Novel regimens versus standard-of-care in NSCLC: a phase II, randomized, open-label, platform trial using a master protocol

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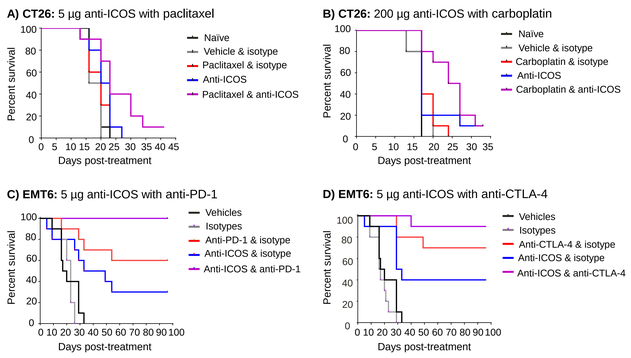
Introduction

Unmet need

Although the role of immunotherapy in NSCLC is well documented, a large unmet need following first-line PD-1/PD-L1 immunotherapy exists due to inherent or emerging resistance

Study rationale

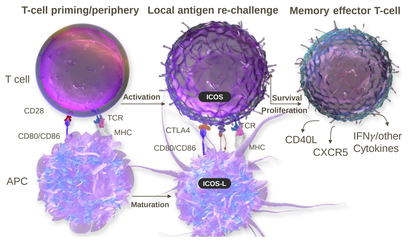
- Treatment regimens combining agents that target different processes within the cancer immunity cycle have the potential to enhance response in relapsed or refractory NSCLC
- This platform trial aims to study novel immunotherapy regimens compared with the current SoC (docetaxel) in patients with advanced NSCLC who have progressed on prior anti-PD-1/PD-L1 and platinum–based combination chemotherapies
- Inducible T-cell co-stimulator (ICOS) is a co-stimulatory receptor and emerging data suggest that ICOS may promote antitumor immune responses and long-term survival;[1-8] as such ICOS is a potential candidate for combination therapy in NSCLC
- In murine tumor models (CT26 and EMT6), combination of an anti-ICOS surrogate antibody with carboplatin, paclitaxel, or immune checkpoint antibodies (anti-PD-1 or anti-CTLA-4) demonstrates improved efficacy relative to monotherapeutic approaches



Kaplan–Meier plots illustrating the survival of CT26 **(A-B)** or EMT6 **(C-D)** tumor-bearing mice (BALB/c, n=10/group, 80-150 mm^3) following treatment with 5 µg **(A,C,D)** or 200 µg **(B)** anti-ICOS (7E.17G9-mIgG1, Q4D x 3, IP) alone or in combination with **(A)** paclitaxel (24 mg/kg, Q4D x 3, IV), **(B)** carboplatin (75 mg/kg, QW x 2, IV), **(C)** anti-PD-1 (200 µg, RMP1-14-rIgG2a, Q4D x 3, IP), or **D)** anti-CTLA-4 (5 µg, 9H10-hamster IgG, Q4D x 3, IP)

ICOS Mechanism of Action

- ICOS is a member of the **B7/CD28 Ig receptor superfamily**[9]
- **GSK3359609** is an IgG4 ICOS agonist antibody that is designed to enhance T cell function and enable anti-tumor responses without depletion of ICOS-expressing cells
- ICOS is **highly expressed in tumor infiltrating lymphocytes** (CD4$^+$ T helper cells, CD8$^+$ cytotoxic T cells, and Treg cells) in many tumors[10]



ENTRÉE-Lung | An adaptive platform trial designed to evaluate multiple treatments in the post PD-1/PD-L1 setting

This trial (NCT03739710) is a

Randomized · Phase II · Open-label · Platform trial

utilizing a master protocol in patients with **advanced NSCLC** who have progressed on initial PD-1/PD-L1-based immunotherapy and platinum-based chemotherapies

Will consist of several sub-studies, with each sub-study comparing

Novel regimens with Current SoC

No treatment crossover permitted

Sub-study 1 is ongoing and will evaluate

SoC (docetaxel) alone compared with **GSK3359609 (ICOS agonist) in combination with SoC**

Participants in sub-study 1 will be randomized in a 1:2 ratio; randomization ratios for subsequent sub-studies will vary and are defined by the study protocol

Additional sub-studies to be added based on emerging non-clinical and clinical data via future protocol amendment(s); additional novel immunotherapy treatment regimens will be analyzed relative to SoC

Sample size is not fixed in the SoC arm; however, there will be

105 patients in sub-study 1 (**35** SoC arm; **70** experimental arm)

with a maximum of **70 patients** in additional experimental arms —

this will provide at least **81% power** with a type 1 error of ≤2.3% for each pairwise comparison

Ongoing treatment arms may be dropped based on interim OS results performed approximately every 3 to 6 months

Interim analyses of OS will be done at regular intervals

The study will employ **a Bayesian decision-making framework**

Advanced NSCLC

Progressed on prior anti-PD-1/PD-L1 & platinum–based chemotherapies

Stratified by histology (squamous vs non-squamous) and line of PD-1/PD-L1 therapy (1st vs 2nd)

Randomization

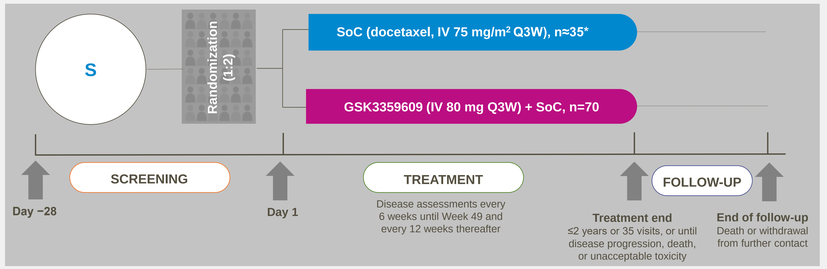
- Sub-study 1 randomization 1:2
- Randomization for subsequent sub-studies: ratios will vary and are defined by the protocol

Sub-study 1 (1:2) *Ongoing*: **SoC (docetaxel), n≈35*** / **ICOS agonist (GSK3359609) + SoC, n=70**

Sub-study 2: **SoC (docetaxel)*** / **Experimental combination (to be determined), n=70**

Sub-study 3: **SoC (docetaxel)*** / **Experimental combination (to be determined), n=70**

*10%–20% of newly enrolled participants in subsequent sub-studies (depending on the number of experimental arms in the trial) will be randomized to SoC once the initial 35 participants have been enrolled on control



Sub-study 1 — Study initiated in January 2019; accrual is on target

Follow-up: every 12 weeks by phone until death or patient withdrawal from further contact

Key inclusion criteria

- ≥ 18 years with NSCLC and measurable disease
- Documented disease progression during or after a maximum of 2 lines of systemic treatment for locally/regionally advanced recurrent, Stage IIIb/ Stage IV or metastatic disease
- 1 line of platinum-containing chemotherapy regimen
- 1 line of PD-1/PD-L1 mAb–containing regimen
- BRAF mutations must have had disease progression on local SoC for the molecular alteration

Key exclusion criteria

- Prior treatment with docetaxel or ICOS agonists
- ≥3 prior lines of therapy for NSCLC, including BRAF mutation participants
- Known EGFR/ALK/ROS1 molecular alterations
- Symptomatic CNS metastases

Primary endpoint

OS, as measured by time from randomization to death

Secondary endpoints

- Survival rate at 12 and 18 months
- Tumor response according to RECIST 1.1 and iRECIST criteria
- PK parameters of the novel immunotherapy
- Safety

Exploratory endpoints

- Tumor and blood-based biomarker evaluations including, but not limited to, evaluation of soluble analytes, TIL immune phenotyping and tumor mutational burden

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Abbreviations

ADCC: antibody-dependent cellular cytotoxicity; ALK: anaplastic lymphoma kinase; APC: antigen-presenting cell; BRAF: proto-oncogene b-RAF; CD: cluster of differentiation; CNS: central nervous system; CTLA4: cytotoxic T-lymphocyte–associated protein 4; CXCRS: CXC chemokine receptors; EGFR: epidermal growth factor receptor; ICOS: inducible T-cell co-stimulator; IFNγ: interferon γ; Ig: immunoglobulin; IP: intraperitoneal; IV: intravenous; mAb: monoclonal antibody; MHC: major histocompatibility complex; NSCLC: non-small cell lung cancer; OS: overall survival; PD-1/PD-L1: programmed cell death protein 1/programmed cell death ligand 1; PK: pharmacokinetics; Q3W: every 3 weeks; Q4D: every 4 days; QW: every week; (i)RECIST: Response Evaluation Criteria in Solid Tumors and modified RECIST 1.1 for immune-based therapeutics; ROS1: ROS proto-oncogene 1; SoC: standard of care; TCR: T-cell receptor; TIL: tumor infiltrating lymphocytes.

Disclosures

SC and M Barve have no conflicts of interest to report. AA, ALS, DR, SB and SY are employees of and stock holders in GSK. OA is an employee of GSK and holds stock in GSK and Biogen Idec. AH is an employee of and stock holder in GSK and Imugene. M Ballas is an employee in GSK and holds stock in GSK, BMS, Abbott and Novartis. MS reports research funding from: BMS, Roche, Merck Serono, Merck Sharpe Dome, Astellas, AstraZeneca, Amgen, Eli Lilly, Pfizer, Mylan, Samsung, Bioven, Pharma Mar, Regeneron; AS has participated in consulting/advisory boards for AstraZeneca and Bayer, and reports honoraria from AstraZeneca, Merck, Genentech-Roche and Bayer. BB has received research funding from: AbbVie, Amgen, AstraZeneca, Biogen, Blueprint Medicines, BMS, Celgene, Eli Lilly, GSK, Ignyta, IPSEN, Merck KGaA, MSD, Nektar, Onveo, Pfizer, Pharma Mar, Sanofi, Spectrum Pharmaceuticals, Takeda, Tiziana Pharma. DS reports institute research funding from GSK. MR reports honoraria from: AbbVie, Amgen, AstraZeneca, BMS, Boehringer-Ingelheim, Celgene, Lilly, Merck, MSD, Novartis, Pfizer, Roche. MG has received honoraria for speaker/advisory/consultancy roles from Otsuka Pharma, BMS, Inivata, MSD, Boehringer Ingelheim, Eli Lilly, Roche, AstraZeneca, Novartis, Celgene, Pfizer, Takeda, Incyte, SeaGen International GmbH, Spectrum Pharmaceuticals, Blueprint Medicines; reports funding from Takeda Pharmaceuticals, Incyte Corporation, Clovis, Eli Lilly, Merck Serono, Bayer, Merck KGaA, AstraZeneca, Roche, MSD, Novartis, Pfizer, GSK, Tiziana Sciences, BMS, Celgene, Otsuka Pharmaceutical, United Therapeutics, Spectrum Pharmaceuticals, Exelixis, Blueprint Medicines; and has non-financial interests in MSD, Pfizer, Eli-Lilly, MSD, Fondazione AIRC per la Ricerca sul Cancro (AIRC), Italian Medicines Agency (AIFA).

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Preclinical studies were conducted in accordance with the GSK Policy on the Care, Welfare and Treatment of Laboratory Animals, and were reviewed by the Institutional Animal Care and Use Committee either at GSK or by the ethical review process at the institution where the work was performed.

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