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CytoDyn – Oncology

CYDY : OTCQB

The pursuit of precision medicine
Mechanism of Action

Leronlimab has unique immunomodulating properties
“CCR5, a seven trans-membrane G-protein coupled receptor (GPCR), is normally expressed only in the immune system; however, CCR5 becomes overexpressed in several malignancies and is overexpressed in breast cancer” (1,2)

“CCR5 receptor levels correlate with poor prognosis in breast cancer” (2,3,4)

“Upon transformation of breast epithelial cells, the increased expression of CCR5 results in increased motility and homing behavior to metastatic sites” (1,2)

“The efficiency of leronlimab binding to CCR5-positive human breast cancer cells was up to 98%”
Multiple Potential MOA’s of Leronlimab in the Tumor Microenvironment

“Prevents overexpression of CCR5 which promotes tumor invasion, migration, and metastasis. In the analysis of > 2200 breast cancer patients, > 50% of patient’s tumors were CCR5⁺ and > 95% of triple-negative breast cancer (TNBC) were CCR5⁺” (1)


Inhibition of T regs that turn off the anti-tumor response - CCR5 is more express in regulatory T cells compared with effector T-cells

“In this study, we also demonstrated that Treg migration to the tumor microenvironment is mediated by CCR5, and these cells are promoting tumor growth via inhibition of antitumor cells such as cytotoxic CD8⁺ T cells. Our findings reinforce the therapeutic potential of CCR5 inhibition for cancer treatment, and indicate an attractive approach for SCC treatment. Mol Cancer Ther; 16(12); 2871–80. ©2017 AACR.”

https://mct.aacrjournals.org/content/16/12/2871
Multiple Potential MOA’s of Leronlimab in the Tumor Microenvironment

Conversion of M2 macrophages (pro-tumor) into M1 macrophages (anti-tumor)

Chemotherapy resistance has been associated with overexpression of CCR5

Prevents tumor angiogenesis - CCL5 (RANTES) promotes VEGF-dependent angiogenesis — the formation of blood supply to support tumor growth

CCL5 suppresses cytotoxic T cell activity, increases recruitment of Tregs, promotes Th2 responses, and promotes tumor angiogenesis.
Potential Synergies with Leronlimab in the Tumor Microenvironment

**DNA damaging agents**
The presence of CCR5 augments resistance to DNA damaging agents and is sufficient to induce cancer metastasis and “stemness.” It enhances DNA repair.
CCr5 antagonists enhanced cell killing by DNA damaging therapeutic agents

**Potential to lower dose of radiation and chemotherapy**
The finding that CCR5 inhibitors enhance cell killing by radiation and DNA-damaging chemotherapeutic agents suggests the potential for combining these biologic agents with chemotherapeutics in order to potentially reduce the dose-dependent side-effects of chemotherapy.
Chemotherapy causes increased CCr5 expression

**Checkpoint Inhibitors**
Combining CCR5 antagonist and anti-PD-L1 inhibited tumor growth and improved overall survival in pancreatic ductal adenocarcinoma xenograft models \(^7\) and conducted a clinical trial (COMBAT study, NCT02826486).
Tumors that initiated from cells expressing CCR5 most strongly (Hi) generated tumors that grew faster than cells that had the lowest CCR5 expression (Lo), n=4, p=0.019 (Fig. 1C). Hence, in the absence of drug treatment, tumor cells that expressed high numbers of CCR5 displayed a growth advantage in vivo.
Leronlimab binds to CCRR5 + Breast Cancer Cells

The efficiency of leronlimab binding to CCR5-positive cells was up to 98% compared with CCR5 antibody (FAB1802A)

https://breast-cancer-research.biomedcentral.com/articles/10.1186/s13058-021-01391-1/figures/1
Nascent (1 – 2 mm) SW480 tumors inoculated in the dermis were assayed for peri-tumoral vessel formation. The utilization of VESGEN software allowed detailed comparisons between treatment groups and revealed marked reduction in multiple key properties of the vascular network feeding the tumor, including 62% reduction in total vessel area (pixels) (p=0.013). Blockade of CCR5 signaling clearly interfered with host processes required for neo-vessel proliferation surrounding growing tumors. Angiogenesis is critical for tumors to progress beyond 2 mm in diameter. 

The utilization of VESGEN software allowed detailed comparisons between treatment groups and revealed marked reduction in multiple key properties of the vascular network feeding the tumor, including 62% reduction in total vessel area (pixels) (p=0.013), 53% reduction in vessel length density (p=0.0011), 61% reduction in number of large vessels (p=0.0082) and 80% reduction in number of small vessels (p=0.017). Thus, primary tumors from animals with the same initial tumor burden exhibited decreased angiogenesis following treatment with leronlimab.
Leronlimab Effect on Angiogenesis

Fig. 7

IgG

Leronlimab

Total vessel area (pixels) Mean ± SE

VEGF level density Mean ± SE

No. of vessels

Vessel area Mean ± SE

G1-G3 largest

G4-G9 smallest

Ler

IgG

P=0.013

P=0.0011

P=0.0082

P=0.017

P=0.91

P=0.011
Leronlimab blocks human CCL5-CCR5-mediated signaling in human breast cancer cells

Leronlimab blocks human CCR5-mediated signaling by CCL3 and CCL4 in human breast cancer cells.

Leronlimab blocks CCR5-mediated invasion of human breast cancer cells into the extracellular matrix in 3D Matrigel invasion assay

In humanized NSG mice **leronlimab effectively delayed tumor progression** compared to IgG treatment, and the effect persisted out to day 80 (Fig. 3), p=0.004.

**Fig. 3**

*Effect of mouse humanization on leronlimab anti-tumor activity. NSG mice were either humanized (normal human BM, 10^7 mononuclear cells) or sham-injected, and then inoculated with SW480 (2.5x10^5 cells s.c.) on d35. Humanized mice received either IgG (h-IgG) leronlimab (h-Ler). Non-humanized mice received IgG (IgG) or leronlimab (Ler). All groups received 2 mg Ab i.p. twice weekly, starting d7, n=8 mice/group.*
Liver metastatic burden was decreased 59% in leronlimab-treated mice.

Lung metastatic burden was decreased 87% in leronlimab-treated mice compared to IgG-treated animals (p=0.012).
Metastasis
“Leronlimab reduced lung metastatic burden > 98% at 8 weeks (99.6%). Collectively, these results provide evidence that the CCR5 antagonist leronlimab reduces the formation of lung metastasis in a murine xenograft model.”

Animal Study Results for Leronlimab in Oncology - Metastasis
“In humanized mice that also received tumor cells, treatment with leronlimab again prolonged survival compared to IgG mice.”

“The tumor volume in humanized mice was significantly delayed, compared to non-humanized mice. Most importantly, humanized mice that received leronlimab had slower tumor growth compared to humanized mice that received IgG. This data suggested that effects of leronlimab upon the human immune cells played a role in tumor suppression.”

“Leronlimab-treated mice had over 2-fold reduction in neo vessel formation compared to IgG treated mice, evidenced by decrease in total pixel count, vessel length density, and overall number of vessels. Most dramatic was reduction of smaller vessels, as compared to larger vessels. The mechanism of angiogenesis inhibition by leronlimab suggests that this agent may inhibit the growth of several solid tumors that are dependent upon this process, especially during the establishment of metastatic lesions.”
“In pancreatic cancer, Treg cells express high levels of CCR5, which are recruited to CCL5 overexpressing tumors. Knockdown of CCL5 or pharmacologic inhibition of CCL5 inhibits pancreatic tumor growth.” (Tan et al., 2009)

“CCL5 may also modulate activity of MDSCs from the bone marrow, and suppress activity cytotoxic T cells, as demonstrated in a model of triple negative breast cancer.” (Zhang, Lv et al., 2013; Zhang, Qin, et al., 2013)

“In addition to modulating immune cell recruitment and activity, CCL5 promotes VEGF-dependent angiogenesis in tumors, as demonstrated for chondrosarcoma and osteosarcoma.” (Liu et al., 2014; Wang et al., 2015).
“The CCL5/CCR5 axis has been reported as a mechanism of tumor progression in pancreatic (5), gastric (6), and breast cancer (7). The CCL5-receptors’ signaling can favor cancer progression, directly affecting proliferation, migration, and cell survival of cancer cells by autocrine signaling, or indirectly by paracrine signaling recruiting pro-tumor and/or anti-inflammatory effector cells into the tumor microenvironment (TME) (8).”

“In this study, we report that CCR5 is highly expressed and associated with poor prognosis in human GBM. CCL5/CCR5 mediates the activation of Akt, and subsequently induces proliferation and invasive responses in U87 and U251 cells. These results suggest that CCR5 over-expression in glioma is essential for tumor proliferation, invasion, and progression.”

https://academic.oup.com/abbs/article/47/11/890/1412
“These studies indicate that within the primary tumor, CCL5 suppresses cytotoxic T-cell activity, increases recruitment of Tregs, promotes Th2 responses, and promotes tumor angiogenesis. CCL5 signals directly on cancer cells to promote survival, invasion, and stem cell renewal.”

(Molecular and Cellular Basis of Metastasis: Road to Therapy
M. Yao, ... N. Cheng, in Advances in Cancer Research, 2016)
“CCR5 is overexpressed in breast cancer (4, 5), gastric adenocarcinoma (24), prostate cancer (25), colorectal carcinoma (26, 27), melanoma (28), Hodgkin lymphoma (29), head and neck cancer (30), gastric cancer (31), esophageal cancer (32), pancreatic cancer (33), acute lymphocytic leukemia (33, 34), and other tumors (Fig. 1B).”

https://cancerres.aacrjournals.org/content/79/19/4801
The role of leronlimab in the tumor microenvironment - potential for enhancing the effectiveness of checkpoint inhibitors, PARP Inhibitors, antibody-drug conjugates, chemotherapy, and radiation.

Safety profile – over 1,200 patients have received leronlimab without strong safety signals including HIV, COVID-19, and oncology patients.

Timeline to expected approval – potential expedited timeline due to unmet medical need, Fast Track Designation for mTNBC, potential for label expansion based on anticipated approval for multidrug resistant HIV, and potential Breakthrough Designation.

Potential for multiple approvals based on mechanism of action study in basket trial (approximately 22 solid tumors)
Summary

Colon Cancer:
Liver metastatic burden was decreased 59% in leronlimab-treated mice
Lung metastatic burden was decreased 87% in leronlimab-treated mice compared to IgG-treated animals (p=0.012) (Fig. 6, lower panels)
leronlimab effectively delayed tumor progression and prolonged survival.

Angiogenesis:
Treatment with leronlimab resulted in a 62% reduction in total vessel area (pixels) (p=0.013), 53% reduction in vessel length density (p=0.0011), 61% reduction in number of large vessels (p=0.0082) and 80% reduction in number of small vessels (p=0.017).
Thus, primary tumors from animals with the same initial tumor burden exhibited decreased angiogenesis following treatment with leronlimab.
Breast Cancer:
leronlimab was shown to bind CCR5 in multiple breast cancer cell lines. Leronlimab reduced human breast cancer metastasis in mouse xenografts by more than 98% over 6 weeks. Leronlimab enhanced the BCa cell killing of the BCa chemotherapy reagent, doxorubicin.
Summary

“Herein, leronlimab was shown to bind CCR5 in multiple breast cancer cell lines. Binding of leronlimab to CCR5 reduced ligand-induced Ca$^{+2}$ signaling, invasion of TNBC into Matrigel, and transwell migration. Leronlimab enhanced the BCa cell killing of the BCa chemotherapy reagent, doxorubicin. In xenografts conducted with Nu/Nu mice, leronlimab reduced lung metastasis of the TNBC cell line, MB-MDA-231, by > 98% at 6 weeks. Treatment with leronlimab reduced the metastatic tumor burden of established TNBC lung metastasis.”

In Closing – Human Studies

Anecdotal evidence – bladder cancer, breast, colon, and prostate

n=30 patients with mTNBC receiving Leronlimab as part of the Emergency Use, Compassionate Use, mTNBC, or Basket Trial had clinical outcome data available for 12 month analysis

72% of patients had a decrease in CAMLs after 30 days

73% of all 30 patients had either reduced Circulating Cells after induction, or had small Circulating Cells at baseline, and had significantly better PFS and OS

Leronlimab appears to have efficacy superior to standard of care in specific populations


References


