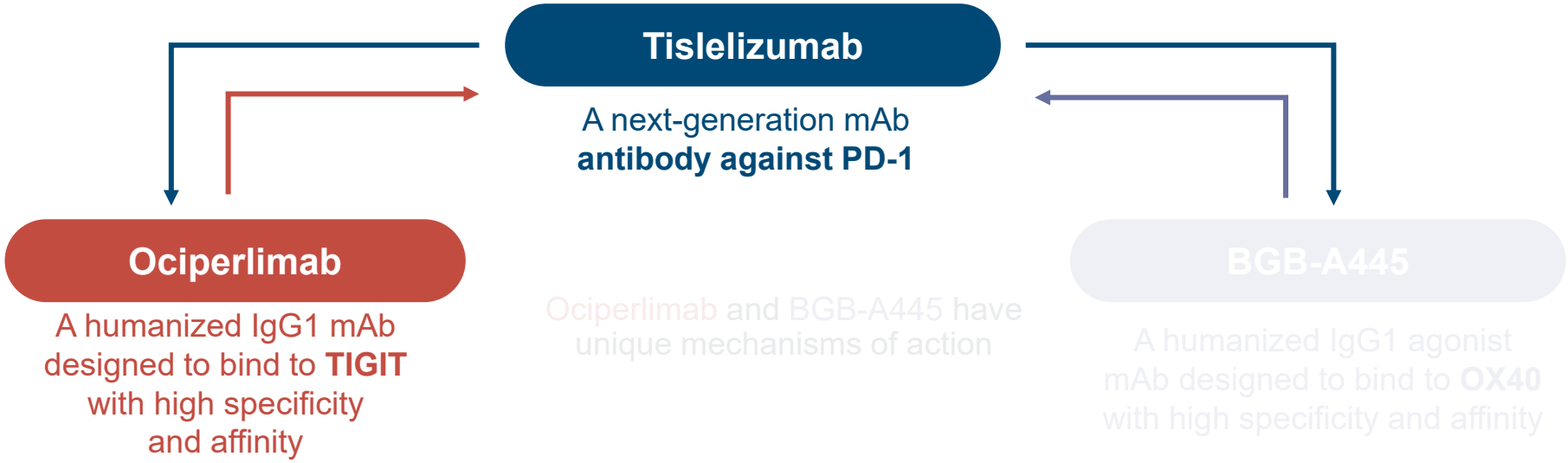


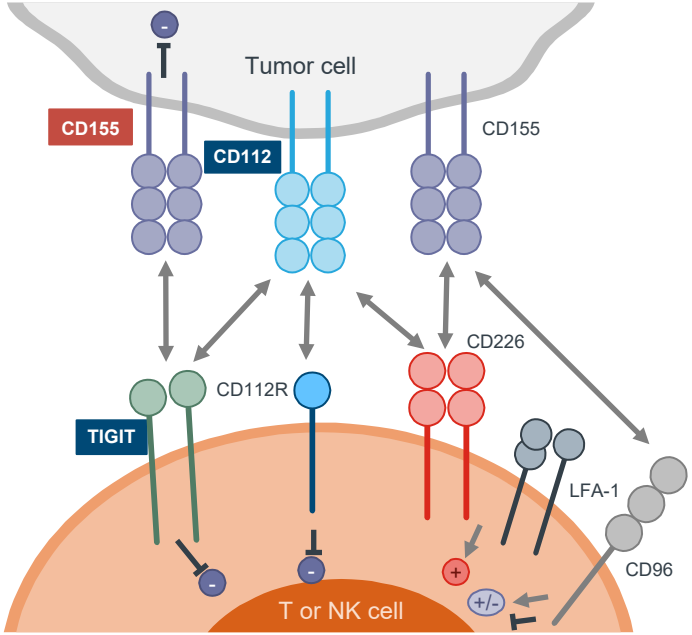
IgG1, immunoglobin G1; mAb, monoclonal antibody; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TIGIT, T-cell immunoreceptor with immunoglobulin and tyrosine-based inhibitory motif domains

1. Sun L et al. Sci Rep. 2020 Feb 7;10(1):2083. doi: 10.1038/s41598-020-58674-4; 2. Haslam A et al. JAMA Netw Open. 2019;2:e192535; 3. Lei Q et al. Front Cell Dev Biol. 2020 Jul 21;8:672; 4.Chen X et al. AACR 2021; 5. Rodriguez-Abreu D et al. J Clin Oncol. 2020;38:9503

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]



Chaiuvn JM and Zarour HM. J Immunother Cancer 2020

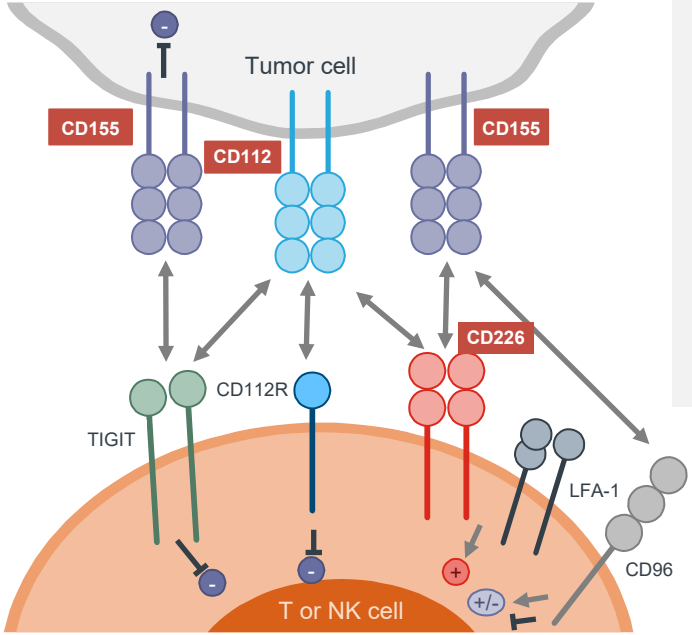
CD155 (PVR) is the main ligand to which TIGIT binds. CD155 is expressed on tumor cells and antigen-presenting cells[2]

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

CD, cluster of differentiation; LFA-1, lymphocyte function-associated antigen 1; NK, natural killer; P, phosphorylation site; PVR, poliovirus receptor; TIGIT, T cell immunoreceptor with immunoglobulin and tyrosine-based inhibitory motif domains; Treg, regulatory T cells. 1. Manieri NA et al. Trends Immunol. 2017;38:20–8; 2. Harjunpää H and Guillerey C. Clin Exp Immunol. 2020;200:108–119; 3. Kurtulus S et al. J Clin Invest. 2015;125:4053–62; 4. Joller N et al. Immunity. 2014;40:569–81

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]



Chauvin JM and Zarour HM. J Immunother Cancer 2020

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

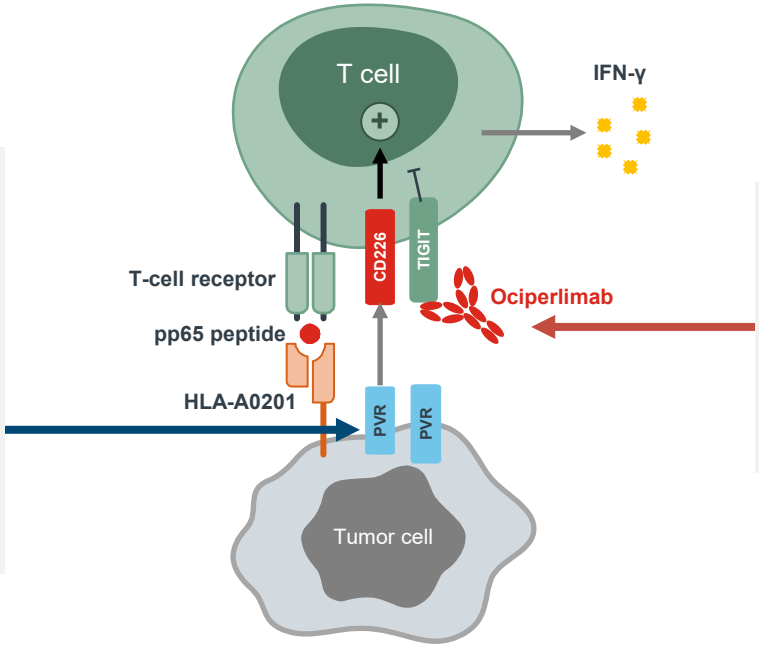
CD226 is expressed on NK and cytotoxic T cells[1]

CD, cluster of differentiation; LFA-1, lymphocyte function-associated antigen 1; NK, natural killer; P, phosphorylation site; R, receptor; TIGIT, T cell immunoreceptor with immunoglobulin and tyrosine-based inhibitory motif domains; Treg, regulatory T cells. 1. Levin SD et al. Eur J Immunol. 2011;41:902–15; 2. Chen X et al. Presented at AACR 2021; 3. Blake S et al. Clin Cancer Res 2016;22:3057–66

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

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

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. 1. Chen X, et al. Presented at AACR 2021

Preclinical data: Ociperlimab reduces Tregs *in vitro*

Anti-TIGIT antibodies were incubated with human PMBC and NK cells

Anti-TIGIT antibodies were incubated overnight with human PMBCs from a lung cancer donor, and NK cells from a healthy donor

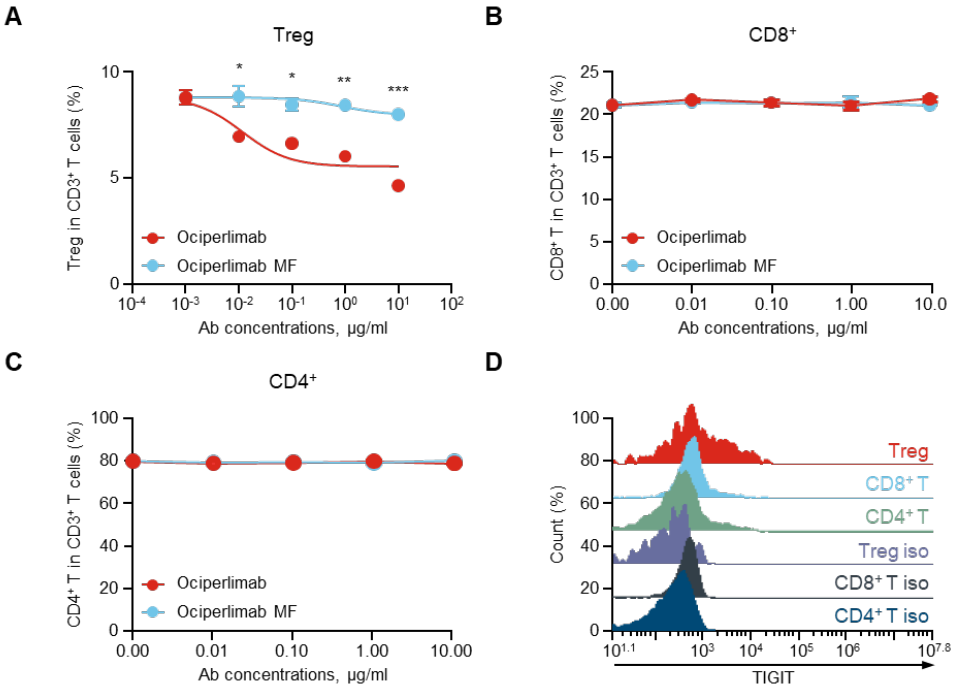
FACS was used to assess:

A) Treg levels

B) $CD8^+$ T cells

C) $CD4^+$ T cells

D) TIGIT expression on T cells



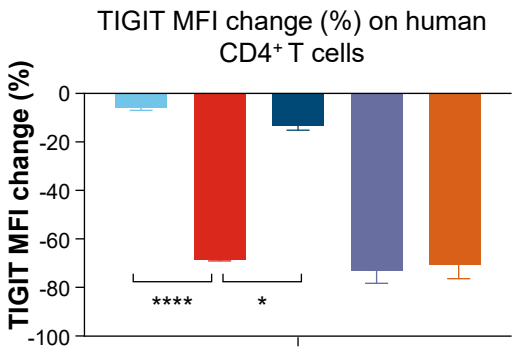
*p<0.05, **p<0.01,***p<0.001. Ociperlimab MF = variant with "silent Fc" mutations.Ab, antibody; CD, cluster of differentiation; FACS, fluorescence-activated cell sorting; iso, isolated; NK, natural killer; PMBC, peripheral blood mononuclear cells; TIGIT, T-cell immunoreceptor with immunoglobulin and 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

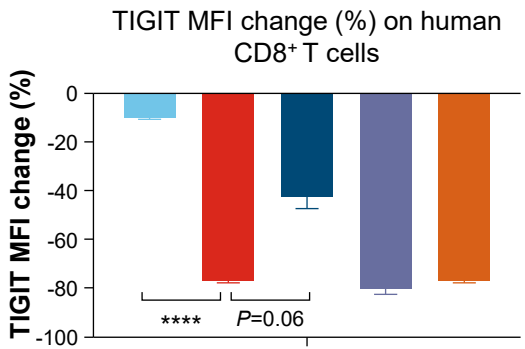
Ociperlimab induced trogocytosis on CD4+ and CD8+ T cells

CD4+ T cells



Ociperlimab MF	+	-	-	-	-
Ociperlimab	-	+	+	+	+
FcgRI blockade	-	-	+	-	-
FcgRII blockade	-	-	-	+	-
FcgRIII blockade	-	-	-	-	+

CD8+ T cells



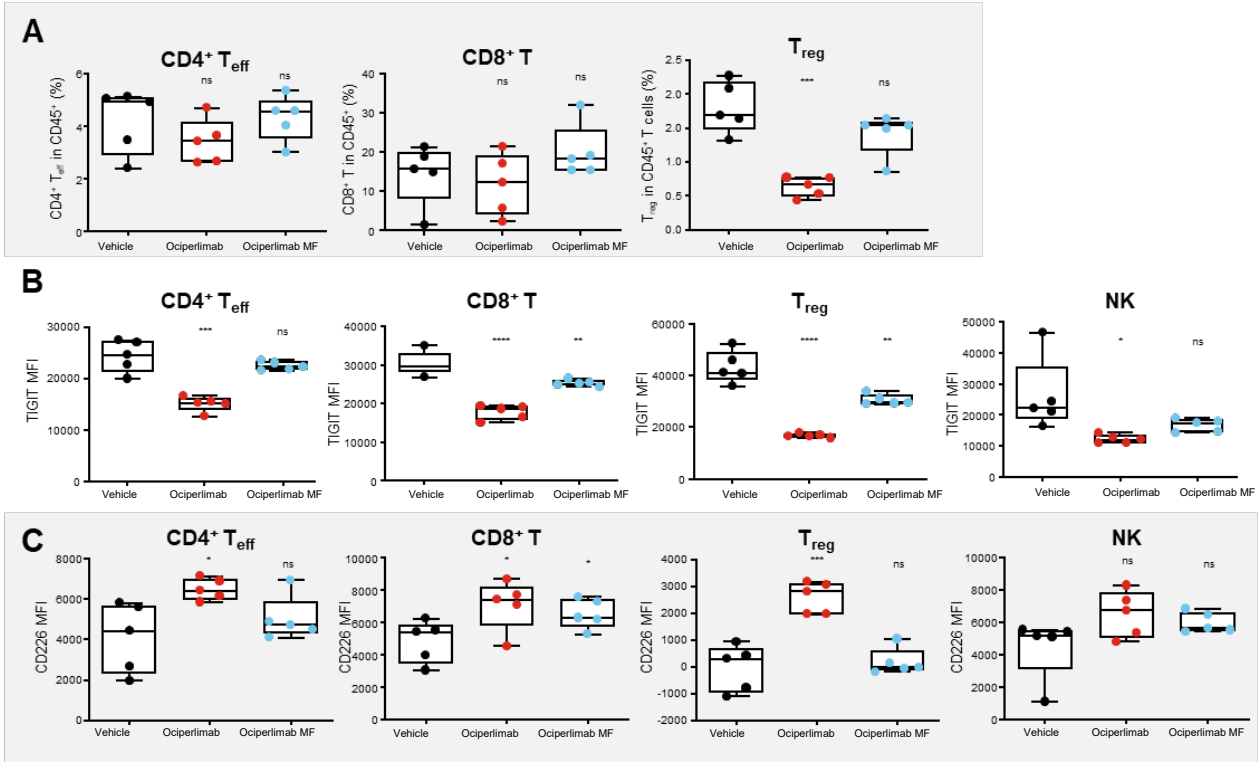
Ociperlimab MF	+	-	-	-	-
Ociperlimab	-	+	+	+	+
FcgRI blockade	-	-	+	-	-
FcgRII blockade	-	-	-	+	-
FcgRIII blockade	-	-	-	-	+

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

Preclinical data: The Fc effector function is critical for the antitumor activity of ociperlimab



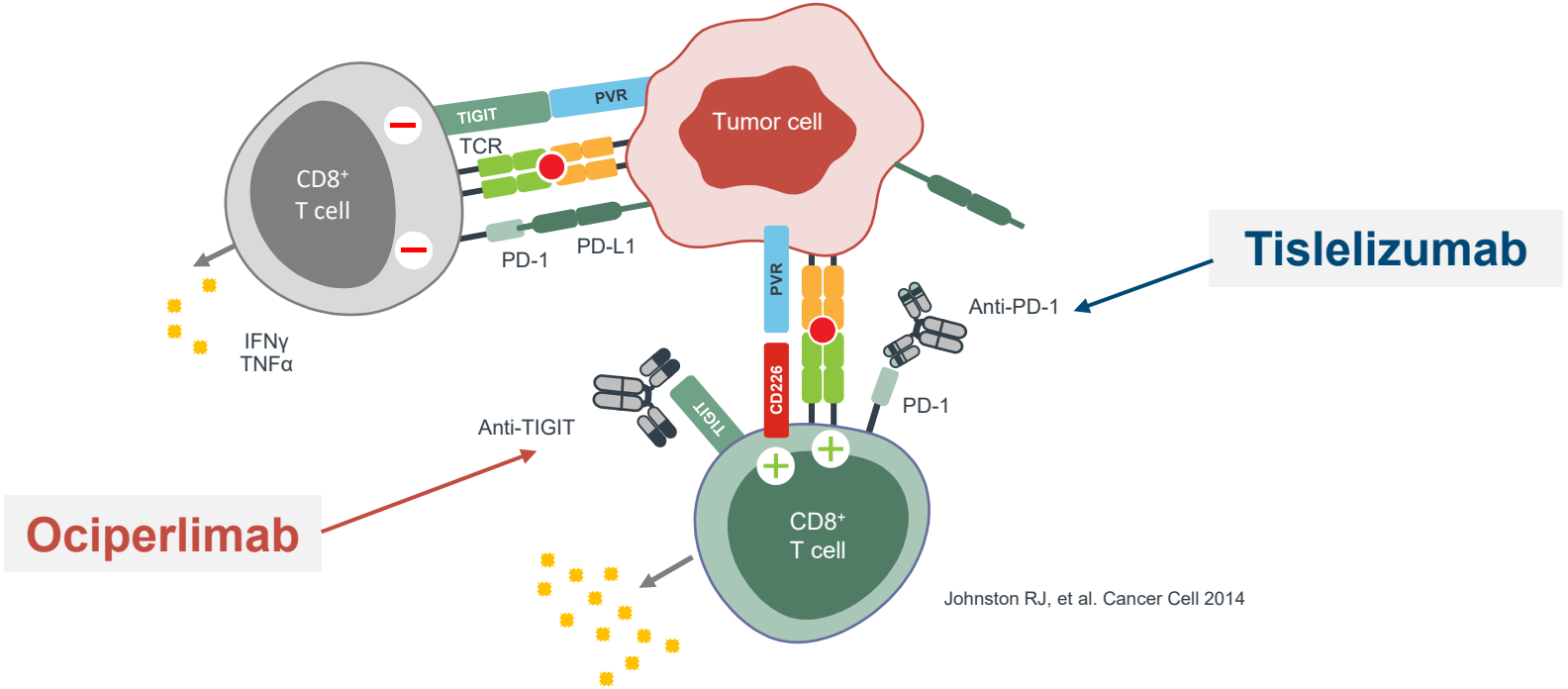
Ociperlimab reduced Tregs **(A)**, down-regulated TIGIT **(B)**, and up-regulated CD226 **(C)** on T cells in a Fc effector function-dependent manner *in vivo*

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 I

Rationale for combining ociperlimab with tislelizumab

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



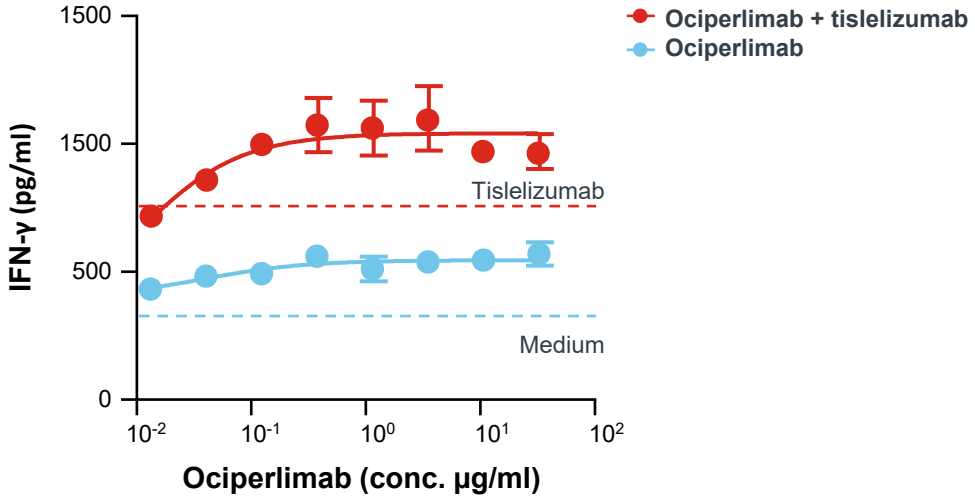
Johnston RJ, et al. Cancer Cell 2014

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



IFNγ 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

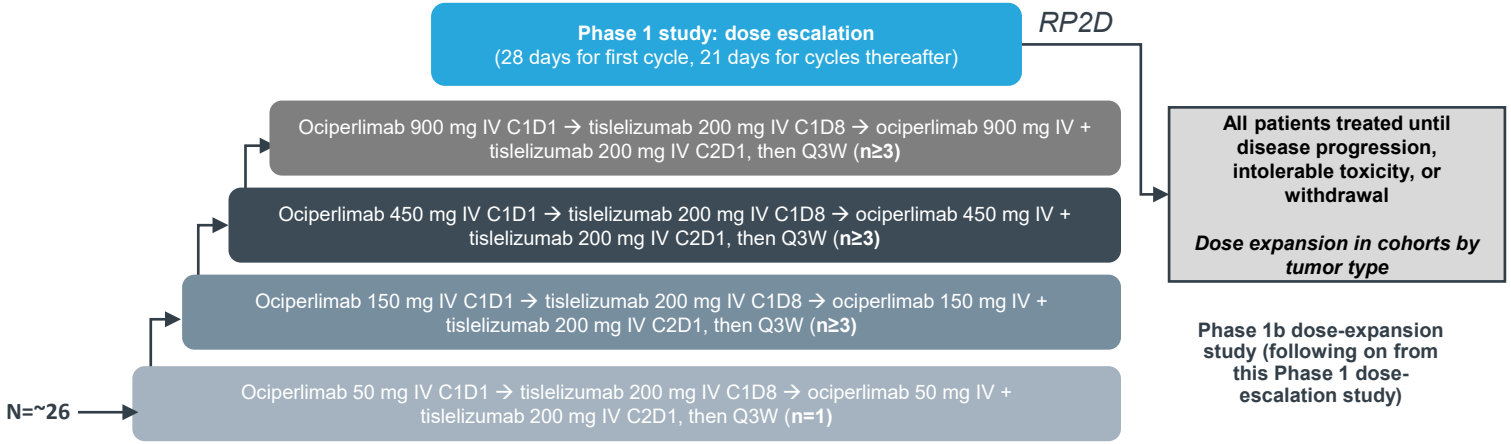
- AEs and serious AEs
- MTD or MAD

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

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



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

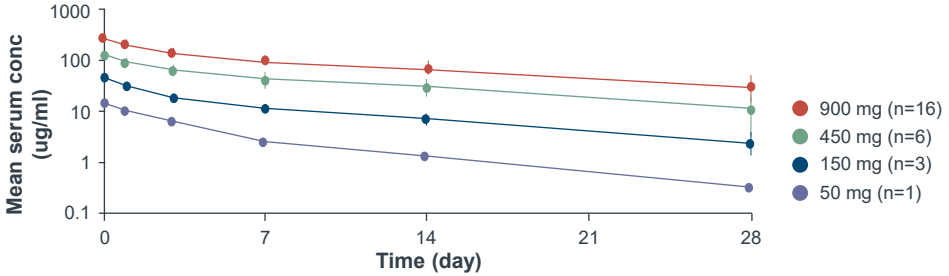
	OCI 50 mg plus TIS 200 mg (n=1)	OCI 150 mg plus TIS 200 mg (n=3)	OCI 450 mg plus TIS 200 mg (n=6)	OCI 900 mg plus TIS 200 mg (n=16)	Total (N=26)
Number of patients treated with any study drug, n (%)	1 (100.0)	3 (100.0)	6 (100.0)	16 (100.0)	26 (100.0)
Patients discontinued from ociperlimab, n (%)	1 (100.0)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

Data cut-off: February 21, 2021
NSCLC, non-small cell lung cancer; OCI, ociperlimab; TIS, tislelizumab
1. Frentzas et al. Presented at ASCO 2021

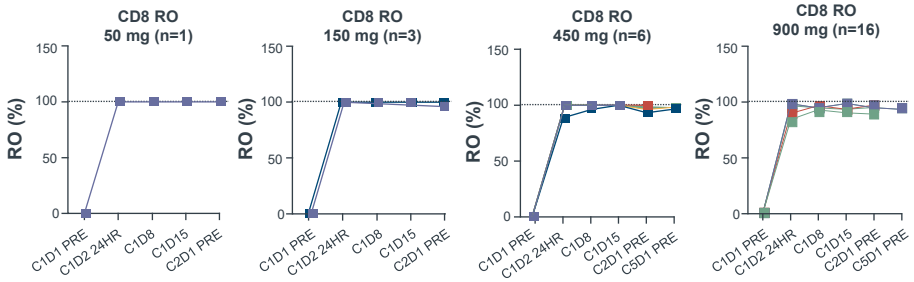
Ociperlimab was administered at a starting dose of 50 mg

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 in peripheral blood mononuclear cells was observed at ≥50 mg doses of ociperlimab and at all timepoints



Data cut-off: February 21, 2021

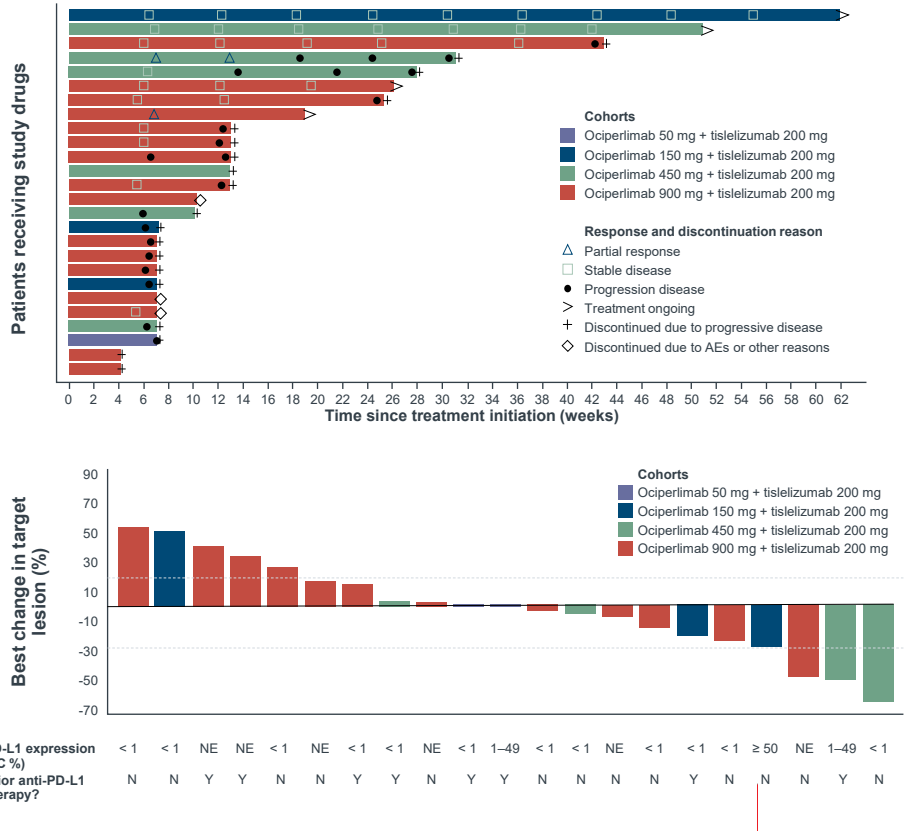
Conc., concentration; C, cycle; D, day; CD, cluster of differentiation; HR, hour; IV, intravenous; PRE, pre; RO, receptor occupancy

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 900mg). 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

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

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

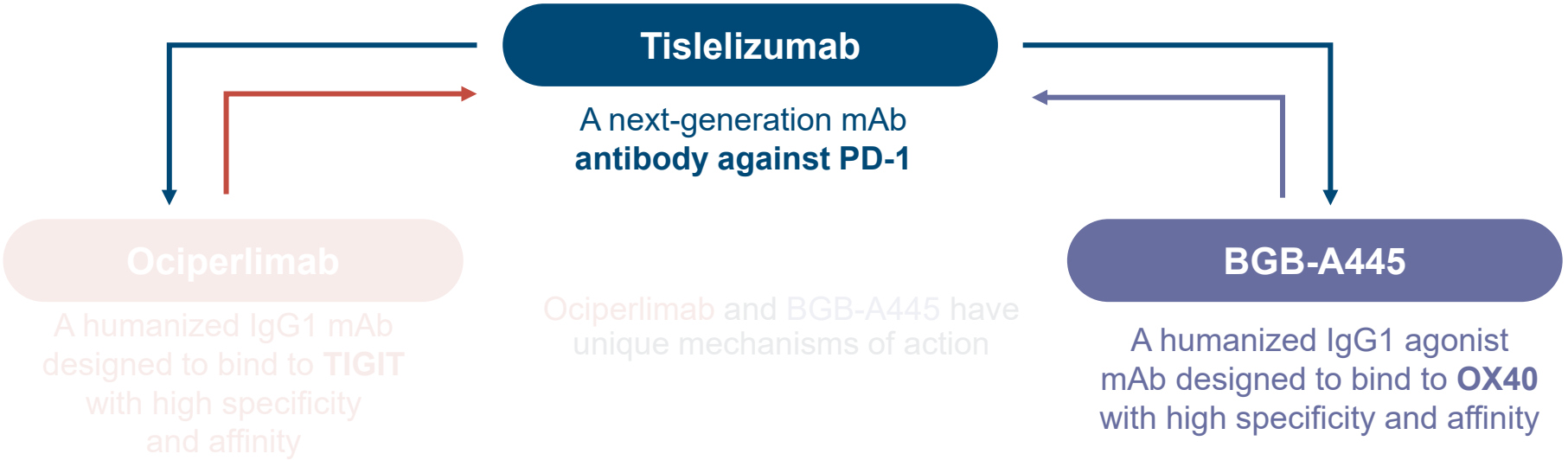
	Phase	Key objectives		Tumor type	Locations
AdvanTIG-202[1]	2	Antitumor efficacy and safety of tislelizumab with or without ociperlimab	2L	Cervical cancer	18 global locations, inc. **Korea**
AdvanTIG-203[2]	2	Antitumor efficacy and safety of tislelizumab + ociperlimab vs tislelizumab + placebo	2/3L	ESCC	100 global locations, inc. **Korea**
AdvanTIG-204[3]	2	Evaluate the efficacy and safety tislelizumab + ociperlimab + cCRT, followed by ociperlimab + tislelizumab vs tislelizumab + cCRT followed by tislelizumab vs cCRT alone	1L	LS-SCLC	32 global locations, inc. **Korea**
AdvanTIG-206[4]	2	Efficacy and safety of ociperlimab in combination with tislelizumab plus BAT1706*, and tislelizumab plus BAT1706	2L	HCC	25 global locations
AdvanTIG-301[5]	3	Efficacy and safety of tislelizumab + ociperlimab + cCRT followed by tislelizumab + ociperlimab vs tislelizumab + cCRT followed by tislelizumab vs cCRT followed by durvalumab	1L	NSCLC	200 locations globally inc. **Korea**
AdvanTIG-302[6]	3	Efficacy and safety of tislelizumab + ociperlimab vs pembrolizumab + placebo	1L	NSCLC	170 global locations, inc. **Korea**

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

1. NCT04693234 2. NCT04732494; 3. NCT04952597; 4. NCT04948697; 5. NCT04866017; 6. 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[1–3]

Dual targeting of signaling pathways may produce synergistic immune cell activation and enhance antitumor activity[4,5]



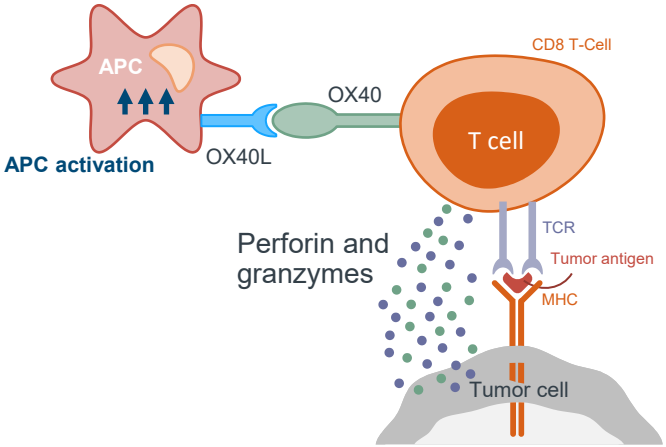
IgG1, immunoglobin G1; mAb, monoclonal antibody; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TIGIT, T-cell immunoreceptor with immunoglobulin and tyrosine-based inhibitory motif domains

1. Sun L et al. Sci Rep. 2020 Feb 7;10(1):2083. doi: 10.1038/s41598-020-58674-4; 2. Haslam A et al. JAMA Netw Open. 2019;2:e192535; 3. Lei Q et al. Front Cell Dev Biol. 2020 Jul 21;8:672; 4. Chen X et al. AACR 2021; 5. Rodriguez-Abreu D et al. J Clin Oncol. 2020;38:9503

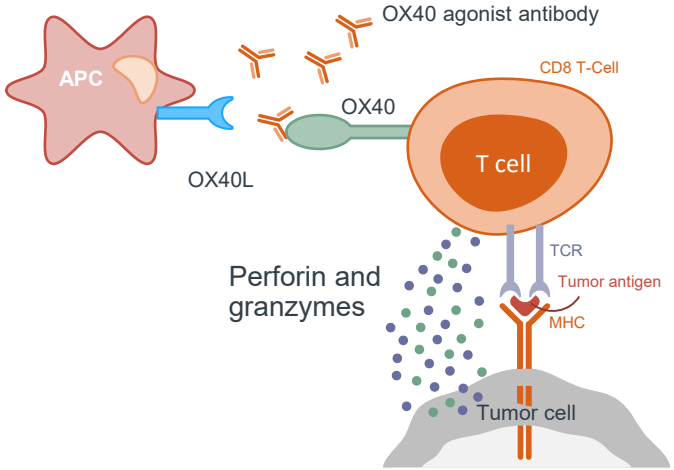
OX40 is an immune co-stimulatory receptor primarily expressed on activated T cells

- 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*

OX40-OX40L engagement



OX40 agonist antibody-OX40L engagement



APC, antigen-presenting cell; MHC, major histocompatibility complex; TCR, T cell receptor

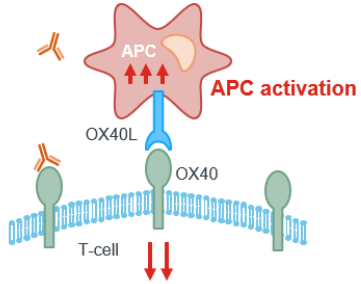
1. Croft M et al. Immunol Rev. 2009 May; 229(1):173–191

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

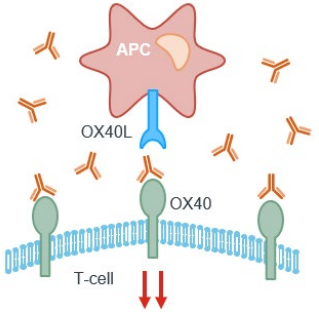
- Unlike ligand-blocking OX40 antibodies, BGB-A445 does not disrupt OX40-OX40L engagement
- BGB-A445 achieves maximal T-cell activation by keeping natural ligand (OX40L) stimulation from APCs

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

Ligand-blocking OX40 agonist



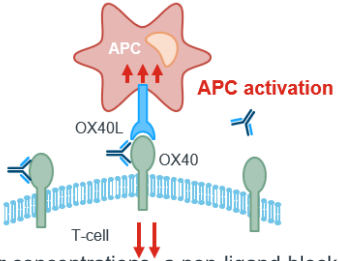
At lower concentrations, a ligand-blocking anti-OX40 agonist promotes T cell proliferation and activation



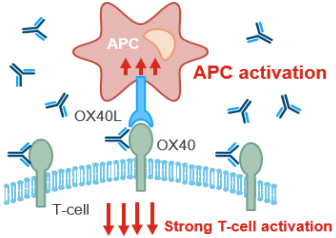
At higher concentrations, a ligand-blocking OX40 agonist Ab blocks OX40-OX40L interaction, impairing APC activation of T cell

Increasing OX40 agonist antibodies concentration

BGB-A445



At lower concentrations, a non-ligand blocking OX40 agonist, promotes T cell proliferation and activation



At higher concentrations, a non-ligand blocking OX40 agonist, such as BGB-A445, does not affect OX40-OX40L interaction, maintaining APC activation and promoting maximum T-cell proliferation and activation

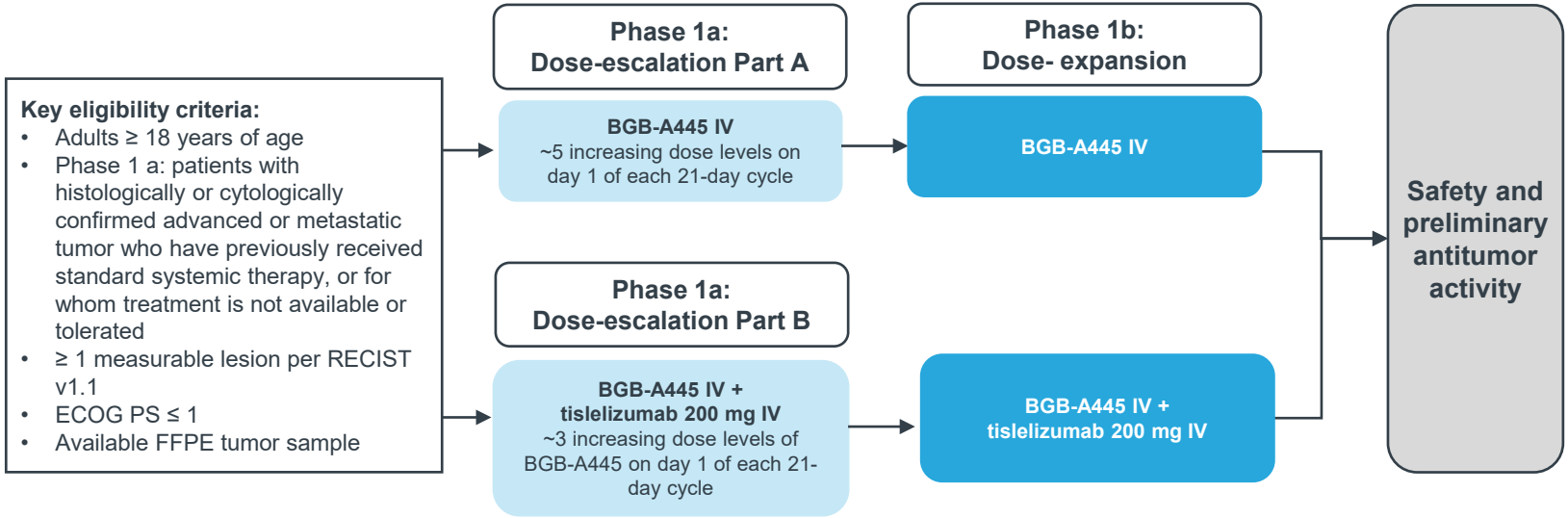
Ab, antibody; APC, antigen-presenting cells

1. Croft M et al. Immunol Rev. 2009 May; 229(1): 173–191

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



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

1.Chen X et al. AACR 2021; 2. Liu Y et al. J Immunother Cancer 2020;8(Suppl 3):A1–A559; 3. Vilgelm AE et al. J Leukoc Biol 2016;100:275–290; 4. Croft M et al. Immunol Rev. 2009; 229:173–191

Any questions?