Abstract 1047P AXA-042, a Systemically Administered TLR2/6 agonist, Demonstrates Target Engagement and TLR Pathway Activation in Patients with Advanced Solid Tumors.

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BACKGROUND

- AXA-042 is a novel synthetic potent and selective TLR2/6 agonist designed for systemic delivery to re-engage the innate immune response.
- AXA-042 induces a pro-inflammatory cytokine/ chemokine release by tumor-localized monocytes/ macrophages (**1**), increases tumor cell killing and antigen release (**2**), enhances DC activation (**3**) and potentiates T cell response to checkpoint blockade (**4**).

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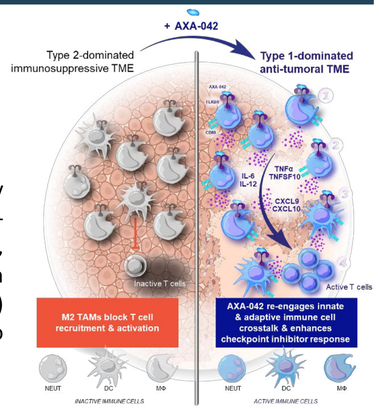
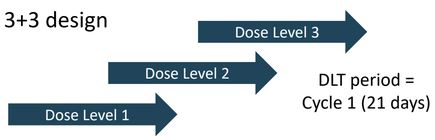


A MULTI-CENTER OPEN-LABEL DOSE ESCALATION, DOSE EXPANSION PHASE 1 STUDY

- Subjects with advanced metastatic solid tumors
- 3+3 design



AXA-042
IV once every 3-weeks

PRIMARY ENDPOINTS

- Safety and Tolerability of AXA-042

SECONDARY ENDPOINTS

- Pharmacokinetic parameters of AXA-042
- Immunogenicity of AXA-042

EXPLORATORY ENDPOINTS

- Pharmacodynamic (PD) effects of AXA-042
- Preliminary AXA-042 anti-tumor efficacy

PD BIOMARKER COLLECTION TIMEPOINTS

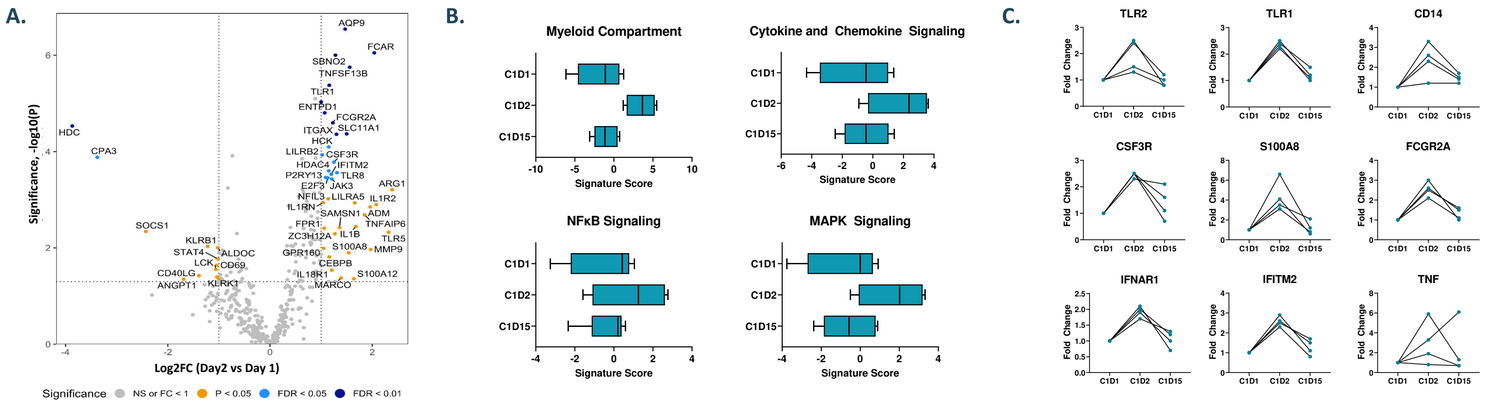
- Cytokines: C1D1 pre-dose, 1h, 4h, C1D2;
- C2D1 pre-dose, 4h; C3D1 pre-dose, 4h
- Nanostring: C1D1 pre-dose, C1D2, C1D15
- CYTOF: C1D1 pre-dose, C1D2, C1D15

COHORT 1 PATIENT CHARACTERISTICS

Age/ Gender	Cancer Type	Prior Lines of Therapy
60/F	Metastatic ovarian granulosa tumor (GCT)	7
50/M	Metastatic GIST	6
69/F	Metastatic mucinous appendiceal adenocarcinoma (AMN)	3
43/F	Metastatic colorectal adenocarcinoma	2
71/F	Metastatic PDAC	2
73/F	High grade serous, platinum-resistant ovarian cancer	3

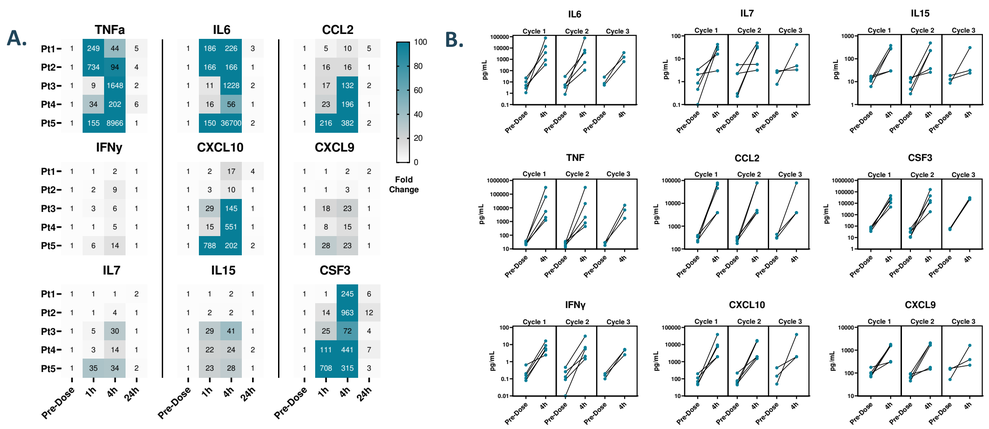
RESULTS

Figure 1. AXA-042 Whole Blood Gene Signature is Consistent with TLR Pathway Activation and Myeloid Cell Engagement



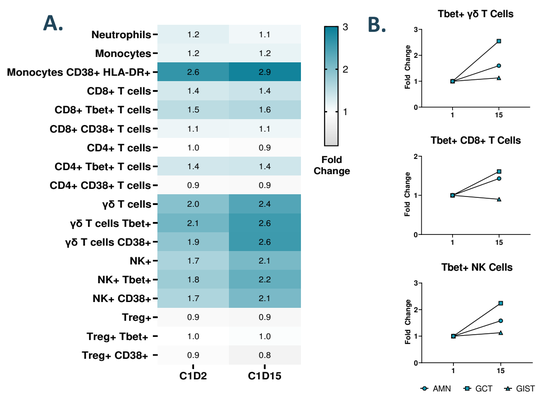
A. Volcano plot displaying differentially expressed genes on Cycle 1 Day 2 (C1D2) relative to C1D1 pre-dose timepoint in whole blood samples collected from AXA-042 treated patients (n=4). Genes with significance P-value < 0.05 and absolute fold change > 1 (log2) are labelled. **B.** Box plots displaying Pathway Signature Scores for whole blood samples collected on C1D1 (pre-dose), C1D2 and C1D15. Min and max values are indicated **C.** Representative examples of AXA-042 differentially expressed genes across individual patients (n=4). Data is shown as fold change relative to C1D1 (pre-dose) timepoint.

Figure 2. AXA-042 Cytokine/Chemokine Induction is Transient and Reproducible Across Cycles



A. Heat Map displaying kinetics of cytokine and chemokine induction in individual patient whole blood samples collected pre-dose or at indicated time points post infusion on C1D1. Data is shown as fold change relative to C1D1 pre-dose timepoint. **B.** Representative cytokine and chemokine induction 4h post AXA-042 infusion in individual patients across Cycles 1, 2 and 3. Cytokine data for n=5 patients was available for Cycles 1-2 and n=3 patients for Cycle 3 at time of data cut-off. Data is shown as pg/mL.

Figure 3. AXA-042 Impacts Distribution of Immune Cell Subsets in Patient Whole Blood



A. Impact of AXA-042 treatment on whole blood immune cell subsets in GCT patient on C1D2 and C1D15. **B.** Impact of AXA-042 treatment on Tbet+ γδ T cell, CD8+ T cell and NK cell subsets across three independent patients in cohort 1. Data in both panels is shown as Fold Change relative to C1D1 pre-dose timepoint

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CONCLUSIONS

- Systemic administration of AXA-042 demonstrates strong engagement of the TLR signaling pathway as reflected by on-target induction of gene expression and cytokines/chemokines associated with myeloid cell activation in patient whole blood samples.
- AXA-042 target engagement response is transient and reproducible across treatment cycles.
- AXA-042 transient TLR2 engagement enhances proportion of Tbet+ peripheral T- and NK- cell subsets in subsets of patients on C1D15.

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