4MO Preclinical evaluation of novel CDK4/6 inhibitor GLR2007 in breast and lung cancer models
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Background: Cyclin-dependent kinases (CDKs) such as CDK4/6 are essential in regulating the cell cycle, which is disrupted in many cancers. Currently marketed CDK4/6 inhibitors abemaciclib, palbociclib, and ribociclib have shown preclinical efficacy in solid tumors including breast cancer and non-small cell lung cancer. GLR2007 is an investigational CDK4/6 inhibitor with potential to treat advanced solid tumors. In vitro and in vivo antitumor effects of GLR2007 were investigated in breast and lung cancer cell line preclinical models.

Methods: In vitro proliferation inhibition was evaluated through live cell counts in 7 human and murine breast cancer cell lines and 21 human lung cancer cell lines after culture for 72 h with 0.01–10,000 nM GLR2007 or 1.5–10,000 nM abemaciclib, reported as half maximal inhibitory concentration (IC50). In vivo antitumor efficacy was determined in MCF-7 breast cancer orthotopic xenografts in NOD/SCID mice, and NCI-H1975 and NCI-H2228 lung cancer subcutaneous xenografts in BALB/c nude mice treated with 50 mg/kg GLR2007 by once-daily oral gavage.

Results: GLR2007 inhibited proliferation at lower IC50 values compared to abemaciclib in 5 breast cancer cell lines (IC50 fold difference range = 0.08–0.92; median = 0.33) and in 20 lung cancer cell lines (IC50 fold difference range = 0.03–0.99; median = 0.31). In MCF-7 breast cancer orthotopic xenografts, compared to vehicle control, 50 mg/kg GLR2007 induced 49.6% tumor growth inhibition (TGI) (P = 0.001) in mice treated for 21 days, and 81.4% TGI (P = 0.037) on day 25 in mice treated for 28 days. In lung cancer subcutaneous xenograft models, compared to vehicle control, 50 mg/kg GLR2007 induced 46.9% tumor growth inhibition (TGI) (P = 0.001) in mice treated for 21 days, and 81.4% TGI (P = 0.037) on day 25 in mice treated for 28 days. In lung cancer subcutaneous xenograft models, compared to vehicle control, 50 mg/kg GLR2007 inhibited proliferation at lower IC50 values compared to abemaciclib. GLR2007 demonstrated significant antitumor efficacy in xenograft models compared to vehicle controls. These preclinical studies demonstrate the potential of GLR2007 as a novel CDK4/6 inhibitor for the treatment of breast and lung cancer.

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5MO CDK4/6 blockade is as effective as immune-checkpoint inhibition in tumor growth control of Mlh1–/– and Msh2loxP/flloxP villin-Cre mice
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Background: Mismatch-repair deficiency (dMMR) is a hallmark of Lynch syndrome-associated cancers, often resulting from inactivating mutations in MLH1 or MSH2. These tumors have a high likelihood of responding to immune checkpoint inhibitors (ICIs). Still, intrinsic or acquired resistance mechanisms impair patients’ outcomes. Here, we compared the therapeutic potential of an anti-CDK11 inhibitor with the CDK4/6 inhibitor abemaciclib in two preclinical mouse models of dMMR-driven carcinogenesis.

Methods: In this ongoing trial, Mlh1–/– or Msh2loxP/flloxP villin-Cre mice with gastrointestinal tumors were either treated with anti-CDK11 monoclonal antibody (clone: 6E11, 2.5 mg/kg bw, i.p., q2wx3) or abemaciclib (75 mg/kg bw, p.o., q1wx8). Control mice received the isotype (anti-IgG1 2.5 mg/kg bw, i.p., q2wx3) or were left untreated. Blood phenotyping was performed regularly. The tumor microenvironment was studied by immunofluorescence.

Results: Both therapies prolonged overall survival of mice significantly: Mlh1–/–: 9.1 weeks (anti-CDK11) vs. 3.5 weeks (control); Msh2loxP/flloxP villin-Cre: 6.0 weeks (6E11, ongoing) and 8.2 weeks (abemaciclib, ongoing) vs. 1.0 weeks (control). One Mlh1–/– mouse received complete remission upon abemaciclib, while anti-CDK11 therapy primarily induced stable disease at best (PET/CT). Therapeutic effects of abemaciclib were accompanied by increased numbers of tumor-infiltrating CD4+CD8+ T-cells and lower numbers of M2-macrophages. Blood phenotyping revealed PD-L1 upregulation under abemaciclib therapy. Conclusions: While ICI-based therapies are effective and FDA approved for dMMR cancer, abemaciclib constitutes a promising alternative therapy option. The strong immune stimulation upon abemaciclib treatment renders this compound ideal for ICI-refractory or intrinsically resistant tumors.

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6MO PCSK9 inhibitor evolocumab reduces cardiotoxicity and inflammation induced by doxorubicin-trastuzumab sequential treatment through MyD88/NF-κB/mTORC1 pathways
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Background: Inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) has emerged as a novel therapy to treat hypercholesterolemia and related cardiovascular diseases. Evolocumab, a PCSK9 inhibitor, reduced the risk of cardiovascular events in patients with atherosclerotic cardiovascular diseases when added to maximally tolerated statin therapy (i.e., ezetimibe), and recent data from the ODYSSEY OUTCOMES trial indicate that abrocilax added to maximally tolerated statin therapy (i.e., other lipid-lowering drugs) reduces the risk of cardiovascular events in patients with a recent acute coronary syndrome.

Methods: Human fetal cardiomyocytes (HFC cell line) were exposed to subclinical concentration of doxorubicin, trastuzumab, sequential treatment of both (all 100 nM), alone or in combination with evolocumab (50 nM) for 48 h. After the incubation period, we performed the following tests: determination of cell viability, through analysis of mitochondrial dehydrogenase activity, study of lipid peroxidation (quantifying cellular Malondialdehyde and 4-hydroxyxynenal), intracellular Ca2+ homeostasis. Moreover, pro-inflammatory studies were also performed (activation of NLRP3 inflammasome; expression of TLR4/MYD88; mTORC1 FoxO1/3a; transcriptional activation of p65/NF-κB and secretion of cytokines involved in cardiotoxicity (Interleukins 1β, 8, 6).

Results: Evolocumab co-incubated with doxorubicin alone or in sequence with trastuzumab exerts cardioprotective effects, enhancing cell viability of 35-43% compared to untreated cells (p<0.05 for all); Evolocumab reduced significantly the cardiotoxicity through MyD88/NF-κB/mTORC1 mediated mechanisms.

Conclusions: We demonstrated, for the first time, that the PCSK9 inhibitor evolocumab exerts direct effects in cardiomyocytes during doxorubicin and trastuzumab exposure turning on a new light on its possible use in cancer patients.

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7MO Effect of anti-CTLA-4 immunotherapy on lymphocyte subset and activation profiles and clonal composition on the B16F0 mouse melanoma model
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Background: One of most promising strategies for cancer immunotherapy is immune checkpoint blockade. However, the remarkable responses to the therapy are currently limited to a minority of patients and indications, highlighting the importance of understanding of immune mechanisms. The purpose of this study was to investigate the effect of anti-CTLA-4 immunotherapy on lymphocyte subset and activation profiles and clonal composition on the B16F0 mouse melanoma model.

Methods: The experiments were carried out on C57BL/6 mice bearing B16F0 mouse melanoma. Mice were treated with 250 µg anti-CTLA-4 (Bio X Cell, USA). T-lymphocytes were obtained from tumor or lymphatic nodules (LN), analyzed by flow cytometry using a FACSAria III cell sorter, sorted and evaluated by RNA- and TCR (T cell receptor)-seq.

Conclusions: While ICI-based therapies are effective and FDA approved for dMMR cancer, abemaciclib constitutes a promising alternative therapy option. The strong immune stimulation upon abemaciclib treatment renders this compound ideal for ICI-refractory or intrinsically resistant tumors.

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