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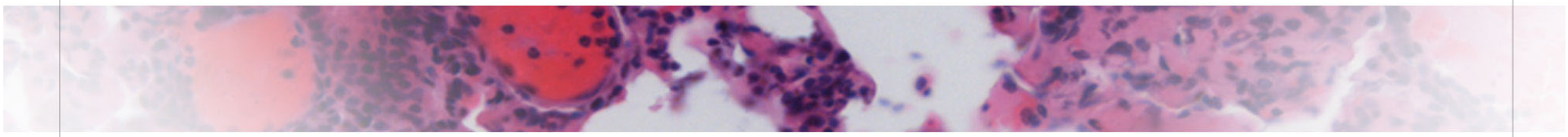

A phase 1 dose-escalation study of IGM-2323, a novel anti-CD20 x anti-CD3 IgM T-cell engager in patients with advanced B-cell malignancies

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Conflict of interest disclosure: Elizabeth Budde

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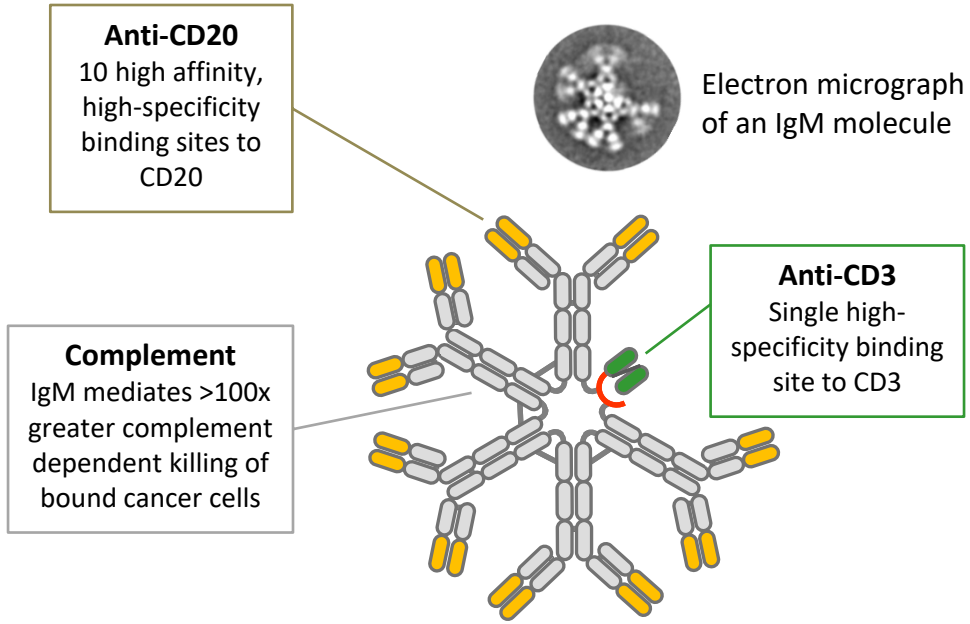
IGM-2323 is a novel engineered high-affinity, high-avidity CD20xCD3 IgM bispecific T-cell engager

IGM-2323 is a novel bispecific antibody, based on an engineered pentameric IgM framework, with a recombinant J-chain that is fused to an anti-CD3 scFv

In preclinical studies, **IGM-2323** has been shown to bind irreversibly to CD20-expressing cells, including cancer cells expressing *very low* levels of CD20, and eliminate them through cell-dependent (TDCC) and cell-independent mechanisms (CDC)[1,2]



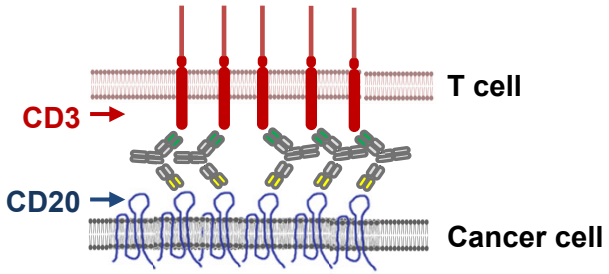
CD, cluster of differentiation; CDC, complement dependent cytotoxicity; IgG/M, immunoglobulin G/M; scFv, single-chain variable fragment; TDCC, T cell-dependent cytotoxicity

1. Baliga et al. Blood 2019;134(Suppl. 1):1574
2. Baliga et al. PEGS 2016

IGM-2323 engagement of T cells

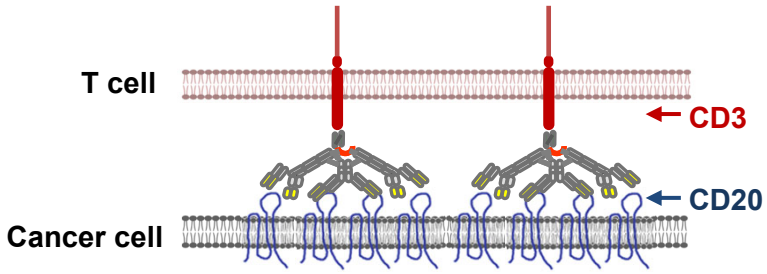
Existing bispecific T-cell engaging antibodies:
IgG or single chain

Supraphysiologic T-cell stimulation



Novel bispecific T-cell engaging antibodies:
IgM

More physiologic T-cell stimulation



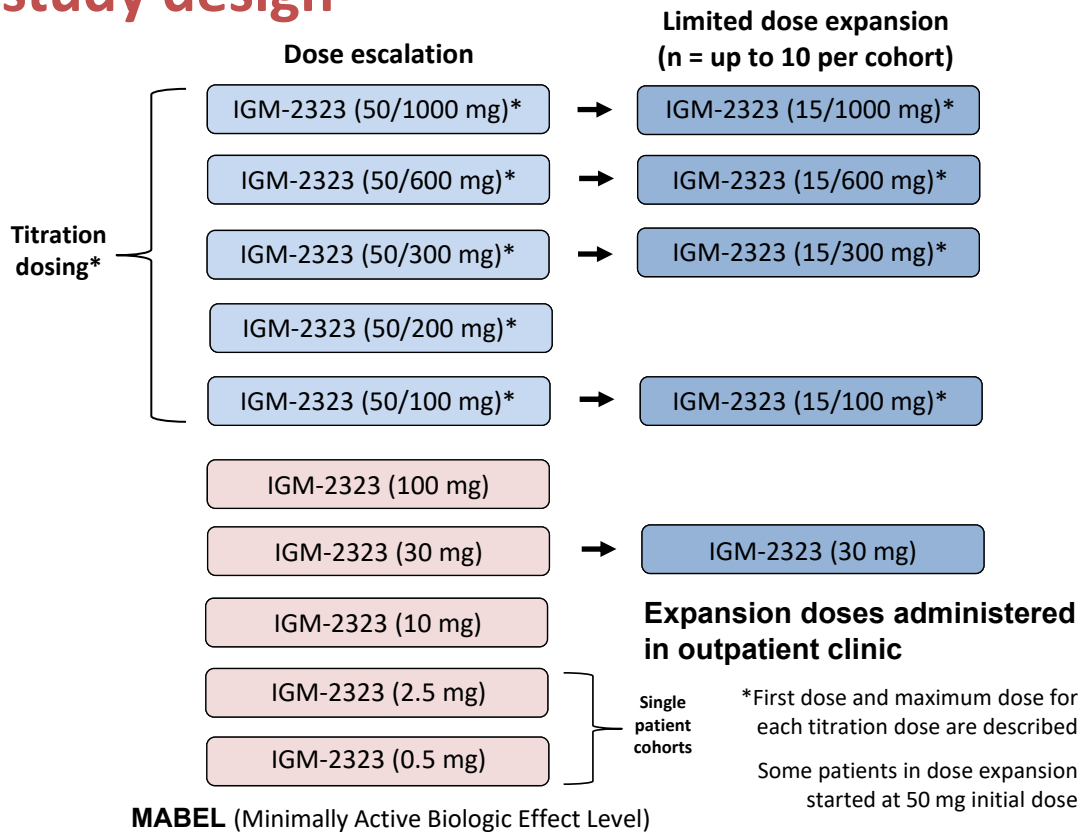
IGM-2323 may provide **more controlled T-cell activation** compared with existing bispecific T-cell engaging antibodies[1–3]

1. Faroudi et al. Proc Natl Acad Sci U S A. 2003;100:14145–50
2. Purbhoo et al. Nat Immunol 2004;5:524–30
3. Itoh et al. J Exp Med 1997;186:757–6

IGM-2323-001: Phase 1 study design

Phase 1

- Single-patient cohorts followed by standard 3+3 design
- R/R B-cell NHL (DLBCL, FL, MCL, MZL)
- 1 cycle: 21 days
- Weekly dosing: D1, D8, D15
- Dexamethasone premedication
- DLT window C1 d1–21
- Q3 week dosing allowed once CR achieved
- All planned dose escalation cohorts completed. Currently enrolling in limited dose-expansion cohorts.
- Intra-patient dose escalation allowed



Baseline demographics

Characteristic	Dosed patients (n=40)
Median age, years (range)	64 (36–84)
Gender, n (%)	
Male / Female	28 (70%) / 12 (30%)
Region, n (%)	
United States / Australia / South Korea	29 (73%) / 6 (15%) / 5 (13%)
Tumor type, n (%)	
DLBCL / MCL	18 (45%) / 4 (10%)
FL / MZL	14 (35%) / 4 (10%)
Disease stage at study entry, n (%)	
I–II	7 (18%)
III-IV	33 (82%)
Prior CAR-T therapy, n (%)	8 (20%)
Prior ASCT, n (%)	3 (8%)
Median prior lines of treatment (range)	3 (2–9)
No. of prior lines of treatment, n (%)	
2 / 3 / ≥4	14 (35%) / 10 (25%) / 16 (40%)
Median time from last treatment, months (range)	3.4 (0.6–37.2)
No. of patients who were refractory to last treatment, n (%)	25 (63%)

Data cut off: September 10, 2021

Disposition/exposure

	Dosed patients (n=40)
Median duration of treatment, months (range)	3.2 (0.0–16.3)
Median duration of study follow-up, months (range)	7.8 (0.4–23.7)
Number of patients ongoing, n (%)	12 (30%)
Discontinued from treatment, n (%)	
Progression	23 (58%)
Investigator/patient decision	5 (13%)
Adverse Event	0
Deaths*, n (%)	
Any cause	0
Related to study drug	0

*Within 30 days of last dose of study drug

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Most common treatment-related adverse events (events occurring in >10% of patients)

Non-laboratory AEs, n (%)	Titration dose levels (n=28)		All dose levels (n=40)	
	All grades	Grade ≥3	All grades	Grade ≥3
Infusion-related reaction	7 (25)	1 (4)	12 (30)	2 (5)
Cytokine release syndrome	5 (18)	1 (4)	10 (25)	1 (3)
Nausea	7 (25)	0	10 (25)	0
Fatigue	6 (21)	0	7 (18)	0
Anemia	2 (7)	1 (4)	6 (15)	2 (5)
Back pain	5 (18)	1 (4)	5 (13)	1 (3)
Laboratory AEs, n (%)	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Hypophosphatemia	6 (21)	1 (4)	9 (23)	1 (3)

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*Cytokine release syndrome graded by ASTCT Consensus Grading (Lee et al. Biol Blood Marrow Transplant 2019)

Adverse events of special interest

Titration cohorts (n=28)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
CRS*	3 (11)	1 (4)	1 (4)	0	0
ICANS^	0	0	0	0	0
Neutropenia	1 (4)	0	0	0	0
IRR	3 (11)	3 (11)	1 (4)	0	0

All patients (n=40)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
CRS*	7 (18)	2 (5)	1 (3)	0	0
ICANS^	0	0	0	0	0
Neutropenia	1 (3)	0	1 (3)	1 (3)	0
IRR	3 (8)	7 (18)	2 (5)	0	0

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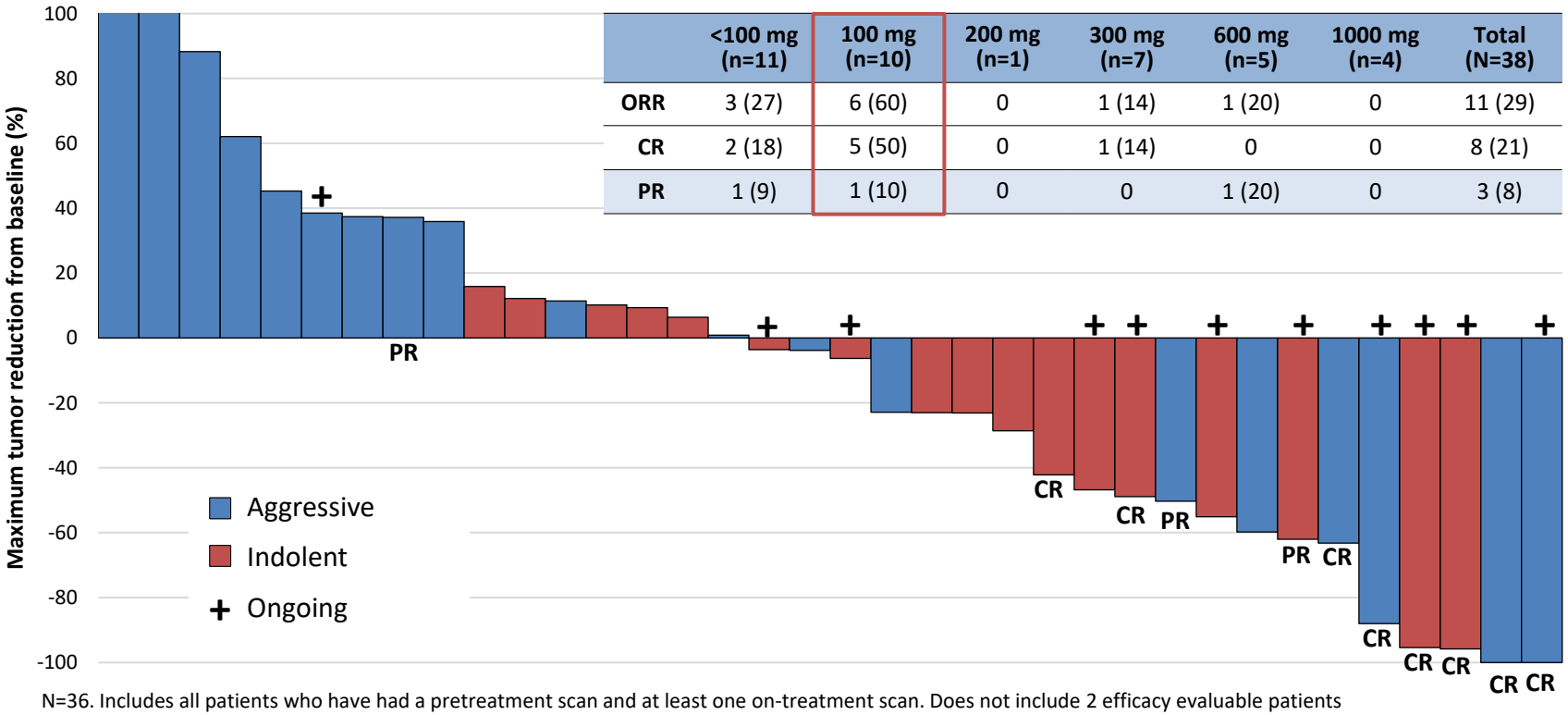
*Cytokine release syndrome graded by ASTCT Consensus Grading (Lee et al. Biol Blood Marrow Transplant 2019)
*Distinction between CRS and IRR were made by the treating investigator
*3 of 5 CRS cases in titration cohorts and 8 of 10 overall occurred in the first cycle
^ICANS: immune effector cell-associated neurotoxicity syndrome

Overall NHL cohort: best post-baseline tumor reduction and responses

	<100 mg (n=11)	100 mg (n=10)	200 mg (n=1)	300 mg (n=7)	600 mg (n=5)	1000 mg (n=4)	Total (N=38)
ORR	3 (27)	6 (60)	0	1 (14)	1 (20)	0	11 (29)
CR	2 (18)	5 (50)	0	1 (14)	0	0	8 (21)
PR	1 (9)	1 (10)	0	0	1 (20)	0	3 (8)



N=36. Includes all patients who have had a pretreatment scan and at least one on-treatment scan. Does not include 2 efficacy evaluable patients who came off treatment prior to first scan. Response assessments per Lugano

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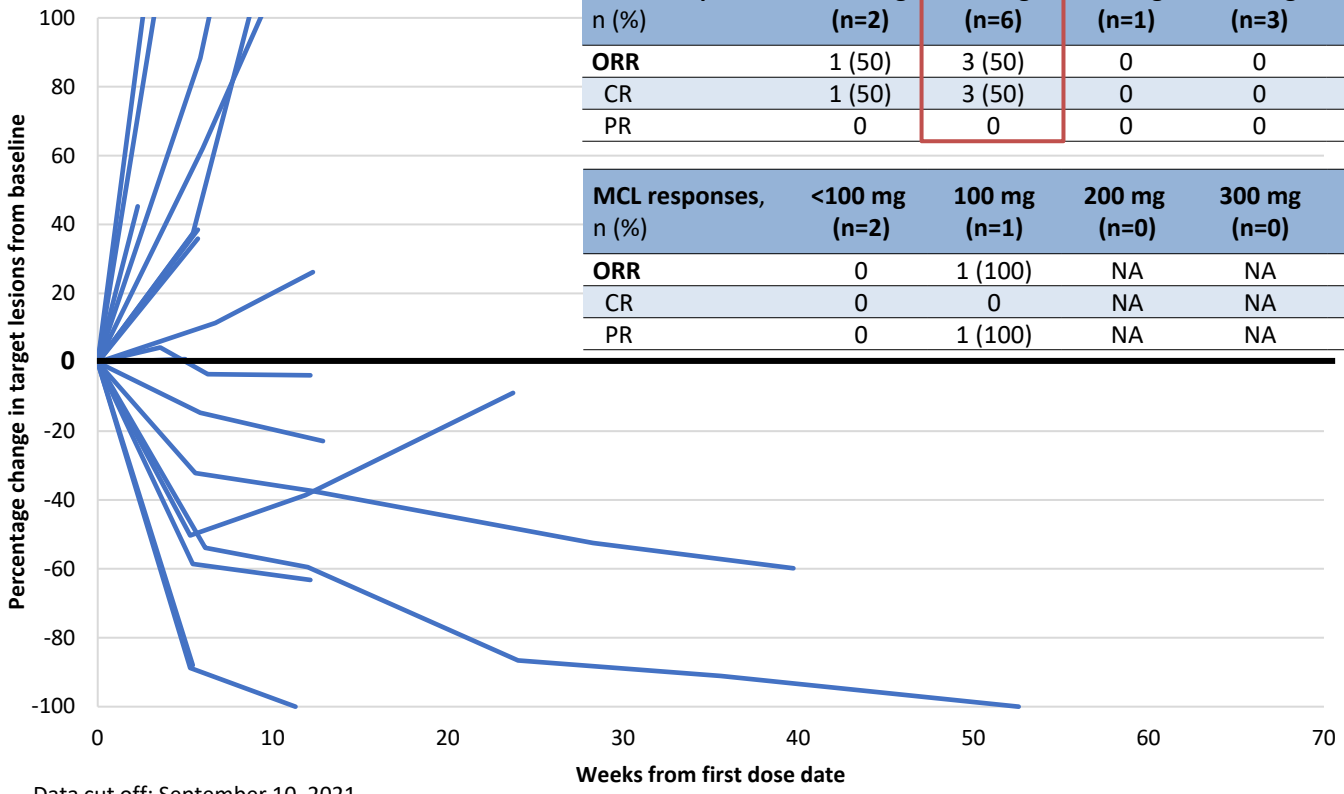
Aggressive NHL cohort (DLBCL and MCL): tumor responses



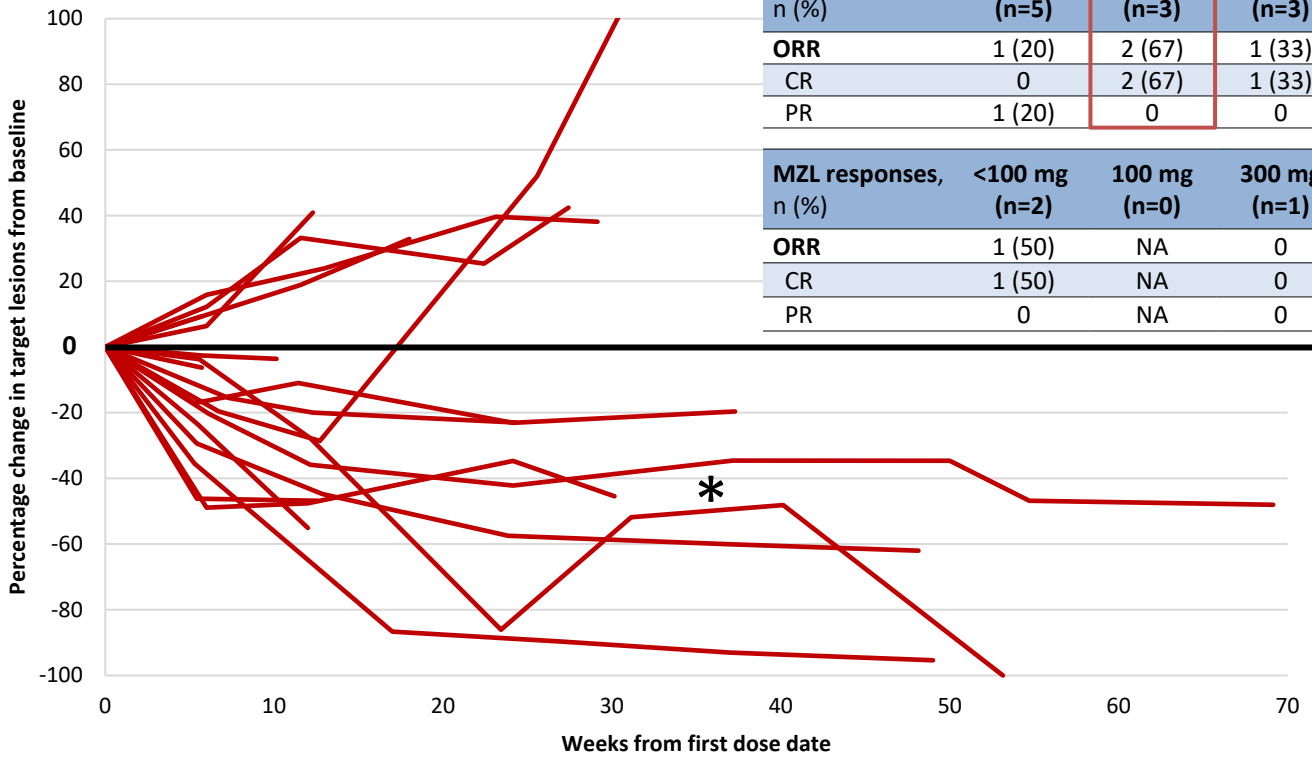
DLBCL responses, n (%)	<100 mg (n=2)	100 mg (n=6)	200 mg (n=1)	300 mg (n=3)	600 mg (n=3)	1000 mg (n=1)	All doses (n=16)
ORR	1 (50)	3 (50)	0	0	1 (33)	0	5 (31)
CR	1 (50)	3 (50)	0	0	0	0	4 (25)
PR	0	0	0	0	1 (33)	0	1 (6)

MCL responses, n (%)	<100 mg (n=2)	100 mg (n=1)	200 mg (n=0)	300 mg (n=0)	600 mg (n=1)	1000 mg (n=0)	All doses (n=4)
ORR	0	1 (100)	NA	NA	0	NA	1 (25)
CR	0	0	NA	NA	0	NA	0
PR	0	1 (100)	NA	NA	0	NA	1 (25)

NA: not applicable

Data cut off: September 10, 2021

Indolent NHL cohort (FL and MZL): tumor responses



FL responses, n (%)	<100 mg (n=5)	100 mg (n=3)	300 mg (n=3)	600 mg (n=1)	1000 mg (n=2)	All doses (n=14)
ORR	1 (20)	2 (67)	1 (33)	0	0	4 (29)
CR	0	2 (67)	1 (33)	0	0	3 (21)
PR	1 (20)	0	0	0	0	1 (7)

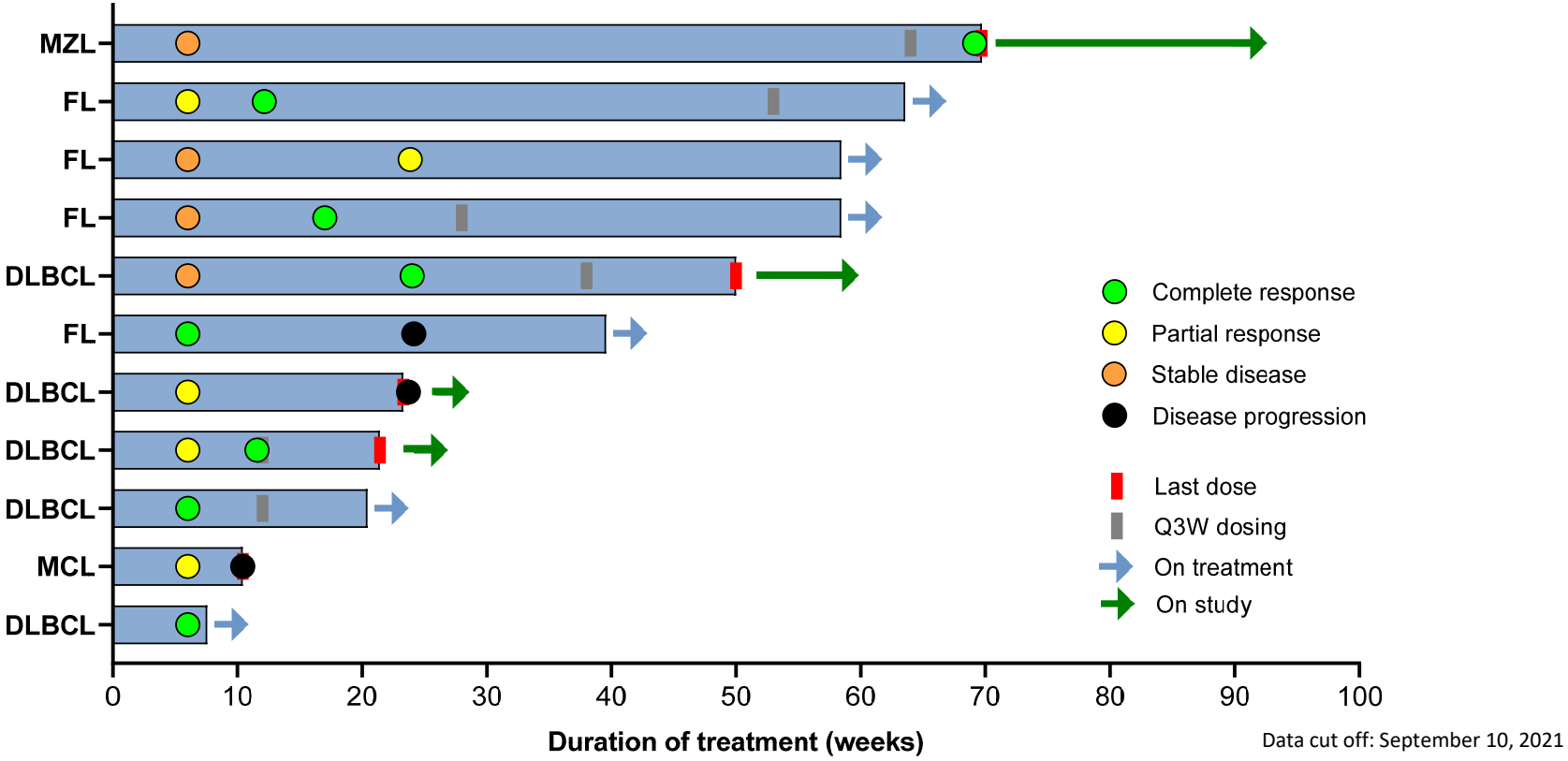
MZL responses, n (%)	<100 mg (n=2)	100 mg (n=0)	300 mg (n=1)	600 mg (n=0)	1000 mg (n=1)	All doses (n=4)
ORR	1 (50)	NA	0	NA	0	1 (25)
CR	1 (50)	NA	0	NA	0	1 (25)
PR	0	NA	0	NA	0	0

NA: not applicable

*FL patient with CR, possible pseudoprogression, and continued treatment with ongoing benefit

Data cut off: September 10, 2021

Patient status: responders only



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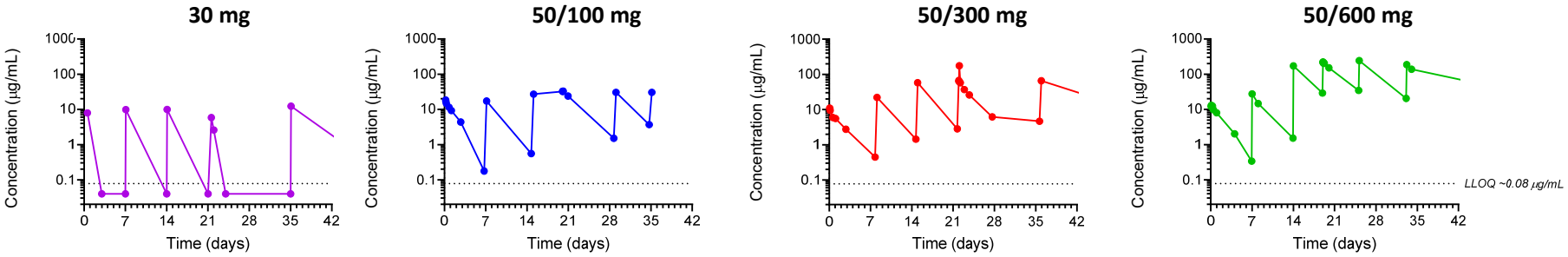
IGM-2323 pharmacokinetics

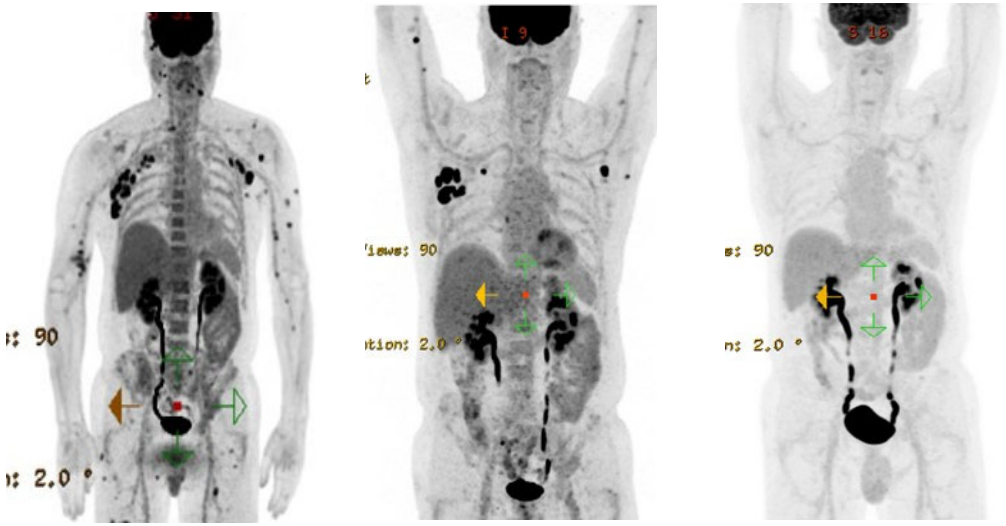
Representative PK profiles: 30 mg expansion & titration cohorts



- No drug-induced antidrug antibodies detected to date
- Sustained and dose-dependent effect on IGM-2323 levels throughout dosing interval at ≥100 mg
- Preliminary population estimate of $t_{1/2}$ is ~1.5 days

63-year-old male with Stage II FL- CR at week 12

PET imaging

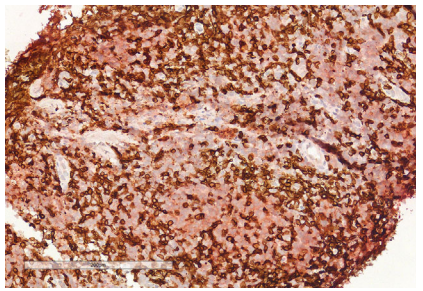


Baseline **Week 6** **Week 12**

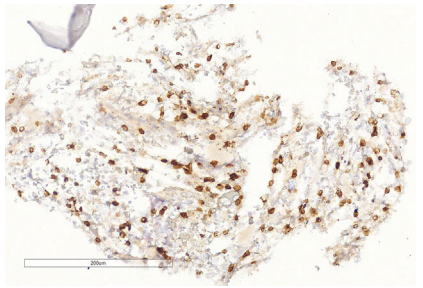
- 63-year-old male with Grade 2 FL; diagnosed in January 2018
- s/p R-CHOP (CR) and R-utomilumab/avelumab (PR)
- Off treatment for 7 months prior to IGM-2323
- Patient remains on treatment in CR
- Images courtesy of Dana Farber Cancer Institute

Tumor CD20/CD3 expression

Pre-treatment



Cycle 7 Day 2



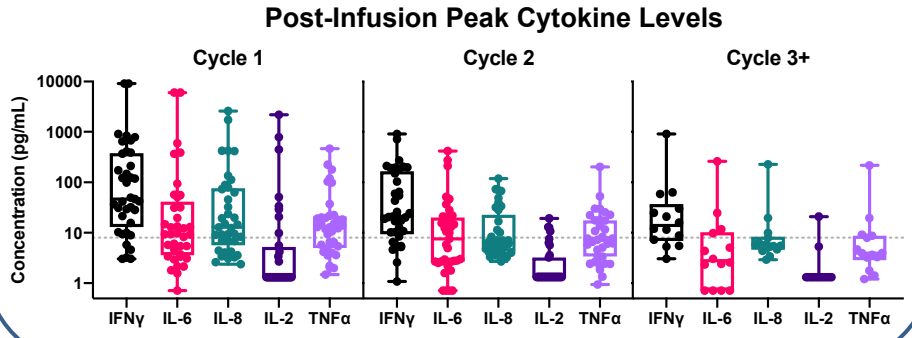
Dual IHC:
CD20
CD3

- 3 of 3 patients with pre-/post-biopsy had CD20 decrease/CD3 increase
- 2 of 4 CR patients with tissue available had low CD20 expression at baseline (H-score=15 and 30)

IGM-2323 induces potent T-cell effector cytokines while minimizing cytokines associated with CRS

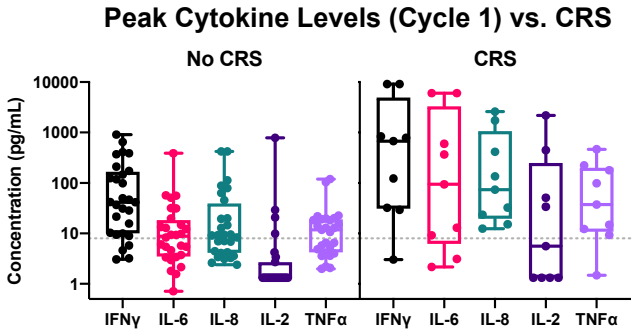
IGM-2323 induces IFNγ dominant immune activity in majority of patients

- Biologically active dose starting at 10 mg
- Transient cytokine elevations (~2–12 hours) over multiple infusions



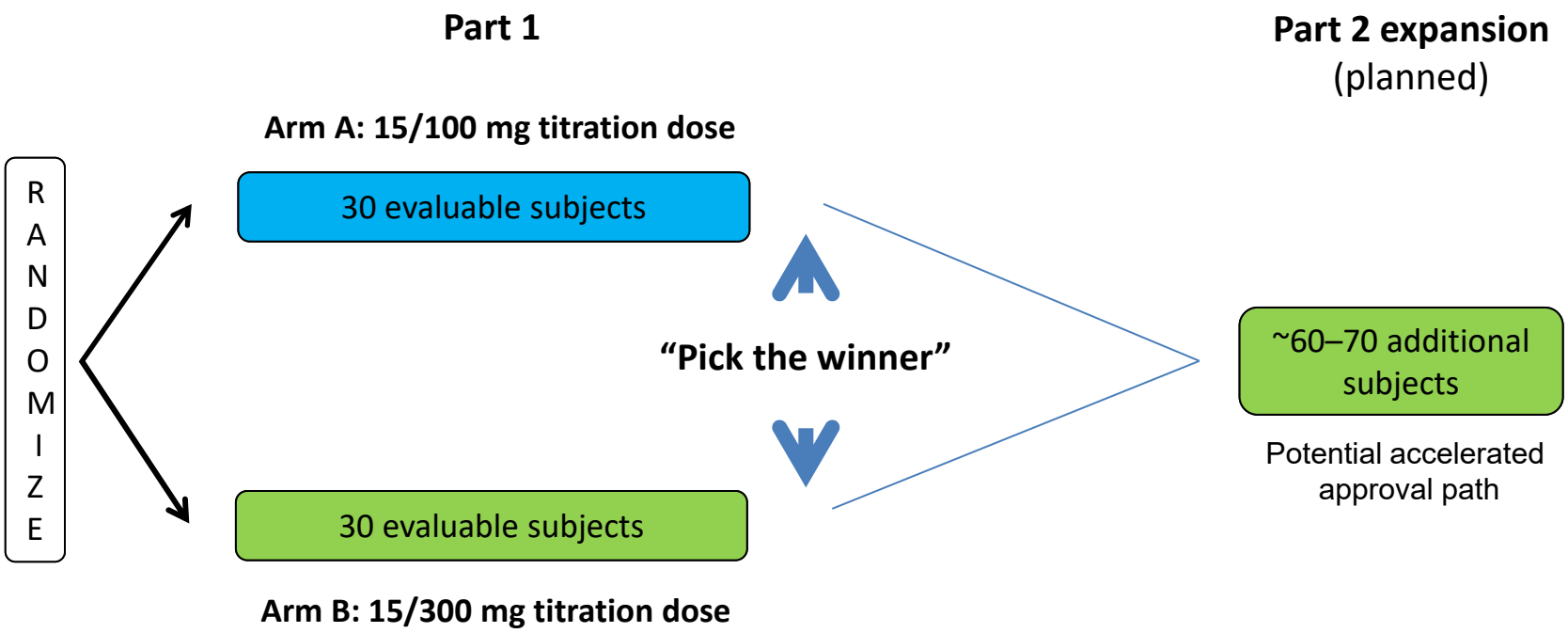
Poly-cytokine response may be associated with CRS

- Timing of poly-cytokine increase matches CRS onset



Box plots show highest concentration of plasma cytokines from n=39 patients. Dotted line indicates median of baseline cytokine levels

Phase 2 randomized dose-selection studies[a]



[a]There will be two dose-selection studies: one in DLBCL; the other in FL

Conclusions

IGM-2323 is active against R/R NHLs and demonstrates a highly favorable safety profile

- Active in heavily pre-treated NHLs with evidence of prolonged DOR as a single agent, including those who have received prior CAR-T
- Low rates of grade 2 or higher CRS, no ICANS, and minimal neutropenia
- Repeatable IFNγ dominant T-cell activation due to a potentially more physiologic immune stimulation, which is in contrast to other T-cell engagers

Phase 2 randomized dose-selection studies underway

- Select optimal phase 2 dose in R/R DLBCL and FL, aligning with FDA guidance (Project Optimus)
- Further exploration of q3 week dosing after first cycle

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  - Study sites and staff
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