TGFβR1 Kinase Inhibitor
Galunisertib, LY2157299 H₂O

Drug Discovery Platform: Cancer Angiogenesis and Tumor Microenvironment/Immuno-Oncology
The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.

A Phase 1b/2 Dose-Escalation and Cohort-Expansion Study of the Safety, Tolerability, and Efficacy of a Novel Transforming Growth Factor-Beta Receptor I Kinase Inhibitor (Galunisertib) Administered in Combination With Anti-PD-1 (Nivolumab) in Advanced Refractory Solid Tumors (Phase 1b) and in Recurrent or Refractory Non-small Cell Lung Cancer, Hepatocellular Carcinoma, or Glioblastoma [Phase 2]*

Key Inclusion Criteria
• For phase 1b: Must have advanced refractory solid tumors in any line of therapy
• For phase 2:
  - Recurrent or refractory non-small cell lung cancer (NSCLC; any histology), hepatocellular carcinoma (HCC) with elevated alpha-fetoprotein ≥ 200 ng/mL, or glioblastoma (primary)
  - Disease progression or was refractory or intolerant to one prior line of therapy and has refused currently approved second-line therapy
• For NSCLC: Prior lines of therapy must include a platinum-based therapy
• For HCC:
  - Received one prior line of therapy with sorafenib or has progressed or been intolerant to sorafenib for participants not eligible for transarterial chemoembolization
  - Child-Pugh class A only
  - Participants may have any viral status (hepatitis B, C, or none) with a viral load < 100 IU/mL
  - Participants with hepatitis B must be on a nucleoside analog reverse transcriptase inhibitor
• For glioblastoma (GB): Previous first-line therapy with at least radiotherapy and temozolomide, except for participants with O6-methylguanine-DNA methyltransferase (MGMT) unmethylated newly diagnosed GB. Participants with MGMT unmethylated newly diagnosed GB may have received radiation therapy only
• Adequate organ function
• Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

Key Exclusion Criteria
• History of a serious cardiac condition within 6 months prior to enrollment, such as unstable angina pectoris, congestive heart failure New York Heart Association class 3/4, or uncontrolled hypertension
• Documented major electrocardiogram abnormalities (not responding to medical treatment)
• Echocardiogram abnormalities, such as heart valve function defect
• Conditions consistent with predisposition for aneurysms
• Evidence of interstitial lung disease or active, noninfectious pneumonitis

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT02423343].

* This clinical trial is being conducted globally in partnership with Bristol-Myers Squibb.

Dose escalation of galunisertib + nivolumab†

Primary endpoint: Safety and tolerability of galunisertib in combination with nivolumab

Galunisertib + nivolumab (NSCLC, HCC, or glioblastoma)‡§

Primary endpoint: Safety of combination therapy

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† Galunisertib is administered PO BID for the first 14 days of a 28-day cycle. Nivolumab is administered intravenously (IV) every 2 weeks for two cycles.
‡ Galunisertib is administered PO BID for the first 14 days of a 28-day cycle. Nivolumab is administered IV every 2 weeks of a 28-day cycle.
§ Participants continue study treatment until discontinuation criteria are met.

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A Phase 1b Dose-Escalation and Cohort-Expansion Study of the Safety, Tolerability, and Efficacy of a Novel Transforming Growth Factor-β Receptor I Kinase Inhibitor (Galunisertib) Administered in Combination With the Anti-PD-L1 Antibody Durvalumab (MEDI4736) in Recurrent or Refractory Metastatic Pancreatic Cancer*

Key Inclusion Criteria

- Recurrent metastatic pancreatic adenocarcinoma
- Disease progression, or refractory or intolerant to no more than two prior systemic regimens for locally advanced or metastatic pancreatic cancer
- Participants who have received prior neoadjuvant therapy and who now have metastatic disease must have received one of the following regimens for their metastatic disease prior to enrollment in this study:
  - FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin)
  - Nab-paclitaxel/gemcitabine
  - TS-1 (tegafur gimeracil oteracil potassium)
  - Liposomal irinotecan/5-fluorouracil/leucovorin
  - Single-agent gemcitabine
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

Key Exclusion Criteria

- History of a serious cardiac condition within 6 months prior to enrollment (e.g., unstable angina pectoris, congestive heart failure New York Heart Association class 3/4, or uncontrolled hypertension)
- Electrocardiogram abnormalities (e.g., cardiac arrhythmia, left bundle-branch block, or myocardial infarction within 6 months prior to enrollment)
- Echocardiogram abnormalities (e.g., heart valve function defect or aneurysm)
- Conditions consistent with predisposition to aneurysms
- Interstitial lung disease or active, noninfectious pneumonitis
- Prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA4 antibody, or small molecules specifically targeting T-cell co-stimulation or checkpoint pathways (e.g., CD137, GITR, TIM-3, and LAG CAR-T cells and vaccines) within 6 months prior to starting study treatment
- Prior treatment with a TGFβR1 kinase inhibitor
- Prior therapy with a monoclonal antibody within 28 days prior to starting study treatment or not recovered (grade ≤ 1 at baseline) from adverse events (except for fatigue or alopecia) due to agents administered more than 28 days earlier

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT02734160].

*This clinical trial is being conducted globally in partnership with AstraZeneca.

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Target
The transforming growth factor β (TGFβ) signaling pathway is complex and results in tumor suppressor or tumor-promoting activity depending on the cellular context in which the pathway is active. As many cancers progress to more aggressive disease states, the tumor suppressor arm of TGFβ signaling is lost and, instead, tumor cells proliferate. In contrast, TGFβ overexpression in advanced disease enhances tumor growth, suppresses the immune system, and exacerbates invasive and metastatic tumor cell behavior.\textsuperscript{3} TGFβ worsens immunosuppression by inhibiting cytotoxic cells such as CD8+ CTLs and NK cells and enhancing suppressive immune cells called T regulatory cells and myeloid-derived suppressor cells.\textsuperscript{2}

Molecule
Galunisertib (LY2157299 monohydrate) is a small molecule that has been shown in vitro to block TGFβ signaling.\textsuperscript{4-7}

Clinical Development
Galunisertib is being investigated in phase I clinical trials, including combination clinical trials in immuno-oncology, and in clinical trials in patients with hepatocellular carcinoma and pancreatic cancer.