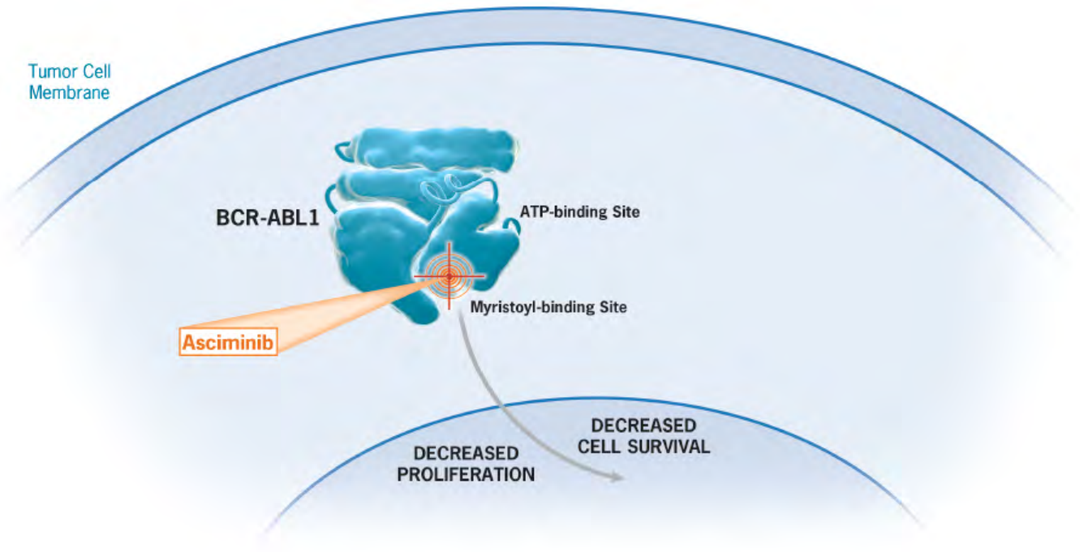
Novartis Oncology

Compounds in Development

Compendium 2019

NOVARTIS

Inhaltsverzeichnis



Novartis internal

Asciminib (ABL001)

BCR-ABL1 small-molecule allosteric inhibitor

Compound Description

Asciminib (ABL001) is an investigational, specific allosteric inhibitor of the BCR-ABL1 kinase.[1–3] Preclinically, asciminib has been demonstrated to maintain activity against clinically relevant adenosine triphosphate (ATP)-binding–site mutations in BCR-ABL1, including T315I, that confer resistance to other BCR-ABL1 tyrosine kinase inhibitors (TKIs) used for the treatment of Philadelphia chromosome–positive (Ph+) chronic myeloid leukemia (CML) and Ph+ acute lymphoblastic leukemia (ALL).[1]

Areas of Research

Ph+ CML and Ph+ ALL

Proposed Mechanism of Action

Asciminib is an investigational, specific inhibitor of BCR-ABL1.[1–3] The binding of the myristoylated N-terminus of ABL1 to an allosteric site in the ABL1 kinase domain plays a key role in negatively regulating ABL1 kinase activity; however, this regulatory component of ABL1 is lost upon fusion with the BCR protein, resulting in a constitutively active tyrosine kinase.[4] By binding to the vacant myristoyl-binding site of BCR-ABL1, asciminib may functionally restore this negative regulation of ABL1 kinase activity in the BCR-ABL1 fusion protein.[1–3]

Key Preclinical Data

In preclinical studies, asciminib specifically inhibited the proliferation of cell lines expressing BCR-ABL1 and was active in the KCL-22 mouse xenograft model of CML.[1,2] In the KCL-22 xenograft model, treatment with either single-agent asciminib or nilotinib resulted in tumor regressions; however, tumor relapses occurred within 30 to 60 days and the resistant tumors showed evidence of point mutations in BCR-ABL1.[1,2] In contrast, combined upfront treatment with both asciminib and nilotinib in this model resulted in sustained tumor regressions, with no evidence of disease relapse, for the entire duration of the study, which included 77 days of treatment and >176 days of follow-up after treatment discontinuation.[2]

Clinical Status

- A Phase I, open-label study of ABL001 in patients with CML or Ph+ ALL is currently recruiting (NCT02081378)[5]
- A Phase II study to evaluate the safety and efficacy of ABL001 in combination with imatinib in patients with CML-CP is also underway (NCT03578367).[6]
- A Phase III, multicenter, open-label, randomized study of oral ABL001 versus bosutinib in patients with CML-CP, previously treated with 2 or more TKIs is ongoing (NCT03106779).[7]

Asciminib is an investigational compound. Efficacy and safety have not been established. There is no guarantee that asciminib will become commercially available. MOA data are based on in vitro/in vivo data. Clinical benefit is unknown.

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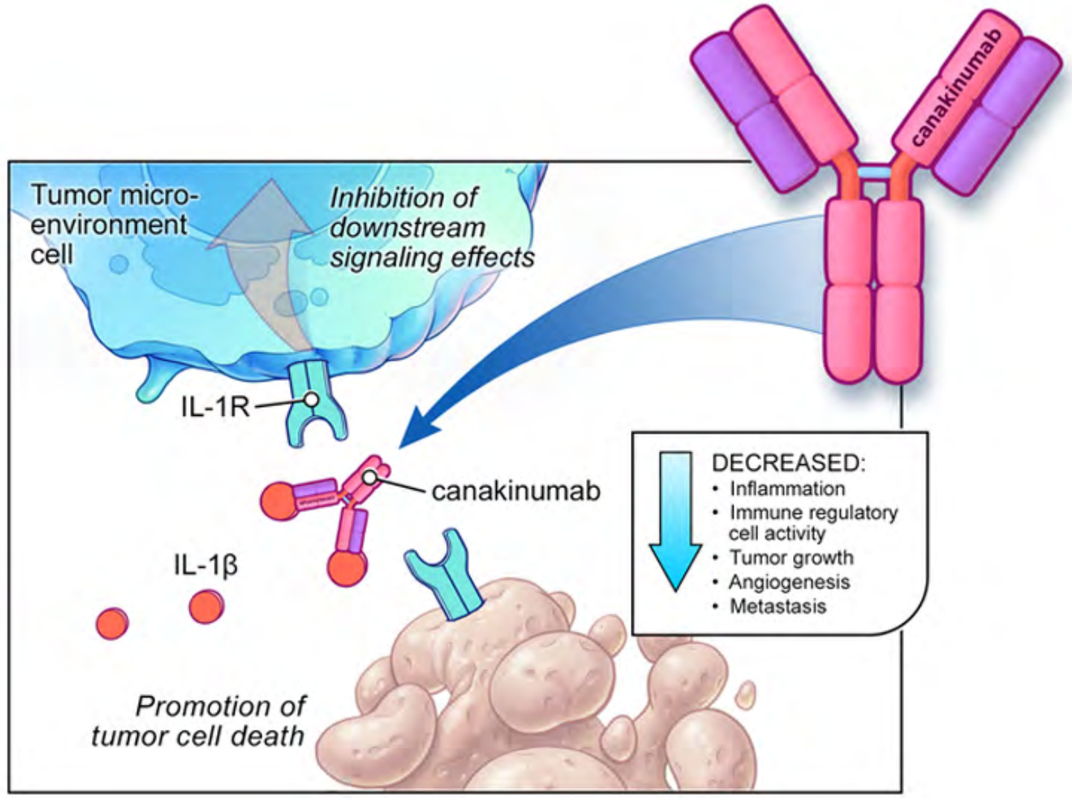


CANAKINUMAB (ACZ885)

Anti–IL-1β monoclonal antibody

Compound Description

Canakinumab (ACZ885) is a human monoclonal antibody that is thought to specifically bind with high affinity to human interleukin 1β (IL-1β), and blocks the interaction of IL-1β with the IL-1 receptor. This neutralizes the biological proinflammatory activity of human IL-1β.[1-3]

Areas of Research

Advanced malignancies, including colorectal cancer (CRC), triple-negative breast cancer (TNBC), non-small cell lung cancer (NSCLC), and adenocarcinoma[4*]

Proposed Mechanism of Action

IL-1β is a potent proinflammatory cytokine that can influence the growth and invasion of many tumor types.[5] IL-1β is released by various cell types, including immune, neural, and endothelial cells and is abundantly expressed at the tumor site and in patient serum.[2,3] IL-1β supports carcinogen-induced tumorigenesis in vivo and determines the invasive propensity of tumor cells.[6] Blockade of IL-1β may suppress tumor progression and enhance antitumor immunity by inducing maturation of immature myeloid cells (MDSCs) into M1 (antitumor) macrophages within the tumor.[7] Canakinumab (ACZ885) is a human monoclonal antibody that is thought to have high affinity and specificity for IL-1β, and the complex formed with the cytokine is unable to attach to the receptor, thereby potentially blocking IL-1β–dependent signaling.[2,3,8,9]

Key Preclinical Data

Canakinumab (ACZ885) has high affinity and specificity for IL-1β that have been demonstrated in both in vitro and in vivo studies.[8,9] Its in vitro biological activity was determined in primary human cell cultures, and exposure of human dermal fibroblasts to canakinumab (ACZ885) inhibited IL-1β–stimulated IL-6 secretion.[2,3] Canakinumab (ACZ885) was shown to fully suppress IL-β–mediated joint inflammation and cartilage destruction in the mouse models of arthritis; however, it does not interfere with IL-1β signaling.[2,3,8,9]

Clinical Status

Phase Ib:

- spartalizumab (PDR001) + canakinumab (ACZ885), CJM112, nazartinib (EGF816), or trametinib in advanced CRC, NSCLC, or TNBC; currently recruiting (NCT02900664).[4]

Phase II:

- CANOPY-N: Canakinumab or Pembrolizumab as Monotherapy or in Combination as Neoadjuvant Therapy in resectable NSCLC (NCT03968419) [10]

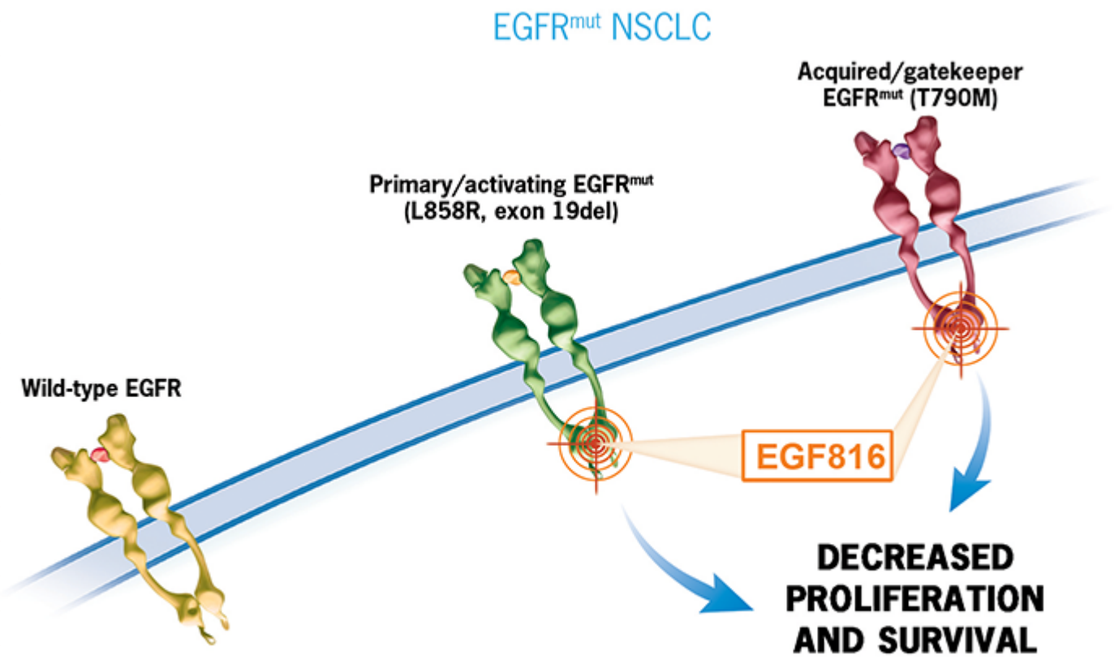
Phase III:

- CANOPY-A: Canakinumab vs Placebo as Adjuvant Therapy in Stages AJCC/UICC v. 8 II -IIIA and IIIB (T>5cm N2) Completely Resected (R0) NSCLC; currently enrolling (NCT03447769)[11]
- CANOPY-1: Pembrolizumab + Platinum-based Doublet Chemotherapy ± Canakinumab as 1L Therapy for Locally Advanced or Metastatic NSCLC and Non-squamous and Squamous NSCLC; currently enrolling (NCT03631199)[12]
- CANOPY-2: Canakinumab + Docetaxel vs Placebo + Docetaxel in NSCLC Previously Treated With PD-(L)1 Inhibitors and Platinum-based Chemotherapy; currently enrolling (NCT03626545)[13]

*Canakinumab (aka ACZ885) is a human monoclonal antibody targeted at IL-1β. It is marketed in the United States and Europe under the name Ilaris®. Since 2009, it has been approved for the treatment of cryopyrin-associated periodic syndromes (CAPS), a spectrum of autoinflammatory syndromes including familial cold autoinflammatory syndrome, Muckle–Wells syndrome, and neonatal-onset multisystem inflammatory disease. In 2016, the United States Food and Drug Adminstration approved the use of canakinumab for the treatment of three additional rare and serious auto-inflammatory diseases: tumor necrosis factor receptor associated periodic syndrome (TRAPS), hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD), and familial Mediterranean fever (FMF).[1]

Canakinumab (ACZ885) is an investigational compound. Efficacy and safety have not been established. There is no guarantee that canakinumab (ACZ885) will become commercially available. MOA data are based on in vitro/in vivo data. Clinical benefit is unknown.

REFERENCES: 1. Ilaris (canakinumab) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2016. **2.** Watkins LR, Milligan ED, Maier SF. Glial proinflammatory cytokines mediate exaggerated pain states: implications for clinical pain. *Adv Exp Med Biol.* 2003;521:1–21. **3.** Ren K, Torres R. Role of interleukin-1beta during pain and inflammation. *Brain Res Rev.* 2009;60:57–64. **4.** ClinicalTrials.gov. https://clinicaltrials.gov/show/NCT02900664. Updated February 6, 2018. Accessed February 23, 2018. **5.** Setrerrahmane S, Hanmel X. Tumor-related interleukins: old validated targets for new anti-cancer drug development. *Mol Cancer.* 2017;16:153. **6.** Krelin Y, Voronov E, Dotan S, et al. Interleukin-1beta-driven inflammation promotes the development and invasiveness of chemical carcinogen-induced tumors. *Cancer Res.* 2007;67(3):1062–1071. **7.** Song X, Voronov E, Dvorkin T, et al. Differential effects of IL-1 alpha and IL-1 beta on tumorigenicity patterns and invasiveness. *J Immunol.* 2003;171:6448–6456. **8.** Alten R, Gram H, Joosten LA, et al. The human anti-IL-1 beta monoclonal antibody ACZ885 is effective in joint inflammation models in mice and in a proof-of-concept study in patients with rheumatoid arthritis. *Arthritis Res Ther.* 2008;10:R67. **9.** Gram H. Preclinical characterization and clinical development of ILARIS® (canakinumab) for the treatment of autoinflammatory diseases. *Curr Opin Chem Biol.* 2016;32:1–9. **10.** ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03968419. Accessed August 28, 2019. **11.** ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03447769. Accessed August 28, 2019. **12.** ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03631199. Accessed August 28, 2019. **13.** ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03626545. Accessed August 28, 2019.



NAZARTINIB (EGF816)

Selectively inhibiting mutant epidermal growth factor receptor

Compound Description

Nazartinib (EGF816) is an investigational, irreversible tyrosine kinase inhibitor (TKI) that is thought to target mutant epidermal growth factor receptor (EGFR^{mut}). It is equally potent against primary activating (EGFR L858R and exon 19del) and secondary/resistance (EGFR L858R/T790M and EGFR exon 19del/T790M) mutations observed in non-small cell lung cancer (NSCLC), and does not inhibit wild-type (WT) EGFR at efficacious doses in mouse xenograft models.[1]

Areas of Research

NSCLC

Proposed Mechanism of Action

The predominant oncogenic EGFR mutations are L858R and exon 19del, accounting for about 90% of EGFR^{mut} NSCLC cases.[2-5] These EGFR-activating mutations respond to first- and second-generation EGFR TKIs. Patients who initially respond will develop acquired resistance to EGFR TKIs within 6 to 14 months.[6,7] In up to 60% of patients with NSCLC harboring a primary EGFR mutation treated with first-generation EGFR TKIs, a secondary "gatekeeper" T790M mutation develops.[6,8]

Key Preclinical Data

Nazartinib (EGF816) is an investigational, irreversible inhibitor of EGFR that targets activating and resistance mutations with equal potency. Furthermore, EGF816 demonstrates selectivity for mutant EGFRs compared with WT EGFR in mouse xenograft models.[1,9]

Nazartinib (EGF816) demonstrated tumor regression in several EGFR-activating and -resistant tumor models in vivo. These include H1975 (L858R; T790M), HCC827 (exon 19del), and H3255 (L858R), which are representative of the relevant clinical settings.[1]

Nazartinib (EGF816) has been demonstrated to selectively target both activating and resistance EGFR mutations without inhibiting WT EGFR at tolerated doses. In preclinical studies, EGF816 has demonstrated single-agent activity against EGFR^{mut} models that are representative of the relevant clinical settings, and is currently being evaluated in patients with EGFR^{mut} NSCLC.[1]

Clinical Status

Several studies evaluating nazartinib (EGF816) in patients with EGFR^{mut} solid tumors (including NSCLC) are currently recruiting patients, including:

- A Phase Ib/II, multicenter, open-label study of nazartinib (EGF816) in combination with capmatinib (INC280) in adult patients with EGFR^{mut} NSCLC (NCT02335944)[10]
- A Phase II, multicenter, open-label study of nazartinib (EGF816) in combination with nivolumab in adult patients with EGFR^{mut} NSCLC (NCT02323126)[11]

Nazartinib (EGF816) is an investigational compound. Efficacy and safety have not been established. There is no guarantee that nazartinib (EGF816) will become commercially available. MOA data are based on in vitro/in vivo data. Clinical benefit is unknown.

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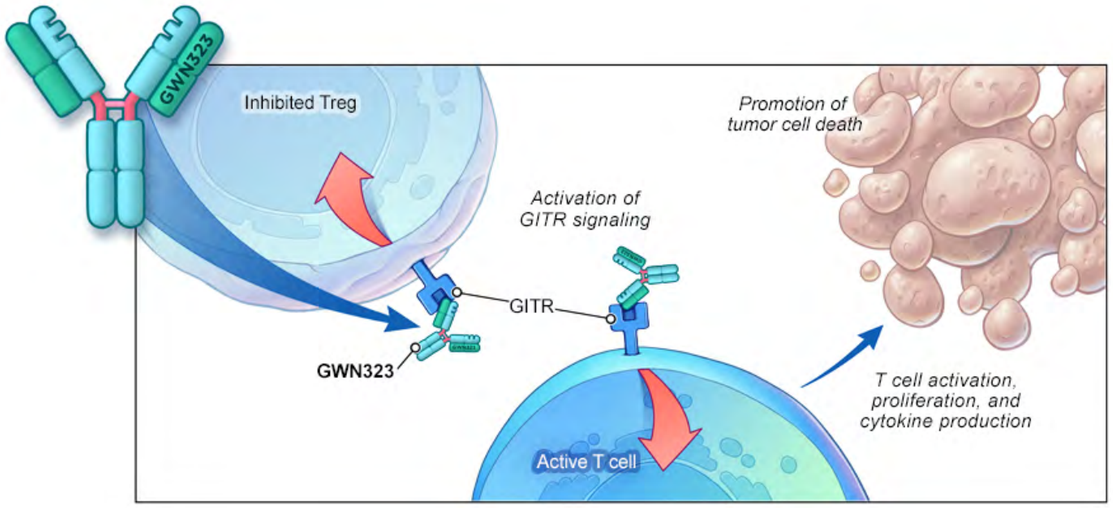

Areas of Research

Advanced malignancies and lymphomas[2]

Proposed Mechanism of Action

GWN323 is an investigational IgG1 agonistic antibody that is thought to target GITR. GITR is a member of the tumor necrosis factor receptor superfamily and is a costimulatory receptor expressed on T cells.[3,4] GITR stimulation results in enhanced proliferation, survival, and activation of effector T cells.[3,5] Effector T-cell function is suppressed by regulatory T cells,[6,7] which shut down immune responses under normal conditions and may also be used by tumors to decrease antitumor immunity.[6] Targeting GITR with an agonistic antibody may decrease regulatory T cells and increase effector T cells.[8]

Key Preclinical Data

Preclinical studies have shown that targeting GITR with an agonistic antibody enhanced the activation of effector T cells and reversed the suppressive effects of regulatory T cells.[3,5] Treatment of animal tumor models with anti-GITR antibodies has been shown to deplete regulatory T cells, increase antitumor immune cell numbers, and induce antitumor immune memory.[3,9,10]

Clinical Status

A Phase I/Ib, open-label, dose-escalation study that is evaluating GWN323 as a single agent or in combination with spartalizumab (PDR001) in advanced solid tumors and lymphomas is currently recruiting (NCT02740270).[2]

GWN323

A GITR agonist antibody

Compound Description

GWN323 is an investigational immunoglobulin G subclass 1 (IgG1) antibody against human GITR (glucocorticoid-induced tumor necrosis factor receptor-related gene); it is both agonistic and antibody-dependent cellular cytotoxicity (ADCC) competent.[1]

GWN323 is an investigational compound.Efficacy and safety have not been established. There is no guarantee that GWN323 will become commercially available. MOA data are based on in vitro/in vivo data. Clinical benefit is unknown.

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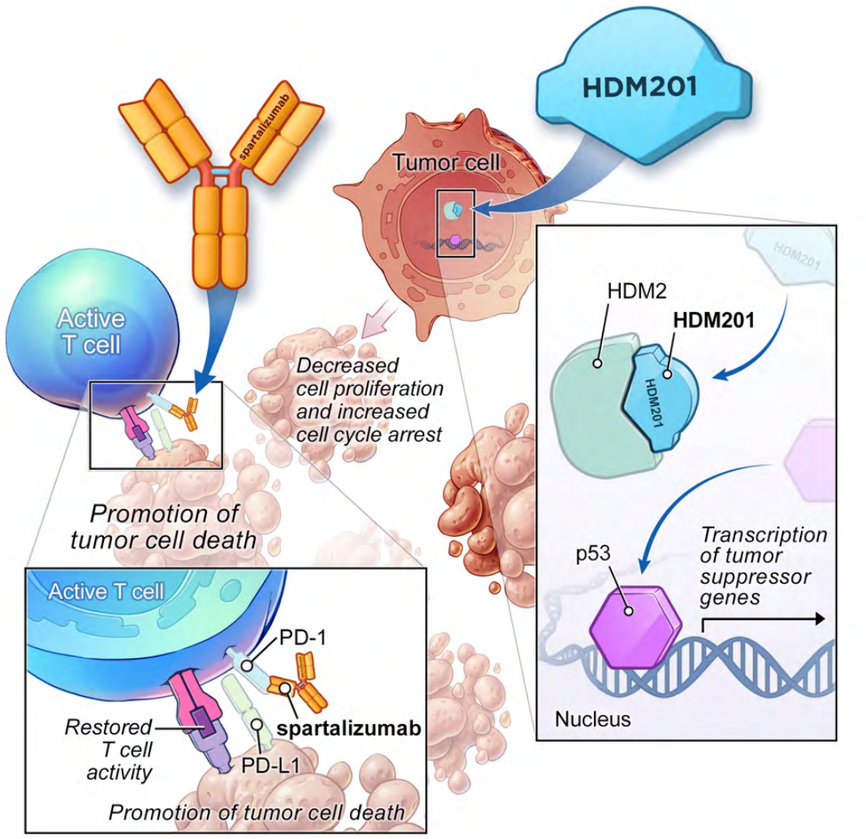

Novartis internal

SPARTALIZUMAB (PDR001) and HDM201

PD-1-targeting monoclonal antibody and HDM2-p53 small molecule inhibitor

Proposed Mechanism of Action

- Programmed death-1 (PD-1) is an immunoinhibitory receptor, largely expressed on activated T cells, regulatory T cells and B cells, that can cause T-cell exhaustion/dysfunction when activated.[1,2]
- Blocking PD-1 activation restores effector T-cell activation, resulting in T-cell proliferation, interferon-γ secretion, and cytolytic function.[1,2]
- Inhibiting the interaction of human double minute 2 (HDM2), an E3 ubiquitin ligase, to p53, a tumor suppressor protein, leads to p53 restoration which has been shown to induce apoptosis in cancer cell lines.[3–5]

Proposed Areas of Research

- *TP53*–wild-type colorectal cancer (CRC) and renal cell carcinoma (RCC)[6,7]

Key Preclinical Data

- In a *TP53*–wild-type mouse model, the combination of spartalizumab and HDM201 resulted in complete tumor regressions and induced lasting antitumor immunity and long-term survival.[7]

Clinical Status

- A Phase Ib, open-label, multicenter study to characterize the safety, tolerability, and pharmacodynamics of spartalizumab treatment combinations, including spartalizumab plus HDM201 in patients with TP53–wild-type CRC and RCC, is currently enrolling patients (NCT02890069).[6]

Spartalizumab in combination with HDM201 is investigational. Efficacy and safety have not been established. There is no guarantee that spartalizumab and HDM201, or this combination will become commercially available for the use(s) under investigation. MOA data are based on in vitro/in vivo data. Clinical benefit is unknown.

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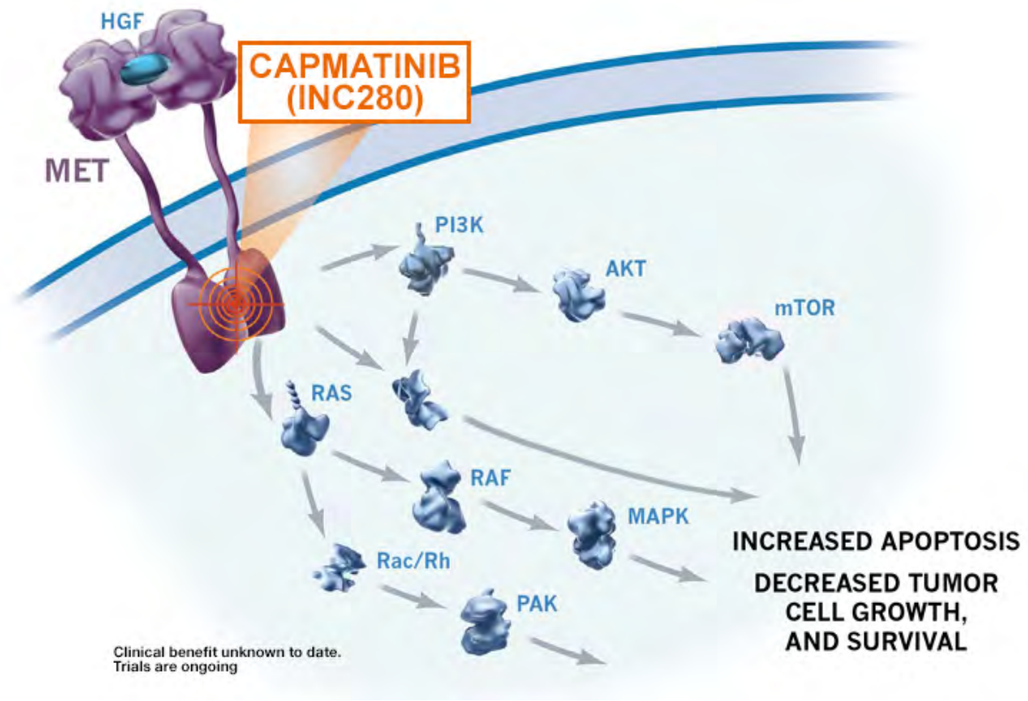


CAPMATINIB (INC280)

Inhibiting MET Receptor Tyrosine Kinase

Compound Description

Investigational, oral, selective cell surface receptor of the mesenchymal epithelial transition factor (MET) receptor tyrosine kinase (RTK) inhibitor

Areas of Research

Solid tumors

Proposed Mechanism of Action

Capmatinib (INC280*) is an investigational, highly selective inhibitor of MET. In human malignant disease, the MET pathway is one of the dysregulated pathways.[1] Inappropriate signaling through the MET RTK occurs in multiple types of human cancers due to receptor overexpression, gene amplification, gene mutation, and/or ligand-dependent activation, and may contribute to malignant progression through increased cell proliferation, survival, invasion, and metastasis.[1–3] Aberrant MET signaling has been documented in many tumor types, including most carcinomas.[1–3]

Key Preclinical Data

Capmatinib (INC280) has demonstrated inhibitory activity (IC_{50} values: 0.2–2 nM) in cell-based biochemical and functional assays that measure MET signaling and MET-dependent cell proliferation, survival, and migration.[3,4] Oral administration of capmatinib (INC280) conferred in vivo activity in blocking both MET phosphorylation and tumor growth in mouse tumor models.[3,4] Capmatinib (INC280) is thought to be highly specific for MET kinase inhibition.[3,5] It has demonstrated >10,000-fold selectivity to c-MET over a panel of more than 50 human kinases in in vitro assays.[3,5]

Clinical Status

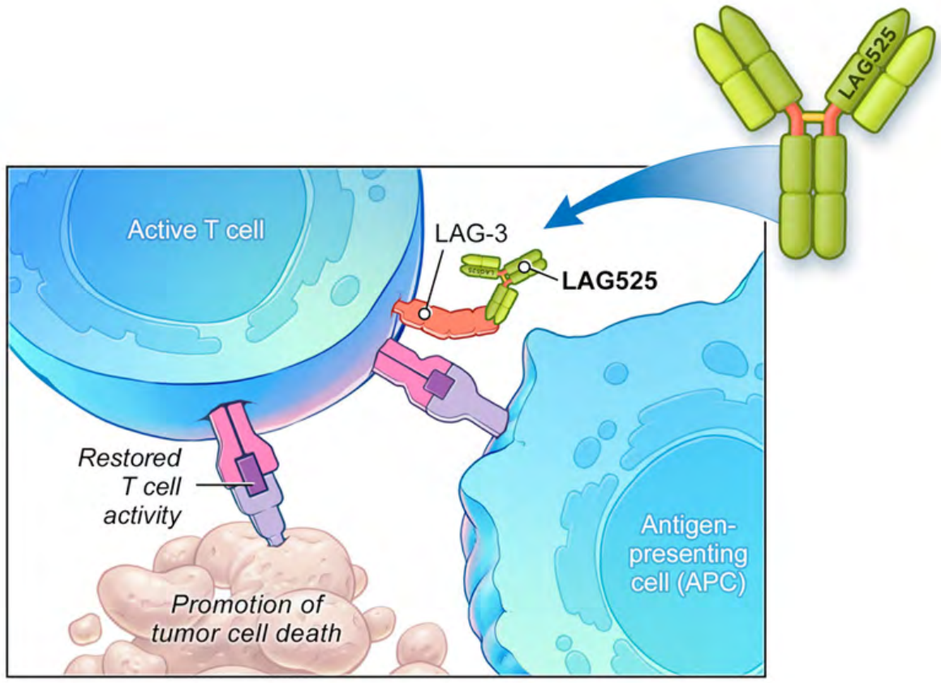
There are several active clinical trials evaluating capmatinib (INC280) that are currently recruiting patients, including:

- A Phase II, multicenter, multicohort study to evaluate antitumor activity of oral MET inhibitor capmatinib (INC280) in adult patients with epithelial growth factor receptor (EGFR), wild-type, advanced non-small cell lung cancer (NSCLC) (NCT02414139)[6]
- A Phase Ib/II, open-label, multicenter study of INC280 in combination with spartalizumab (PDR001) or spartalizumab (PDR001) single agent in advanced hepatocellular carcinoma (NCT02795429)[7]
- A Phase Ib/II, multicenter, open-label study of nazartinib (EGF816) in combination with capmatinib (INC280) in adult patients with EGFR mutated NSCLC (NCT02335944)[8]

* Capmatinib (also known as INC280 or INCB028060) is licensed from Incyte Corp.

Capmatinib (INC280) is an investigational compound. Efficacy and safety have not been established. There is no guarantee that capmatinib (INC280) will become commercially available. MOA data are based on in vitro/in vivo data. Clinical benefit is unknown.

REFERENCES: 1. Liu X, Yao W, Newton RC, et al. Targeting the c-MET signaling pathway for cancer therapy. *Expert Opin Investig Drugs*. 2008;17(7):997–1011. **2.** Birchmeier C, Birchmeier W, Gherardi E, et al. Met, metastasis, motility and more. *Nat Rev Mol Cell Biol*. 2003;4(12):915–925. **3.** Liu X, Koblish H, Wang Q, et al. Discovery and characterization of INCB028060, a novel, potent and selective Met RTK inhibitor for cancer treatment. In: Proceedings from the 99th Annual Meeting of the American Association for Cancer Research (AACR); April 12–16, 2008; San Diego, CA. Abstract 2577. **4.** Koblish HK, Liu X, Hall L, et al. Preclinical in vivo characterization of INCB028060, a novel, potent and highly selective c-MET inhibitor. In: Proceedings from the 44th Annual Meeting of the American Society of Clinical Oncology (ASCO); May 30–June 3, 2008; Chicago, IL. Abstract 14561. **5.** Liu X. INCB028060, a novel, potent and selective Met RTK inhibitor for cancer treatment. Paper presented at: 4th Annual Summit of the Modern Drug Discovery and Development; October 15–17, 2008; San Diego, CA. **6.** ClinicalTrials.gov. www.clinicaltrials.gov/ct2/show/NCT02414139. Updated November 13, 2017. Accessed January 25, 2018. **7.** ClinicalTrials.gov. www.clinicaltrials.gov/ct2/show/NCT02795429. Updated November 6, 2017. Accessed January 25, 2018. **8.** ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02335944. Updated January 17, 2018. Accessed January 25, 2018.



Novartis internal

LAG525

A LAG-3 receptor-targeting monoclonal antibody

Compound Description

LAG525 is an investigational immunoglobulin G4 humanized monoclonal antibody that is thought to bind to LAG-3, an inhibitory receptor expressed on immune cells.[1,2]

Areas of Research

Advanced solid and hematologic malignancies

Proposed Mechanism of Action

The inhibitory receptor LAG-3 is expressed on activated CD4+ and CD8+ T cells, subsets of regulatory T cells (Tregs), natural killer cells, and plasmacytoid dendritic cells.[1] LAG-3 negatively regulates T-cell signaling and function in effector T cells by binding major histocompatibility complex (MHC) class II molecules, which are expressed on epithelial cancer cells, tumor-infiltrating T macrophages, and dendritic cells.[1,3] In addition, LAG-3 signaling supports the suppressive phenotype of regulatory T cells. In preclinical studies, blockade of the LAG-3 interaction with MHC class II molecules restored activity of anti-tumor effector cells and enhanced anti-programmed death-1 (PD-1) anti-tumor activity.[3] Additionally, dual blockade of LAG-3 and PD-1, coexpressed on tumor-infiltrating lymphocytes, was synergistic for tumor growth inhibition.[4-6]

Clinical Status

- A Phase I/II, open-label, multicenter study of the safety and efficacy of LAG525 single agent and in combination with spartalizumab (PDR001) administered to patients with advanced solid tumors, including non-small cell lung cancer, melanoma, and renal cancer, is currently recruiting (NCT02460224).[7]

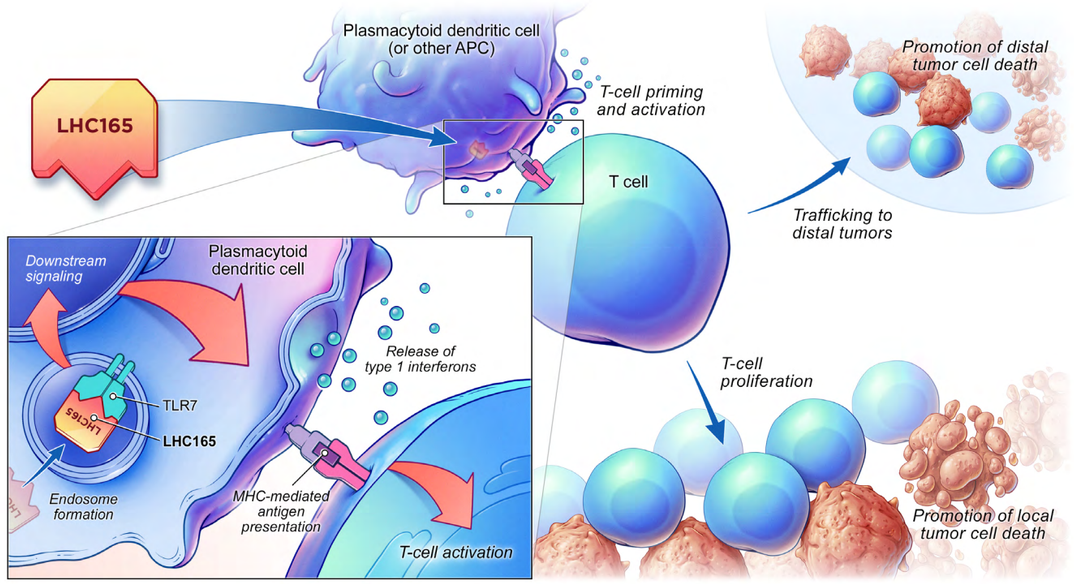
- A Phase II, open-label, parallel-cohort study to determine the efficacy and safety of treatment of the combination of spartalizumab (PDR001) and LAG525 across multiple tumor types that are relapsed and/or refractory is currently recruiting (NCT03365791).[8]

Clinical Data

- Spartalizumab (PDR001) and LAG525 showed promising activity in NET, SCLC and DLBCL[9]
- LAG525 in combination with spartalizumab was well tolerated in patients with solid tumors and hematologic malignancies, with no unexpected safety concerns[9]

LAG525 is an investigational compound. Efficacy and safety have not been established. There is no guarantee that LAG525 will become commercially available. MOA data are based on in vitro/in vivo data. Clinical benet is unknown.

REFERENCES: 1. Freeman GJ, Sharpe AH. A new therapeutic strategy for malaria: targeting T cell exhaustion. *Nat Immunol.* 2012;13(2):113–115. **2.** Data on le. Novartis; 2015. **3.** Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer.* 2012;12(14):252–264. **4.** Grosso JF, Goldberg MV, Getnet D, et al. Functionally distinct LAG-3 and PD-1 subsets on activated and chronically stimulated CD8 T cells. *J Immunol.* 2009;182(11):6659–6669. **5.** Baitsch L, Legat A, Barba L, et al. Extended co-expression of inhibitory receptors by human CD8 T-cells depending on differentiation, antigen-specicity and anatomical localization. *PLoS One.* 2012;7(2):e30852. **6.** Woo SR, Turnis ME, Goldberg MV, et al. Immune inhibitory molecules LAG-3 and PD-1 synergistically regulate T-cell function to promote tumoral immune escape. *Cancer Res.* 2012;72(4):917–927. **7.** ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02460224. Updated February 23, 2018. Accessed March 8, 2018. **8.** ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03365791. Updated March 6, 2018. Accessed March 19, 2018. **9.** DOI: 10.1200/JCO.2019.37.15_suppl.2553 *Journal of Clinical Oncology* 37, no. 15_ suppl (May 20, 2019) 2553-2553



Proposed Areas of Research

Solid tumors[4]

Key Preclinical Data

- In vitro and in vivo assays demonstrated the ability of LHC165 to bind to TLR7 and activate downstream signaling pathways leading to cytokine expression.[1]
- Dose-dependent inhibition of tumor growth was observed following intratumoral injection of LHC165 in tumor mouse models.[1]
- Preclinical murine models demonstrated that combination of LHC165 with an anti-programmed death-ligand 1 (PD-L1) agent led to more effective tumor growth inhibition than either agent alone.[1]

Clinical Status

- A Phase I/Ib, open-label, multicenter dose-escalation and dose-expansion study of the safety and tolerability of intratumorally administered LHC165 single agent and in combination with spartalizumab (PDR001) in patients with advanced malignancies is currently enrolling patients (NCT03301896).[4]

LHC165

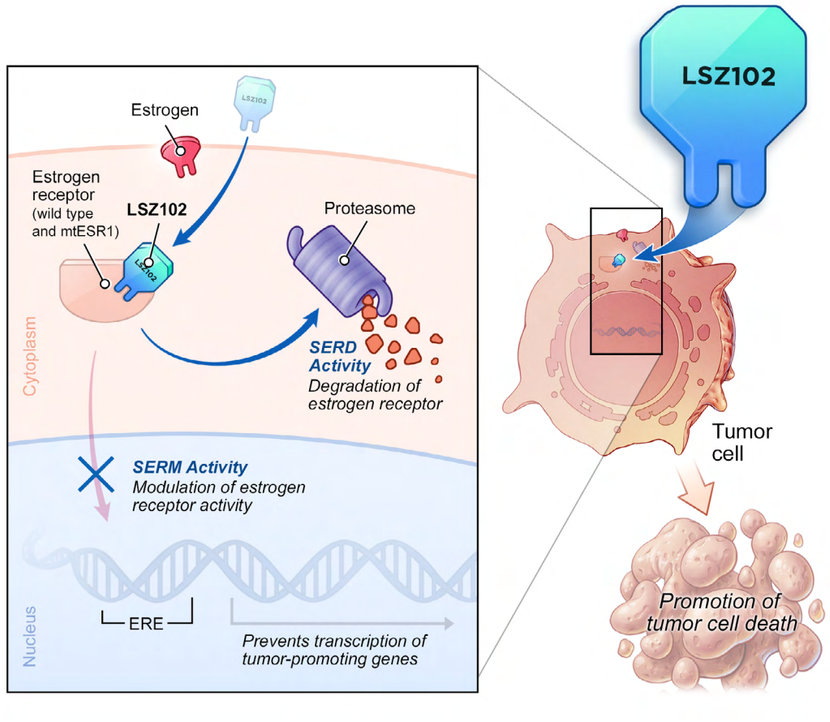
TLR7 agonist

Proposed Mechanism of Action

- LHC165 is an investigational synthetic toll-like receptor 7 (TLR7) agonist.[1]
- TLRs, including TLR7, are intracellular endosome receptors able to initiate innate immune signaling in response to damage- and pathogen-associated molecular patterns.[2]
- TLR7 agonists can induce activation of the innate and adaptive antitumor immune response in tumor models.[1–3]

LHC165 is an investigational compound. Efficacy and safety have not been established. There is no guarantee that LHC165 will become commercially available. MOA data are based on in vitro/in vivo data. Clinical benefit is unknown.

REFERENCES: 1. Data on file. Novartis; 2017. **2.** Chi H, Li C, Zhao FS, et al. Anti-tumor activity of toll-like receptor 7 agonists. *Front Pharmacol.* 2017;8:304. **3.** Spinetti T, Spagnuolo L, Mottas I, et al. TLR7-based cancer immunotherapy decreases intratumoral myeloid-derived suppressor cells and blocks their immunosuppressive function. *Oncoimmunology.* 2016;5:e1230578. **4.** ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show/NCT03301896. Updated December 12, 2018. Accessed March 15, 2019.



Novartis internal

LSZ102

A selective estrogen receptor downregulator

Compound Description

LSZ102 is an investigational orally bioavailable small molecule with selective estrogen receptor degrader (SERD) and selective estrogen receptor modulator (SERM) proper ties.

Areas of Research

ER+ breast cancer

Proposed Mechanism of Action

LSZ102 is an investigational orally bioavailable small molecule that is thought to: 1) target the estrogen receptor (ER) for proteasome-dependent degradation; and 2) act as a high affinity, competitive ER antagonist.[1] ERα, a nuclear hormone receptor that regulates a large set of genes promoting cell proliferation and cell cycle progression, is a potential therapeutic target in ER+ breast cancer. LSZ102 exhibits pharmacokinetic properties that may lead to enhanced ER inhibition and potentially improved clinical outcomes.[1]

Key Preclinical Data

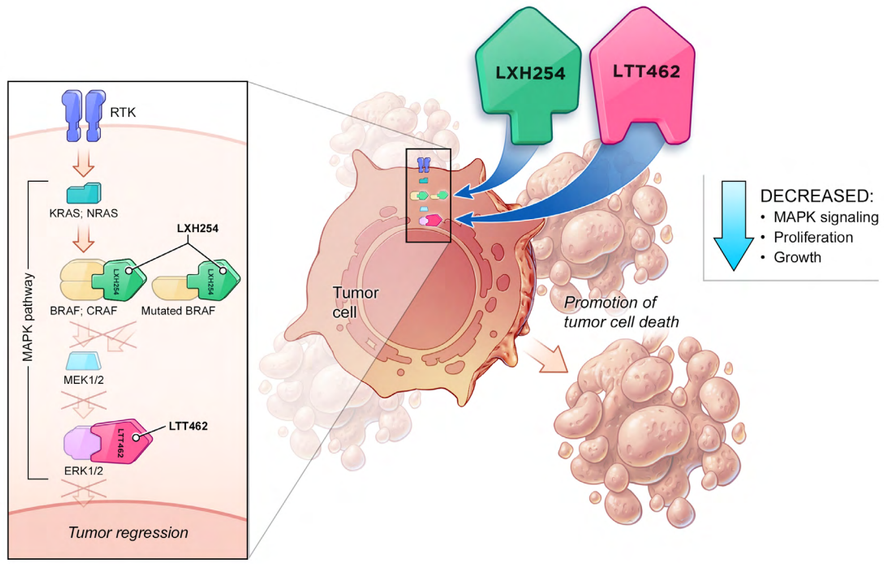
In vitro, LSZ102 demonstrated SERD properties through potent ER antagonism and degrader activity in an estrogen-sensitive, MCF7 ER+ breast cancer cell model. LSZ102 also inhibited insulin-driven MCF7 cell proliferation and dose-dependently inhibited the expression of ER target genes.[1] In vivo, LSZ102 showed activity against xenografts of an estrogen-sensitive, ER+ breast cancer cell line and of patient-derived tumor cells.[1]

Clinical Status

A Phase I/Ib, open-label study of LSZ102 single agent and LSZ102 in combination with either LEE011 (LSZ102 + LEE011) or BYL719 (LSZ102 + BYL719) in patients with advanced or metastatic ER+ breast cancer who have progressed after endocrine therapy (NCT027346152) is underway.

LSZ102 is an investigational compound. Efficacy and safety have not been established. There is no guarantee that LSZ102 will become commercially available. MOA data are based on in vitro/in vivo data. Clinical benefit is unknown.

REFERENCES: 1. Data on file. Novartis; 2016. **2.** ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02734615. Updated September 6, 2017. Accessed January 30, 2018.



LXH245 and LTT462

BRAF/CRAF and ERK small-molecule inhibitors

Compound Description

LXH254 is an investigational, small-molecule inhibitor of BRAF/CRAF.[1] LTT462 is an investigational, small-molecule inhibitor of extracellular signal–regulated kinase 1 and 2 (ERK1/2).[1]

Areas of Research

Mitogen-activated protein kinase (MAPK)-altered solid tumors, with focus on RAS/RAF mutations[2–5]

Proposed Mechanism of Action

LXH254 is an investigational type II adenosine triphosphate (ATP)-competitive inhibitor that selectively inhibits both monomeric and dimeric BRAF/CRAF, thereby inhibiting MAPK signaling with reduced paradoxical activation relative to currently approved RAF inhibitors. LTT462 is an investigational, selective, orally bioavailable, ATP-competitive inhibitor of ERK1 and ERK2.[1]

Key Preclinical Data

In vitro, LTT462 demonstrated antiproliferative activity with submicromolar half maximal inhibitory concentration (IC_{50}) in cancer cell lines with BRAF, KRAS, NRAS and MEK mutations.[1] LXH254 inhibited RAF/MEK pathway signaling and proliferation in human tumor cells expressing mutant KRAS, NRAS, and BRAF, with IC_{50} values ranging from 0.2 to 1.5 μM.[1]

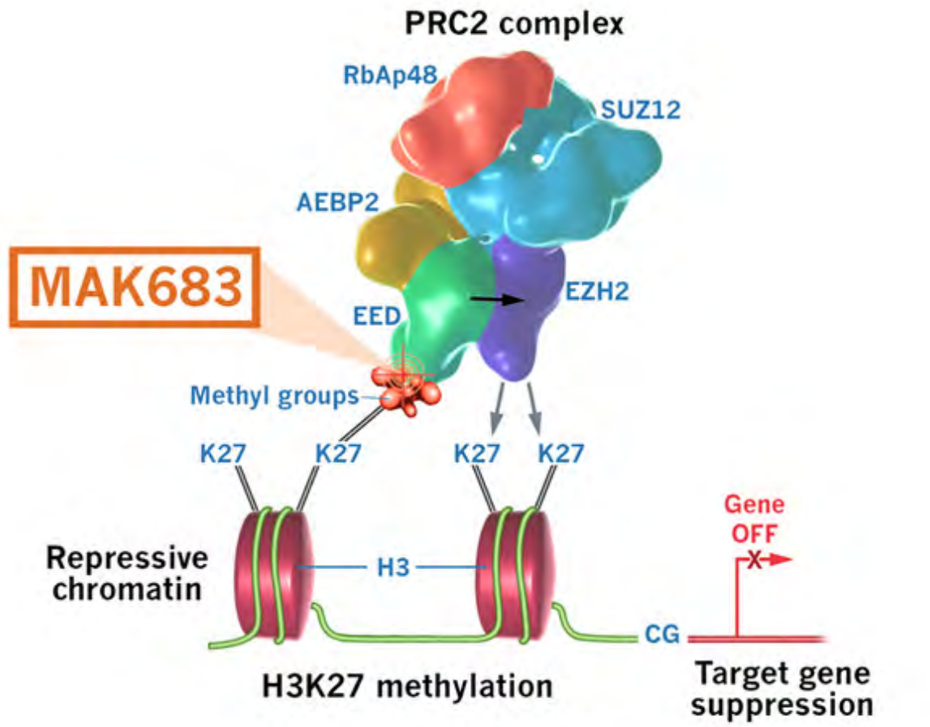
In vivo, both LXH254 and LTT462 showed antitumor effects in tumor xenograft models harboring KRAS, NRAS, and BRAF mutations, both as single agents, in combination, or in combination with the MEK inhibitor trametinib.[1]

Clinical Status

- A first-in-human, Phase I study of LXH254 in patients with advanced solid tumors harboring MAPK pathway alterations is currently recruiting (NCT02607813).[2]
- A first-in-human, Phase I study of LTT462 in patients with advanced solid tumors harboring MAPK pathway alterations is currently recruiting (NCT02711345).[3]
- A Phase Ib, open-label, multicenter study of LXH254 and LTT462 or LXH254 and trametinib in adult patients with advanced or metastatic KRAS- or BRAF-mutant non-small cell lung cancer (NSCLC) or NRAS-mutant melanoma is currently recruiting (NCT02974725).[4]
- A Phase Ib, open-label, dose-escalation study of EGF816 in combination with ribociclib, trametinib, or LXH254, followed by dose expansion of EGF816 in combination with ribociclib, trametinib, LXH254, INC280, or gefitinib in patients with advanced EGFR-mutant NSCLC is currently recruiting (NCT03333343).[5]

LXH254 in combination with LTT462 is investigational. Efficacy and safety have not been established. There is no guarantee that LXH254 and LTT462 or this combination will become commercially available for the use(s) under investigation. MOA data are based on in vitro/in vivo data. Clinical benefit is unknown.

REFERENCES: 1. Data on file. Novartis; 2016. **2.** ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show/NCT02607813. Updated September 24, 2018. Accessed October 11, 2018. **3.** ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show/NCT02711345. Updated July 6, 2018. Accessed October 11, 2018. **4.** ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show/NCT02974725. Updated April 20, 2018. Accessed October 11, 2018. **5.** ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show/NCT03333343. Updated August 27, 2018. Accessed October 11, 2018.



Novartis internal

MAK683

EED small-molecule inhibitor

Compound Description

MAK683 is an investigational selective inhibitor of embryonic ectoderm development (EED), a component of the polycomb repressive complex 2 (PCR2). MAK683 inhibits interaction between EED and trimethylated lysine 27 on histone H3 (H3K27me3).[1]

Areas of Research

Advanced malignancies, including lymphoma, nasopharyngeal carcinoma, and other solid tumors.[2]

Proposed Mechanism of Action

EED is essential for the histone methyltransferase activity of PRC2 because EED directly binds to H3K27me3.[1] Disruption of the EED-EZH2 protein-protein interaction by MAK683 results in a loss of H3K27me3-stimulated PRC2 activity and prevents H3K27 trimethylation.[1] This decrease in histone methylation alters gene expression patterns associated with cancer pathways and results in decreased tumor cell proliferation in EZH2-mutated and PRC2-dependent cancer cells.[1]

Key Preclinical Data

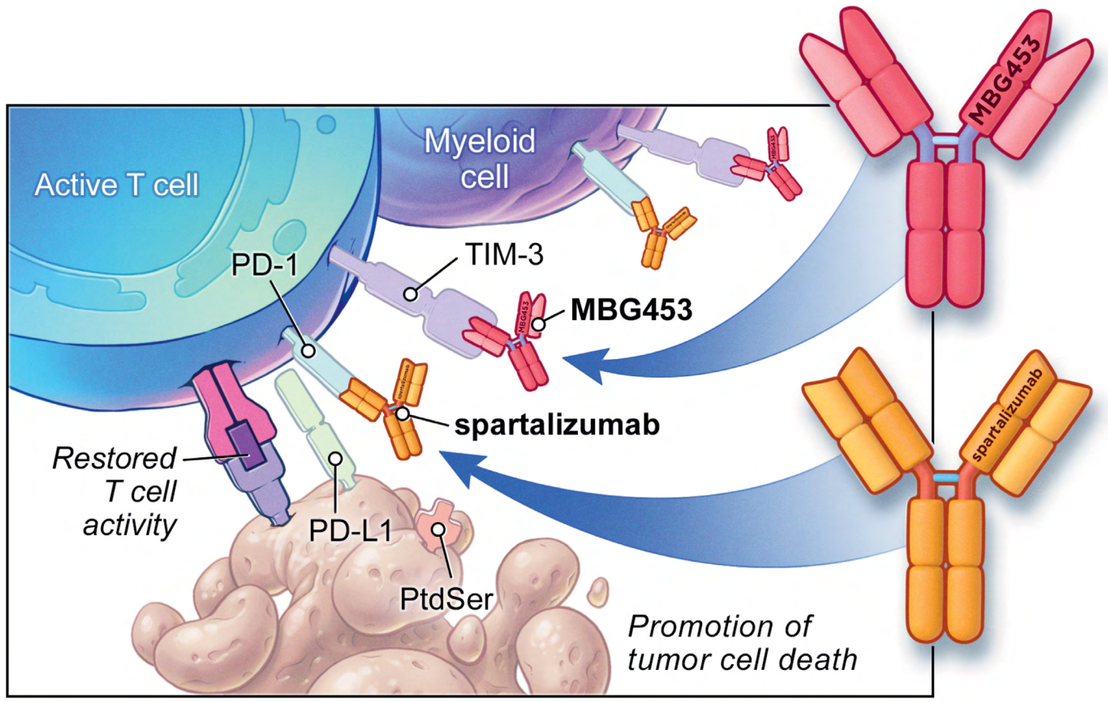
In preclinical studies, MAK683 inhibited H3K27 methylation and led to decreased proliferation in EZH2-mutated DLBCL cell lines and resulted in tumor regressions in mouse and rat xenograft models.[1]

Clinical Status

A Phase I/II, multicenter, open-label study of MAK683 in patients with DLBCL, nasopharyngeal carcinoma, or gastric cancer, ovarian cancer, prostate cancer, and sarcoma is currently recruiting patients (NCT02900651).[2]

MAK683 is an investigational compound. Efficacy and safety have not been established. There is no guarantee that MAK683 will become commercially available. MOA data are based on in vitro/in vivo data. Clinical benefit is unknown.

REFERENCES: 1. Date on file. Novartis; 2017; **2.** ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show/NCT02900651. Updated June 6, 2018. Accessed October 16, 2018.



SPARTALIZUMAB (PDR001) & MBG453

PD-1-targeting monoclonal antibody and TIM-3-targeting monoclonal antibody

Compound Description

Spartalizumab (PDR001) and MBG453 are investigational monoclonal antibodies that bind with subnanomolar affinity in vitro to programmed death-1 (PD-1) and T-cell immunoglobulin mucin (TIM-3), respectively.[1,2]

Areas of Research

Advanced malignancies, acute myeloid leukemia (AML), and myelodysplastic syndromes (MDS)[3,4]

Proposed Mechanism of Action

PD-1 is an immunoinhibitory receptor expressed on activated T cells, regulatory T cells, and B cells.[5] When bound to programed death-ligand 1 (PD-L1), a ligand expressed in many tumor types, PD-1 is activated leading to T-cell exhaustion/dysfunction.[5,6] Blocking PD-1 activation has been demonstrated to restore effector T-cell function, leading to T-cell proliferation, interferon-γ secretion, and cytolytic function.[5]

TIM-3 is an inhibitory receptor expressed in the majority of leukemic stem cells (LSCs) and leukemic progenitors in AML but not in normal hematopoietic stem cells. MBG543 may have a direct effect on LSCs and AML progenitors.[7] TIM-3 blockade has also been demonstrated to restore activity of exhausted T cells and may diminish suppressor activity of regulatory T cells, enhancing anti-tumor activity of PD-1/PD-L1 inhibition.[8–10]

Clinical Status

- A Phase I-Ib/II, open-label, multicenter study of the safety and efficacy of MBG453 as a single agent and in combination with spartalizumab (PDR001) in adult patients with advanced malignancies, including melanoma, non-small cell lung cancer, and renal cell carcinoma, is currently recruiting (NCT02608268).[3]
- A Phase Ib, multiarm, open-label study of spartalizumab (PDR001) and/or MBG453 in combination with decitabine in patients with AML or high-risk MDS is currently recruiting (NCT03066648).[4]

Clinical Data

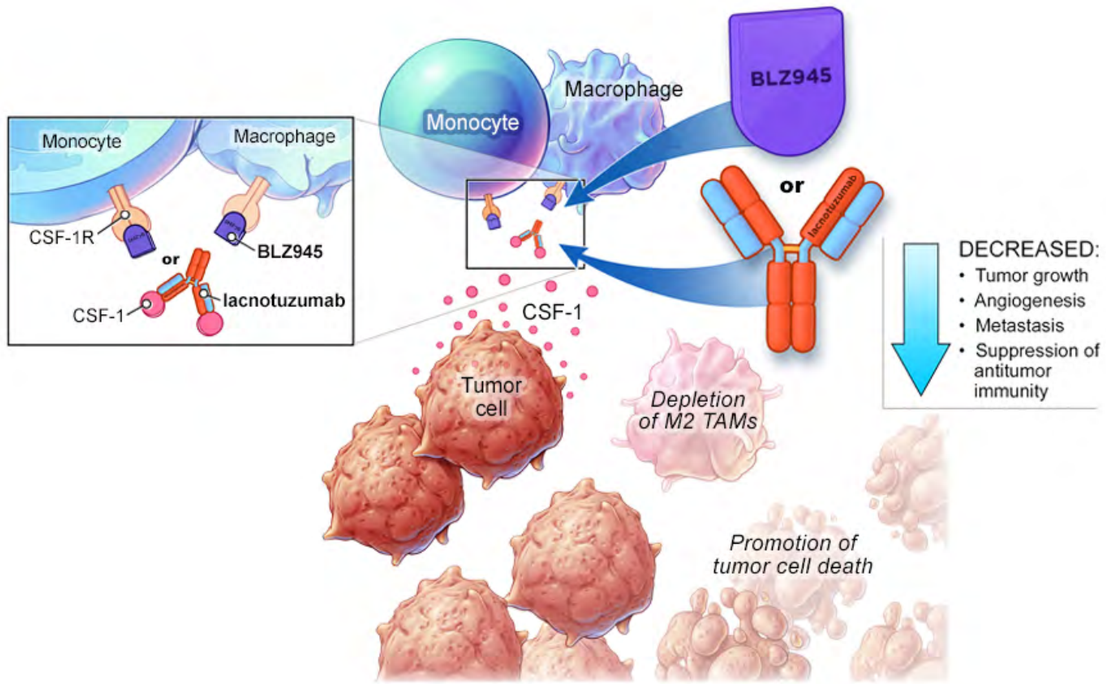
Ph I/II Study of MBG453 ± Spartalizumab (PDR001) in pts with Advanced Malignancies

- MTD were not identified with the tested dose/schedule
- MBG453 800 mg Q4W (n=9 pts treated) and MBG453 800 mg + spartalizumab 400 mg Q4W (n=6 pts treated) were declared as RP2Ds
- Of 86 MBG453 + spartalizumab pts, PRs were seen in 4 pts (5%); 1 anti-PD-1/PD-L1 pre-treated pt, 3 anti-PD-1/PD-L1 naïve; SD was seen in 34/86 (40%) MBG453 + spartalizumab pts; 10 of 34 pts with SD were anti-PD-1/PD-L1 pre-treated

Cancer Res July 1 2019 (79) (13 Supplement) CT183; DOI: 10.1158/1538-7445.AM2019-CT183

Spartalizumab in combination with MBG453 is investigational. Efficacy and safety have not been established. There is no guarantee that spartalizumab and MBG453 or this combination will become commercially available for the use(s) under investigation. MOA data are based on in vitro/in vivo data.

REFERENCES: 1. Data on file. Novartis; 2018. **2.** Sabatos-Peyton C, MBG453: A high affinity, ligand blocking anti-TIM-3 monoclonal Ab. Presented at: AACR Annual Meeting 2016; April 16-20, 2016; New Orleans, LA. **3.** ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show/ NCT02608268. Updated October 2, 2016. Accessed October 11, 2018. **4.** ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show/ NCT03066648. Updated June 20, 2018. Accessed October 11, 2018. **5.** Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. *Annu Rev Immunol.* 2008;26:677–704. **6.** Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer.* 2012;12(14):252–264. **7.** Kikushige Y, Shima T, Takayanagi S, et al. TIM-3 is a promising target to selectively kill acute myeloid leukemia stem cells. *Cell Stem Cell.* 2010;7(6):708-717. **8.** Ngiow SF, Teng MW, Smyth MJ. Prospects for TIM3-targeted antitumor immunotherapy. *Cancer Res.* 2011;71(21):6567–6571. **9.** Du W, Yang M, Turner A, et al. TIM-3 as a target for cancer immunotherapy and mechanisms of action. *Int. J. Mol. Sci.* 2017;18:645. **10.** Sakuishi K, Apetoh L, Sullivan JM, et al. Targeting Tim-3 and PD-1 pathways to reverse T cell exhaustion and restore anti-tumor immunity. *J Exp Med.* 2010;207(10):2187–2194. **11.** Ngiow SF, von Scheidt B, Akiba H, Yagita H, Teng MW, Smyth MJ. Anti-TIM3 antibody promotes T cell IFN-γ-mediated antitumor immunity and suppresses established tumors. *Cancer Res* 2011;71: 3540–3551.



LACNOTUZUMAB (MCS110) and BLZ945

CSF-1 targeting monoclonal antibody and CSF-1R small-molecule inhibitor

Compound Description

Lacnotuzumab is an investigational monoclonal antibody specific to macrophage colony-stimulating factor 1 (CSF-1),[1] and BLZ945 is an investigational selective small-molecule inhibitor of the CSF-1 receptor (CSF-1R).[2]

Areas of Research

Immunomodulatory subtype of triple-negative breast cancer (TNBC) and other solid tumors[3,4]

Proposed Mechanism of Action

Lacnotuzumab is an investigational humanized monoclonal antibody that binds to the CSF-1[1] ligand, a cytokine involved in the proliferation and differentiation of monocytes to macrophages.[5] BLZ945 is an investigational selective small-molecule inhibitor targeting CSF-1R.[2] CSF-1 is expressed in over 50% of breast cancers,[6] and its expression is correlated with chemoresistance.[5,7] CSF-1 secreted from tumor cells recruits tumor-associated macrophages (TAMs), which can stimulate tumor growth, angiogenesis, invasion, and/or metastasis, as well as suppress antitumor immunity.[8]

Key Preclinical Data

Preclinical studies have shown that CSF-1 is a viable target for breast cancer therapy. Deleting CSF-1 in mice susceptible to breast cancer resulted in reduced macrophage recruitment and delayed metastasis.[9]

Antibody-mediated blockade of CSF-1 in mice bearing human, chemoresistant MCF-7 breast cancer xenografts suppressed CSF-1 tissue expression and macrophage recruitment and restored sensitivity to chemotherapy, resulting in a 56% reduction in tumor growth.[7] Additionally, CSF-1R inhibition increased CD8+ T-cell tumor infiltration and enhanced antitumor response to paclitaxel in xenograft models.[10] Furthermore, CSF-1R inhibition with BLZ945 blocked tumor growth and regressed established tumors in preclinical models.[2]

Clinical Status

There is 1 trial currently evaluating lacnotuzumab in oncology.

- A Phase Ib/II study (NCT02807844) is evaluating lacnotuzumab in combination with PDR001 in patients with advanced malignancies[3]

There is currently 1 trial underway evaluating BLZ945.

- A Phase I/II, open-label, multicenter study (NCT02829723) is evaluating BLZ945 as single agent and in combination with PDR001 in patients with advanced solid tumors[4]

Lacnotuzumab and BLZ945 are investigational compounds. Efficacy and safety have not been established. There is no guarantee that lacnotuzumab or BLZ945 will become commercially available. MOA data are based on in vitro/in vivo data. Clinical benefit is unknown.

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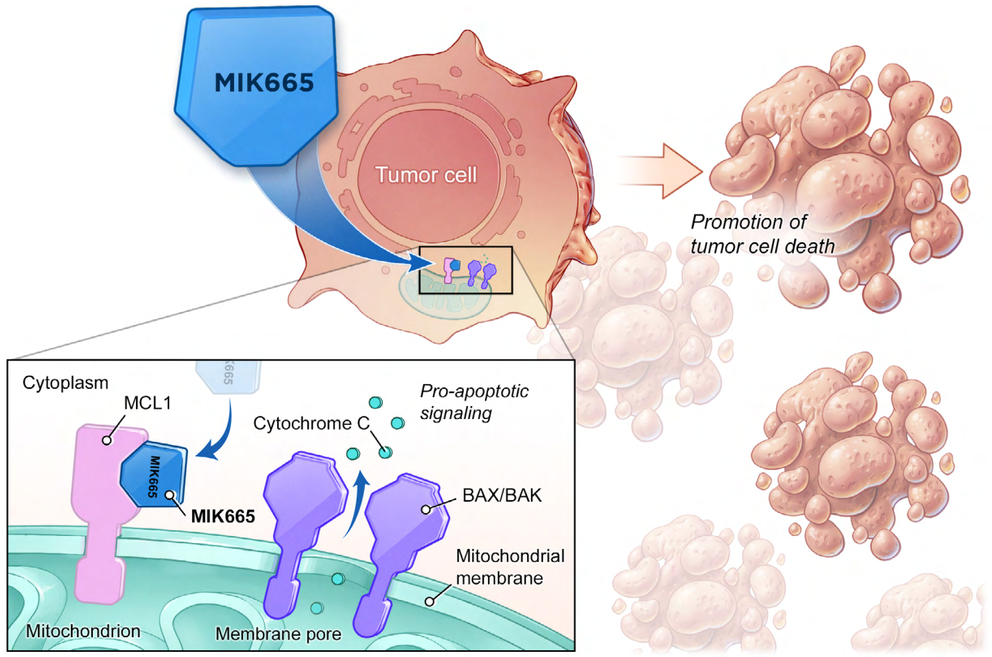


MIK665 (S64315)

A myeloid leukemia differentiation protein Mcl-1 (MCL1) inhibitor; BCL2-homology domain 3 (BH3) mimetic

Compound Description

MIK665 is an investigational, selectively induced myeloid leukemia differentiation protein Mcl-1 (MCL1) inhibitor that is being codeveloped with SERVIER. MIK665 is also known as S64315. MIK665 is administered intravenously.[1]

Areas of Research

Refractory or relapsed lymphoma or multiple myeloma (MM), acute myeloid leukemia (AML), and myelodysplastic syndrome (MDS).[1,2]

Proposed Mechanism of Action

MCL1 is a member of the antiapoptotic B-cell lymphoma 2 (BCL2) family of proteins. Expression of antiapoptotic BCL2-family members is a hallmark of myeloid malignancies and plays a crucial role in disease pathogenesis. MCL1 is commonly upregulated in MM and AML cells, thereby representing a potential therapeutic target alone or in combination with other treatments.[3,4] MCL1 inhibits apoptosis through sequestration of the proapoptotic BCL2-homology domain 3 (BH3)–only proteins BCL2-like 11 (BIM) or phorbol-12-myristate-13-acetate-induced protein 1 (NOXA), or by direct interaction with proapoptotic proteins BCL2-associated X (BAX) and BCL2 antagonist/killer 1 (BAK).[1] MIK665 is a BH3 mimetic that selectively inhibits MCL1 in vitro by binding to its BH3 binding groove, disrupting its interaction with BAX/BAK, potentially leading to disruption of the mitochondrial outer membrane (MOM), followed by cytochrome C release, caspase activation, and subsequent cell death.[1,5]

Key Preclinical Data

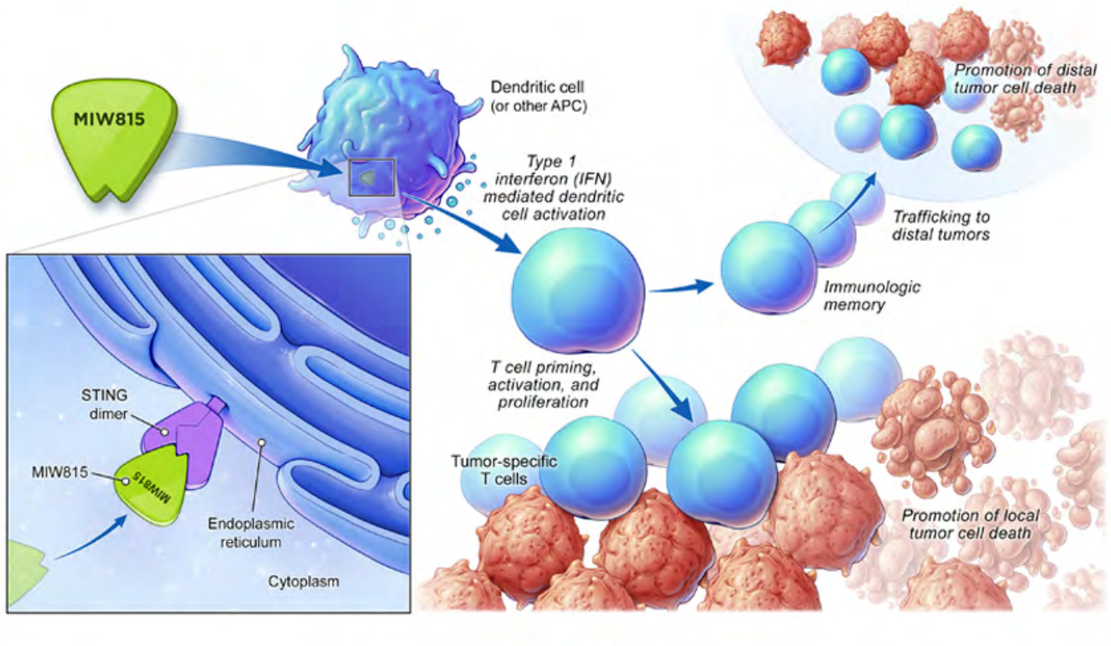
MIK665 is a highly selective MCL1 inhibitor with higher affinity for MCL1 than for the antiapoptotic proteins BCL2 or BCL-X_L.[1] In vitro cellular assays demonstrated antiproliferative activity across a panel of human acute myeloid leukemia, lymphoma, and MM cell lines.[1] In vivo, MIK665 showed antitumor activity in several hematologic cancer models in mice and rats.[1]

Clinical Status

- A Phase I, open-label study to characterize the safety, tolerability and pharmacokinetics of MIK665 (S64315), an MCL1 inhibitor, in patients with refractory or relapsed lymphoma or multiple myeloma is active and recruiting (NCT02992483).[2]
- Phase I, open-label study to characterize the safety, tolerability and pharmacokinetics of MIK665 (S64315), an MCL1 inhibitor, in patients with refractory or relapsed lymphoma or multiple myeloma (NCT02992483) and in AML (Acute Myeloid Leukemia) and MDS (Myelodysplastic Syndrom) (EudraCT 2016-003768-38, NCT02979366) is active and recruiting.[2]

MIK665 is an investigational compound. Efcacy and safety have not been established. There is no guarantee that MIK665 will become commercially available. MOA data are based on in vitro/in vivo data. Clinical benet is unknown.

REFERENCES: 1. Data on le. MIK665 Investigators Brochure, Edition 1. Novartis Pharmaceuticals Corp; 2016. **2.** ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02992483. Accessed August 8, 2018. **3.** Wuilleme-Toumi S, Robillard N, Gomez, P, et al. Mc-1 is overexpressed in multiple myeloma and associated with relapse and shorter survival. *Leukemia.* 2005;19(7):1248–1252. **4.** Ramsey HE, Fischer MA, Lee T, et al. A novel MCL-1 inhibitor combined with venetoclax rescues venetoclax resistant acute myelogenous leukemia. *Cancer Discov.* 2018; [Epub ahead of print]. **5.** Anderson MA, Huang D, Roberts A. Targeting BCL2 for the treatment of lymphoid malignancies. *Semin Hematol.* 2014;51:219–227.



MIW815 (ADU-S100)

A STING agonist

Compound Description

MIW815[a,b] is an investigational cyclic dinucleotide (CDN) that is thought to stimulate the body's innate immune response to tumors.[1,2] It is delivered through a direct injection to the tumor to activate the STING (stimulator of interferon genes) pathway.[2]

Areas of Research

Solid tumors or lymphomas

Proposed Mechanism of Action

Type 1 interferon signaling plays an essential role in tumor-initiated T-cell priming.[1] The STING pathway is activated through binding of exogenous or endogenous CDNs to STING dimers on the endoplasmic reticulum, initiating a type 1 interferon immune response potentially promoting tumor-initiated T-cell priming against an individual's tumor.[1,3,4]

This MOA can potentially be achieved by intratumoral injection of STING agonists, such as MIW815, to activate the STING pathway.[1] Activation of the STING pathway has been observed to lead to antitumor immunity, both locally and distally.[5]

The intratumoral injection of MIW815 may promote tumor regression and immunologic memory.[5]

Clinical Status

- A Phase I, open-label, multicenter study of the safety and efficacy of MIW815 (ADU-S100) administered by intratumoral injection to patients with advanced/metastatic solid tumors or lymphomas is currently enrolling patients (NCT02675439).[6]
- A Phase Ib, open-label, multicenter study evaluating the safety and efficacy of MIW815 in combination with spartalizumab (PDR001) in patients with advanced or metastatic solid tumors or lymphomas is currently enrolling patients (NCT03172936).[7]

Clinical Data

Ph Ib Study of MIW815 + Spartalizumab (PDR001) in pts with advanced/metastatic solid tumors or lymphoma (NCT03172936)

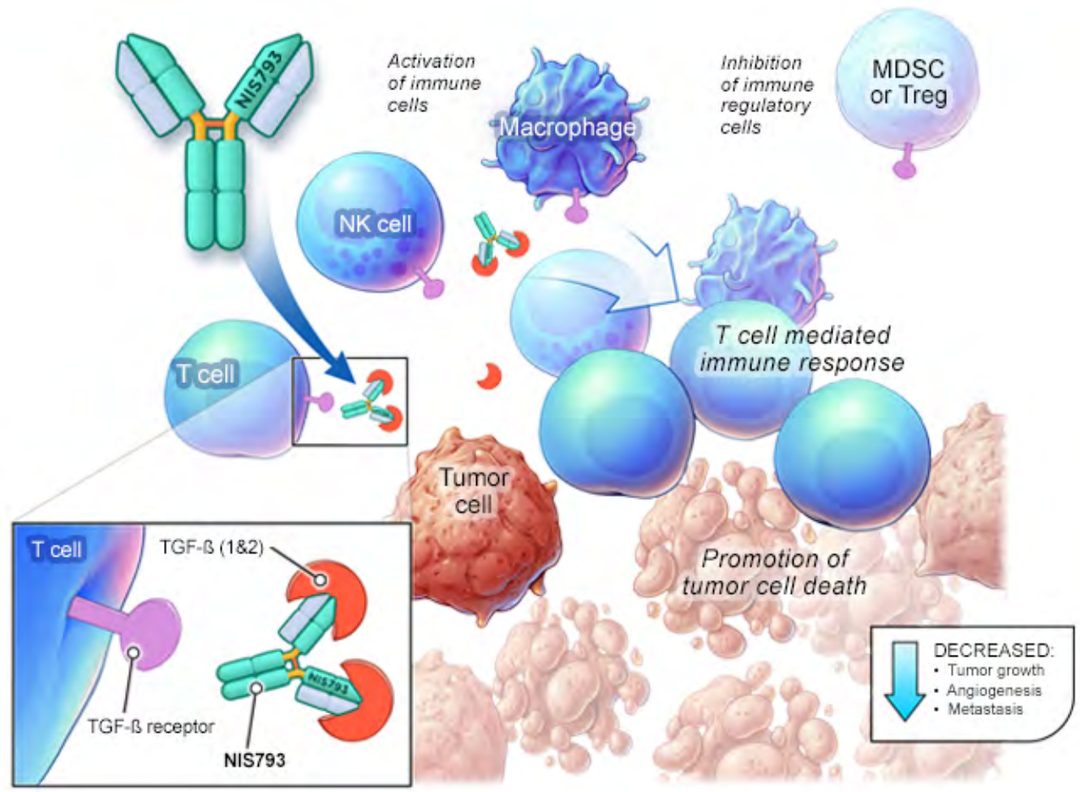
- MIW815 (ADU-S100) + spartalizumab was generally well tolerated in patients with solid tumors or lymphomas, with no DLTs reported as of the data cut-off
- The MTD has not been reached and dose-escalation is ongoing
- MIW815 plasma exposure increase dose-proportionally
- INF-β concentrations appeared to increase with increasing exposure to MIW815 (ADU-S100)
- The combination has demonstrated anti-tumor activity in PD-1-naive TNBC and PD-1-relapsed/refractory melanoma

Journal of Clinical Oncology 2019 37:15_suppl, 2507-2507

[a] MIW815 is codeveloped in partnership with Aduro Biotech, Inc.
[b] MIW815 is also known as ADU-S100.

MIW815 is an investigational compound. Efficacy and safety have not been established. There is no guarantee that MIW815 will become commercially available. MOA data are based on in vitro/in vivo data.

REFERENCES: 1. Data on Ie. MIK665 Investigators Brochure, Edition 1. Novartis Pharmaceuticals Corp; 2016. **2.** ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02992483. Accessed August 8, 2018. **3.** Wuilleme-Toumi S, Robillard N, Gomez, P, et al. Mc-1 is overexpressed in multiple myeloma and associated with relapse and shorter survival. *Leukemia.* 2005;19(7):1248–1252. **4.** Ramsey HE, Fischer MA, Lee T, et al. A novel MCL-1 inhibitor combined with venetoclax rescues venetoclax resistant acute myelogenous leukemia. *Cancer Discov.* 2018; [Epub ahead of print]. **5.** Anderson MA, Huang D, Roberts A. Targeting BCL2 for the treatment of lymphoid malignancies. *Semin Hematol.* 2014;51:219–227.



MDSC, myeloid-derived suppressor cell; NK, natural killer; Treg, regulatory T cells

Novartis internal

NIS793

A humanized anti-transforming growth factor β (TGFβ) monoclonal antibody

Compound Description

NIS793 is an investigational monoclonal antibody that binds to TGFβ1 and TGFβ2 with high affinity, and TGFβ3 to a lesser extent.[1]

Areas of Research

Advanced or metastatic solid tumors[2]

Proposed Mechanism of Action

NIS793 is an investigational, humanized monoclonal antibody that has been shown in vitro to neutralize TGFβ1, TGFβ2, and, to a lesser extent, TGFβ3[1]; these cytokines are involved in cell proliferation, differentiation, and tissue homeostasis.[3,4] In many cancers, it has been demonstrated that genetic alterations in the TGFβ pathway promote tumor initiation and progression, leading to increased TGFβ production in the tumor microenvironment.[5,6] Elevated TGFβ expression can, in turn, indirectly stimulate tumor progression and metastasis through structural remodeling of the tumor microenvironment and suppression of immune surveillance.[5,6] These findings support the rationale to investigate the potential of NIS793 to block TGFβ in solid tumors where TGFβ plays a key role in tumor immune escape.

Key Preclinical Data

Preclinical data have demonstrated that inhibition of TGFβ1 and TGFβ2 restores immune-mediated tumor control in mouse syngeneic models.[7] NIS793 inhibits tumor growth in preclinical models of head and neck cancer.[1]

Clinical Status

A Phase I/Ib open-label, multicenter, dose-escalation study of NIS793 as a monotherapy and in combination with spartalizumab (PDR001) in adult patients with advanced malignancies is currently recruiting.[2]

NIS793 is an investigational compound. Efficacy and safety have not been established. There is no guarantee that NIS793 will become commercially available. MOA data are based on in vitro/in vivo data. Clinical benefit is unknown.

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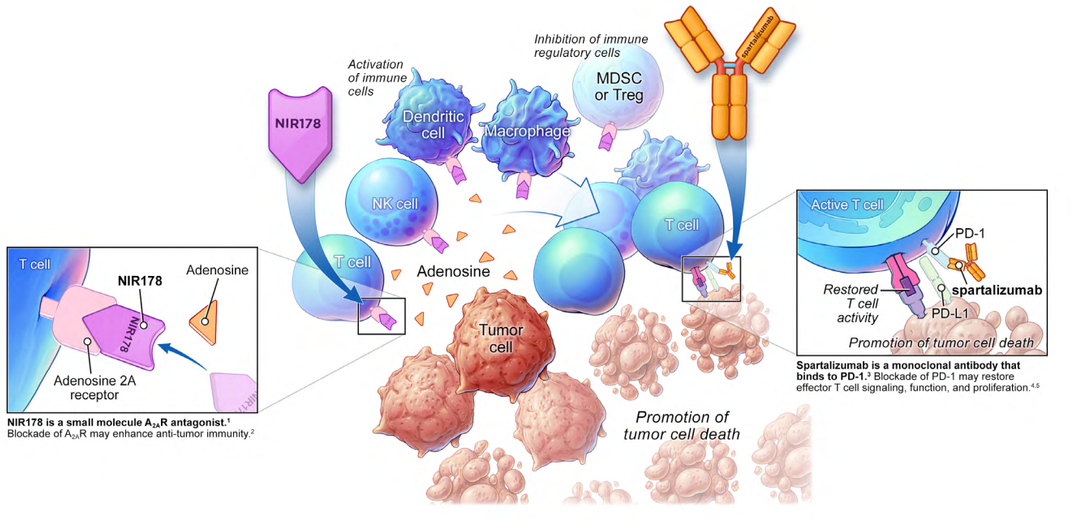


NIR178 is a small molecule $A_{2A}R$ antagonist.[1]
Blockade of $A_{2A}R$ may enhance anti-tumor immunity.[2]

Spartalizumab is a monoclonal antibody that binds to PD-1.[3] Blockade of PD-1 may restore effector T cell signaling, function, and proliferation.[4,5]

A2AR, adenosine 2A receptor; MDSC, myeloid-derived suppressor cell; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; Treg, regulatory T cell.

Novartis internal

SPARTALIZUMAB (PDR001) and NIR178 (PBF-509)

PD-1-targeting monoclonal antibody and adenosine 2A receptor antagonist

Compound Description

Spartalizumab (PDR001) is an investigational monoclonal antibody that binds with sub-nanomolar affinity in vitro to programmed death-1 (PD-1).[1] NIR178 (also known as PBF-509)[a] is an investigational, orally bioavailable, small-molecule adenosine 2A receptor ($A_{2A}R$) antagonist.[2]

Areas of Research

Non-small cell lung cancer (NSCLC), advanced solid tumors, and non-Hodgkin lymphoma[3–5]

Proposed Mechanism of Action

PD-1 is an immunoinhibitory receptor expressed on activated T cells, regulatory T cells, and B cells.[6] When bound to programmed death-ligand 1 (PD-L1), a ligand expressed in many tumor types, PD-1 is activated, leading to T-cell exhaustion/dysfunction.[6,7] Blocking PD-1 activation restores effector T-cell function, leading to T-cell proliferation, interferon-γ secretion, and cytolytic function.[6]

$A_{2A}Rs$ are expressed on various immune cells, including T cells and natural killer (NK) cells; binding of adenosine in the tumor microenvironment leads to the suppression of T- and NK-cell function.[8,9] Blockade of $A_{2A}Rs$ may counteract the immunosuppressive effects of tumor-derived adenosine and enhance immune responses.[8,9]

Key Preclinical Data

Spartalizumab (PDR001) binds to PD-1 with subnanomolar affinity in vitro, blocking interaction with ligands, PD-L1 and PD-L2.[1] Preclinical studies showed that $A_{2A}R$ antagonists reduced tumor burden in mouse models of NSCLC, and may further drive T-cell function in combination with PD-1 or PD-L1 checkpoint inhibitors.[10]

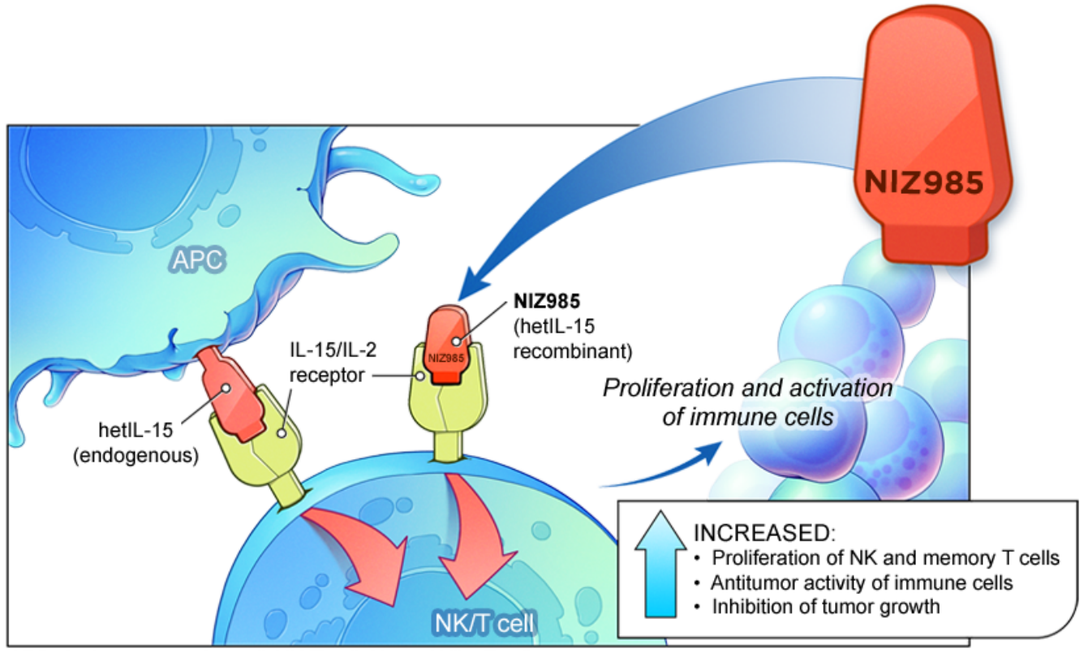
Clinical Status

- A Phase I/Ib trial of NIR178 (PBF-509) as a single agent and in combination with spartalizumab (PDR001) in patients with advanced NSCLC is currently enrolling patients (NCT02403193).[3]
- A Phase II, multicenter, open-label study of NIR178 (PBF-509) in combination with spartalizumab (PDR001) in patients with selected advanced solid tumors and non-Hodgkin lymphoma is currently enrolling patients (NCT03207867).[4]
- A Phase I/Ib, multicenter, open-label study of NZV930 alone and in combination with spartalizumab (PDR001) ±NIR178 (PBF-509) in patients with advanced malignancies is currently enrolling patients (NCT03549000).[5]

[a]NIR178 is codeveloped in partnership with Palobiofarma S.L.

Spartalizumab in combination with NIR178 is investigational. Efficacy and safety have not been established. There is no guarantee that spartalizumab and NIR178 or this combination will become commercially available for the use(s) under investigation. MOA data are based on in vitro/in vivo data. Clinical benefit is unknown.

REFERENCES: 1. Data on file. Novartis; 2018. **2.** Pinna A. Adenosine A2A receptor antagonists in Parkinson's disease: progress in clinical trials from the newly approved istradefylline to drugs in early development and those already discontinued. *CNS Drugs.* 2014;28:455–474. **3.** ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show/NCT02403193. Updated September 16, 2016. Accessed October 11, 2018. **4.** ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show/NCT03207867. Updated June 7, 2018. Accessed October 11, 2018. **5.** ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show/NCT03549000. Updated August 13, 2016. Accessed October 11, 2018. **6.** Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. *Annu Rev Immunol.* 2008;26:677–704. **7.** Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer.* 2012;12:252–264. **8.** Fishman P, Ba-Yehuda S, Synowitz M, et al. Adenosine receptors and cancer. *Handb Exp Pharmacol.* 2009;193:399–441. **9.** Leone RD, Lo YC, Powell JD. A2aR antagonists: next generation checkpoint blockade for cancer immunotherapy. *Comput Struct Biotechnol J.* 2015;13:265–272. **10.** Mediavilla-Varela M, Castro J, Chiappori A, et al. A novel antagonist of the immune checkpoint protein adenosine A2a receptor restores tumor-infiltrating lymphocyte activity in the context of the tumor microenvironment. *Neoplasia.* 2017;19:530–536.



APC=Antigen-presenting cell; NK/T cell=Natural killer T cell

Proposed Mechanism of Action

IL-15, in association with IL-15Rα, is presented in trans by antigen-presenting cells to natural killer (NK) cells and T cells expressing IL-2/IL-15Rß and common γc chains.[3–5] IL-15 promotes the expansion of NK cells and T cells and enhances the survival of CD8+ memory T cells.[3] In preclinical models, different soluble forms of IL-15/IL-15Rα showed enhanced CD8+ T-cell expansion and increased antitumor activity.[1,6–8] Treatment with NIZ985, a soluble, heterodimeric complex of IL-15/IL-15Rα, may increase the expansion and survival of memory CD8+ T cells.

Clinical Status

A Phase I study of subcutaneous recombinant human NIZ985 (hetIL-15) alone and in combination with spartalizumab (PDR001) in adults with metastatic cancers is currently recruiting.[2]

Clinical Data

Ph I/Ib study of NIZ985 with and Without Spartalizumab (PDR001) in pts with Metastatic/Unresectable Solid Tumors

- No DLTs were reported
- In 13 evaluable NIZ985 pts, BORs were SD (n=3, 23%), PD (n=8, 62%), and unknown (n=2, 15%)
- BORs in 11 evaluable NIZ985 + spartalizumab pts were SD (n=5, 45%) and PD (n=6, 55%)
- RDE was declared as 1 µg/kg NIZ985 (TIW; 2 weeks on/2 weeks off) for monotherapy and with spartalizumab (400 mg, Q4W)

Cancer Res July 1 2019 (79) (13 Supplement) CT082; DOI: 10.1158/1538-7445.AM2019-CT082

NIZ985

Recombinant human interleukin-15 agonist

Compound Description

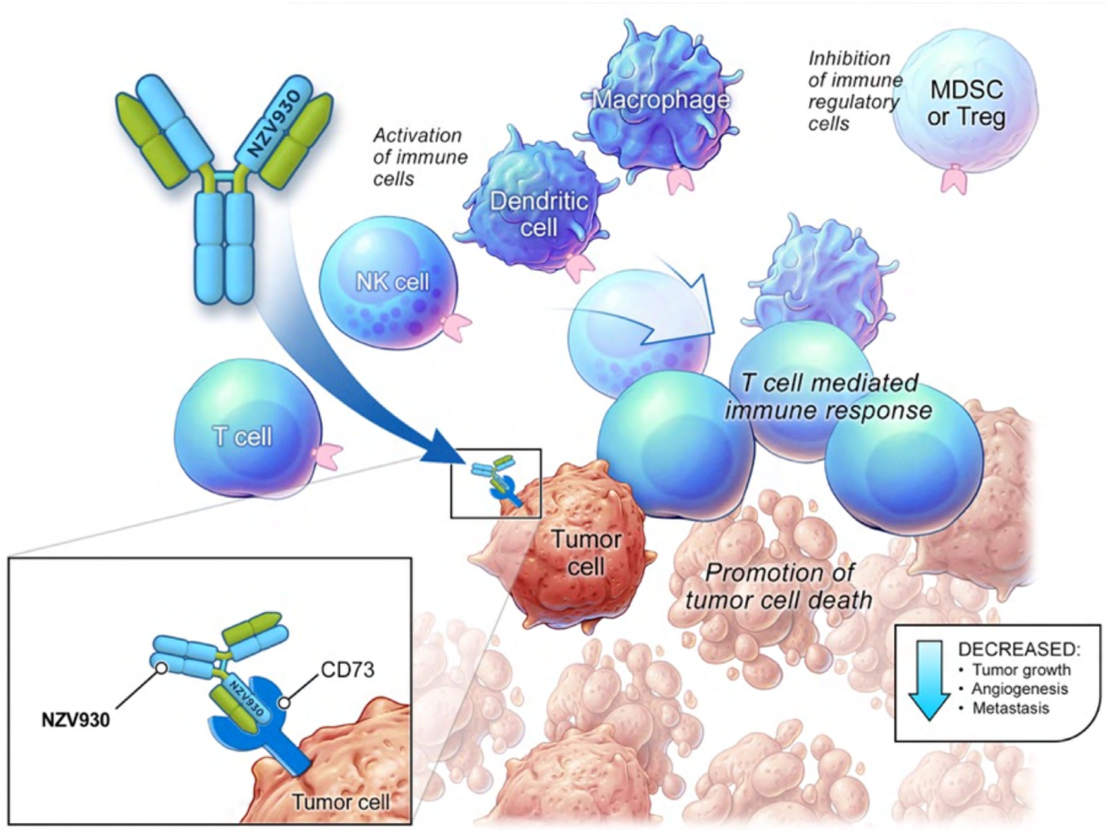
NIZ985 is an investigational recombinant heterodimer of interleukin (IL)-15/IL-15 receptor alpha (IL-15Rα) (hetIL-15).[1]

Areas of Research

Metastatic solid tumors, including melanoma, renal cell cancer, non-small cell lung cancer, and head and neck squamous cell carcinoma.[2]

NIZ985 is an investigational compound. Efficacy and safety have not been established. There is no guarantee that NIZ985 will become commercially available. MOA data are based on in vitro/in vivo data. Clinical benefit is unknown.

REFERENCES: 1. Ng SS, Nagy BA, Jensen SM, et al. Heterodimeric IL-15 treatment enhances tumor infiltration, persistence and effector functions of adoptively transferred tumor-specific T cells in the absence of lymphodepletion. *Clin Cancer Res.* 2016; 2016 Dec 16. [Epub ahead of print]. **2.** ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02452268. Accessed August 21, 2018. **3.** Dubois S, Mariner J, Waldmann TA, et al. IL-15Rα recycles and presents IL-15 in trans to neighboring cells. *Immunity.* 2002;17:537–547 **4.** Schluns KS, Klonowski KD, Lefrancois L. Transregulation of memory CD8 T-cell proliferation by IL-15Rα+ bone marrow-derived cells. *Blood.* 2004;103:988–994. **5.** Mortier E, Woo T, Advincula R, et al. IL-15Rα chaperones IL-15 to stable dendritic cell membrane complexes that activate NK cells via trans presentation. *J Exp Med.* 2008;205:1213–1225. **6.** Dubois S, Patel HJ, Zhang M, et al. Preassociation of IL-15 with IL-15Rα-IgG1-Fc enhances its activity on proliferation of NK and CD8+/CD44^{high} T cells and its antitumor action. *J Immunol.* 2008;180:2099–2106. **7.** Klebanoff CA, Finkelstein SE, Surman DR, et al. IL-15 enhances the in vivo antitumor activity of tumorreactive CD8+ T cells. *Proc Natl Acad Sci U S A.* 2004;101:1969–1974. **8.** Bessard A, Sole V, Bouchaud G, et al. High antitumor activity of RLI, an interleukin-15 (IL-15)-IL-15 receptor alpha fusion protein, in metastatic melanoma and colorectal cancer. *Mol Cancer Ther.* 2009;8:2736–2745. **9.** Bergamaschi C, Kulkarni V, Rosati M, et al. Intramuscular delivery of heterodimeric IL-15 DNA in macaques produces systemic levels of bioactive cytokine inducing proliferation of NK and T cells. *Gene Ther.* 2015;22:76–86. **10.** Chertova E, Bergamaschi C, Chertov O, et al. Characterization and favorable in vivo properties of heterodimeric soluble IL-15·IL-15Rα cytokine compared to IL-15 monomer. *J Biol Chem.* 2013;288:18093–18103.



Novartis internal

NZV930

CD73-targeting monoclonal antibody

Proposed Mechanism of Action

- CD73 is overexpressed in many cancers and acts to hydrolyze adenosine monophosphate, releasing extracellular adenosine.[1,2]
- Adenosine signaling through adenosine receptor-mediated pathways contributes to suppression of the antitumor immune response by inhibiting CD8+ T-cell and natural killer cell responses,[3] and expanding/enhancing differentiation of suppressive cell types, including regulatory T cells and myeloid-derived suppressor cells.[4]
- NZV930 is an investigational human CD73-targeting monoclonal antibody;[5] CD73 inhibition has been shown to alleviate adenosine-induced immunosupression.[2]

Proposed Areas of Research

Advanced malignancies[6]

Key Preclinical Data

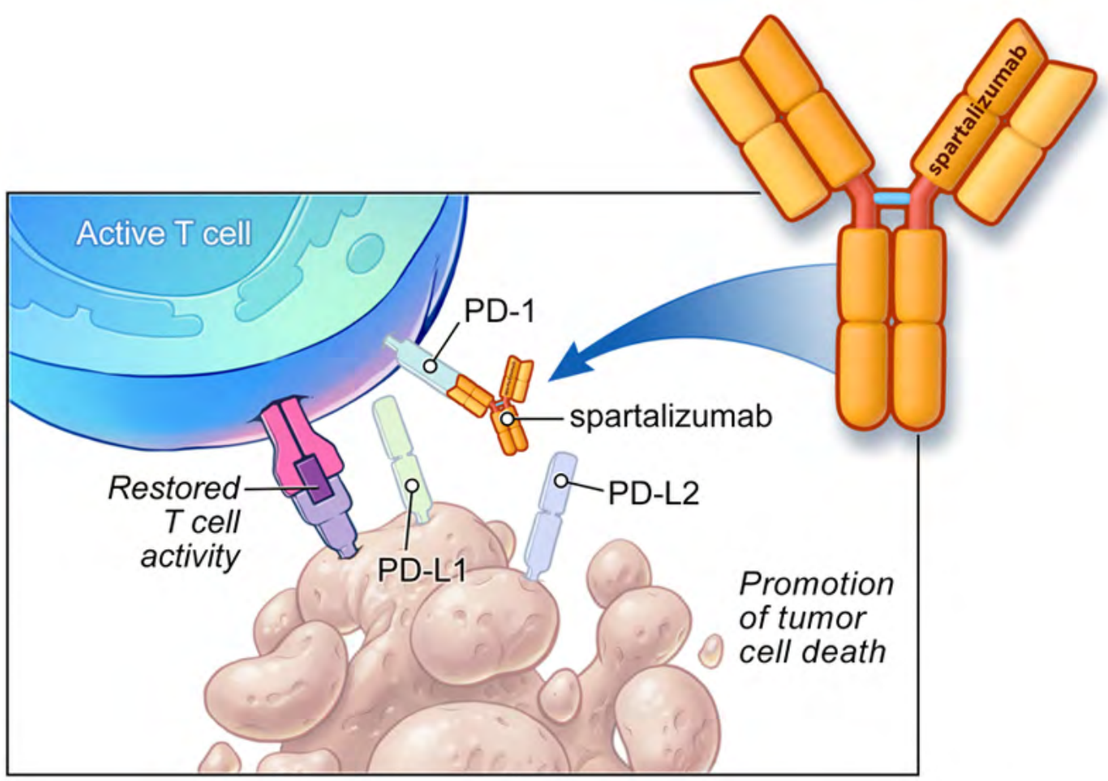
- Co-blockade of the CD73 and programmed death-1 (PD-1) pathways in mouse syngeneic tumor models demonstrated enhanced tumor growth inhibition (88%) compared with single-agent treatment with anti-CD73 (31%) or anti-PD-1 (52%) antibodies.[5]

Clinical Status

- A Phase I/Ib, open-label, multicenter study of NZV930 as a single agent and in combination with spartalizumab (PDR001) and/or NIR178 in patients with advanced malignancies is currently enrolling patients (NCT03549000).[6]

NZV930 is an investigational compound. Efficacy and safety have not been established. There is no guarantee that NZV930 will become commercially available. MOA data are based on in vitro/in vivo data. Clinical benefit is unknown.

REFERENCES: 1. Jiang T, Xu X, Qiao M, et al. Comprehensive evaluation of NT5E/CD73 expression and its prognostic significance in distinct types of cancers. *BMC Cancer.* 2018;18:267. **2.** Allard B, Longhi MS, Robson S, et al. The ectonucleotidases CD39 and CD73: novel checkpoint inhibitor targets. *Immunol Rev.* 2017;276:121-144. **3.** Young A, Ngiow SF, Gao Y, et al. A2AR adenosine signaling suppressed natural killer cell maturation in the tumor microenvironment. *Cancer Res.* 2018;78(4):1003-1016. **4.** Allard D, Allard B, Gaudreau PO, et al. CD73-adenosine: a next-generation target in immuno-oncology. *Immunotherapy.* 2016;8(2):145-163. **5.** Data on file. Novartis; 2018. **6.** ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show/NCT03549000. Updated February 18, 2019. Accessed March 18, 2019.



Novartis internal

SPARTALIZUMAB (PDR001)

PD-1 receptor-targeting monoclonal antibody

Compound Description

Spartalizumab (PDR001) is an investigational monoclonal antibody that in vitro binds with subnanomolar affinity to programmed death-1 (PD-1).[1,2]

Areas of Research

Advanced solid tumors

Proposed Mechanism of Action

PD-1 is an immunoinhibitory receptor expressed on activated T cells, regulatory T cells, and B cells.[1] When bound to programmed death-ligand 1 (PD-L1), a ligand expressed in many types of human tumors, PD-1 is activated, leading to upregulation of effector cell function towards exhaustion, anergy, and apoptosis.[3] In preclinical studies, blocking PD-1 activation by PD-L1 with monoclonal antibodies restores effector T-cell function, leading to T-cell proliferation, interferon-γ secretion, and cytolytic function.[1]

Clinical Status

Several clinical trials are currently enrolling patients and evaluating spartalizumab (PDR001) as single-agent therapy, including:

- An open-label, multicenter, Phase I/II study of the safety and efficacy of spartalizumab (PDR001) administered to patients with advanced malignancies (NCT02404441).[4]
- A Phase II, open-label, randomized controlled study of spartalizumab (PDR001) in patients with moderately differentiated/undifferentiated, locally advanced, recurrent, or metastatic nasopharyngeal carcinoma who progressed on standard treatment (NCT02605967).[5]

Clinical Data

Activity in anaplastic thyroid cancer (ATC)

Overall response rates (ORR 20-22%) were observed with single-agent spartalizumab in ATC, including 1 response at >15 months; 8/41 PR and 1/41 CR (irRECIST)[6]

Activity in NSCLC

- population was unselected for PD-L1-positivity[7]
- 33.3% of patients treated at 300 mg Q3W were PD-L1 positive; 46.8% of patients treated at 400 mg Q4W were PD-L1 positive[7]
- ORRs were 6.8% (300 mg Q3W) and 15.3% (400 mg Q4W)[7]
- ORRs were 10.5% (6/57) in patients with baseline PD-L1 <1%, 7.1% (1/14) in PD-L1 level 1–49%, and 20.8% (5/24) in PD-L1 ≥50%[7]

Activity in melanoma

- ORR in the melanoma cohort was 27.9% including 3 CRs[7]
- Patients were heavily pretreated (64% had received ≥1 prior therapies) and ~25% of patients had non-cutaneous melanoma[7]
- The ORR was 16.7% (3/18) in patients with baseline CD8 <1% and 42.9% (9/21) in patients with CD8 ≥1%[7]

Safety

The spectrum of immune-related AEs reported in the studies were consistent with published results with approved anti-PD-1 mAbs[7,8]

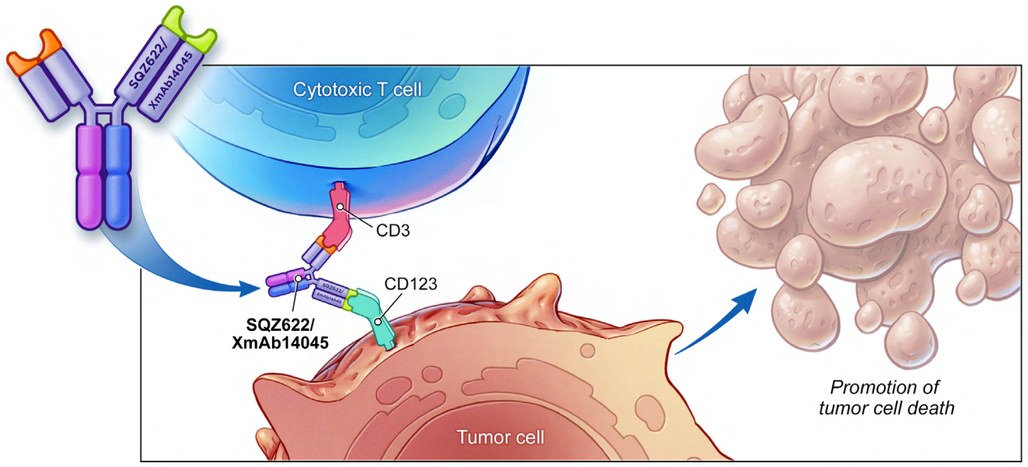
Spartalizumab is being characterized across a number of key indications[6,7,9]

6. Wirth L, et al. ASCO 2018; abstract 6024; 7. Lin CC, et al. ESMO 2018; abstract 1159P; 8. Wang P-F, et al. Front Pharmacol 2017;8:730; 9. Yao JC, et al. ESMO 2018; abstract 1308O;

Spartalizumab has the potential to act as an IO backbone for investigation of combinations with other novel agents that may work synergistically to further enhance immune response (various combination trials are ongoing).

Spartalizumab (PDR001) is an investigational compound. There is no guarantee that spartalizumab (PDR001) will become commercially available. MOA data are based on in vitro/in vivo data.

REFERENCES: 1. Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. *Annu Rev Immunol.* 2008;26:677–704. **2.** Data on file.Novartis; 2015. **3.** Annibali O, Crescenzi A, Tomarchio V, et al. PD-1/PD-L1 checkpoint in hematological malignancies. *Leuk Res.* 2018;67:45–55. **4.** ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02404441. Updated February 26, 2018. Accessed February 26, 2018. **5.** ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02605967. Updated February 8, 2018. Accessed February 26, 2018.



Novartis internal

SQZ622/ XmAb®14045

CD3- and CD123-targeting bispecific antibody

Compound Description

SQZ622/XmAb14045[a] is an investigational full-length bispecific antibody against CD3 and CD123 antigens.[1]

Areas of Research

Acute myeloid leukemia (AML) and other CD123-expressing hematologic malignancies[2]

Proposed Mechanism of Action

CD123 is expressed on leukemic stem cells and blasts, and at much lower levels in normal hematopoietic stem cells.[3] SQZ622/XmAb14045 is thought to act by potentially recruiting and stimulating cytotoxic T cells to initiate apoptosis in CD123-expressing leukemic stem cells and blasts.[1]

Key Preclinical Data

SQZ622/XmAb14045 recruited cytotoxic T cells to initiate apoptosis of CD123-expressing tumor cells in vitro, depleted CD123-expressing cells in blood and bone marrow in animal models, and reduced xenograft tumor burden in an animal model.[1,4]

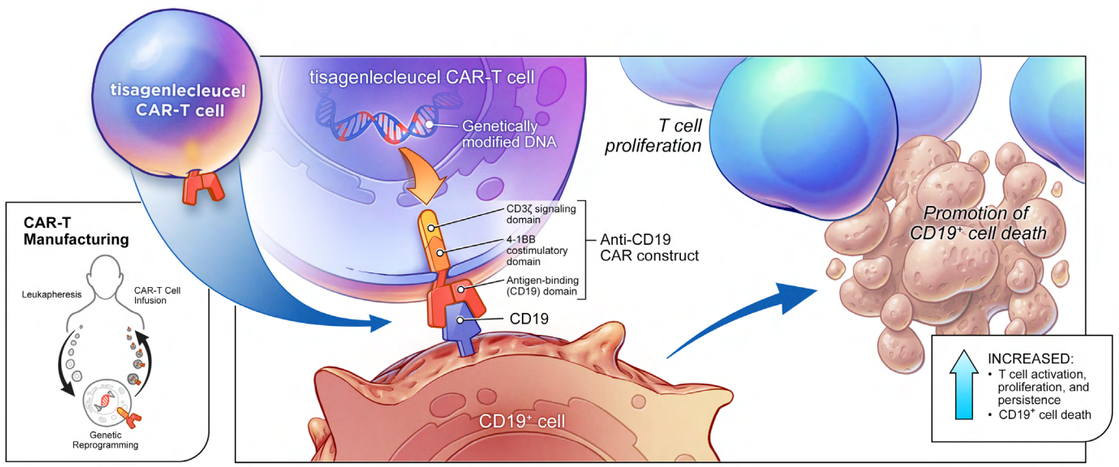
Clinical Status

A Phase I study is now enrolling to evaluate the safety and tolerability of SQZ622/XmAb14045 in patients with CD123-expressing hematologic malignancies (NCT02730312).[2]

[a]SQZ622/XmAb14045 is codeveloped in partnership with Xencor, Inc.

SQZ622/XmAb14045 is an investigational compound. Efficacy and safety have not been established. There is no guarantee that SQZ622/XmAb14045 will become commercially available. MOA data are based on in vitro/in vivo data. Clinical benefit is unknown.

REFERENCES: 1. Chu SY, Pong E, Chen H, et al. Immunotherapy with long-lived anti-CD123 x anti-CD3 bispecific antibodies stimulates potent T cell-mediated killing of human AML cell lines and of CD123+ cells in monkeys: a potential therapy for acute myelogenous leukemia. Poster presented at: 56th ASH Annual Meeting and Exposition; December 6–9, 2014; San Francisco, CA. Abstract 2316. **2.** ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02730312. Updated March 15, 2018. Accessed October 10, 2018. **3.** Testa U, Pelosi E, Frankel A. CD123 is a membrane biomarker and a therapeutic target in hematologic malignancies. *Biomarker Res*. 2014;2:4. **4.** Data on file. XmAb14045 Investigators Brochure, Edition 1. Xencor, Inc; 2016.



Novartis internal

Tisagenlecleucel

CD19-targeted CAR-T cell therapy

Compound Description

Tisagenlecleucel (CTL019) is an investigational, adoptive immunocellular therapy that uses autologous peripheral blood T cells genetically reprogrammed ex vivo with a chimeric antigen receptor (CAR) that targets CD19 on the surface of B cells.[1] Using lentiviral vector technology for gene transfer, engineered T cells express a second-generation CAR in which an anti-CD19 single-chain variable fragment is coupled with a CD3-zeta signaling domain to activate T cells and a CD137 (4-1BB) costimulatory domain to potentially improve T-cell activation and endurance of responses.[1,2]

Areas of Research

High-risk B-cell acute lymphoblastic leukemia (ALL) in pediatric and young adult patients, relapsed or refractory (r/r) B-cell ALL in adult patients, and r/r non-Hodgkin lymphoma (NHL), including r/r diffuse large B-cell lymphoma (DLBCL) and r/r follicular lymphoma (FL).[3–8]

Proposed Mechanism of Action

CARs are fusion proteins that reprogram cytotoxic T cells to recognize target cells based on surface expression of a specific antigen.[9] Gene transfer technology is used to stably express the tisagenlecleucel CAR on the surface of a patient's T cells, conferring potential specificity to CD19.[2] After infusion into the patient, the tisagenlecleucel cells rapidly expand in vivo and track to cells expressing target antigens.[10] Binding of tisagenlecleucel cells to CD19-positive cells initiates a cascade of events, and has the potential to induce cell death.[10] Thus, tisagenlecleucel therapy uses T-cell cytotoxicity to eliminate target cells in an antigen-specific manner.[1,2]

Key Preclinical Data

In preclinical studies, the intracellular 4-1BB costimulatory domain of the tisagenlecleucel CAR improved T-cell proliferation and persistence,[2] which is possibly attributable to 4-1BB–mediated amelioration of T-cell exhaustion.[11] Tisagenlecleucel cells can persist in vivo for years as memory CAR T cells.[12]

Clinical Status

Several clinical trials are currently underway to evaluate tisagenlecleucel, including:

- Phase Ib, open-label, multicenter study of tisagenlecleucel in combination with pembrolizumab in r/r DLBCL (PORTIA, NCT03630159)[3]
- Phase II, single-arm, multicenter, open-label trial of tisagenlecleucel in pediatric patients with r/r mature B-cell NHL (BIANCA, NCT03610724)[4]
- Phase II, single-arm, open-label, multicenter trial of tisagenlecleucel in 1L high-risk pediatric and young adult patients with B-cell ALL who are minimal residual disease-positive at the end of consolidation therapy (CASSIOPEIA, CCTL019G2201J)8
- Phase II, single-arm, multicenter, open-label trial of tisagenlecleucel in adult patients with r/r FL (ELARA, NCT03568461)[5]
- Phase III, open-label, multicenter, randomized trial comparing tisagenlecleucel to standard of care in adult patients with r/r aggressive B-cell NHL (BELINDA, NCT03570892)[6]
- Phase III, open-label, multicenter, randomized trial to compare tisagenlecleucel vs blinatumomab or inotuzumab for adult patients with r/r B-cell ALL (OBERON, NCT03628053)[7]
- Global, non interventional, multi database, post authorization safety study to monitor the safety and effectiveness of patients treated with tisagenlecleucel in compliance with the health authority guidelines for gene therapy (FDA) and advanced therapy medicinal products (EMA) (PICTOR, CCTL019B2401)[8]

Tisagenlecleucel is being studied for new use(s) for which the efcacy and safety have not been established. There is no guarantee that tisagenlecleucel will become commercially available for the use(s) under investigation. MOA data are based on in vitro/in vivo data.

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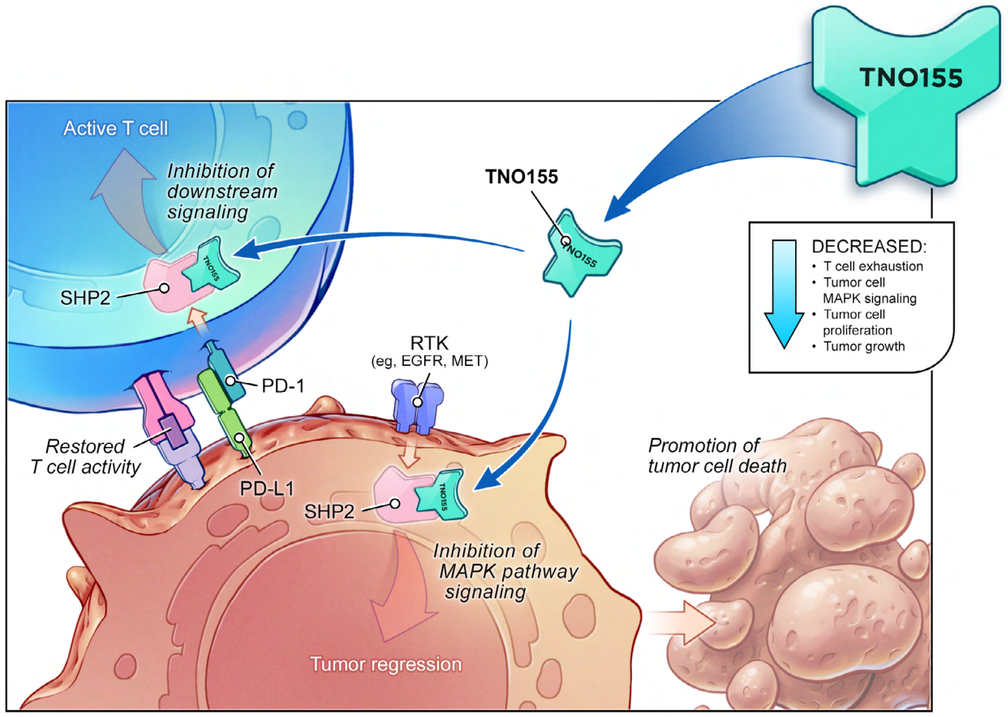

TNO155

An Src homology-2 domain protein tyrosine phosphatase-2 (SHP2) inhibitor

Compound Description

TNO155 is an investigational, orally bioavailable inhibitor of Src homology-2 domain containing protein tyrosine phosphatase-2 (SHP2).[1]

Areas of Research

Solid tumors that are likely to be dependent on receptor tyrosine kinase (RTK) signaling[2]

Proposed Mechanism of Action

SHP2 is a ubiquitously expressed cytoplasmic phosphatase encoded by the *PTPN11* gene.[3] Upon activation of RTKs, SHP2 is recruited to the plasma membrane, where it associates with activated RTKs and several adaptor proteins to relay signaling by activating RTK-dependent signaling pathways, including the RAS/MAPK pathway.[4,5] Inhibiting SHP2 with TNO155 may inhibit this activation.

Key Preclinical Data

In vitro, TNO155 demonstrated antiproliferative activity in RTK-dependent cell lines, including epidermal growth factor receptor (EGFR)–dependent head and neck cancer cell lines, Fms-related tyrosine kinase 3 internal tandem duplication (FLT3-ITD) acute myeloid leukemia (AML) cell lines, and EGFR-mutant non-small cell lung cancer (NSCLC) cell lines.[1]

In vivo, TNO155 demonstrated a pharmacokinetic-pharmacodynamic relationship, leading to a dose-dependent anticancer effect in EGFR-dependent esophageal cancer (KYSE-520), EGFR-dependent head and neck cancer (Detroit-562), and FLT3-dependent AML (HAMLX-5340) xenograft models.[1]

Rationale for Targeting Advanced Solid Tumors With Documented RTK Dependence

Patients with metastatic or unresectable RTK-driven cancers can potentially derive benefit from molecules that directly target these RTKs, but resistance to these agents regularly occurs.[6,7] Mechanisms of resistance frequently include drug-resistant mutations in the targeted RTK and/or activation of bypass RTK pathways.[8,9] Targeting SHP2 with TNO155 may potentially offer an alternative treatment option for these patients.

Clinical Status

An open-label, multicenter, Phase I, dose-finding study of oral TNO155 in patients with advanced solid tumors, including EGFR-mutant NSCLC, esophageal squamous cell cancer, head and neck squamous cell cancer, and other RAS/RAF wild-type solid tumors is active and recruiting (NCT03114319).[2]

TNO155 is an investigational compound. Efficacy and safety have not been established. There is no guarantee that TNO155 will become commercially available. MOA data are based on in vitro/in vivo data. Clinical benefit is unknown.

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The Novartis IO portfolio targets the cancer-immunity cycle

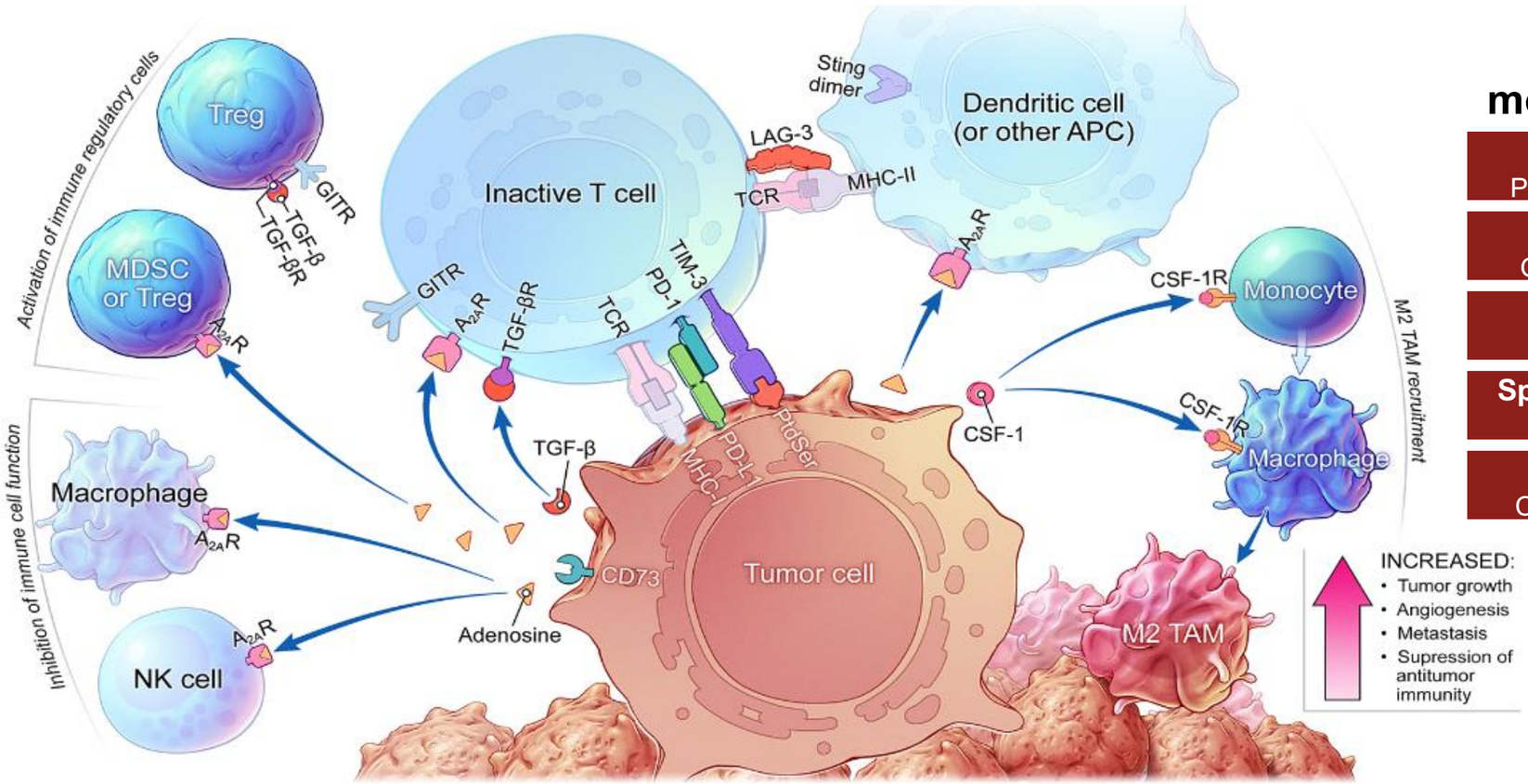
Immune priming

LHC165
TLR7 agonist

MBG453
TIM-3 mAb

MIW815
STING agonist

NIZ985
IL-15 agonist



T-cell modulation

FAZ053
PD-L1 inhibitor

GWN323
GITR agonist

LAG525
LAG-3 mAb

Spartalizumab
PD-1 mAb

SQZ622
CD123 × CD3

Tumor environment

BLZ945
CSF-1R inhibitor

FAZ053
PD-L1 inhibitor

Lacnotuzumab
CSF-1 mAb

LAG525
LAG-3 mAb

MBG453
TIM-3 mAb

NIR178
A2AR inhibitor

NIS793
TGF-β mAb

Spartalizumab
PD-1 mAb

All compounds are either investigational or being studied for new use(s). Efficacy and safety have not been established. There is no guarantee that they will become commercially available for the use(s) under investigation.

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