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1 **Pre-clinical characterization of ISB 1342, a CD38xCD3 T-cell engager for**  
2 **relapsed/refractory multiple myeloma**

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10

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#### 54 **Key points**

- 55 • ISB 1342 exhibits potent killing of primary MM cells and MM cell lines with low  
56 sensitivity to daratumumab.
- 57 • ISB 1342 induced complete MM tumor eradication in two *in vivo* mouse models.

#### 58 **Abstract**

59 Whilst treatment of multiple myeloma (MM) with daratumumab significantly extend patient  
60 lifespan, resistance to therapy is inevitable. ISB 1342 was designed to target MM cells from  
61 patients with relapsed/refractory MM (r/rMM) displaying lower sensitivity to daratumumab.  
62 ISB 1342 is a bispecific antibody with a high affinity Fab binding to CD38 on tumor cells on a  
63 different epitope than daratumumab and a detuned scFv domain affinity binding to CD3ε on T-  
64 cells, to mitigate the risk of life-threatening cytokine release syndrome, using the Bispecific  
65 Engagement by Antibodies based on the TCR (BEAT<sup>®</sup>) platform. *In vitro*, ISB 1342 efficiently  
66 killed cell lines with different levels of CD38 including those with a lower sensitivity to  
67 daratumumab. In a killing assay, wherein multiple modes of action were enabled, ISB 1342  
68 showed higher cytotoxicity towards MM cells compared to daratumumab. This activity was  
69 retained when used in sequential or concomitant combinations with daratumumab. The  
70 efficacy of ISB 1342 was maintained in daratumumab-treated bone marrow patient samples  
71 showing lower sensitivity to daratumumab. ISB 1342 induced complete tumor control in two  
72 therapeutic mouse models, unlike daratumumab. Lastly, in cynomolgus monkeys, ISB 1342  
73 displayed an acceptable toxicology profile. These data suggest that ISB 1342 may be an  
74 option in patients with r/rMM refractory to prior anti-CD38 bivalent monoclonal antibody  
75 therapies. It is currently developed in a phase 1 clinical study.

76

#### 77 **Introduction**

78 Multiple myeloma (MM) is the second most common haematological malignancy  
79 worldwide, with 35,500 and 54,600 new cases anticipated in 2025 in the USA and Europe,  
80 respectively (1). The emergence of CD38-targeted therapies has significantly prolonged the  
81 survival of patients with relapsed/refractory MM (r/rMM) who were previously treated with ≥2  
82 prior therapies. Daratumumab, a human IgG1 monoclonal antibody targeting CD38, is  
83 associated with a median overall survival (OS) of 20.1 months in patients refractory to  
84 proteasome inhibitors and immunomodulatory drugs (2,3). Mechanistically, daratumumab  
85 induces killing of MM cells via antibody-dependent phagocytosis (ADCP), complement-  
86 dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC) and by  
87 inducing direct apoptosis via FcγRs-mediated cross-linking (4–6). Clinical outcomes have  
88 further improved with the approval of daratumumab combinations compared to monotherapy  
89 (4,7,8). Despite such progress, most patients continue to relapse, due to multiple primary and  
90 acquired resistance mechanisms to anti-CD38 therapies (4,9,10). Amongst those  
91 mechanisms, transient down-regulation of CD38 expression on the surface of MM cells, which  
92 never fully recover expression, has been observed in patients treated with daratumumab (11).

93 ISB 1342 was therefore designed to be active regardless of CD38 expression and to  
94 overcome pre-existing resistance to daratumumab's many mechanisms of action. ISB 1342  
95 was engineered using the BEAT<sup>®</sup> platform (**B**ispecific **E**ngagement by **A**ntibodies based on  
96 the **TCR** platform) (12–14) to target the cluster of differentiation (CD)3-epsilon (CD3ε) and  
97 CD38. ISB 1342 aims to treat r/rMM, by targeting and depleting CD38<sup>+</sup> MM cells via a T-cell  
98 redirected killing by crosslinking the CD3ε molecules on T-cells and the CD38 molecules on  
99 MM cells. This bridging activates T-cells in a polyclonal manner, independent of the  
100 involvement of a specific antigenic peptide presented on the major histocompatibility class  
101 (MHC) proteins or costimulatory molecules (15,16).

102 In this study, we evaluated the ability of ISB 1342 to kill MM cells, which model some  
103 resistance mechanisms to daratumumab in patients. We demonstrate that ISB 1342 can  
104 successfully induce the killing of MM cell lines *in vitro* and *in vivo*, as well as of primary MM  
105 cells in bone marrow aspirates (BMA) from patients previously exposed to daratumumab,  
106 whereas the latter possesses limited activity under these conditions. Studies in cynomolgus  
107 monkeys revealed an acceptable toxicology profile and supported the advancement of  
108 ISB 1342 into an ongoing Phase 1 dose-escalation clinical study in r/rMM patients.

## 109 **Material and Methods**

110 Additional detailed methods are presented in the supplemental file.

### 111 **Human samples and cell lines**

112 BMA or peripheral blood samples from MM patients were obtained from University  
113 Hospital Geneva, CHU Nantes (MYRACLE cohort (**17**)), and Oxford University Hospitals with  
114 informed consent under each site ethical approvals. Human PBMCs (hPBMC) from healthy  
115 donors and MM patients, and bone marrow mononuclear cells (BMMC) were isolated using  
116 Ficoll gradients. All cell lines were of human origin (from DSMZ or Sigma-Aldrich) and cultured  
117 in the media recommended by the supplier.

### 118 **Redirected lysis (RDL) assay**

119 MM cell lines were labelled with eFluor<sup>TM</sup>670 dye (2μM) or CFSE (1μM) and co-  
120 cultured for 48-72 hours with hPBMCs at an effector to target ratio (E:T) of 10:1 or 5:1 with  
121 ISB 1342 or control molecules and additional treatments (soluble CD38, dexamethasone). The  
122 MM cell killing was measured as the decrease of the remaining live target cells count after  
123 treatment (based on viability dye staining) normalized with the untreated and non-effector cells  
124 conditions. The T-cell response was measured as the proportion of live CD8<sup>+</sup>T-cells  
125 expressing CD25, Ki-67 and Granzyme B/Perforin (**Supplementary Table 1, 2**).

### 126 **Multiple Mode of Action Killing assay (MMoAK)**

127 hPBMCs were co-cultured with MM cell lines previously labelled with eFluor670 (2μM)  
128 in medium containing 50%Human Serum (HS) and 100U/ml hIL-2 at E:T of 5:1 to enable  
129 ADCC, ADCP, CDC, and T-cell mediated cytotoxicity (**Figure 3F**). Co-cultures were then  
130 incubated with ISB 1342, daratumumab (Darzalex<sup>®</sup>, Janssen Biotech Inc.) or control  
131 molecules. The MM cell killing was measured as the decrease of the remaining live target  
132 cells count after treatment (based on viability dye staining) normalized with the untreated and  
133 non-effector cells conditions. The T-cell response was measured as the proportion of live  
134 CD8<sup>+</sup>T-cells expressing CD25, CD69 and CD107a (**Supplementary Table 1, 2**).

### 135 **Ex vivo assay on MM patient samples**

136 Baseline phenotype analysis was performed on 0.2-0.5x10<sup>6</sup> BMMC and MM cell lines  
137 to assess the phenotype of MM cells and T-cells (**Supplementary Table 1**). Killing assay was  
138 performed on 0.1-0.2x10<sup>6</sup> BMMC treated with ISB 1342 or daratumumab in medium  
139 containing 10%HS and hIL-6 (3ng/ml) for 17-32 hours at 37°C (**Supplementary Table 2**).  
140 Tumor cell killing was calculated as the decrease of the remaining live target cell count,  
141 defined as CD138<sup>+</sup>, after treatment, normalized to the untreated condition. The T-cell  
142 response was measured as the proportion of live CD8<sup>+</sup>T-cells expressing CD25, CD69, and  
143 CD107a.

#### 144 ***In vivo* efficacy mouse model**

145 The *in vivo* study was performed with 6/7-week-old immunodeficient female NSG  
146 (NOD.Cg-Prkdc<sup>scid</sup> Il2rg<sup>tm1Wjl</sup>/SzJ) mice (8 mice per group) from Charles River Laboratories and  
147 conducted according to the Swiss Animal Protection Law with authorization from the cantonal  
148 and federal veterinary authorities. 10x10<sup>6</sup> KMS-12-BM cells were injected s.c. and 10x10<sup>6</sup>  
149 hPBMC were injected intraperitoneally (i.p.). Treatments were injected i.v. 9 days after, when  
150 tumors reached an average volume of 150mm<sup>3</sup> and then once (ISB 1342) or twice  
151 (daratumumab)/week, for 3 weeks. Immunoglobulins (IVIg) were injected i.v. one day before  
152 each treatment injection. When animals reached maximum tumor size (1000 mm<sup>3</sup>) prior to  
153 study endpoint, they were euthanized, and last observation carried forward (LOCF) was used.  
154 Tumor size was evaluated three times/week. For the flow-cytometry analysis, tumors were  
155 harvested 7 days after the first treatment injection and dissociated with an enzymatic cocktail  
156 from a tumor dissociation kit using a GentleMACS dissociator. Cells in suspension were  
157 filtered, red blood cells (RBC) lysed, and stained for human immune cell infiltration and CD38  
158 expression on tumor cells (**Supplementary Table 1**).

#### 159 **Studies in cynomolgus monkeys**

160 Monkey studies were conducted at SNBL USA Ltd, an AAALAC-accredited facility.  
161 Purpose-bred (Cambodian origin), naïve male and female cynomolgus monkeys were used in  
162 the non-GLP study. The study protocol and amendments were approved by the study director  
163 and SNBL's IACUC. All procedures were performed in compliance with the SNBL SOPs.  
164 Cynomolgus monkeys (1 male and 1 female) received a single intravenous (i.v.) bolus  
165 injection at escalating doses of ISB 1342 (1, 100, and 1000 µg/kg at day 1, 29, and 57,  
166 respectively). Clinical observations and blood samples were collected for clinical pathology,  
167 cytokines, anti-drug antibody (ADA), and flow cytometry analysis of leukocyte populations  
168 (**Supplementary Table 1**). The serum concentrations of ISB 1342 were measured using an  
169 exploratory hybrid IP-LC/MS/MS method at Q2 solutions (Ithaca, USA).

## 170 **Results**

### 171 **ISB 1342 Engineering and biophysical characterization**

172 The anti-CD3ε scFv portion of ISB 1342 was genetically engineered by fusing the  
173 variable heavy chain and light chain domains of a humanized version of the SP34 mouse  
174 antibody via a 15-amino acid (aa) linker ((Gly<sub>4</sub>Ser)<sub>3</sub>). The resulting scFv domain is connected  
175 to the hinge region via a short 5-aa linker (Gly<sub>4</sub>Thr). The Fab portion is based on a humanized  
176 mouse anti-human CD38 antibody, 9G7, developed by Ichnos and dubbed humanized 9G7  
177 (h9G7). Fc receptors (FcR) expressed on human peripheral blood cells drive cytotoxic,  
178 phagocytic, and inflammatory functions (18,19). To prevent FcγR-mediated binding, which  
179 may act as an antibody sink and potentially crosslink FcγR-expressing immune cells with T-  
180 cells, and to minimize non-specific T-cell activation (in the absence of target cell engagement),  
181 two mutations, LALA (L234A/L235A, EU numbering), were introduced into the CH2 domains  
182 of ISB 1342 (**Figure 1 A**). These mutations decrease the binding of human IgG1 molecules to  
183 human FcγR (20,21). ISB 1342 interacted weakly with all FcγR compared to its Fc-competent  
184 counterpart (**Supplementary Figure 1A, B**). ISB 1342 was designed to bind to CD38  
185 expressing tumor cells with high affinity while mitigating the risk of life-threatening cytokine  
186 release syndrome (CRS) in the clinic by detuning the affinity to CD3ε still to effective level  
187 (22). ISB 1342 binding to human CD38 and CD3εδ recombinant proteins displayed K<sub>D</sub> of  
188 1.1±0.15nM and 125±2.8nM, respectively, when SPR results were analyzed using the  
189 Langmuir 1:1 model (**Figure 1B and Supplementary Figure 1C**). On MM cell lines  
190 expressing different levels of CD38, such as KMS-12-BM (CD38<sup>+</sup>), NCI-H929 (CD38<sup>++</sup>) and  
191 MOLP-8 (CD38<sup>+++</sup>), ISB 1342 affinity was higher (K<sub>D</sub>=2.5±1.8nM on KMS-12-BM) than on  
192 human CD3<sup>+</sup>CD38<sup>-</sup>T-cells (K<sub>D</sub>=230.4±44.8nM) (**Figure 1B, C**). ISB 1342 was designed to  
193 target an epitope different from daratumumab as shown by the non-overlapping antigen  
194 binding footprints on the 3D structure of CD38 (**Figure 1D**). The lack of competition was

195 confirmed by the ability of ISB 1342 to bind CD38 despite pre-incubation of CD38 with  
196 daratumumab in a biolayer interferometry assay (**Figure 1E**).

### 197 **ISB 1342 induces killing of MM cell lines**

198 We explored the ability of ISB 1342 to specifically kill MM cell lines by engaging T-cells  
199 *in vitro*, using a RDL assay with hPBMC as effectors. First, we evaluated the ability of  
200 ISB 1342 to mediate synapse formation by confocal microscopy. ISB 1342 was located and  
201 enriched at the interface between T-cells and KMS-12-BM after at least 4 hours, suggesting  
202 the formation of an immunological synapse (**Figure 2A, Supplementary Figure 2A**). Next, we  
203 evaluated whether ISB 1342 induced killing of KMS-12-BM cells compared to molecules with  
204 one or both arms replaced by null arms. ISB 1342 killed with an average half-maximal  
205 effective concentration (EC<sub>50</sub>) of 1.23pM while controls did not induce sufficient killing to  
206 calculate an EC<sub>50</sub> (**Figure 2B**). This killing was paired with increased expression of CD25 on  
207 CD8<sup>+</sup> (**Figure 2C**), and CD4<sup>+</sup>T-cells (data not shown), elevated T-cell proliferation (Ki-67  
208 staining), and Granzyme B and Perforin (**Figure 1D-E, Supplementary Figure 2B**). No  
209 significant increases for any of these markers were seen with control molecules. Cell staining  
210 confirmed efficient binding of ISB 1342 (**Supplementary Figure 2C**) to both cell types while  
211 controls bound at similar levels to tumor (CD38 only control) and T-cells (CD3 only control).  
212 We then evaluated potential T-cell fratricide by ISB 1342. A549 cells expressing CD38 and  
213 EGFR were targeted by a T-cell engager (TCE) with the same CD3 arm as ISB 1342 but  
214 targeting EGFR that is not expressed on T-cells and therefore not expected to induce any T-  
215 cell fratricide. In these conditions, both TCE had similar cytotoxic activity and displayed similar  
216 counts of CD8<sup>+</sup>CD38<sup>+</sup>T-cells, which suggests that ISB 1342 is not inducing T-cell fratricide  
217 (**Supplementary Figure 2D, E**). Taken together these data indicate that ISB 1342 induces co-  
218 engagement of CD38 on tumor cells and CD3ε on T-cells, mediating T-cell activation and  
219 killing of tumor cells.

220 We next tested whether the cytotoxicity of ISB 1342 could be influenced by soluble  
221 CD38 (sCD38), which is found in MM patients at concentrations up to 2.8ng/ml in serum  
222 (23,24). At this concentration, no effect was observed on the cytotoxicity of ISB 1342 (**Figure**  
223 **2F**). MM patients undergoing treatment with TCE, often receive corticosteroids, such as  
224 dexamethasone, to treat cytokine-associated toxicities including CRS (25). Treatment with  
225 dexamethasone induced a significant reduction of ISB 1342 cytotoxicity, but no change in  
226 maximum killing (**Figure 2G**). In contrast, maximum cytokine release was reduced for TNF-α,  
227 IL-6 and IL-2 in the presence of dexamethasone (**Figure 2H**). Taken together these data  
228 support that ISB 1342-induced cytokine release may be manageable with dexamethasone,  
229 while maximum killing of tumor cells is sustained.

### 230 **ISB 1342 induces potent killing of MM cells with low sensitivity to daratumumab**

231 Nihof *et al.* show that the level of CD38 expression on patient MM cells is associated  
232 with response to daratumumab therapy (11). To explore the relative impact of CD38  
233 expression on ISB 1342 and daratumumab activities, four cell lines with different CD38  
234 expression levels (**Figure 3A**) were evaluated. KMS-12-BM and NCI-H929 resemble r/rMM  
235 patients with lower CD38 expression, while expression on RPMI-8226 and MOLP-8 is high.  
236 We noted reduced CDC and ADCP on KMS-12-BM and NCI-H929 compared to MOLP-8 with  
237 daratumumab (**Figure 3B, C**). However, similar ADCC levels were observed with all cell lines  
238 (**Figure 3D**). These observations indicate that KMS-12-BM and NCI-H929 indeed exhibit  
239 some resistance features of patient-derived MM cells with reduced sensitivity to  
240 daratumumab-mediated killing. With ISB 1342, similar cytotoxicity was seen for all three cell  
241 lines in a RDL assay (**Figure 3E**), suggesting that the activity of ISB 1342 does not depend on  
242 CD38 expression levels.

243 To evaluate the combined effect of these observations directly in a single assay, we  
244 developed a multiple mode of action killing assay (MMoAK), where ADCC, ADCP, CDC, and  
245 T-cell mediated cytotoxicity are enabled (**Figure 3F**). To achieve this, hPBMC were co-  
246 cultured with MM cells in 50% human serum as a source of complement, and interleukin-2  
247 (hIL-2) in order to facilitate NK cell functions (26). On KMS-12-BM, NCI-H929 and RPMI8226  
248 (CD38++++), we observed a higher cytotoxicity for ISB 1342 compared to daratumumab

249 (Figure 3F-H), notably with both a lower EC<sub>50</sub> in all cell lines tested and a higher maximal  
250 killing for NCI-H929 and RPMI8226. ISB 1342 was able to kill the three cell lines at similar  
251 levels, independently of CD38 expression, and also efficiently activated T-cells in this model  
252 (Figure 3G, Supplementary Figure 3A, B).

253 Given the utilization of daratumumab in early lines of therapy, we then aimed to  
254 determine whether co- or pre-treatment with this drug could influence cytotoxicity of ISB 1342  
255 *in vitro*. In a concomitant MMoAK model (Figure 4A), daratumumab (at pre-determined  
256 EC<sub>50</sub>=0.2nM) did not influence cytotoxicity, maximum killing and T-cell activation/degranulation  
257 of ISB 1342 (Figure 4B, C). In the sequential treatment model (Figure 4D), ISB 1342 potency  
258 and T-cell activation/degranulation were also unchanged before and after pre-treatment with  
259 daratumumab (Figure 4E, F). In both models, the percentage of CD8<sup>+</sup>CD38<sup>+</sup> T-cells was  
260 higher in presence of ISB 1342 but not with daratumumab only, whereas the absolute  
261 numbers were reduced with ISB 1342 in the sequential model only (Supplementary Figure  
262 3C). These results suggest that at 72 hours, in this model, T-cell viability starts reducing upon  
263 activation by ISB 1342 whereas daratumumab is not affecting T-cells. Thus, the use of  
264 ISB 1342 in daratumumab pre-treated patients following a limited wash-out period should be  
265 possible since residual daratumumab should not interfere with ISB 1342 efficacy.

### 266 **ISB 1342 induces killing of primary MM cells from patients**

267 We evaluated the activity of ISB 1342 and daratumumab in samples from patients not  
268 previously treated with daratumumab (dara-naïve), including smoldering MM, newly diagnosed  
269 MM, newly diagnosed Plasma Cell Leukemia (PCL) and patient at relapse versus patients  
270 previously treated with daratumumab (dara-exposed), including heavily treated  
271 relapsed/refractory patients (Supplementary Table 3). Both daratumumab and ISB 1342  
272 achieved efficient killing of dara-naïve MM cells, while only ISB 1342 was able to achieve  
273 efficient killing of dara-exposed MM cells or a single PCL sample (with an EC<sub>50</sub> of 77.7pM)  
274 (Figure 5A-D). Viability of MM cells was similar at baseline and after 18-24h in culture  
275 (Supplementary Figure 4A, B). Dara-exposed patients had significantly lower CD8<sup>+</sup>T-cells,  
276 NK cells and monocytes/macrophages to MM cells ratio than dara-naïve patients (Figure 5E;  
277 Supplementary Figure 4C-E). Thus, the activity of daratumumab correlated with the ratios of  
278 NK cells and monocytes/macrophages to MM cells whereas we observed no correlation  
279 between the CD8<sup>+</sup>T-cell:MM cell ratio and ISB 1342 cytotoxic activity (Supplementary Figure  
280 4F-H). Counts of CD8<sup>+</sup>CD38<sup>+</sup>T-cells were slightly higher in the presence of ISB 1342  
281 compared to daratumumab and counts of NK cells and monocytes/macrophages were not  
282 affected by daratumumab or ISB 1342 treatments (Supplementary Figure 5A-C), suggesting  
283 an absence of on-target off-tumor killing and T-cell fratricide under these conditions. ISB 1342  
284 was also able to efficiently induce cytotoxicity towards tumor cells from patients with  
285 Waldenstrom macroglobulinemia and T-cell acute lymphoblastic leukemia (T-ALL) both  
286 expressing low levels of CD38 (Supplementary Figure 5D, E). Importantly, all patient  
287 samples, irrespective of the group considered, responded to ISB 1342 and showed an  
288 increased fraction of activated CD4<sup>+</sup> and CD8<sup>+</sup>T-cells as measured by the increase in CD25<sup>+</sup>  
289 and CD69<sup>+</sup>T-cells (Figure 5F, G; Supplementary Figure 5F).

### 290 **ISB 1342 exhibits anti-tumor activity *in vivo***

291 We evaluated the anti-tumor activity of ISB 1342 in two mouse models. NSG mice  
292 were engrafted s.c. with KMS-12-BM and injected i.p. with hPBMC (Figure 6A). In this model,  
293 ISB 1342 was able to control tumor growth by day 12, whereas we detected no tumor  
294 regression with daratumumab compared to vehicle control (Figure 6B). Additionally, an  
295 increase in the number of tumor-infiltrating hCD45<sup>+</sup> cells and T-cell were detected specifically  
296 in mice treated with ISB 1342 on day 7 (Figure 6C, D), as expected from TCE mechanism of  
297 action (27–30). We also observed a substantial increase in CD25<sup>+</sup> and/or CD69<sup>+</sup> tumor  
298 infiltrating T-cells reflecting their activated status (Figure 6E). A second model expressing  
299 very high levels of CD38 (Daudi) showed similar tumor control for ISB 1342. In this model,  
300 daratumumab was able to induce partial control of tumor growth and no tumor control was  
301 detected with the CD3 only control (Supplementary Figure 6). These *in vivo* results show



302 that ISB 1342 tumor cell killing is triggered *in vivo* independently of CD38 expression levels  
303 unlike daratumumab.

#### 304 **ISB 1342 shows an adequate profile in PK/PD and safety studies**

305 Cancer immunotherapies are often associated with toxicity and tolerability events generally  
306 caused by elevated cytokine release (31). Since CD38 is expressed on human immune cells,  
307 in particular on NK, B and myeloid cells at similar levels to KMS-12-BM MM cells  
308 (**Supplementary Figure 7A**), we therefore examined the ability of ISB 1342 to influence  
309 peripheral immune cells in a high-density PBMC assay (HD-PBMC). Indeed, this assay has  
310 been previously reported to increase the sensitivity to T-cell responses and is commonly used  
311 for evaluation of toxicity of TCE (32,33). In this assay, we did not observe any depletion of  
312 peripheral leukocytes *in vitro* compared to the untreated condition (**Supplementary Figure**  
313 **7B**). In addition, we found that less ISB 1342 bound to CD38 on RBC compared to  
314 daratumumab and observed no sensitization of RBC to hemagglutination compared to positive  
315 controls (**Supplementary Figure 7C, D**). We then investigated the PD changes in peripheral  
316 leukocyte populations, cytokines levels, and ISB 1342 PK using cynomolgus monkeys injected  
317 i.v. with consecutive doses of ISB 1342. In cynomolgus monkeys, expression of CD38 on  
318 peripheral leukocytes was observed at a significantly higher level on B-cells compared to  
319 monocytes, CD4<sup>+</sup> and CD8<sup>+</sup>T-cells (**Figure 7A**); and resulted in detectable levels of ISB 1342  
320 binding to B-cells (**Figure 7B**). One male and one female cynomolgus monkeys received  
321 ISB 1342 on day 1 (1µg/kg), day 29 (100µg/kg) and day 57 (1000µg/kg). ISB 1342 induced an  
322 initial reduction in B-cell numbers following each dose compared to baseline counts, which  
323 rebounded over time but not to baseline levels (**Figure 7C**). A similar profile was observed for  
324 monocytes, however levels returned to baseline after the first two doses (**Figure 7D**). Such a  
325 transient reduction in peripheral populations could reflect re-distribution of these cells rather  
326 than depletion. The number of CD4<sup>+</sup> and particularly of CD8<sup>+</sup>T-cells, including activated  
327 CD69<sup>+</sup>T-cells, substantially increased above the baseline in the circulation of animals  
328 administrated with 100µg/kg, indicating T-cell activation and expansion in the periphery  
329 (**Figure 7E-H**). A substantial dose-dependent elevation in serum cytokines such as IFN-γ was  
330 also observed (**Figure 7I**). ISB 1342 serum concentration profiles followed a bi-phasic  
331 disposition with a short distribution phase, followed by a longer terminal elimination phase.  
332 The terminal elimination half-life, not confounded by anti-drug antibodies (ADA) was  
333 approximately 4.75 days (**Figure 7J**). The reduced half-life of ISB 1342 observed at  
334 1000µg/kg may be a reflection of ADA appearance at this dose (**Table 1**). These observations  
335 were confirmed with the single dose study at 100µg/kg (**Supplementary Figure 8,**  
336 **Supplementary Table 4**). Overall, in this study, the dose-limiting toxicity (DLT) was  
337 considered to be the CRS and the maximum tolerated dose (MTD) was 100µg/kg using i.v.  
338 route. ISB 1342 therefore revealed the most common DLT of TCE and adequate PD and PK  
339 profiles to highlight a potential therapeutic window.

#### 340 **Discussion**

341 Advancement in the therapy of MM has substantially improved with the introduction of  
342 CD38-targeted monoclonal antibodies (34,35). Daratumumab, the first approved CD38-  
343 targeting monoclonal antibody, has shown significant efficacy in MM (36) both as a single  
344 therapy (37) and as a combination (7,38,39). Despite these results, most patients relapse and  
345 become refractory to daratumumab. Though efficacious, isatuximab, the second approved  
346 anti-CD38 monoclonal antibody (40) cannot be used as salvage therapy, as it targets CD38  
347 with a similar mode of action, and therefore will be unable to overcome escape mechanisms of  
348 daratumumab treatment (10). The use of TCE like ISB 1342, could instead be an option for  
349 these patients. The data presented here show that ISB 1342 exhibits more potent cytotoxicity  
350 than daratumumab when tested on MM cell lines with varying CD38 expression and lower  
351 sensitivity to daratumumab, on patient BMA or *in vivo*. Importantly, the potency of ISB 1342  
352 was not affected when combined with daratumumab or in the presence of soluble CD38.

353 The concept of a CD38xCD3 TCE (12,41) is explored in two other disclosed programs:  
354 1) AMG424, (Xencor and Amgen) (23); and 2) CD38xCD28xCD3 tri-specific antibody (Sanofi)



355 (42). AMG424 showed good killing activity both *in vitro* and *in vivo*. This TCE presents a  
356 higher affinity to CD3 (15nM in SPR) than ISB 1342, a similar affinity to CD38 (7.7nM). Unlike  
357 the observations we describe here for ISB 1342, AMG424 seems to induce significant  
358 depletion of peripheral immune cell populations both *in vitro* and *in vivo* (23). The sponsor is  
359 currently testing this candidate in the context of T-ALL and Acute Myeloid Leukemia (AML)  
360 (NCT05038644). The tri-specific CD38xCD28xCD3 may enhance the potency and persistence  
361 of T-cells by providing costimulatory signals. The reported *in vitro/in vivo* results warranted a  
362 clinical trial (NCT04401020). Another CD3xCD38 TCE was described recently and is not  
363 currently in clinical development (43). The activity of this TCE seems to depend on the  
364 expression levels of CD38 but did not induce depletion of peripheral immune cells. Despite  
365 these advantages in terms of absence of on-target off-tumor activity and the lack of  
366 dependency on CD38 levels of ISB 1342 compared to published CD3xCD38 TCEs, direct  
367 comparison of ISB 1342 to these based on published data is not straightforward without a  
368 side-by-side investigation *in vitro* and *in vivo*.

369 ISB 1342 was designed with the advantage that it targets a different epitope from  
370 daratumumab to avoid long wash-out periods. Indeed, a minimal washout period of 3-6  
371 months is usually necessary with other anti-CD38 therapies targeting overlapping epitopes or  
372 with daratumumab re-treatments due to the decrease in CD38 expression and potential  
373 competition (11). This delay in treating patients can be problematic and favor the occurrence  
374 of resistant clones (44). The key resistance mechanisms described for daratumumab include:  
375 down-regulation of CD38 (11,45), increased expression of complement inhibitors (CD46,  
376 CD55, CD59) limiting CDC (11), and up-regulation of CD47, which interferes with  
377 phagocytosis (10). Here, we modelled lower sensitivity to daratumumab using cell lines  
378 displaying some of these features, and patient samples post-daratumumab therapy. In  
379 agreement with the literature, the activity of daratumumab was also influenced by the ratio of  
380 effector to MM cells in patient samples (46). However, the data presented here show that the  
381 mode of action of ISB 1342 is mediated by T-cells, making it insensitive to the features of  
382 daratumumab resistance such as up-regulation of complement inhibitors proteins or to CD47.  
383 We also show that ISB 1342 can efficiently kill MM cells regardless of CD38 expression, T-cell  
384 to MM cell ratio and recent treatment with daratumumab, providing a rationale for using  
385 ISB 1342 in patients relapsing following daratumumab treatment.

386 MM patients showing a T-cell exhaustion profile are more likely to develop progressive  
387 disease compared to those with less exhaustion (47). Indeed, patients undergoing autologous  
388 stem cell transplantation (ASCT) plus lenalidomide as maintenance therapy, exhibit signs of T-  
389 cell exhaustion before relapsing (48). Similar pre-clinical findings were observed in the context  
390 of TCEs. In fact, when blinatumomab was continuously administered for 28 days, T-cells  
391 developed an exhausted phenotype and could not kill target cells; while with intermittent  
392 dosing, T-cells retained their memory TCF1<sup>+</sup> phenotype and could control tumor growth in the  
393 presence of blinatumomab (49). The quality of T-cells defines the activity of TCEs. Hence,  
394 some bispecific antibodies are displaying potent cytotoxicity on primary MM mostly in the  
395 presence of healthy T-cells (50), but showing reduced activity when exhaustion was detected  
396 (51). Several preclinical studies have also shown that a combination with an anti-PD-1  
397 antibody can enhance tumor control by a TCE (52,53). More studies are required to  
398 understand how treatment with ISB 1342 will influence T-cell phenotype in the long-term,  
399 nevertheless recent studies demonstrate that patients may benefit from a sequence of two  
400 different TCE therapies (54). With the recent approval of teclistamab (BCMA TCE, Janssen  
401 Biotech) in r/rMM patients, these findings are key to support the development of ISB 1342 in  
402 the clinic, which is likely to be administered to patients previously treated with other TCEs.  
403 Despite the development and approval of efficient BCMA-targeted-therapies, studies have  
404 characterized antigen loss, biallelic deletion on chromosome 16 encompassing the BCMA  
405 locus, point mutations, shedding and anti-drug antibodies as mechanisms of resistance to  
406 anti-BCMA therapies (55–59). Therefore, it remains essential to monitor biomarkers indicative  
407 of these mechanisms and to develop TCE against other validated antigens such as CD38, to  
408 guarantee a range of therapeutic options for patients depending on the features associated  
409 with their relapse.

410 TCE therapies are associated with a systemic cytokine release, which is a product of  
411 their mode of action. However, this functional cytokine release can progress into CRS, which  
412 usually requires intensive care (60–63). Mitigating CRS, while maintaining potential for a  
413 beneficial anti-tumor response, is key for TCE therapies, including ISB 1342 (64). However,  
414 risk factors such as tumor burden and co-morbidities often associated with severe CRS should  
415 be considered carefully. Corticosteroid treatment is often used to mitigate CRS in the clinic,  
416 and data shown here demonstrate that use of dexamethasone does not strongly affect  
417 ISB 1342 cytotoxicity and led to a significant reduction of CRS-associated cytokines *in vitro*.  
418 Using a priming dose or step-up dosing regimen could also mitigate CRS. Indeed, in the  
419 teclistamab trial, 40 patients received 1500µg/kg, after 60µg/kg and 300µg/kg step-up doses,  
420 and no dose-limiting toxicities were observed (65). Lastly, the use of monoclonal antibodies  
421 before injection of a TCE to reduce peripheral tumor burden, could also mitigate CRS. For  
422 instance, such an approach was tested for glofitamab (27,66), an anti-CD20 TCE, which was  
423 administered after one dose of obinutuzumab (anti-CD20 antibody, Roche). This strategy  
424 resulted in a manageable CRS while preserving strong potency (67). Whether such  
425 approaches could be used for ISB 1342 remains to be clarified in clinical trials. Although,  
426 preclinical models can assess cytokine release in response to TCE, the field lacks models that  
427 accurately predict the occurrence and intensity of CRS in humans. Thus, more studies are  
428 warranted to fully assess CRS and to design better options to efficiently mitigate it, such as  
429 JAK, mTOR and Src/lck inhibitors currently under investigation (68).

430 In conclusion, ISB 1342 is a potent TCE that may be used immediately after or  
431 concomitantly with daratumumab to circumvent escape via CD38 downregulation and other  
432 mechanisms described previously. Our study suggests that ISB 1342 could elicit anti-tumor  
433 clinical responses in patients with r/rMM who have previously received daratumumab therapy.  
434 Based on this encouraging preclinical data and the differentiation from other CD38-targeting  
435 therapeutics used in the clinic, a phase I clinical trial of ISB 1342 in r/rMM patients is ongoing  
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456 B.P, C.E, P.S, E.N, A.L, T.M, A.C, D.P, L.C, J.M, J. B and M.C contributed to assay design,  
457 data acquisition, interpretation and analysis. Z.K, E.M, C.K, contributed to acquisition of data,  
458 and analysis, interpretation of patient samples experiments. T.M, C.P-D, P.M, C.M.E, J.R.E,  
459 A.M, G.B contributed to the acquisition of patient samples and discussion of data  
460 interpretation. G.G, V.U and V.M supervised, analysed and interpreted the cynomolgus

461 monkey studies. B.P, M.L.M, A.D, M.Pi, M-A.D, A.S, S.B, E.Z, M.P, M.C contributed to project  
462 and resources administration, resources and supervision. B.P, P.S, C.E, A.D, S.B, A.S, M.Pi,  
463 MA.D, E.Z, reviewed and edited the manuscript. B.P, C.E, M.P and M.C wrote, reviewed and  
464 edited the manuscript.

#### 465 **Conflict of interest Statement**

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683

## 684 Tables

685

686 **Table 1: Summary PK Parameters of ISB 1342 in Cynomolgus Monkeys: consecutive**  
687 **doses study**

Dose level (µg/kg)	C <sub>0</sub> (ng/mL)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)	AUC <sub>0-t</sub> (hr*ng/mL)	t <sub>last</sub> (hr)	AUC <sub>0-∞</sub> (hr*ng/mL)	t <sub>1/2</sub> (hr)	ADA detected
1	NE	0.44	4.0	8.8	36	NE	NE	None
100	206	131	4.0	4589	252	4863	58.2 <sup>a</sup>	Day 43
1000	462	165.95	4.0	2193	16	4355 <sup>a</sup>	2.8	Day 43

688

<sup>a</sup> N=1

689 AUC<sub>0-∞</sub> = area under the (serum) concentration time curve extrapolated out to infinity; AUC<sub>0-t</sub> = area  
690 under the plasma concentration-time curve from time zero to time t; C<sub>0</sub> = initial concentration; NE: Not  
691 Estimable; t<sub>1/2</sub> = terminal elimination half-life; t<sub>last</sub> = time of the last measurable (positive) concentration;  
692 T<sub>max</sub> = Time to reach maximum serum concentration following drug administration. ADA = Anti-Drug  
693 Antibodies.

## 694 Figure Legends

695

696 **Figure 1. ISB 1342 properties and binding.** (A) Schematic 3D representation of ISB 1342, a  
697 bispecific antibody based on the BEAT® technology with a Fab targeting CD38, an scFv  
698 targeting CD3ε and Fc carrying the LALA (L234A, L235A) mutation. The model was generated  
699 using the BioLuminate software (Schrödinger, USA). (B) Mean ± SD of K<sub>D</sub> determined either  
700 on CD38<sup>+</sup> T-cells (n=12 donors in 3 independent experiments) and MM cells lines, KMS-12-  
701 BM (20 measures from n=14 independent experiments), NCI-H929 (12 measures from n=5  
702 independent experiments) and MOLP-8 (9 measures from n=3 independent experiments), or  
703 recombinant human proteins CD3εδ (n=5 independent experiments) and CD38 (n=3  
704 independent experiments) (C) Representative binding of ISB 1342 on CD38<sup>+</sup> human healthy T-  
705 cells (mean ± SD of 4 donors) and KMS-12-BM MM cell line (one representative measurement  
706 from one experiment). (D) Epitope mapping of daratumumab and ISB 1342 on CD38.  
707 Residues in dark red represent the CD38 residues in a 4 Å radius from the daratumumab

708 chain in the crystal structure 7DHA. Linear peptides mapping by SPR as well as site-directed  
709 mutagenesis were used to determine the binding epitope of ISB 1342 on CD38, shown in  
710 green on the CD38 chain of crystal structure 7DHA (in beige color). (E) ISB 1342 does not  
711 compete with daratumumab and can engage CD38 prebound by daratumumab. Biotinylated  
712 human CD38 protein was loaded on a streptavidin SA Biosensor. Biosensor with immobilized  
713 CD38 was then dipped in a solution of daratumumab in kinetics buffer to reach saturation of  
714 the surface. Then, saturated biosensor was dipped into a pre-mixed solution of daratumumab  
715 + ISB 1342 at equimolar concentrations (pink curve) or daratumumab only (black curve). Plots  
716 show binding to the sensor tip as a wavelength shift (Response, in nm; Y axis) vs. time (in  
717 sec; X axis).

718 **Figure 2: ISB1342 induces killing of MM cell lines *in vitro* via T-cell engagement.** (A)  
719 Representative confocal image of ISB 1342 (white) at the synapse between T-cell (green) and  
720 KMS-12-BM MM cell line (blue) acquired with Zeiss LSM 800 inverted confocal microscope,  
721 magnification 40X. (B-F) Cytotoxicity of KMS-12-BM MM cell line (B, F) and T-cell activation  
722 (C), proliferation (D) and degranulation (E) after treatment with ISB 1342 or control molecules  
723 in presence (F) or absence (B-E) of soluble CD38 (sCD38) and healthy PBMC (E:T 5:1) for 72  
724 hours. Data represent mean  $\pm$  SD from 3 PBMC donors performed in 2 independent  
725 experiments (B-E) or mean  $\pm$  SD of EC<sub>50</sub> from 3 donors that were compared to the condition  
726 without sCD38 using a one-way ANOVA followed by a Dunnett's post-hoc comparison (F), ns:  
727 not significant. (G-H) Cytotoxicity of RPMI8226 MM cell line (G) and cytokine release (H) in  
728 presence of ISB 1342  $\pm$  Dexamethasone and healthy PBMC (E:T 10:1) for 48 hours. Data  
729 represent mean  $\pm$  SD of EC<sub>50</sub> compared using a paired t-test (G) and mean  $\pm$  SD at the  
730 maximum dose of ISB 1342 tested compared using paired t-test (H) from 6 PBMC donors and  
731 performed in 2 independent experiments; \*\* p<0.01, \*\*\* p<0.001.

732 **Figure 3: ISB 1342 induces potent killing of cell lines showing a reduced sensitivity to**  
733 **daratumumab.** (A) Absolute number of specific Antibody Bound per Cell (sABC) indicating  
734 the relative CD38 density on MM cell lines. Data represent mean  $\pm$  SD and compared using a  
735 one-way ANOVA followed by a Kruskal-Wallis post-hoc comparison using KMS-12-BM as  
736 reference. (B-D) Cytotoxicity of MM cell lines in presence of daratumumab in CDC (B), ADCP  
737 (C) and ADCC (D) assays. Data represent mean  $\pm$  SD of maximum response from 4 donors in  
738 2 independent experiments (B), from up to 10 donors in 3 independent experiments (C) and  
739 from 5 donors in 3 independent experiments (D) that were compared using a one-way ANOVA  
740 followed by a Tukey post-hoc comparison. (E) Cytotoxicity of MM cell lines in presence of  
741 ISB 1342 and healthy PBMC (E:T 5:1) for 72 hours in a RDL assay. Data represent mean  $\pm$   
742 SD of EC<sub>50</sub> from 6 PBMC donors, compared using a one-way ANOVA followed by Dunnett's  
743 post-hoc comparison to KMS-12-BM. (F-H) Schematic representation depicting the Multiple  
744 Mode of Action (MoA) Killing *in vitro* assay (MMoAK) including four MoA: T-cell RDL, ADCC,  
745 ADCP and CDC (F). Cytotoxicity of various MM cell lines in presence of ISB 1342 or  
746 daratumumab, healthy PBMC (E:T 5:1), normal human serum and rhIL-2 for 48 hours in a  
747 MMoAK assay. Data represent mean  $\pm$  SD of duplicates from one representative donor using  
748 non-linear regression analysis (F), mean  $\pm$  SD of EC<sub>50</sub> from up to 10 PBMC donors per  
749 treatment and cell line from 6 independent experiments that were compared using a two-way  
750 ANOVA and Sidak's post-test (G-H); \*p<0.05, \*\*p<0.01, \*\*\*p<0.0001, \*\*\*\*p<0.00001.

751 **Figure 4: ISB 1342 *in vitro* potency is not impacted by the concomitant or pre-treatment**  
752 **with daratumumab.** (A) Schematic representation depicting the MMoAK assay with  
753 concomitant treatment with ISB 1342 and daratumumab. (B, C) Cytotoxicity of NCI-H929 MM  
754 cell line (B) and CD8<sup>+</sup> T-cell response (C) following treatment with increasing doses of ISB  
755 1342 and a fixed dose daratumumab or monoclonal antibody control (mAb) in presence of  
756 healthy PBMC (E:T 5:1), normal human serum and rhIL-2 for 48 hours. Data represent mean  
757  $\pm$  SD of EC<sub>50</sub> or the maximum response from 12 donors in 3 independent experiments that  
758 were compared using an unpaired T-test. (D) Schematic representation depicting the MMoAK  
759 assay of pre-treatment with daratumumab followed by ISB 1342. (E,F) Cytotoxicity of NCI-  
760 H929 MM cell line (E) and CD8<sup>+</sup> T-cell response (F) in presence of healthy PBMC (E:T 5:1),

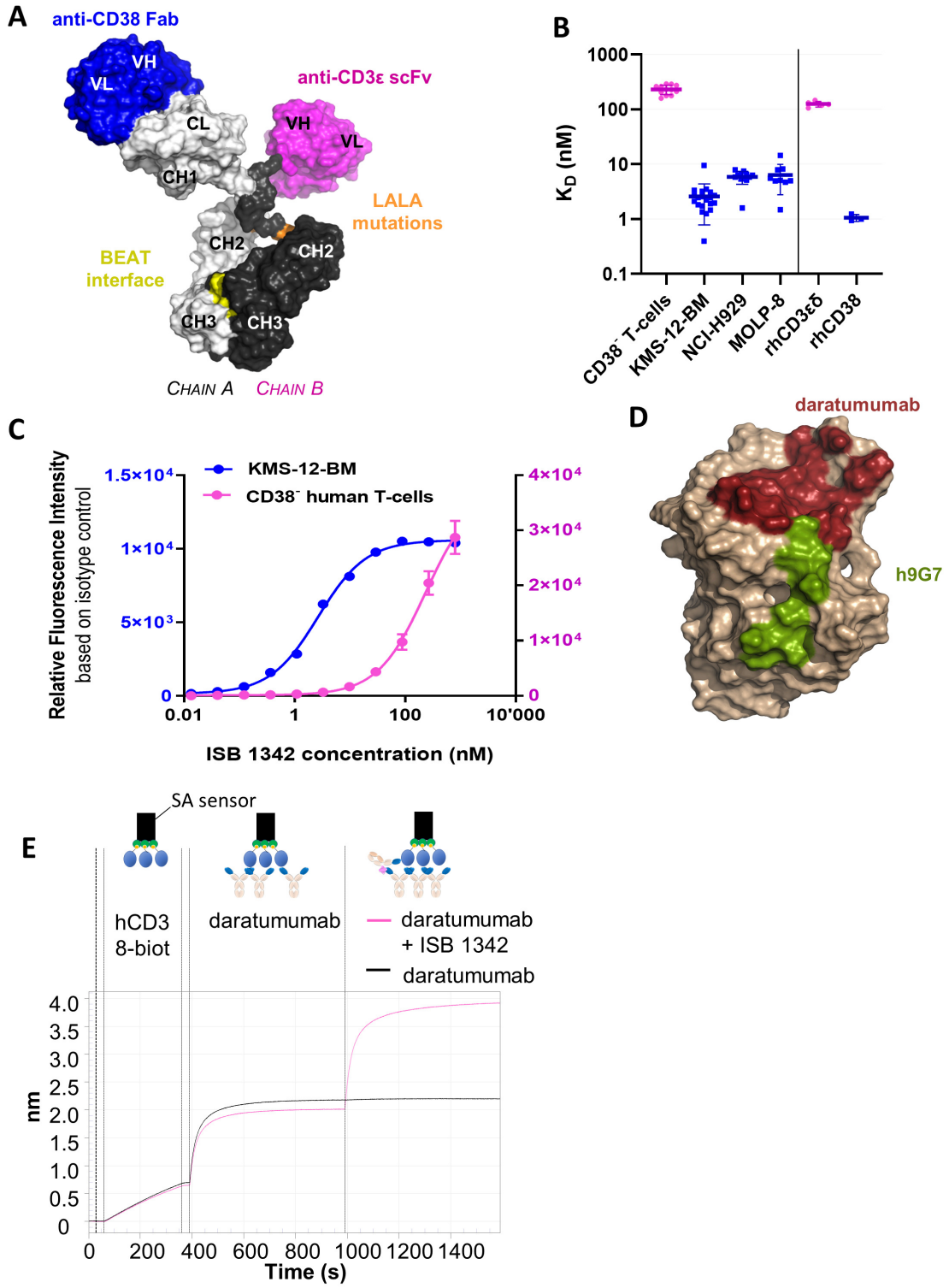
761 normal human serum and rhIL-2 with increasing doses of ISB 1342 for 48 hours after pre-  
762 treatment with a fix dose daratumumab or monoclonal antibody control for 24h. Data represent  
763 mean  $\pm$  SD of EC<sub>50</sub> or the maximum response from up to 9 donors in 3 independent  
764 experiments that were compared using an unpaired T-test; ns: not significant.

765 **Figure 5: ISB 1342 maintains high potency to kill tumour cells from patients previously**  
766 **treated with daratumumab.** (A-C) Representative cytotoxicity curves of CD138<sup>+</sup> MM cells by  
767 ISB 1342 and daratumumab at 18-24h in samples from patients not previously treated with  
768 daratumumab (dara-naïve, patient sample 4) (A), previously treated with daratumumab (dara-  
769 exposed, patient sample 15) (B) and dara-naïve plasma cell leukemia (PCL, patient sample 1)  
770 (C). Data are mean (A, B) or mean  $\pm$  SEM of replicates (C) analysed using non-linear  
771 regression analysis. (D) Maximal cytotoxicity of CD138<sup>+</sup> tumor cells with ISB 1342 (10-100nM)  
772 or daratumumab (100nM) in samples from dara-naïve patients (filled symbols) versus dara-  
773 exposed (open symbols). Dots represent individual samples and data are mean  $\pm$  SD  
774 compared using one-way ANOVA followed by Dunnett's multiple comparison analysis to  
775 daratumumab on dara-naïve samples. (E) Radar plot of average values for CD8<sup>+</sup>T-cells, NK  
776 cells and Monocytes/Macrophages ratio to CD138<sup>+</sup> MM cells in samples from dara-naïve  
777 patients (blue) versus dara-exposed ones (pink). (F) Representative CD8<sup>+</sup> T-cell activation  
778 with ISB 1342 and isotype control measured by flow cytometry with expression of CD69 (blue)  
779 and CD25 (pink) in PCL. Data are mean  $\pm$  SEM of replicates analysed using non-linear  
780 regression analysis. (G) Maximum T-cell activation (CD25 and CD69) and degranulation  
781 (CD107a) on dara-naïve versus dara-exposed patient samples with ISB 1342. Data are mean  
782  $\pm$  SD compared using unpaired t-test.

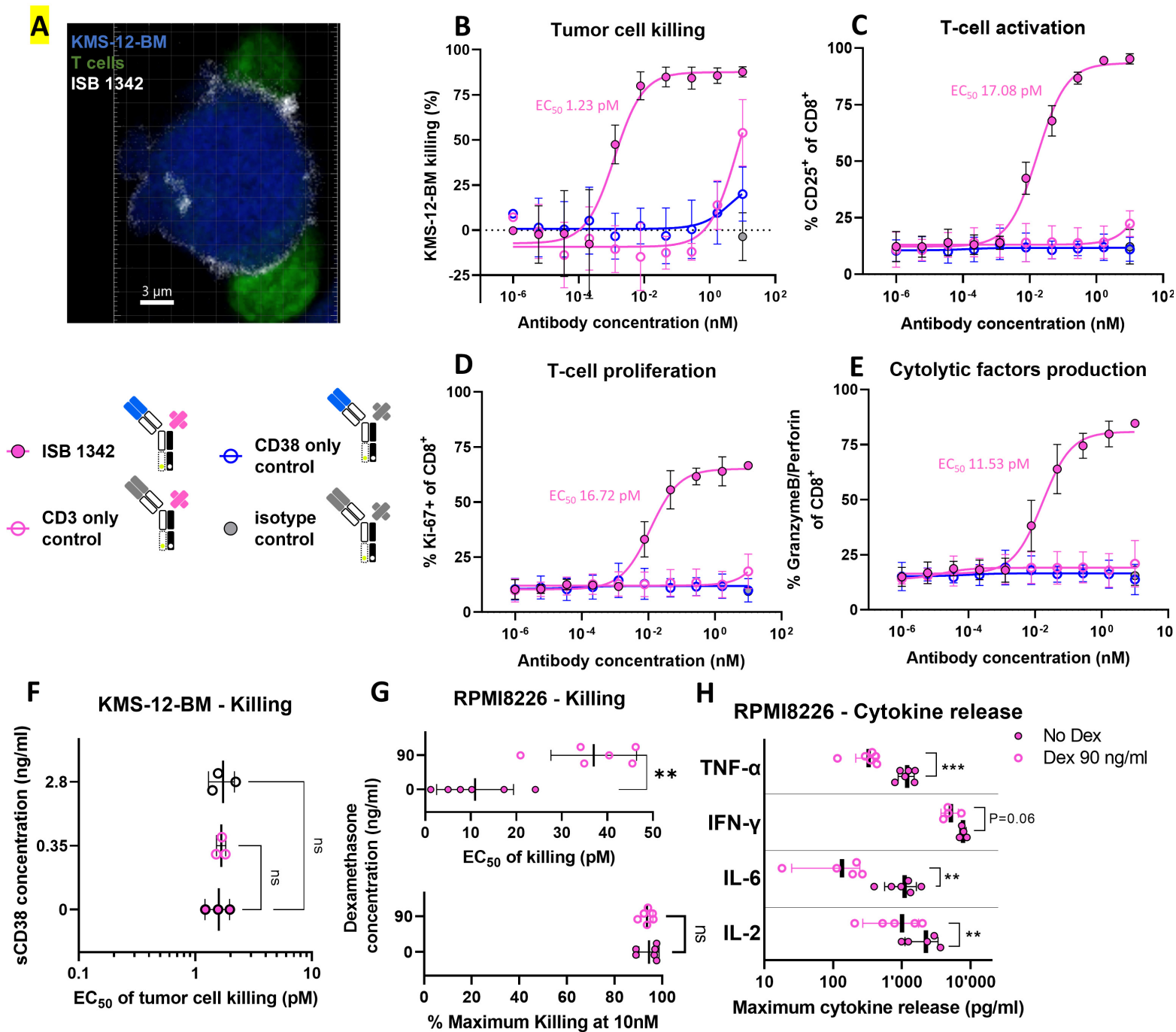
783 **Figure 6: ISB 1342 controlled tumor growth *in vivo* in the KMS-12-BM xenograft**  
784 **hPBMC-transferred NSG mouse model.** (A-B) Experimental design (A) and measurement of  
785 tumor growth (B) in the KMS-12-BM s.c. xenograft human PBMC (hPBMC)-transferred NSG  
786 mouse model. *In vivo* activity was followed for ISB 1342 at 0.5 mg/Kg injected i.v. once per  
787 week and daratumumab at 16 mg/Kg injected i.v. twice per week, both for three weeks with 8  
788 mice per group. Data are mean mm<sup>3</sup>  $\pm$  SD determined by caliper measurements. Data were  
789 compared for both models using two-way ANOVA followed by Tukey's post-hoc comparison. \*  
790 is showing significant differences between ISB 1342 and vehicle control; # is showing  
791 differences between daratumumab and ISB 1342. (C-D) Infiltration of hCD45<sup>+</sup> cells (defined  
792 as live hCD45<sup>+</sup>mCD45<sup>-</sup>) (C) and T-cells (hTCR $\alpha\beta$ <sup>+</sup>CD14<sup>-</sup>CD19<sup>-</sup>CD56<sup>-</sup>CD45<sup>+</sup>) (D) in tumors of  
793 KMS-12-BM xenografted mice after vehicle, ISB1342 or daratumumab treatments. Data are  
794 mean  $\pm$  SD for 5 mice compared using one-way ANOVA followed by Dunnett's post-hoc test to  
795 ISB 1342. (E) Representative dot plots showing activation profile (CD25 and CD69  
796 expression) on tumor-infiltrating T-cell activation in vehicle, daratumumab and ISB 1342-  
797 treated mice. (F) CD38 expression on MM cells in tumors (KMS-12-BM model). Data are  
798 mean  $\pm$  SD compared using one-way ANOVA followed by Tukey's post-hoc test; \*p $\leq$ 0.05.

799 **Figure 7: Impact of ISB 1342 on circulating leukocytes and systemic soluble factors in**  
800 **cynomolgus monkeys.** (A) Expression profile of CD38 on leukocyte populations from  
801 cynomolgus monkeys. Dots represent data the relative fluorescence intensity (RFI) from each  
802 measurement and bars represent mean  $\pm$  SD from 4 animals. Data were compared using a  
803 one-way ANOVA followed by Dunnett's post-hoc comparison, \*p $\leq$ 0.05. (B) Representative  
804 binding of ISB 1342 or isotype control on cynomolgus monkey B-cells. (C-H) Cynomolgus  
805 monkeys (1 male and 1 female) were injected with 3 consecutives doses of ISB 1342 i.v. (1,  
806 100 and 1000  $\mu$ g/kg) at day 1, 29 and 57 respectively. Levels of peripheral B-cells (C),  
807 monocytes (D), CD8<sup>+</sup> T-cells (E), activated CD8<sup>+</sup> CD69<sup>+</sup> T-cells (F), CD4<sup>+</sup> T-cells (G) and  
808 activated CD4<sup>+</sup> CD69<sup>+</sup> T-cells (H) were measured using flow cytometry. Data is mean  $\pm$  SD of  
809 10<sup>3</sup> counts/ $\mu$ l normalized to baseline counts for two animals. (I,J) Levels of circulating IFN- $\gamma$  (I)  
810 and ISB 1342 (J) were measured using ELISA. Data represent levels per animal and LLOQ is  
811 the lower limit of quantification for the assay.

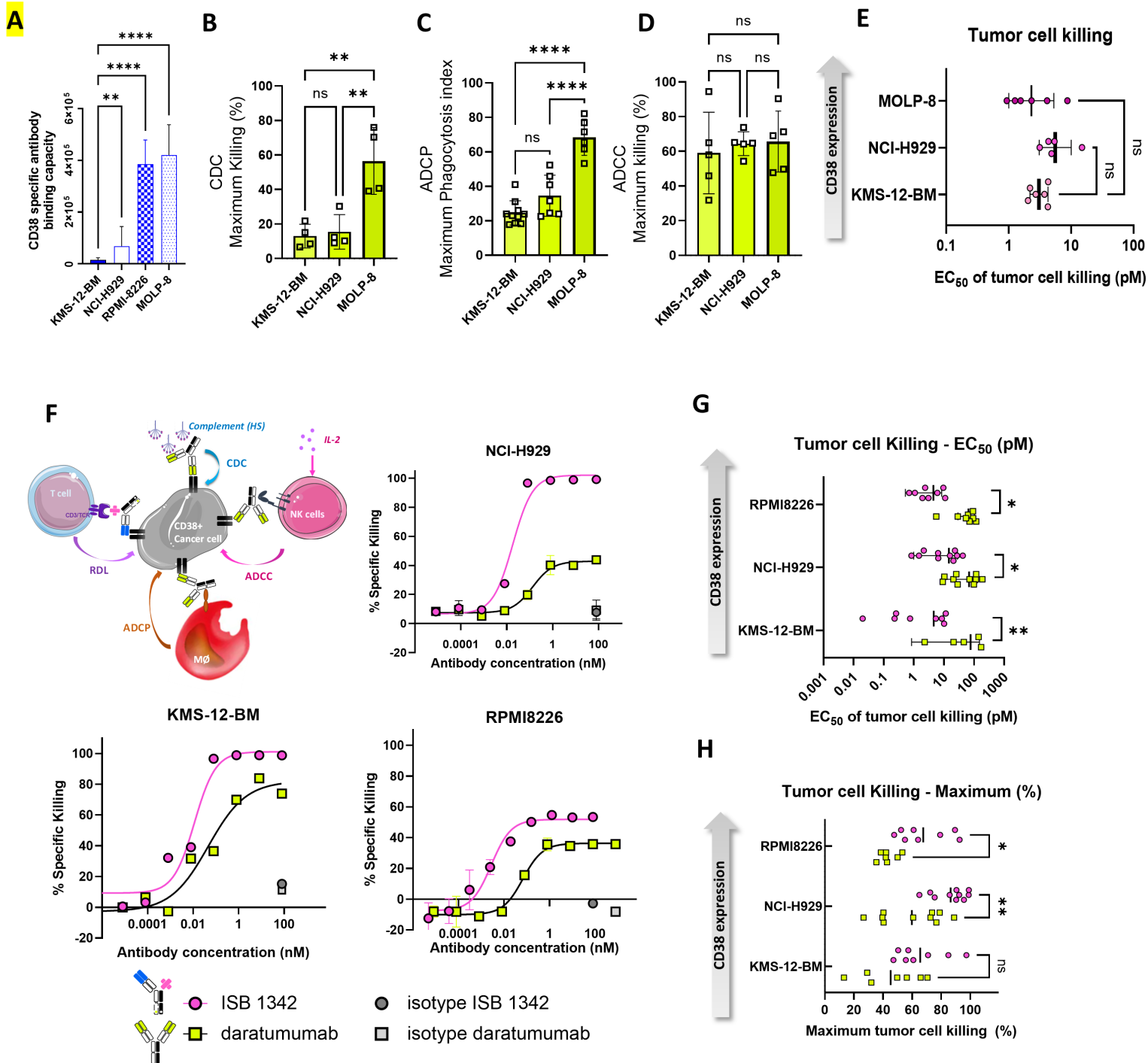
# Figure 1



# Figure 2

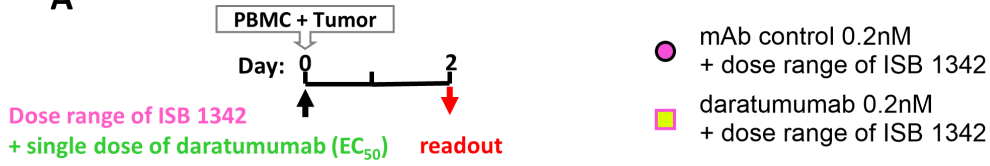


# Figure 3

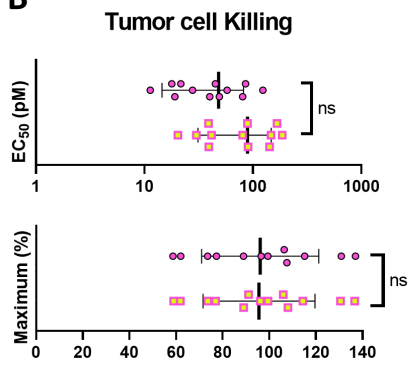


# Figure 4

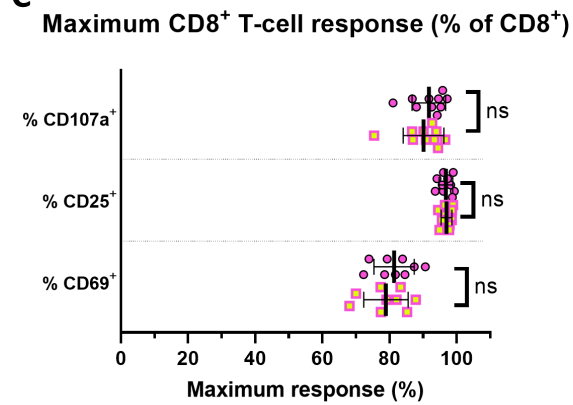
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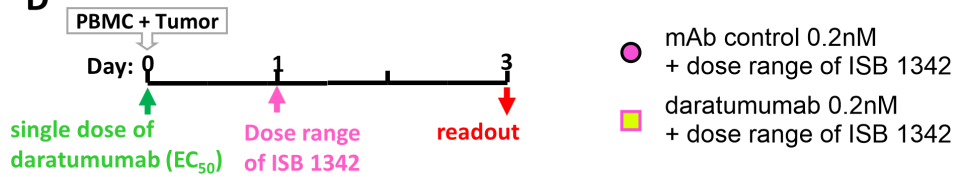
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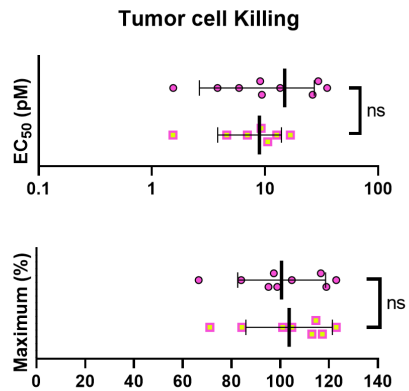
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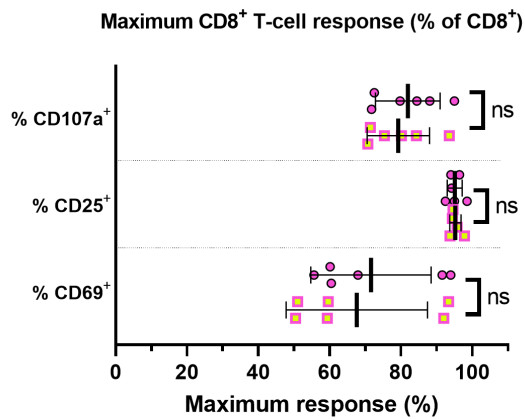
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**E**



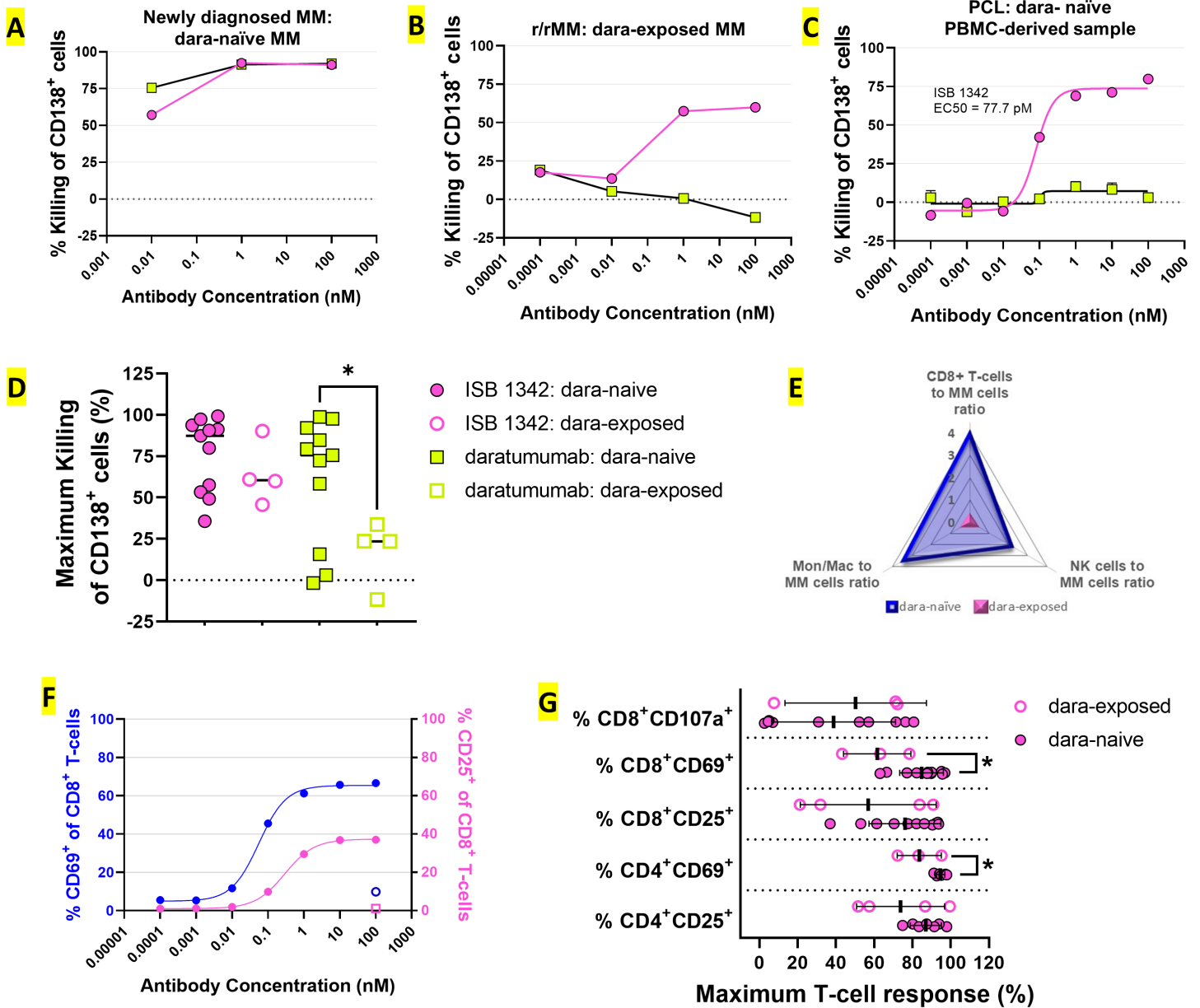
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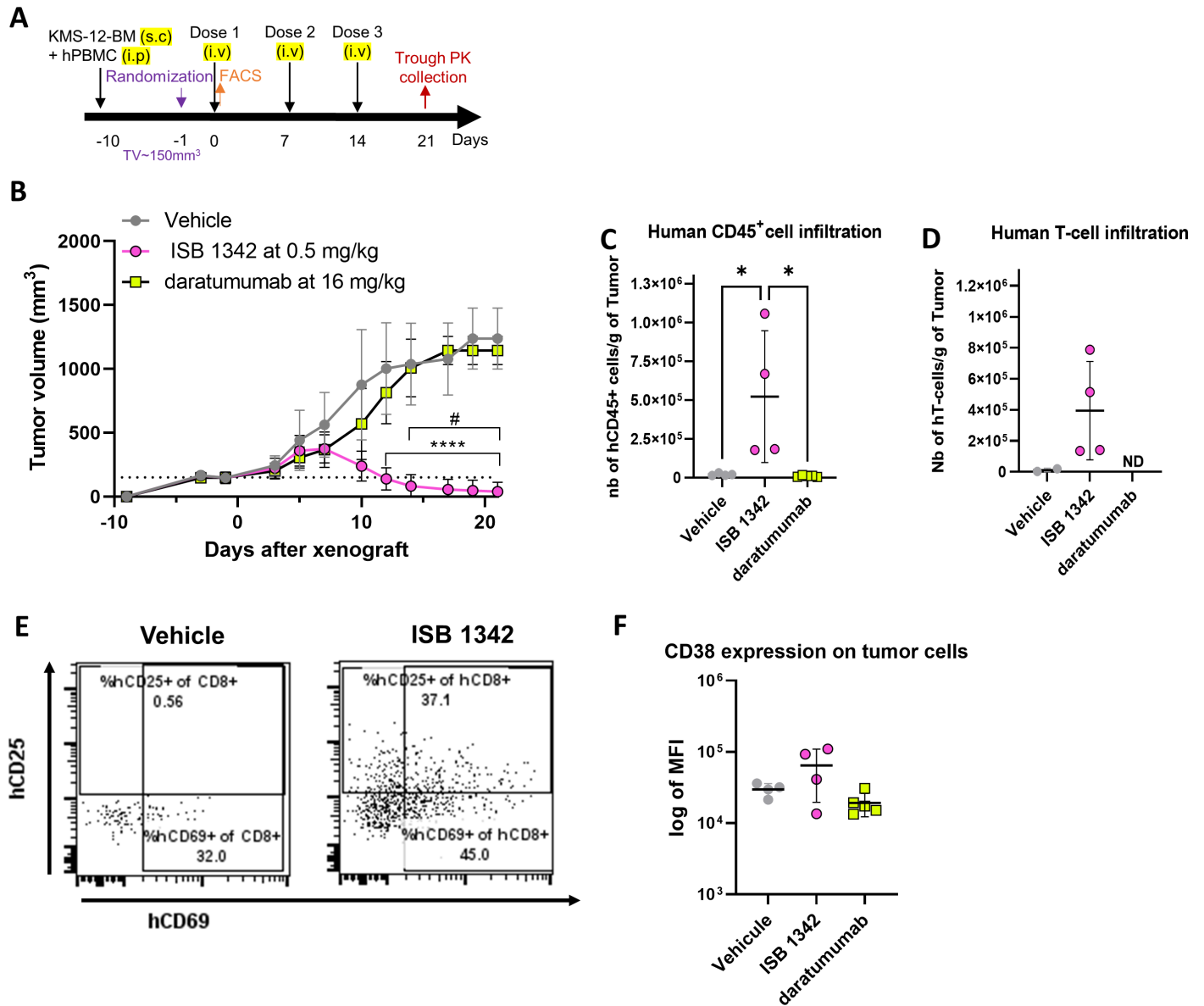


# Figure 5

● ISB 1342  
■ daratumumab



# Figure 6



# Figure 7

