ISB 1342: A FIRST-IN-CLASS CD38 T CELL ENGAGER FOR THE TREATMENT OF RELAPSED REFRACTORY MULTIPLE MYELOMA

Marie-Agnès Doucey
Ichnos Sciences, Epalinges, Switzerland
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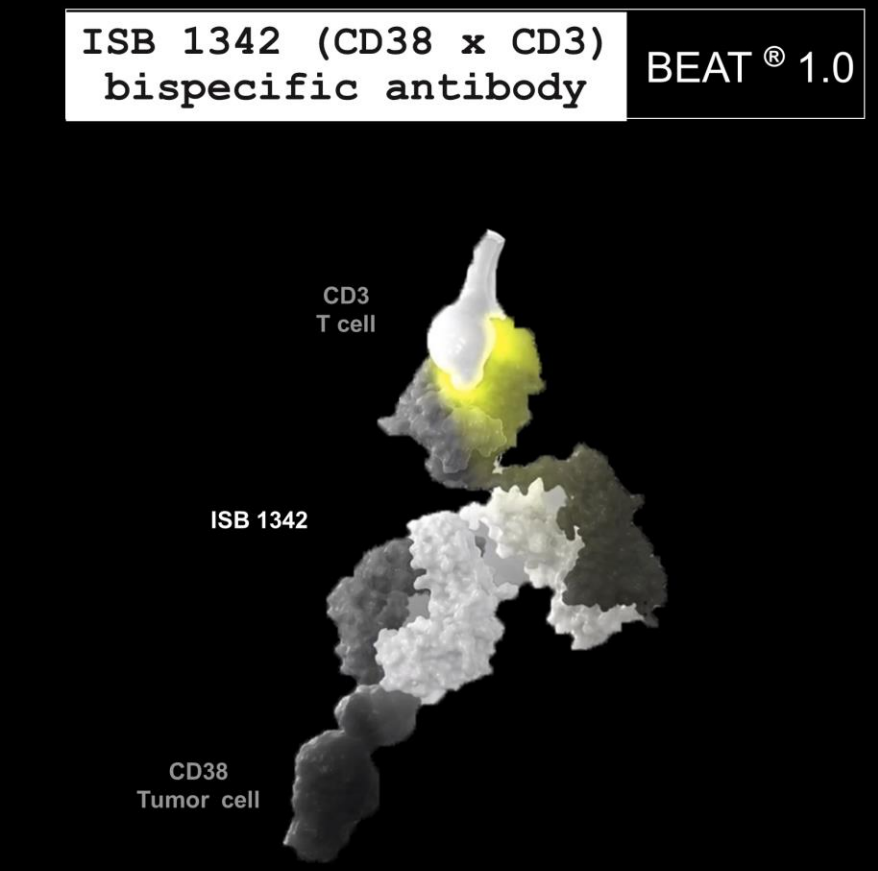

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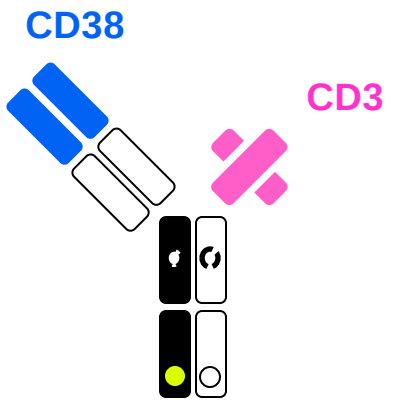
ISB 1342 (CD38 x CD3): Potential First-in-Class Therapy in Relapsed/Refractory Multiple Myeloma

- CD38 is a validated target for multiple myeloma expressed at the surface of tumor cells
- ISB 1342 redirects T lymphocytes to kill CD38-expressing tumor cells in MHC-antigen-independent manner
- ISB 1342 binds to a proprietary anti-CD38 epitope, which is different from that of daratumumab or isatuximab
- ISB 1342 is designed to overcome:
  - + Daratumumab resistance by killing low CD38-expressing tumor cells
  - + Resistance to CDC and ADCC mediated by daratumumab
- Phase 1 dose escalation study is ongoing

Humanized proprietary CD38 binder
Parental Ab 9G7
Cell based affinity 4.3 nM
Cynomolgus monkey cross-reactive



CD3 binder formatted as scFv
Parental Ab SP34
Cell based affinity 230 nM
Cynomolgus monkey cross- reactive

ADCC and CDC functions reduced by LALA-mutations (L234A/L235A)

BEAT® 1.0: **B**ispecific **E**ngagement by **A**ntibodies based on the **T** cell receptor

MHC: Major Histocompatibility Complex, CDC: Complement-Dependent Cytotoxicity, ADCC: Antibody-Dependent Cell-mediated Cytotoxicity.

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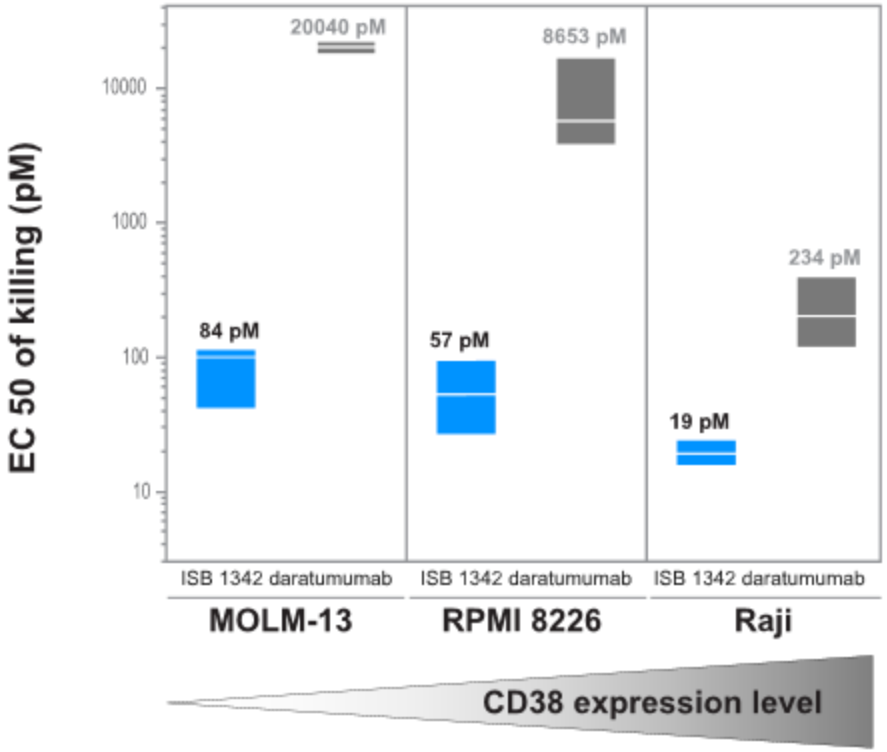
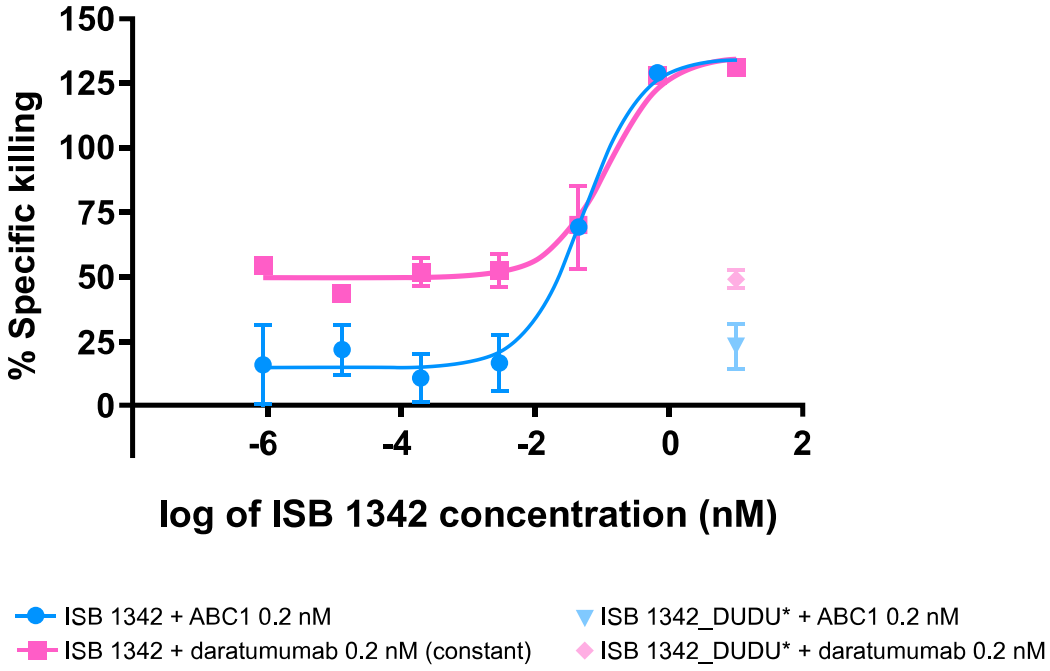
ISB 1342 Demonstrates Superior Potency to Daratumumab *In Vitro* and Retains Potency when Combined with Daratumumab

ISB 1342 shows superior killing potency to daratumumab *in vitro* in tumor cells expressing low, intermediate and high levels of CD38 (left panel) and retains potency when combined concomitantly (right panel) or sequentially (not shown) with daratumumab





*Multiple mode of action killing assay combines Antibody-Dependent Cell-mediated Cytotoxicity (ADCC), Complement-Dependent Cytotoxicity (CDC) and re-directed cell lysis. ISB 1342 induced a statistically significantly better killing than daratumumab (left panel).*DUDU is a control BEAT molecule with two irrelevant binders, ABC1 is a control antibody.*

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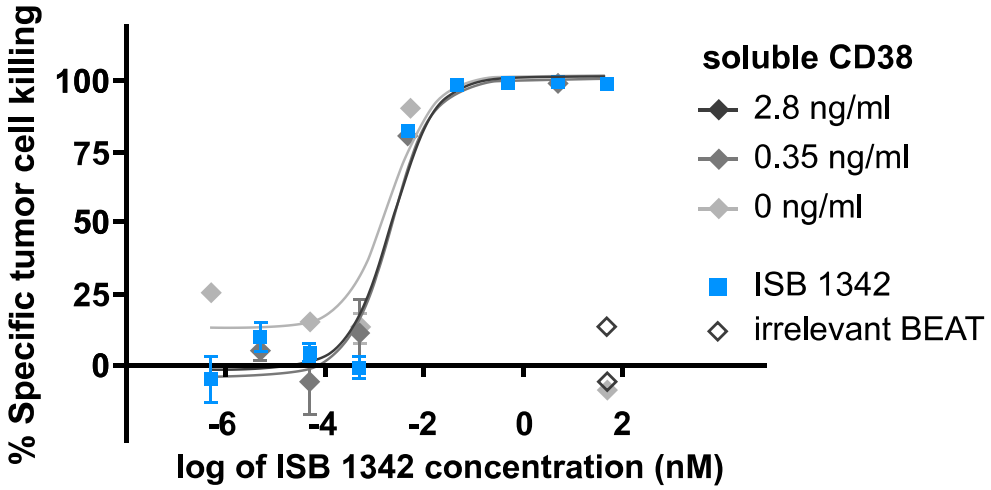
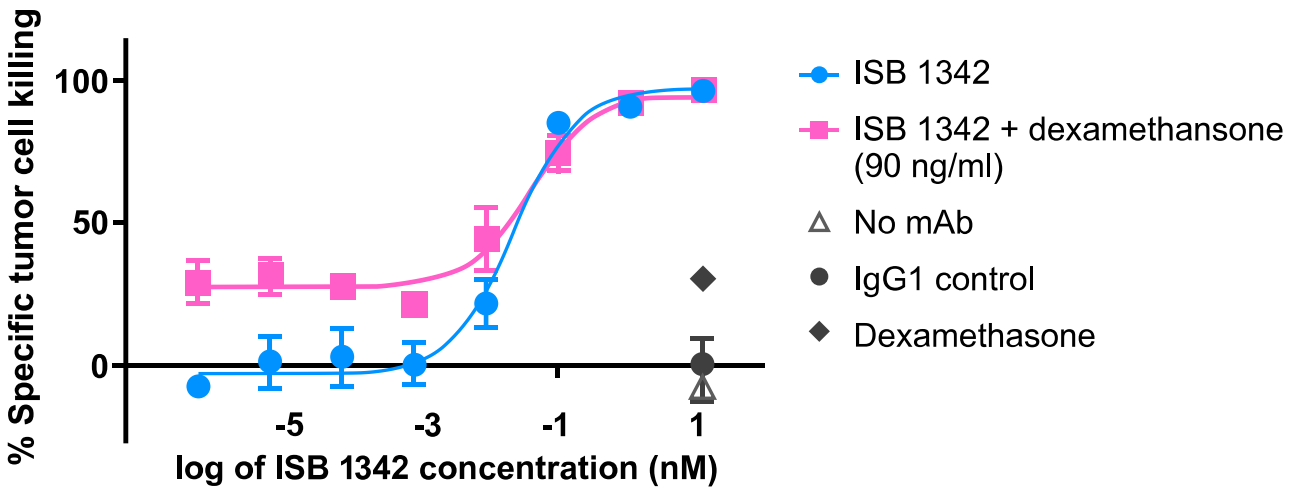
ISB 1342 Killing Potency *In Vitro* is Minimally Impacted by Soluble CD38 and Glucocorticoids

The killing activity of ISB 1342 remains unchanged in the presence of soluble CD38 (left panel) and was only mildly impacted by a relatively high dose of dexamethasone (a 3-4-fold increase in EC50, right panel).





Re-directed cell lysis assay performed in the presence of CD38-expressing tumor cells.

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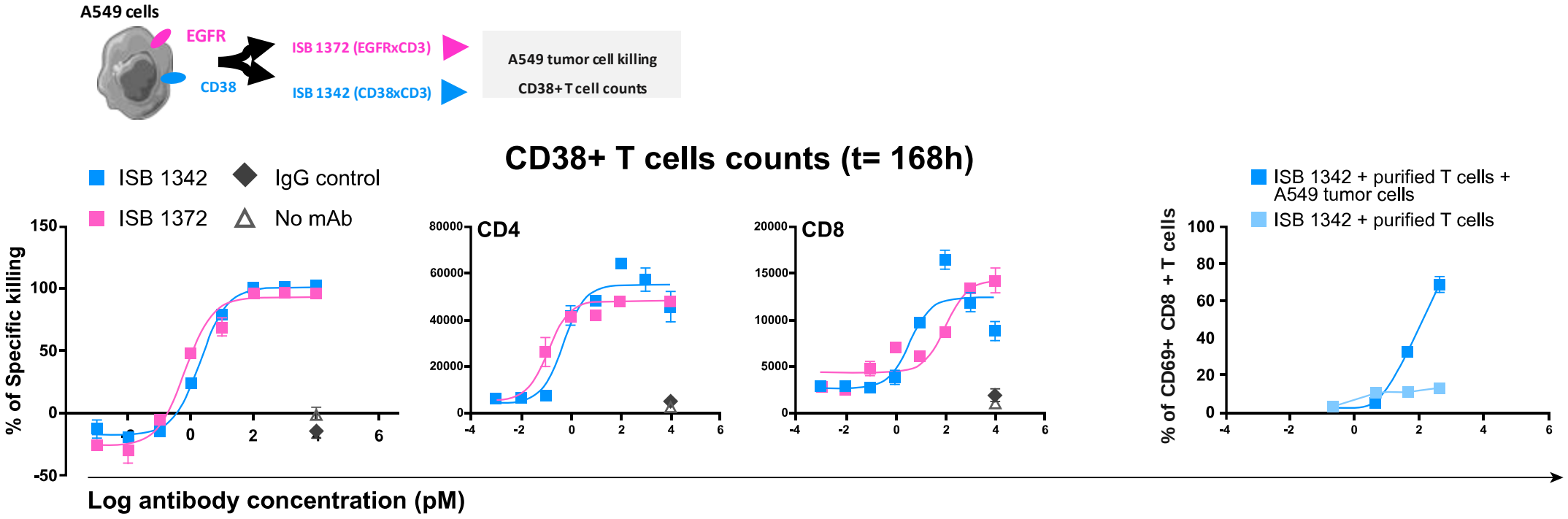
ISB 1342 Shows a Favorable On Target Specificity Profile In Vitro

ISB 1342 does not induce a detectable fratricide of CD38+ T cell *in vitro* (left panel) and induces a limited activation of T cells in the absence of CD38-expressing tumor cells (right panel).



Re-directed cell lysis of A549 tumor cells induced by ISB 1342 (CD38xCD3) and ISB 1372 (EGFRxCD3) and human PBMCs as a source of T cells (left panel). T cell activation induced by ISB 1342 in presence and absence of A549 tumor cells (right panel).

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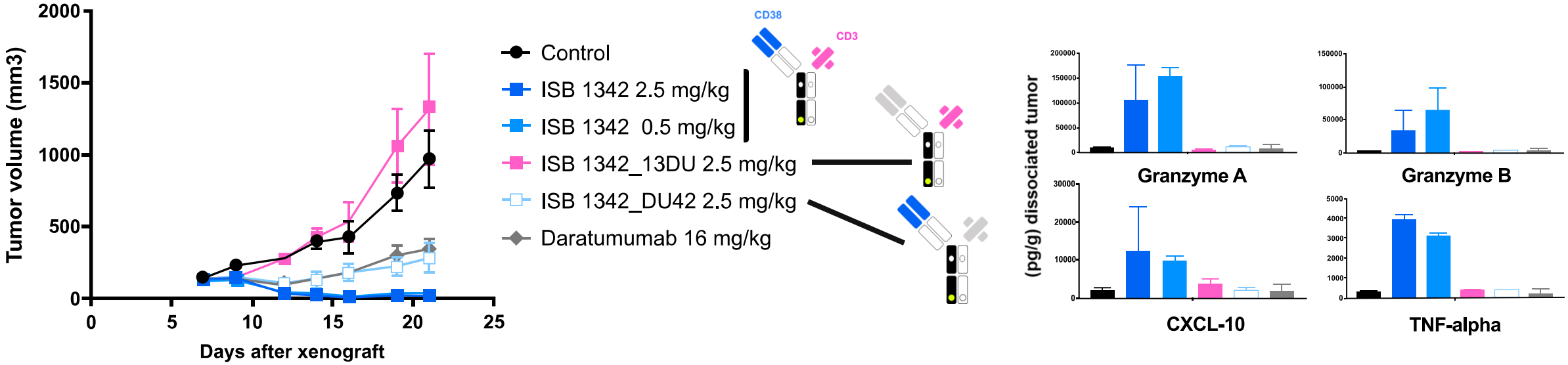
ISB 1342 Demonstrates Superior Potency to Daratumumab *In Vivo*

In contrast to daratumumab, ISB 1342 induces full tumor control (left panel) and increased levels of Granzyme, TNF-alpha and CXCL10 in tumors (right panel); This represents correlates of anti-tumor immunity associated with ISB 1342 efficacy *in vivo*. Control molecules ISB 1342_13DU (made of irrelevant CD38 binder) fails to engage and kill tumor cells while ISB 1342_DU42 (made of irrelevant CD3 binder) partially controls tumor growth through residual effector functions.



NOD-SCID mice were xenografted s.c. with a mix of human PBMC and Daudi tumor cells (CD38 high). Mice were randomized at day 7 post-xenograft when the average tumor volume reached 120 mm^3 and treatments injected i.v. twice per week for 3 weeks. At day 21, ISB 1342 induced a statistically significantly higher tumor control relative to daratumumab (left panel). Cytokines and effector molecules (right panel) were measured in dissociated tumors one week post-treatment.

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Conclusions

ISB 1342 SHOWS A HIGHER POTENCY *IN VITRO* AND *IN VIVO* RELATIVE TO DARATUMUMAB, SUPPORTING ONGOING CLINICAL DEVELOPMENT IN MULTIPLE MYELOMA PATIENTS

- ISB 1342 showed a higher killing potency than daratumumab *in vitro*
- Soluble CD38, glucocorticoids and combination with daratumumab had minimal impact on the killing potency of ISB 1342 *in vitro*
- ISB 1342 did not induce a detectable fratricide of CD38+ T cell in vitro
- ISB 1342 induced a better tumor control than daratumumab *in vivo* in a therapeutic setting

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