XmAb30819, an XmAb® 2+1 ENPP3 x CD3 bispecific antibody for RCC, demonstrates safety and efficacy in vivo preclinical studies

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Introduction

- Ectonucleotide pyrophosphatase/phosphodiesterase 3 (ENPP3 or CD203c), a nucleotide hydrolase known to convert ATP to AMP, is differentially expressed in renal cell cancer (RCC) as measured by bulk RNAseq and IHC.
- A type II integral membrane protein, ENPP3's expression profile makes it a potential target for a CD3 bispecific approach against clear cell and papillary RCC as well as other segments of this patient population.
- Unlike targets for hematopoietic cancers, solid cancer targets like ENPP3 are not tumor restricted and therefore can exhibit baseline levels of expression on normal cells.
- Normal tissue expression of ENPP3 has been described on tubules of the kidney cortex, and subsets of cells in gastrointestinal, adrenal, and endometrial tissues.
- To create a selective T-cell engaging antibody against ENPP3, we extended our XmAb heterodimeric Fc platform to create the 2+1 Fab2-scfvFc format, which is bivalent for ENPP3 and monovalent for CD3.

XmAb 2+1 Fab2-scfvFc format enables selective tumor targeting

- XmAb heterodimeric Fc platform allows for well-behaved, high-yielding, and easily manufactured 2+1 bispecific antibodies
- Modified Fc domain eliminates Fc affinity, but preserves FcRn affinity for antibody-like half-life
- Fc substitutions promote heterodimer formation and facilitate purification by standard methods such as Protein A or ion-exchange chromatography
- An ENPP3 Fv was humanized, affinity-tuned, and inserted into our CD3 bispecific platform.

Affinity-tuned 2+1 bispecific antibodies allow for selective engagement of high-expressing tumor target cells over low-expressing normal cells

- Cell binding performed on KU812 (–/–SKG)
- XmAb30819 was selected based on activity in vivo coupled with tolerability in NHPs

B Cell line proxies for "on-target" and "off-target" tissue identified by IHC

- ENPP3 prevalence was achieved by IHC scoring of tumor and normal tissue FFPE cores
- Antigens cell on various endogenous ENPP3+ cell lines ranged from ~5% to ~1%, and were correlated with tumor and normal tissues by IHC

C Bivalent 2+1 format retains binding despite reduced monovalent affinity

- Monovalent (avidity driven)
- Cell lines were mixed with T cells at E:T of 10:1 then treated with XmAb30819 for 40 hrs

D XmAb30819 selectively kills high expressing cell lines in vitro

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Summary

The XmAb 2+1 ENPP3 x CD3 bispecific antibody XmAb30819:
- Is humanized, well-behaved, and efficiently purified and manufactured.
- Selectively recruits T cells to kill high-expressing ENPP3+ cancer cells in vitro.
- Stimulates expected pharmacodynamics in cynos and features antibody-like half-life.
- Induces potent anti-tumor activity in two tumor models with hPBMC-engrafted NSG mice at doses that are well-tolerated in cyno monkeys.

E XmAb30819 is well-tolerated and shows dose-dependent pharmacodynamics in NHPs

- Phase 1: Cytox monkeys tolerated single doses of XmAb30819 at various dose levels.
- Phase 2: Expanded cohort to iv at the highest dose administered; one monkey experienced dosing-limiting toxicity
- Serum half-life supports antibody-like dosing schedule

F XmAb30819 reverses tumor growth of two "on-target" cell lines in mice

- Engraft KU812 or RXF393 cancer cells intratumorally
- Median KU812 tumor volume over time
- Median RXF393 tumor volume over time

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These results support clinical testing of XmAb30819 as a potential therapeutic option for patients with RCC and subsets of other ENPP3+ indications.

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