Multimeric IgM Antibodies Targeting DR5 are Potent and Rapid Inducers of Tumor Cell Apoptosis *In Vitro* and *In Vivo*

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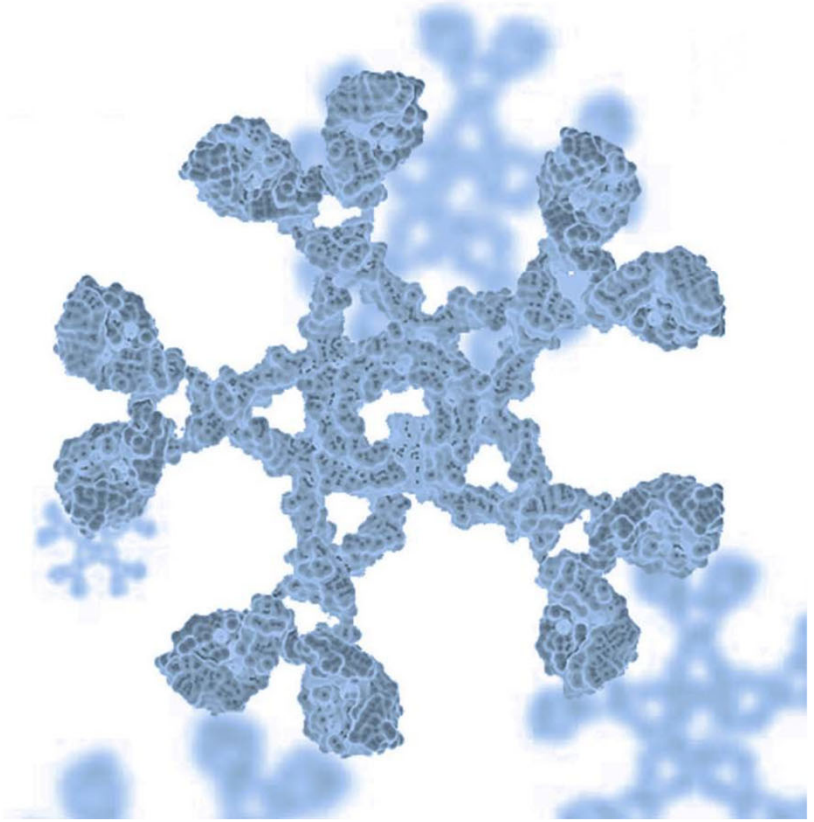
SVP Immuno-oncology Research

PEGS Europe, Barcelona, Spain
November 4th, 2021



Disclosure Information

Angus Sinclair

I have the following financial relationships to disclose:

Employee and Stockholder of IGM Biosciences Inc

-and-

I will not discuss off label use and/or investigational use in my presentation.

IGM's Pipeline

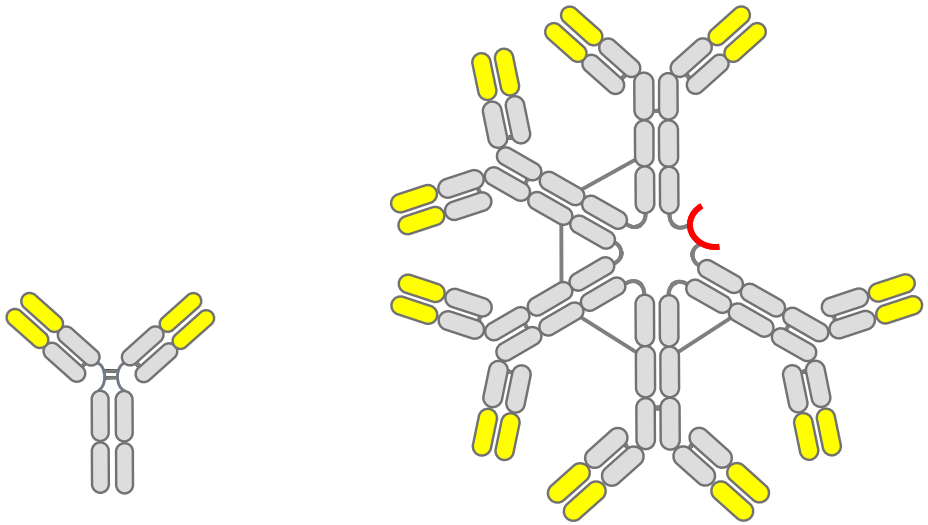
Lead Programs

Mode	Target	Indications	Phase of Development					Worldwide Commercial Rights	Anticipated Milestones
			Discovery	Preclinical	Phase 1	Phase 2	Phase 3		
T cell Engager	IGM-2323 (CD20 x CD3)	NHL, CLL						igm biosciences	Recommended Phase 2 dose: 2021
Receptor Cross-linking Agonist	IGM-8444 (DR5)	Solid and Hematologic Malignancies						igm biosciences	Initial Phase 1 data in solid tumors: 2021
Target Neutralizer	IGM-6268 (SARS-CoV-2)	COVID-19						igm biosciences	Phase 1 initiation: Q4 2021 (anticipated)
Targeted Cytokines	IGM-7354 (IL-15 x PD-L1)	Solid and Hematologic Malignancies						igm biosciences	Phase 1 initiation: 2022 (anticipated)

Research and Discovery Programs

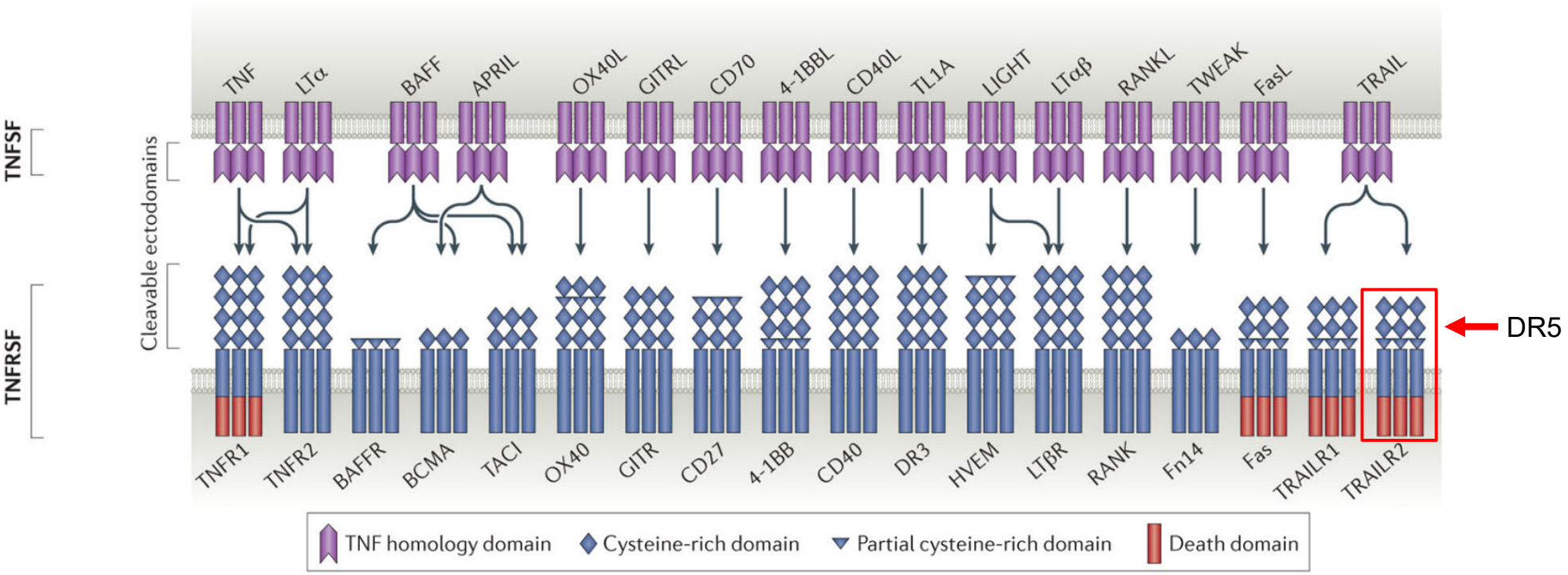
Mode	Target	Indications	Worldwide Commercial Rights
T cell Engagers	CD123 x CD3	Acute Myeloid Leukemia	igm biosciences
	CD38 x CD3	Multiple Myeloma	
	Multiple Targets x CD3	Multiple Solid Tumors	
Receptor Cross-linking Agonists	OX40	Solid and Hematologic Malignancies	igm biosciences
	GITR		

IgM has features that may be advantageous to target receptors



Higher valency may be critical to target receptors expressed at low levels and receptors that require multimerization for agonist activity including TNFrSF: DR5, OX40, GITR etc.

TNF receptors require multimerization for effective signaling



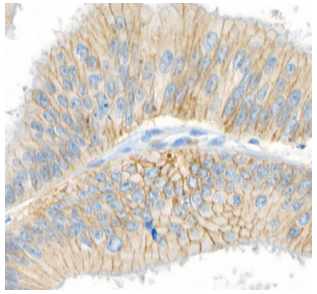
TNFR1, FAS, TRAIL-R1 (Death Receptor 4) and TRAIL-R2 (**Death Receptor 5**) have cytoplasmic 'death domains' which induce apoptosis upon receptor oligomerization

Croft M and Siegel RM, Nat Rev Rheumatol 2017, 13(4): 217-233

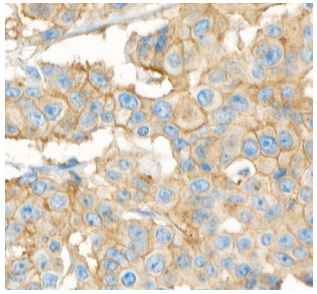
IgM antibodies enhance DR5 signaling via efficient receptor clustering

DR5 Stained Tumor Samples

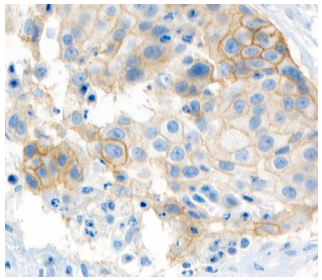
Colon Adenocarcinoma



Gastric Adenocarcinoma

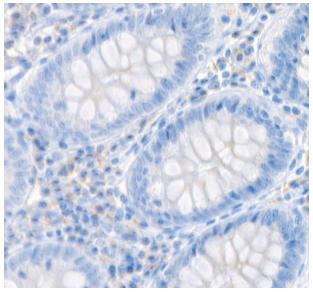


Squamous cell carcinoma

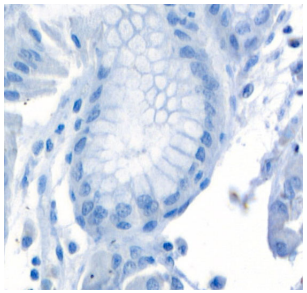


DR5 Stained Normal Tissues

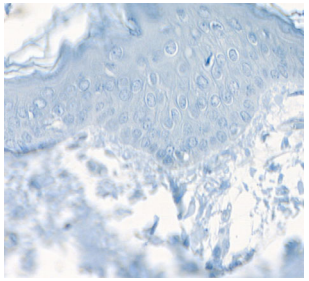
Colon

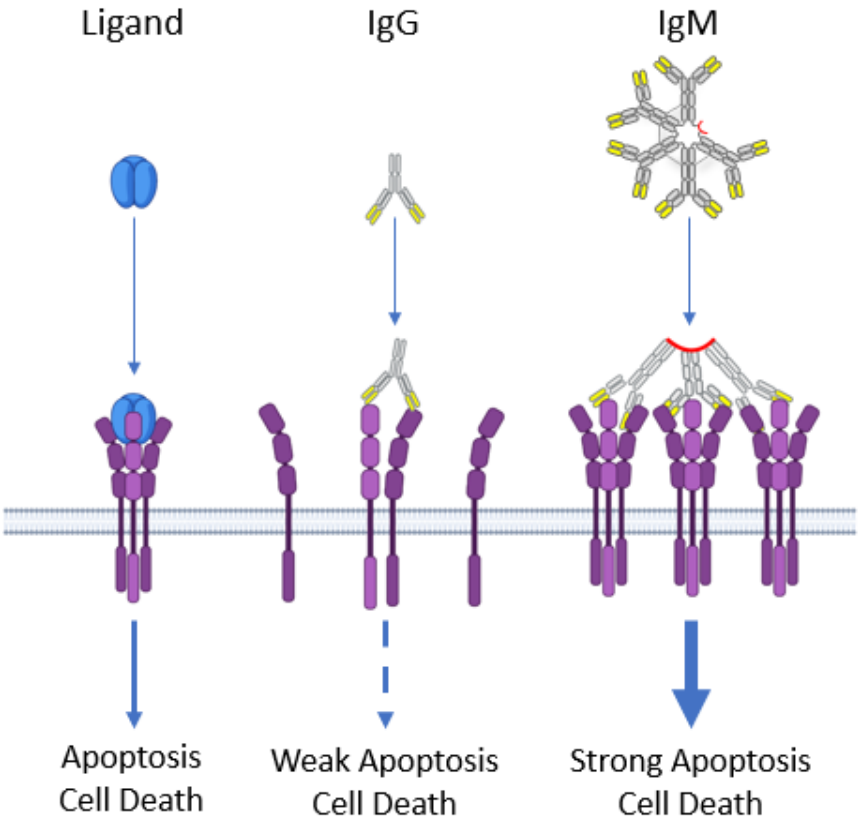


Stomach



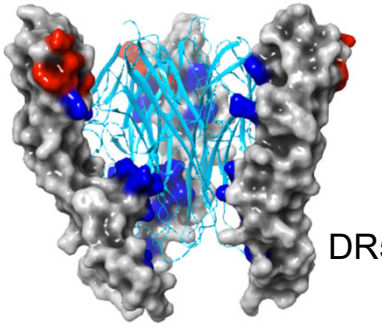
Skin





IGM-8444 binds membrane distal DR5 cysteine rich domain 1 (CRD1)

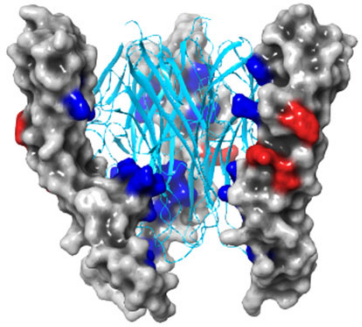
Mab-1



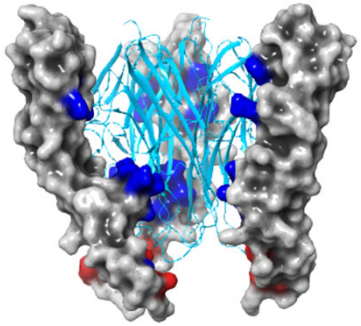
IGM-8444 was derived from Mab-1

	Mab-1	Mab-2	Mab-3	Mab-4	Mab-5
Kd, DR5-Fc (nM)	2.2	1.3	2.3	1.3	0.6
Ligand blocking	Y	N	Y	N	Y

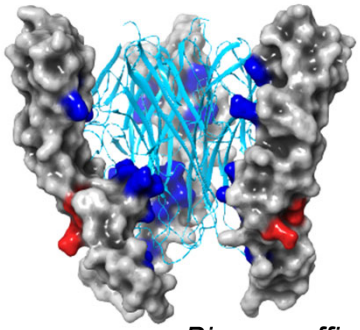
Mab-2



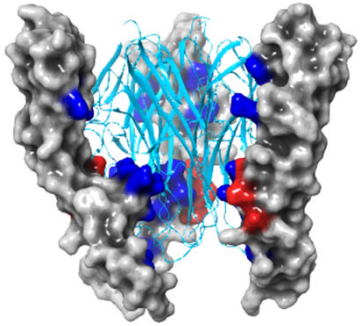
Mab-3



Mab-4



Mab-5

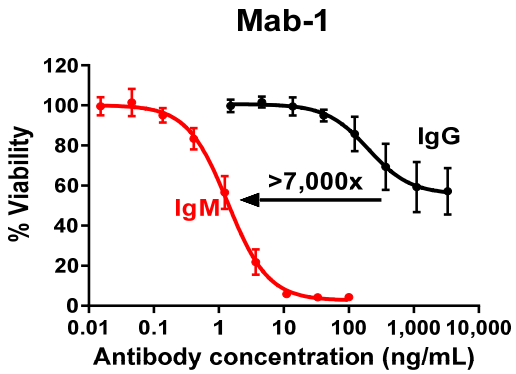


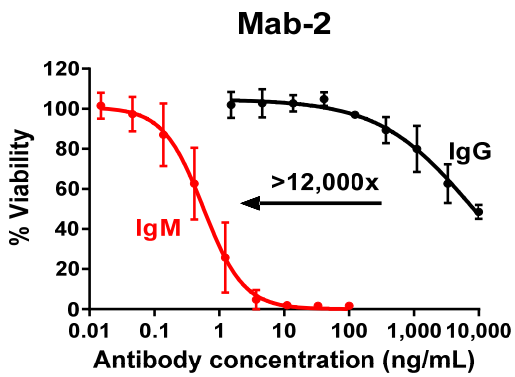
Antibody binding sites in red;
Ligand binding sites in blue

Biacore affinities determined using IgGs;
Epitopes mapped by alanine scanning using IgG Fab fragments

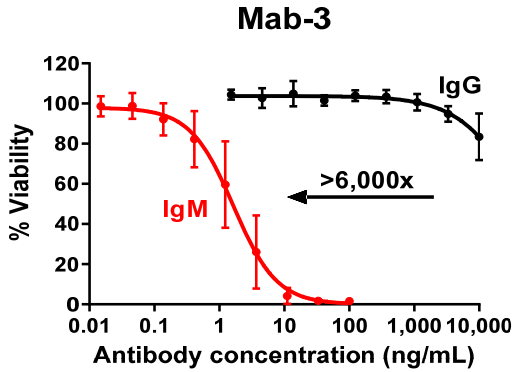
igm biosciences™

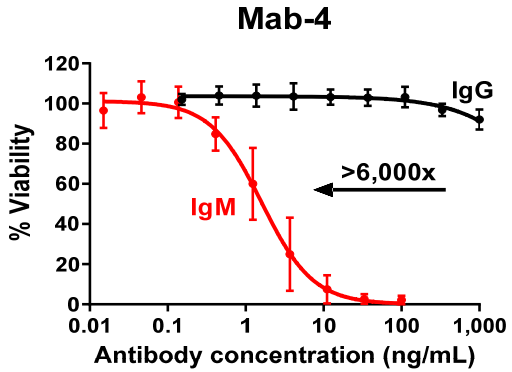
DR5 agonist IgM antibodies are > 5,000-fold more potent than IgG

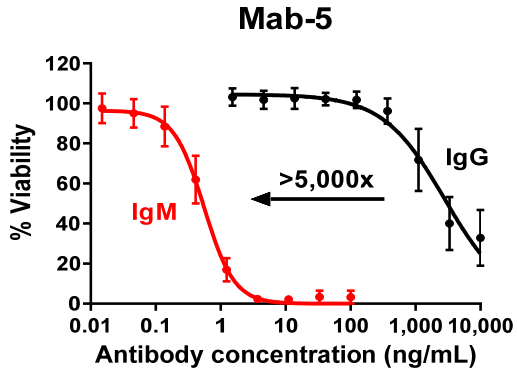




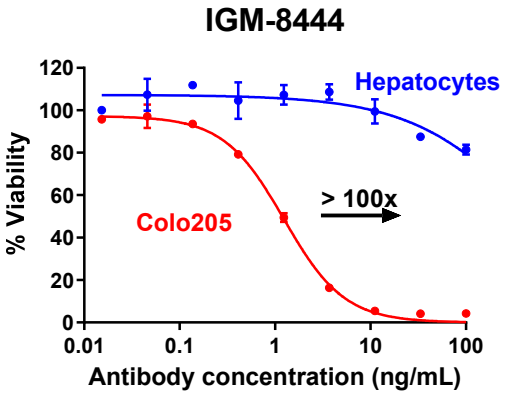
24-hour Colo205 in vitro cytotoxicity assay

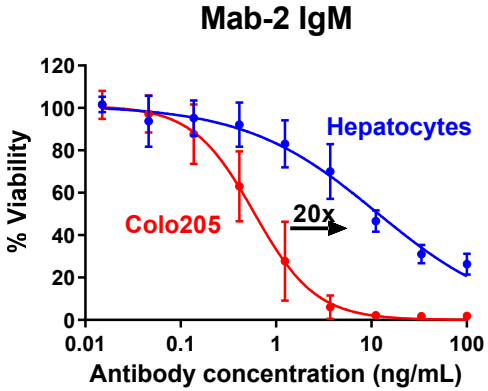




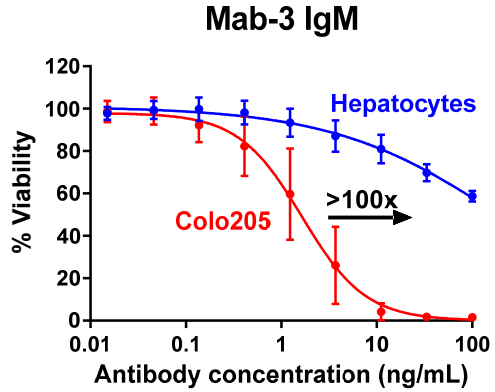


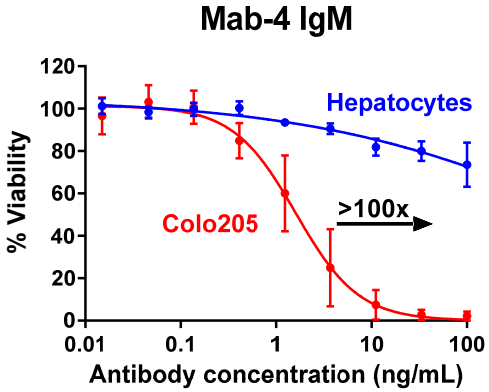
IGM-8444 demonstrates little/no human hepatocyte cytotoxicity

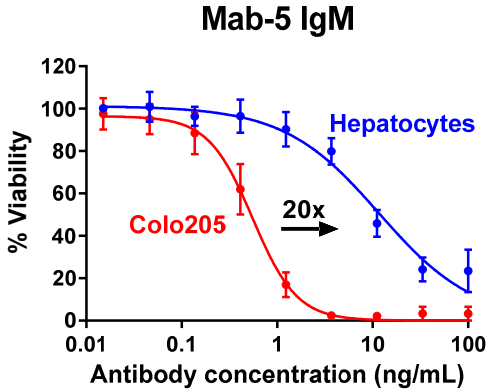




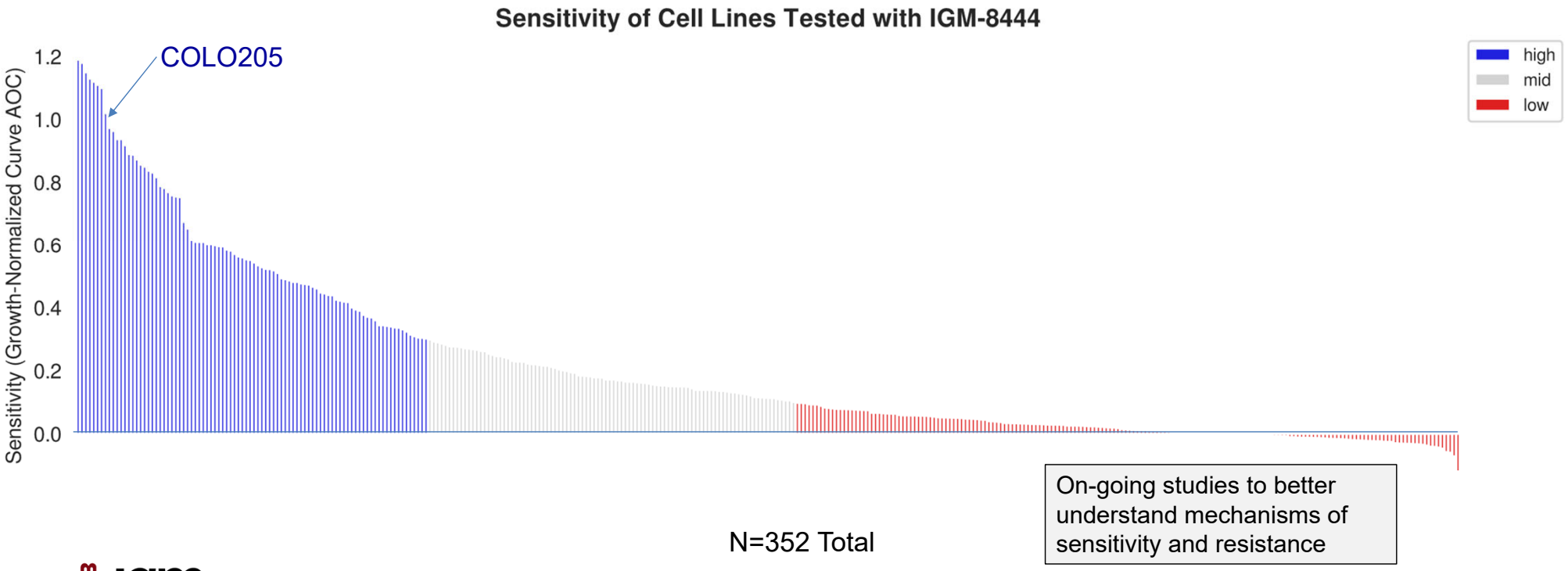
24-hour in vitro cytotoxicity assay comparing Colo205 cells vs primary human hepatocytes



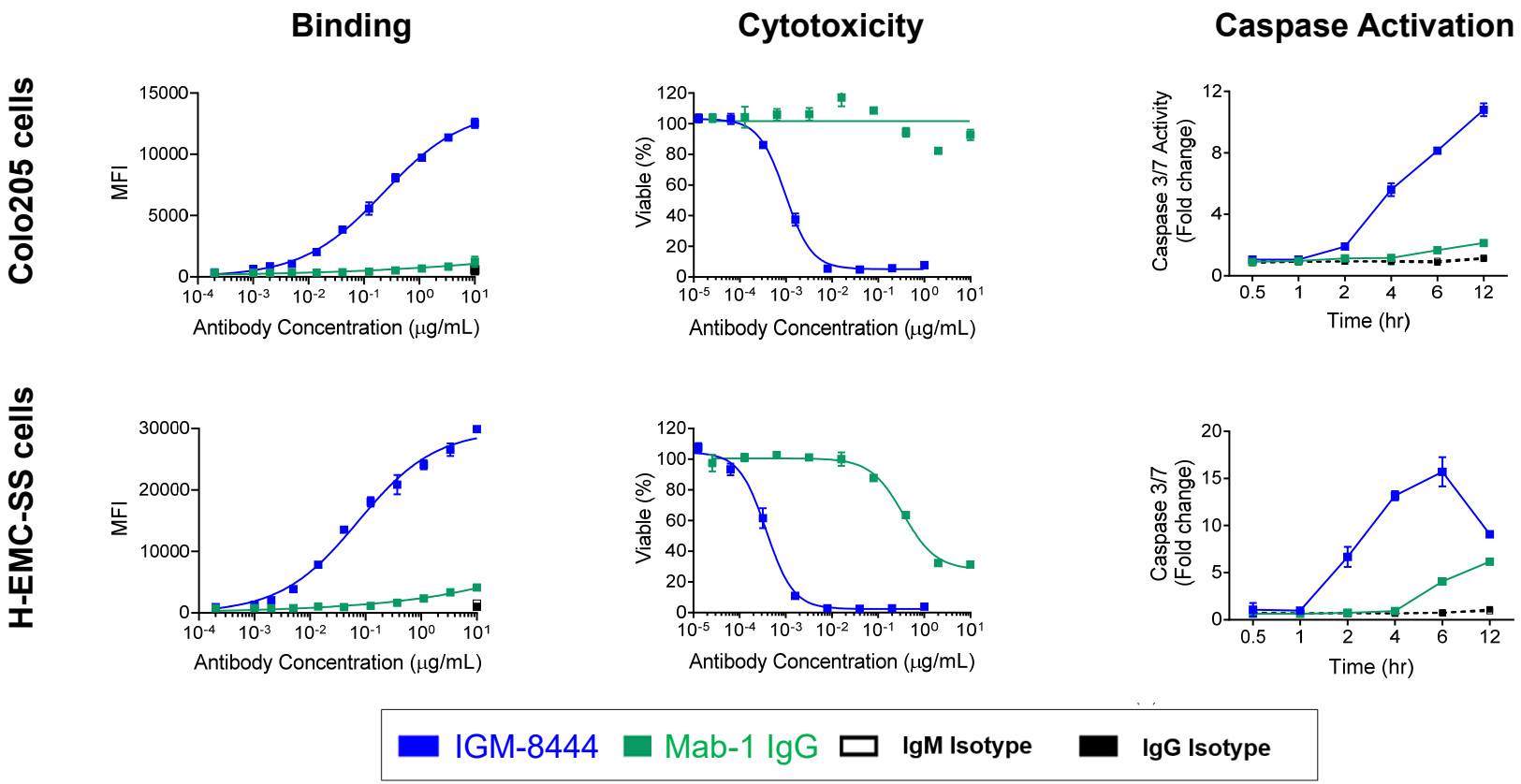




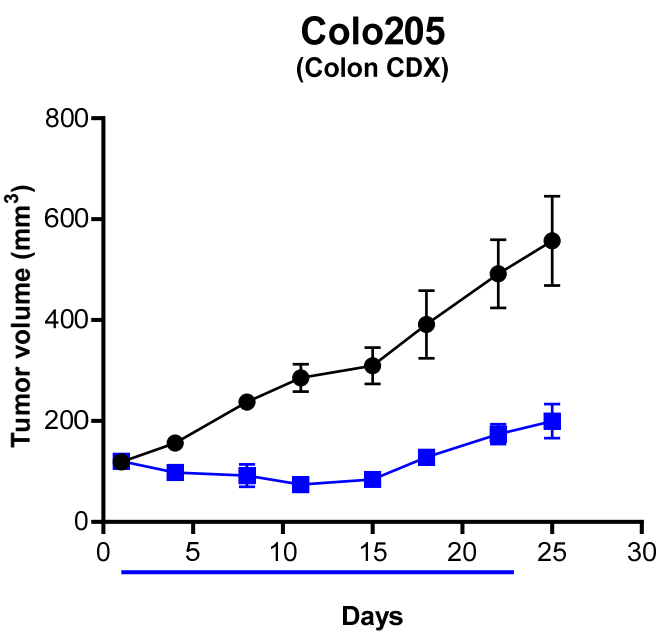
IGM-8444 induces cytotoxicity across multiple tumor cell lines

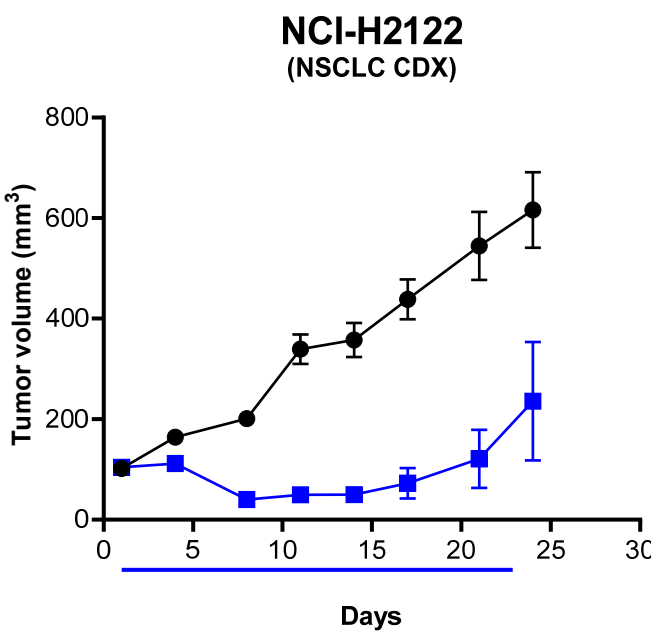


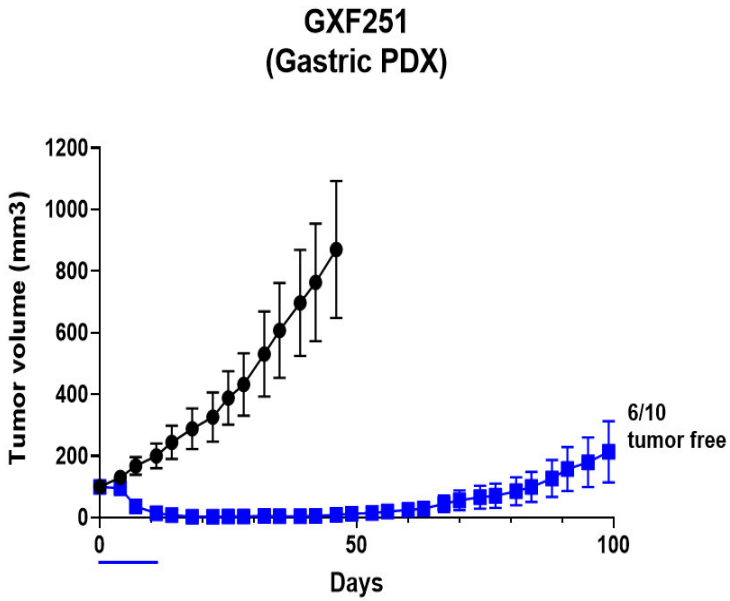
IGM-8444 potently binds DR5 inducing faster apoptosis vs IgG



IGM-8444 inhibits mouse xenograft tumor growth in multiple models

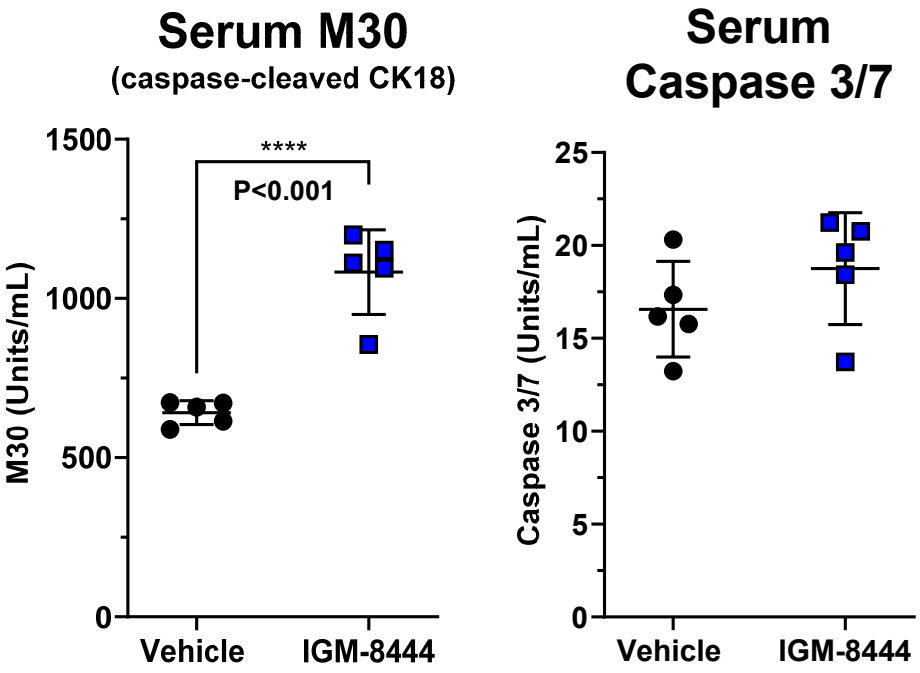


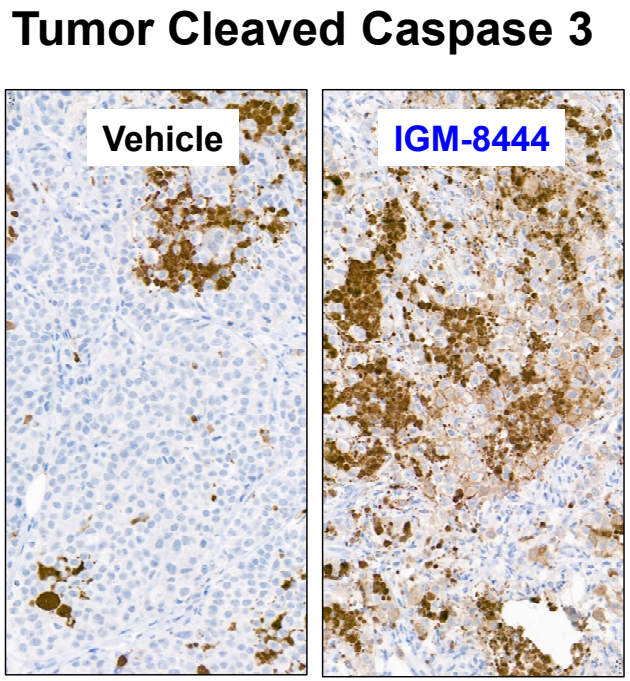




Vehicle; IGM-8444 (5 mg/kg)
Colo205 & NCI-H2122 Q2Dx11; GXF251 Q2Dx7

IGM-8444 induces apoptotic biomarkers in the NCI-H2122 tumor model

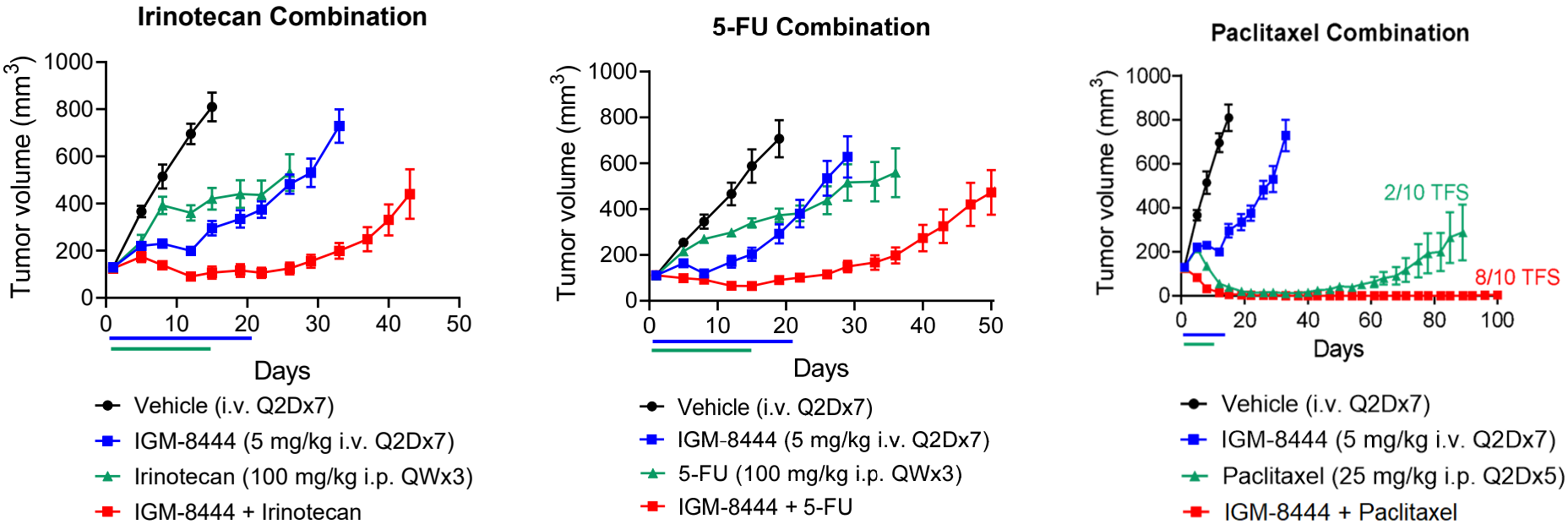




Vehicle; IGM-8444 (5 mg/kg)
Serum & tumor biomarkers measured 24 hours post single dose

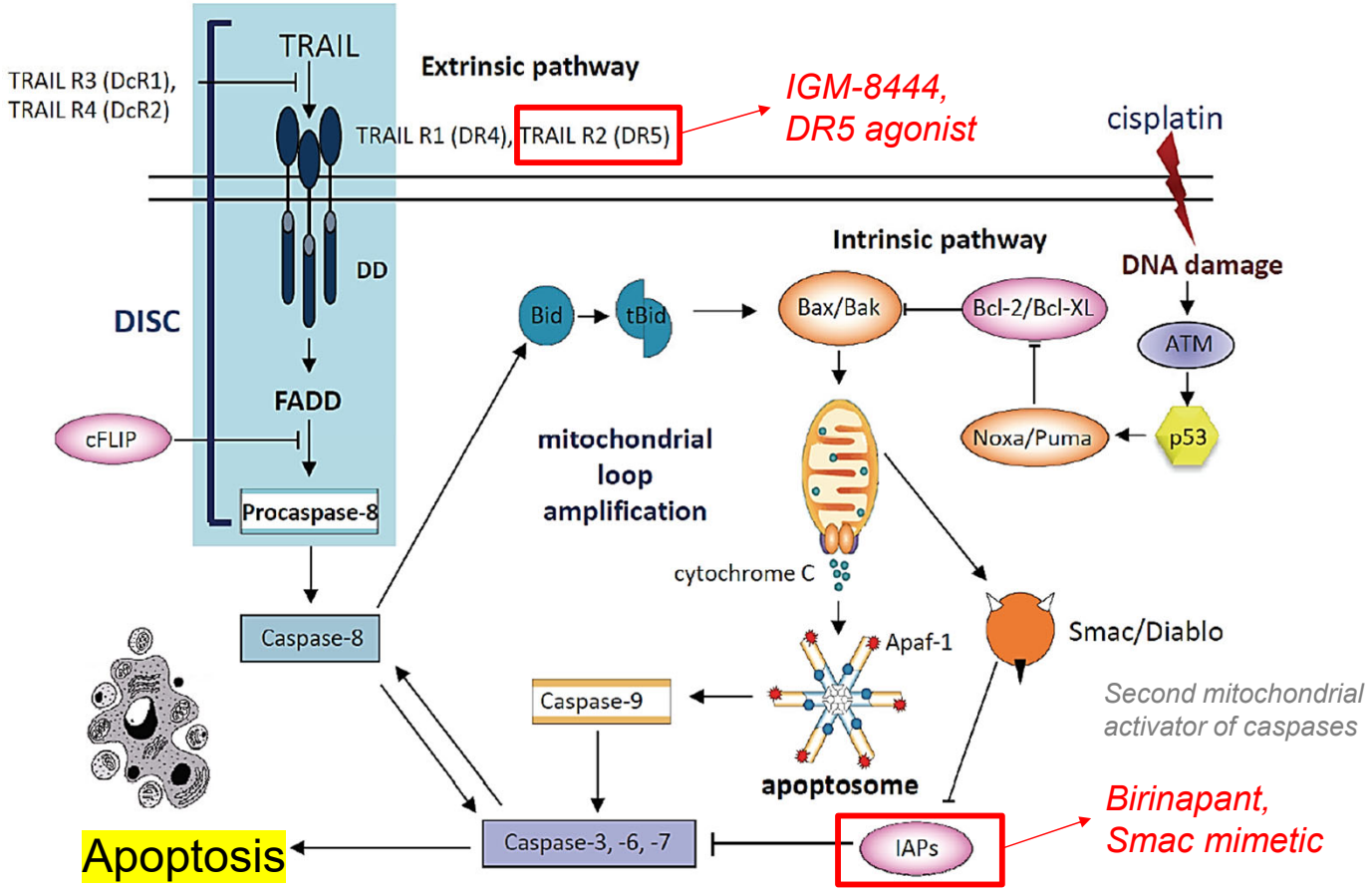
IGM-8444 and chemotherapy combinations enhance tumor regressions

Colorectal Cancer Model Colo205



Combinations of IGM-8444 with chemotherapeutic agents did not induce enhanced hepatotoxicity in vitro

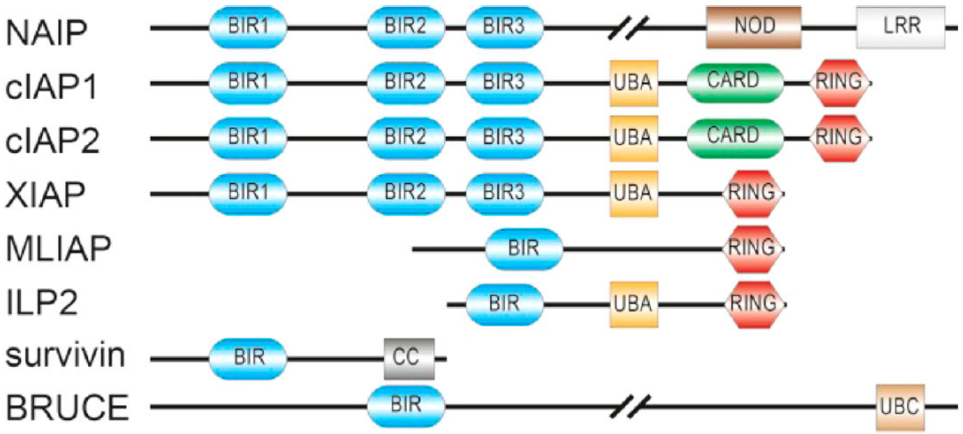
IGM-8444 and SMAC mimetics target distinct apoptosis pathways



Khaider NG et al, Am J Cancer Res 2012.

Birinapant is a clinical stage bivalent IAP antagonist (SMAC mimetic)

IAP Family Members



Birinapant (TL32711)

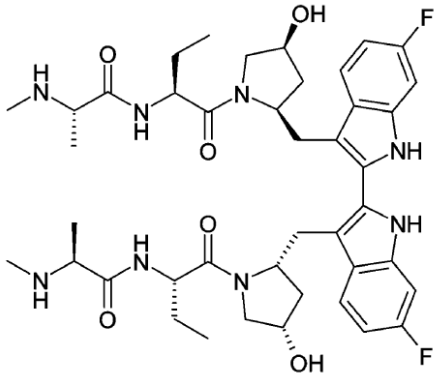


Table 1. Mean K_i Values for 1 and 2 to Selected IAP BIR Domains[a]

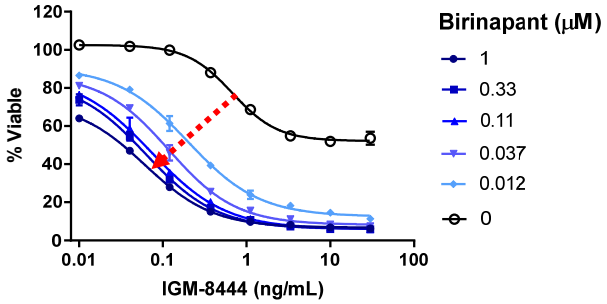
	K_i (nM)			
compd	XIAP BIR3	cIAP1 BIR3	cIAP2 BIR3	ML-IAP BIR
Birinapant	50 ± 23	~1	36	~1

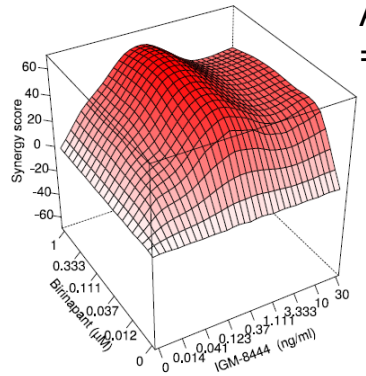
[a]Results are expressed as mean ± standard deviation from four or greater independent assays unless otherwise indicated.

Condon et al 2014 J Med Chem 57:3666

IGM-8444 + birinapant is highly synergistic across multiple cancers

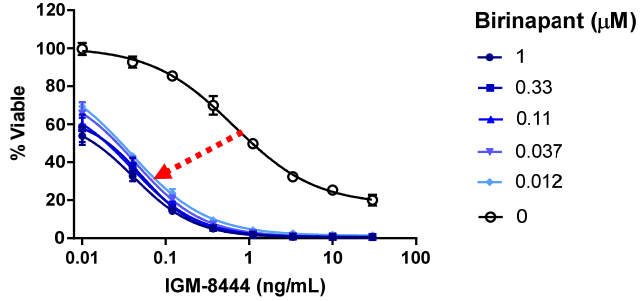
HT-1080 (Fibrosarcoma)

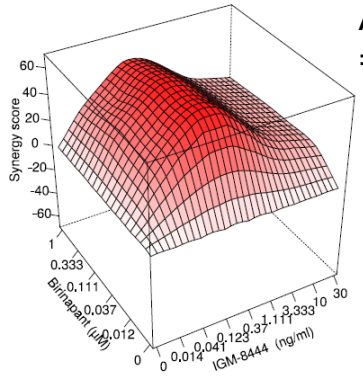




Avg. Bliss = 45

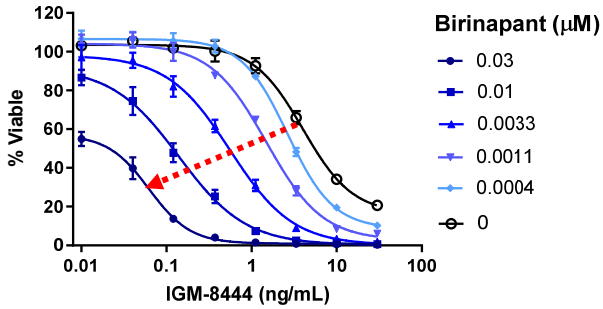
HCT116 (Colorectal)

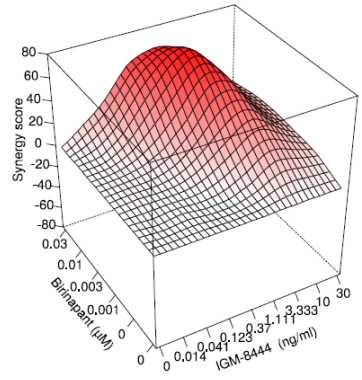




Avg. Bliss = 36

SK-LU-1 (NSCLC)





Avg. Bliss = 25

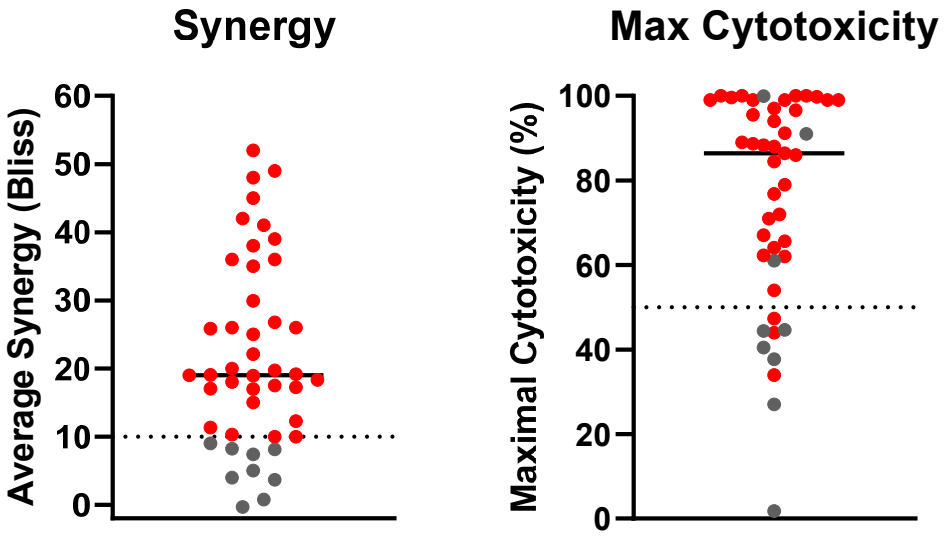
IGM-8444 + birinapant is highly synergistic across multiple cancers

45 cell lines screened:

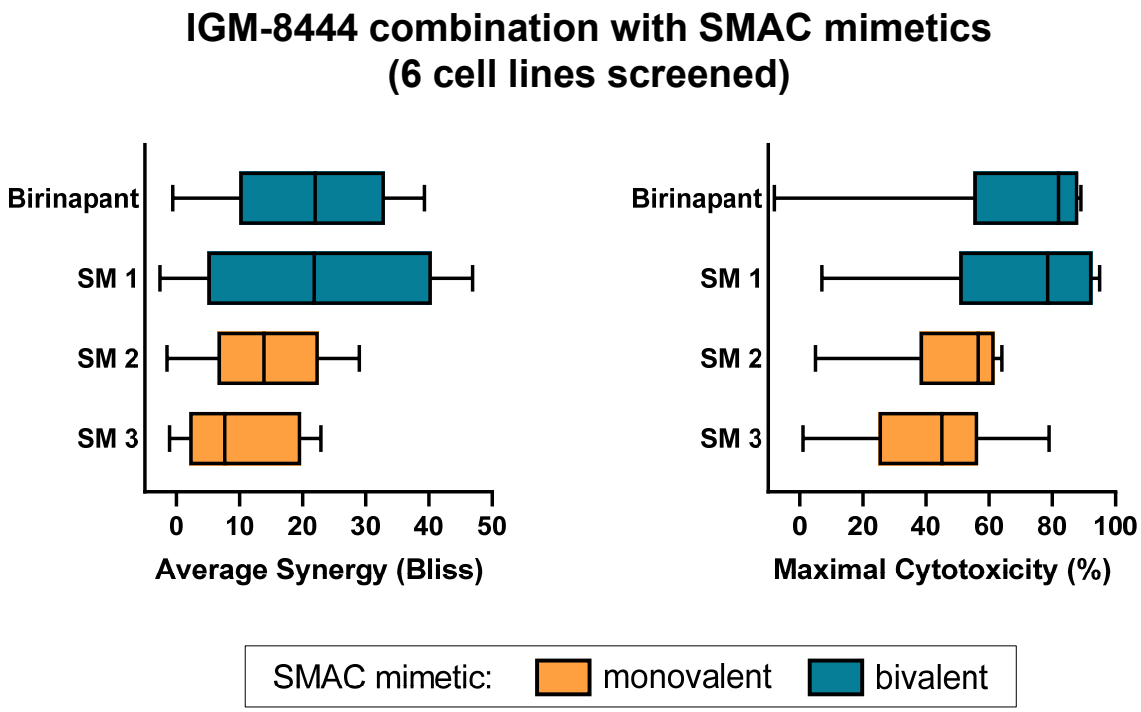
- Colorectal
- NSCLC
- TNBC
- Ovarian
- Sarcomas
- Head & Neck
- Melanoma
- Gastric
- Bladder
- Esophageal
- Pancreatic

- 36/45 (80%) showed strong combinatorial synergy (average Bliss score > 10)

- 36/45 (80%) showed > 50% maximal cytotoxicity

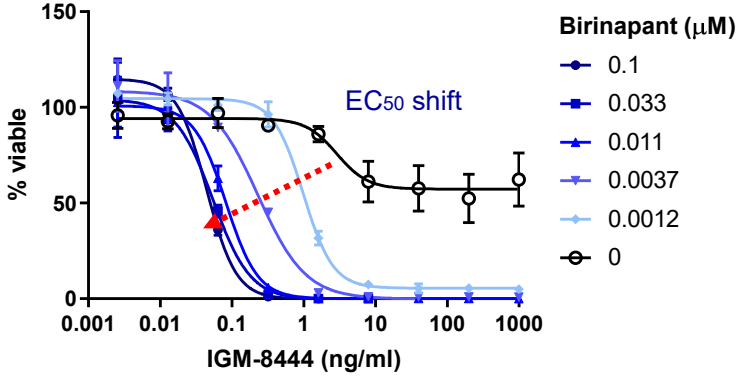


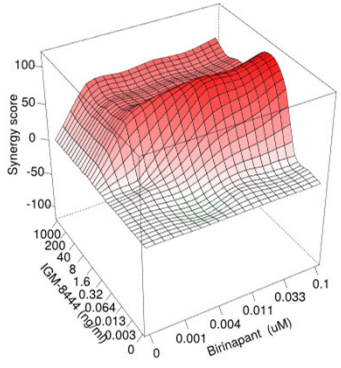
IGM-8444 & bivalent SMAC mimetic combinations are the most potent



IGM-8444 & birinapant are synergistic in an acquired resistant line

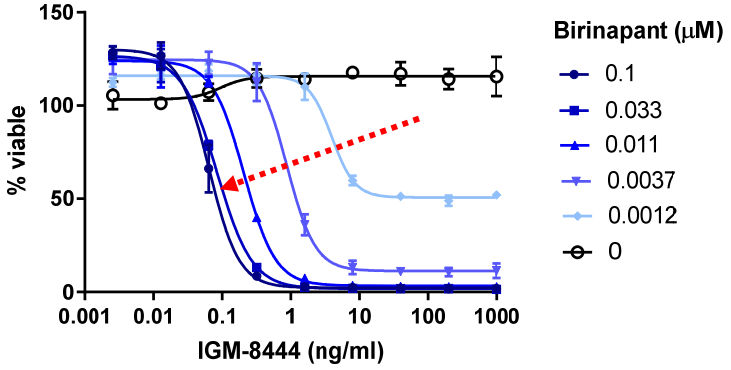
Wild-type MDA-MB-231 cells:

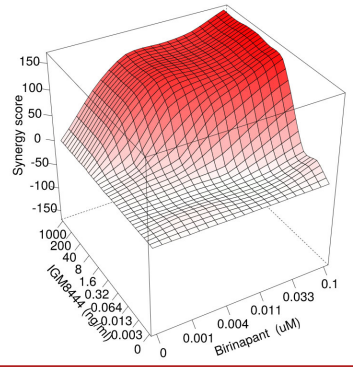




Avg Bliss = 51.9

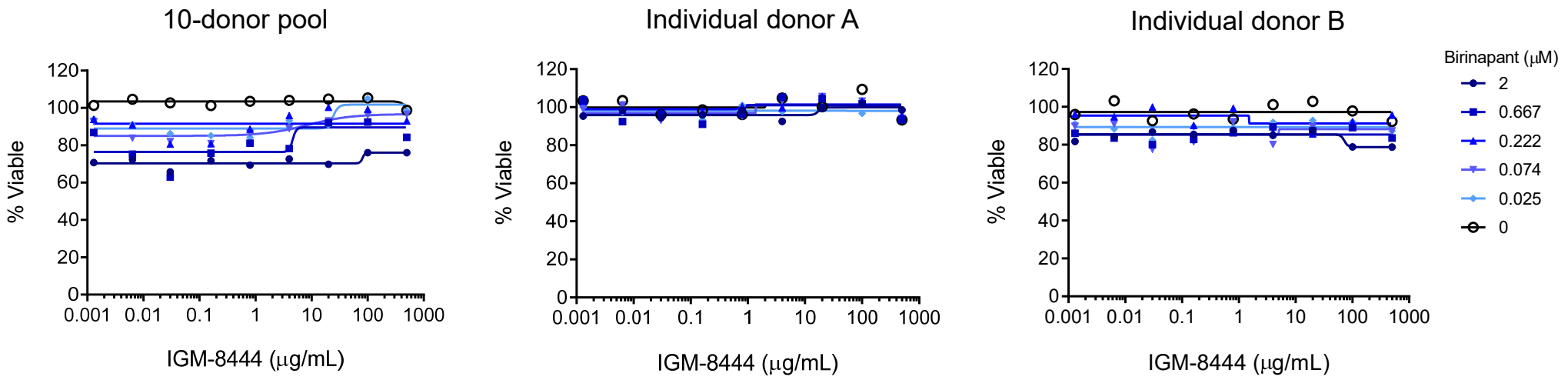
MDA-MB-231 cells with acquired resistance to DR5 agonist IgMs





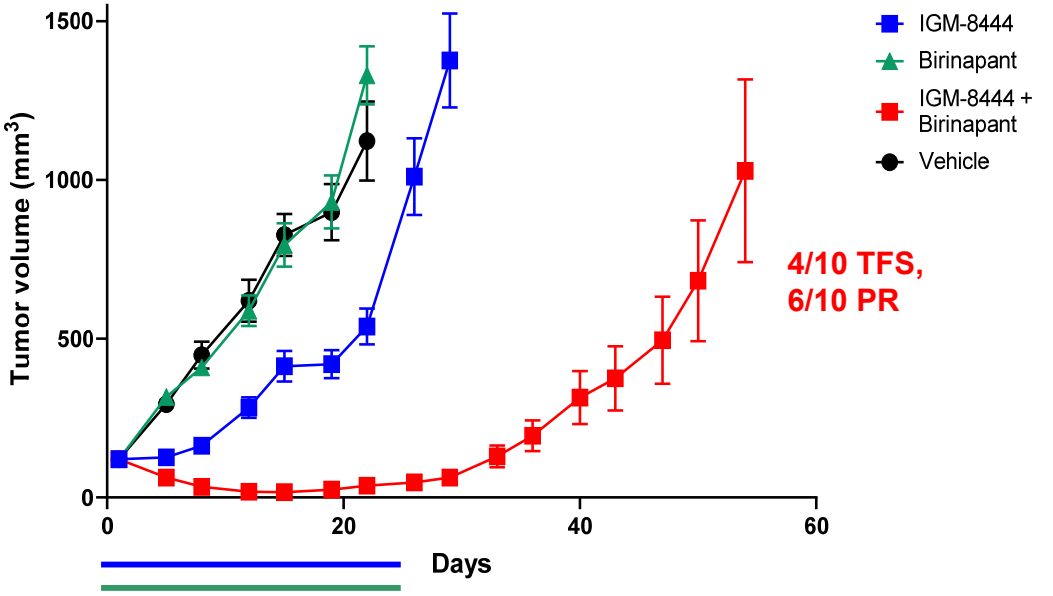
Avg Bliss = 84.4

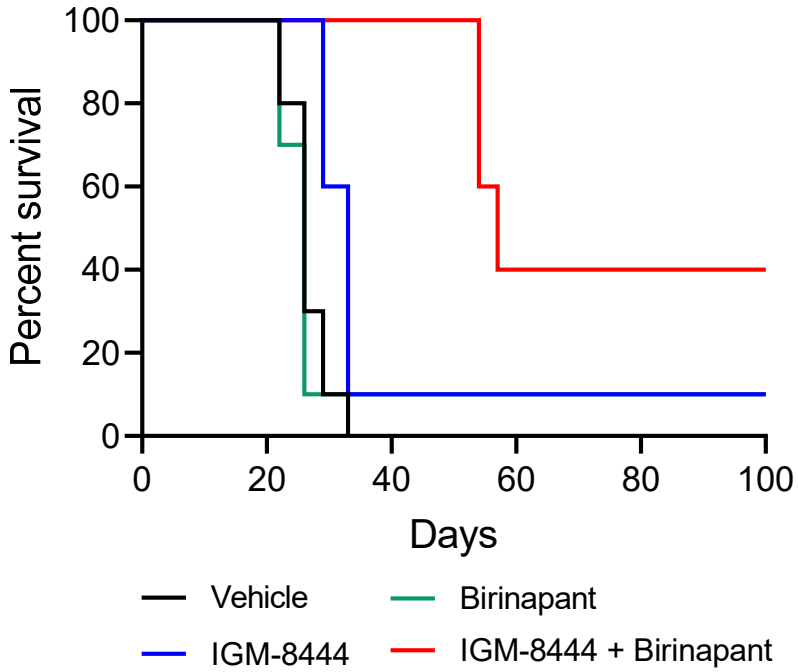
IGM-8444 and birinapant combinations are safe on hepatocytes in vitro



IGM-8444 and birinapant combinations enhance TNBC tumor regressions

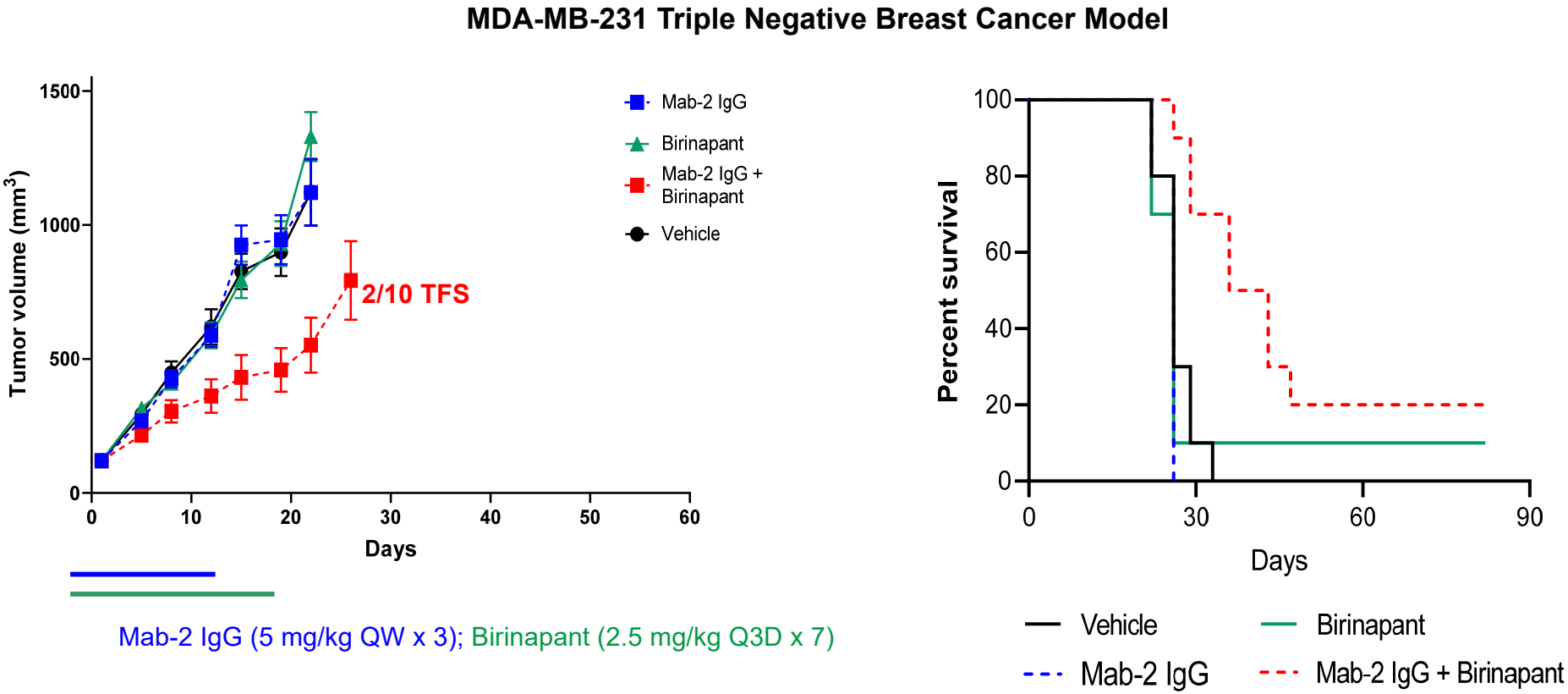
MDA-MB-231 Triple Negative Breast Cancer Model





IGM-8444 (5 mg/kg Q2D x 11); Birinapant (2.5 mg/kg Q3D x 7)

DR5 Mab-2 IgG and birinapant combinations have weaker effects



Mab-2 IgG (5 mg/kg QW x 3); Birinapant (2.5 mg/kg Q3D x 7)

IGM-8444 Phase 1: All-comers solid tumors and lymphoma

- DR5 expressed broadly in solid tumors, leukemias and lymphomas
- Ongoing Phase 1 is testing IGM-8444 in a solid tumors and NHL
- Standard 3+3 design to identify single agent dose and schedule
- IV dose given every 2 weeks; flexibility to test alternative schedules
- Phase 1 is also testing combinations with chemotherapy (FOLFIRI) and planned birinapant and venetoclax combinations
  - ClinicalTrials.gov Identifier: NCT04553692

IGM-8444 summary and conclusions

- **IgM antibodies are potent cross-linking agents of TNFrSF**
- IGM-8444 demonstrates potent agonist activity against DR5 preclinically
  - Strong apoptosis with potent tumor cell killing (EC_{50} < 2 pM)
  - Good hepatotoxicity profile
  - Broad anti-tumor activity using *in vitro* and *in vivo* models
  - Inhibits solid and liquid tumor growth
  - Additive or synergistic activity with chemotherapy, venetoclax and birinapant
  - Safety demonstrated *in vitro* and in non-GLP cyno monkey studies
- A Phase 1 clinical trial for IGM-8444 is ongoing in solid tumors and NHL as a single agent and combinations with FOLFIRI (CRC) and planned birinapant and venetoclax combinations

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