EMERGE: Epigenetic Modulation of the Immune Response in Gastrointestinal Cancers


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BACKGROUND AND RATIONALE

• Response to checkpoint blockade in unselected gastrointestinal (GI) cancers has been disappointing
• Tumours which display a non-T-cell inflamed phenotype such as mismatch repair proficient (MMRpf) or microsatellite unstable (MSI) colorectal cancers (CRC) respond less frequently to checkpoint inhibitors (CPIs)
• Changes in tumour expression of antigens and increased immune infiltrates are associated with improved response to CPIs
• Epigenetic modulation of tumours by HDAC inhibitors may lead to an increase in antigen presentation and immune infiltrates and increase response to immunotherapy in oesophagogastric and colorectal cancers
• Modification of the epigenome using HDAC inhibitors shows promising synergy with immune-oncology drugs in pre-clinical studies1-3

AIMS AND HYPOTHESIS

Aim: To evaluate the safety and efficacy of domatinostat, a selective class 1 histone deacetylase inhibitor in combination with avelumab, an anti-PD-L1 monoclonal antibody

Hypothesis: Domatinostat in combination with avelumab will decrease tumour immune exclusion, result in a T cell inflamed phenotype and increase response rates to avelumab

OBJECTIVES, ENDPOINTS AND STATISTICAL CONSIDERATIONS

Primary endpoint:
• Safety run-in phase (Phase IIA): To recommend a safe and tolerable dose of domatinostat and avelumab for the main efficacy phase
• Main efficacy phase (Phase IIB): Best objective response rate (ORR) as per RECIST v1.1 at 6 months

Secondary endpoints: Safety and tolerability, PFS, OS, duration of objective response and DCR

Statistical considerations:
1. Safety run-in phase: standard 3+3 dose finding design where escalating doses of domatinostat will be examined, dosing of avelumab will remain constant
2. Main efficacy phase: Simon 2-stage optimal design
   • To rule out an ORR of ≤25% in the CRC cohort while aiming for 35%, 2/9 and 9/34 responses are required in the 1st and 2nd stages respectively
   • To rule out an ORR of ≤15% in the OG cohort while aiming for 35%, 2/9 and 9/34 responses are required in the 1st and 2nd stages respectively with a 1-sided alpha of 5% and 80% power

TRIAL DESIGN

• Multicentre phase II study non-randomised design
• The trial is being conducted in 2 stages:

• 1. Safety run-in phase:
   • Dose escalation of domatinostat in combination with avelumab
   • Recruitment of 5 patients has been treated within the safety run-in phase of the trial

• 2. Main efficacy phase:
   • Avelumab Avelumab Avelumab Avelumab
   • Safety run-in (Phase IIA)
   • Multicentre phase II study non-randomised design
   • Dose escalation of domatinostat in combination with avelumab
   • Recruitment of 25 patients in the main efficacy phase

PATIENT ELIGIBILITY

Key inclusion criteria:
• Aged ≥18 years
• Histologically confirmed gastric, gastro-oesophageal junction, oesophageal or colorectal adenocarcinoma
• MMRpf/MSI
• Advanced and inoperable or metastatic
• At least one prior chemotherapy treatment
• PD-L1 unselected
• Adequate liver, renal, bone marrow function
• PS 0-1

Key exclusion criteria:
• Any prior treatment with immunotherapy
• Any immunodeficiency disorder
• Active infection
• Autoimmune disease that might deteriorate on immunotherapy
• Patients receiving corticosteroids for hormone replacement are eligible at doses of ≤10mg prednisolone/day
• Baseline prolongation of the QT/QTc

EXPLORATORY TRANSLATIONAL RESEARCH

FUNDING

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DISCLOSURES

DC: Celgene, Merostim, Astrazeneca, Medimmune, Bayer, Astra, OSI, Eli Lilly, Janssen, Merck; HG: Astrazeneca, Eli Lilly, Merck, Roche, Pfizer, Servier, Pierre Fabre; IC: Astrazeneca, Bayer, Bristol Myers Squibb, OSI, Lilly, Five Prime Therapeutics, Merck Serono, MSD, OncoTherapy International, Pierre Fabre, Roche, Janssen-Cilag, and Sanofi; DC: Boehringer Ingelheim, Roche Diagnostics, Bristol Myers Squibb, Guardant Health, Celgene, Roche; All authors disclose no disclosures.

REFERENCES


CURRENT STATUS

• The study opened for recruitment in January 2019
• 5 patients have been treated within the safety run-in phase of the trial