Maturing Clinical Profile of IMGN779, a Next-Generation CD33-Targeting Antibody-Drug Conjugate, in Patients with Relapsed or Refractory Acute Myeloid Leukemia

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CD33-Targeting ADCs in AML

- **CD33 is a sialic acid binding receptor, expressed on the surface of the majority of AML blasts**
- **CD33 is an established ADC target in AML, as evidenced by the recent re-approval of gemtuzumab ozogamicin (Mylotarg®)**
- **Safety and efficacy limitations of existing CD33-targeting ADCs → opportunity for improvement**
- **Next generation CD33-directed ADCs with alternate MOAs and broader therapeutic windows may provide additional benefit for patients**

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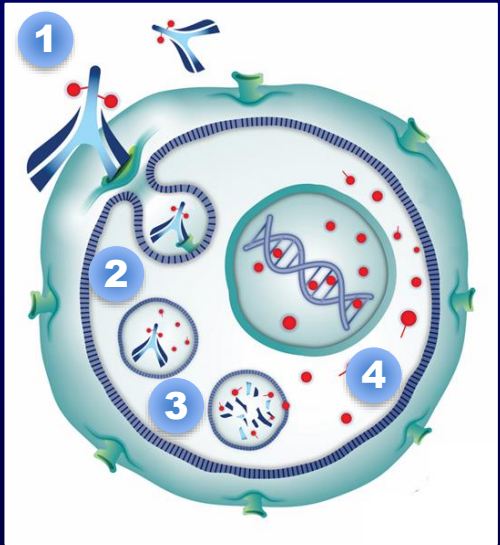
IMGN779
A Next-Generation CD33-Targeting ADC



1 - ADC binds target
2 - ADC internalized
3 - Payload released
4 - Payload alkylates DNA

- High-affinity, humanized anti-CD33 antibody
- Novel DNA-alkylating payload, DGN462, with potent preclinical anti-leukemia activity
- IGNs: novel cytotoxic payload class[1]
  - single strand DNA breaks (vs. double strand breaks)
  - better therapeutic index relative to cross-linking payloads[2]

[1]Miller 2016 *Mol Cancer Ther* 15:1870-78; [2]Miller 2018 *Mol Cancer Ther* 17:650-660

IMGN779 Phase 1 Study
Study Objectives

Primary

- **Establish the MTD and RP2D of IMGN779 administered as monotherapy using once every two weeks (Q2W) and once weekly (QW) dosing schedules**

Secondary

- **Evaluate safety and tolerability of IMGN779, including determination of dose-limiting toxicities (DLT)**
- **Characterize the preliminary antitumor activity, pharmacokinetic (PK), and pharmacodynamic (PD) profiles**

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IMGN779 Phase 1 Study
Study Design

- Adults (≥18 years) with relapsed or refractory CD33^{+} AML
- CD33^{+} defined as ≥20% of blasts expressing CD33 by local flow cytometry
- Dose escalation follows a 3+3 design
- Two schedules tested
  - Q2W: administered i.v. on Days 1 and 15 of a 28-day cycle
  - QW: administered i.v. on Days 1, 8, 15, and 22 of a 28-day cycle

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IMGN779 Phase 1 Study
Dose Escalation and Patient Allocation

Dose (mg/kg)	0.02	0.04	0.08	0.16	0.26	0.39	0.54	0.7	0.91	1.2	1.5	Total	
Q2W schedule	3	3	3	3	5*	3	3	4*	3	3	3	36	57
QW schedule	-	-	-	-	-	7*	6*	5*	-	3		21	

- **Based on PK/PD and safety data through 0.54 mg/kg Q2W, opening of the QW schedule was initiated at the 0.39 mg/kg dose**

* Includes replaced and expansion patients

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IMGN779 Phase 1 Study
Patient Demographics

Characteristic (N = 57)		Median [range], or N (%)
Age, y		68 [26-88]
Sex	Female	31 (54)
Prior therapy*	Non-intensive only	17 (30)
	Intensive	40 (70)
Prior SCT		9 (16)
Disease status	First relapse	13 (23)
	Primary refractory	16 (28)
	Relapsed refractory	28 (49)

* Non-intensive therapy includes HMA, IDH inhibitors; intensive therapy includes 7+3, HiDAC, Vyxeos, SCT

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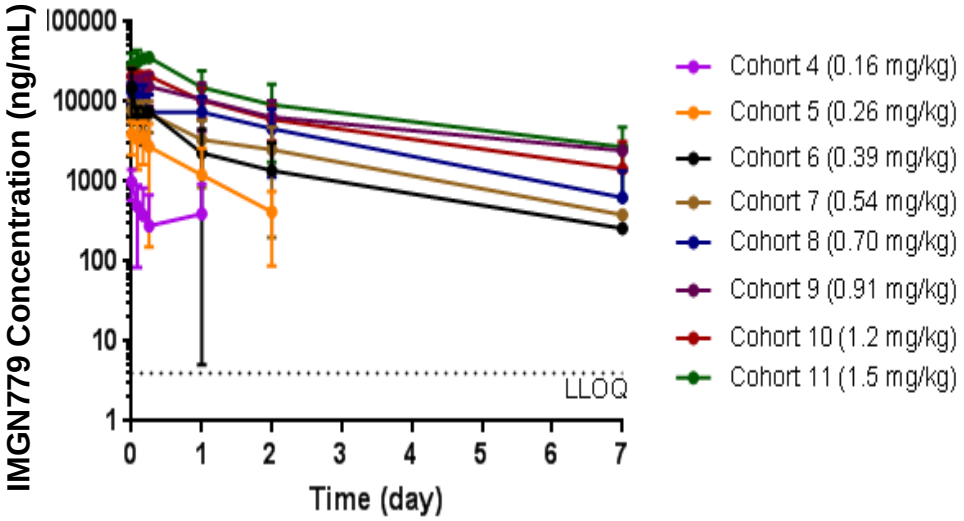
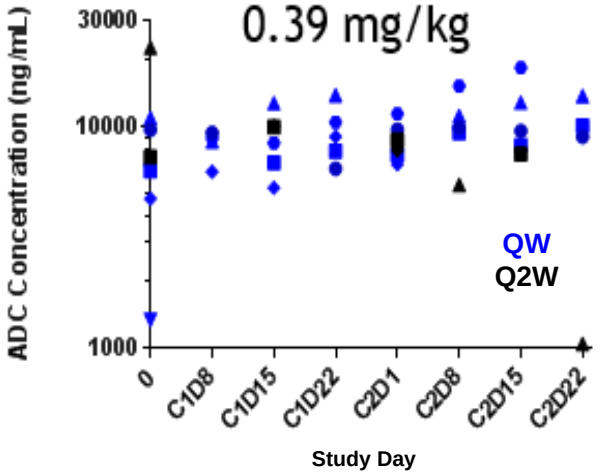
Pharmacokinetics





Preliminary analyses

- **Plasma IMGN779 concentrations indicate consistent and sustained exposure through 7 days at doses ≥0.39 mg/kg**
- **With QW dosing, trend for modestly higher end of infusion values with 0.39 mg/kg compared to Q2W schedule; similar for 0.54 and 0.7 mg/kg doses**

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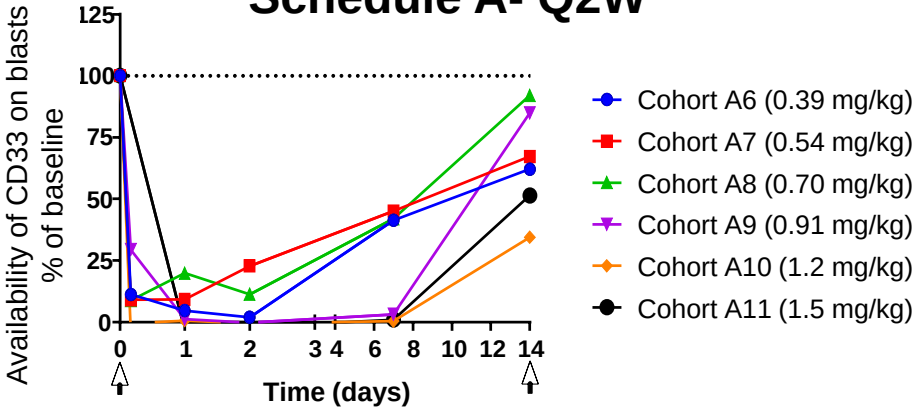
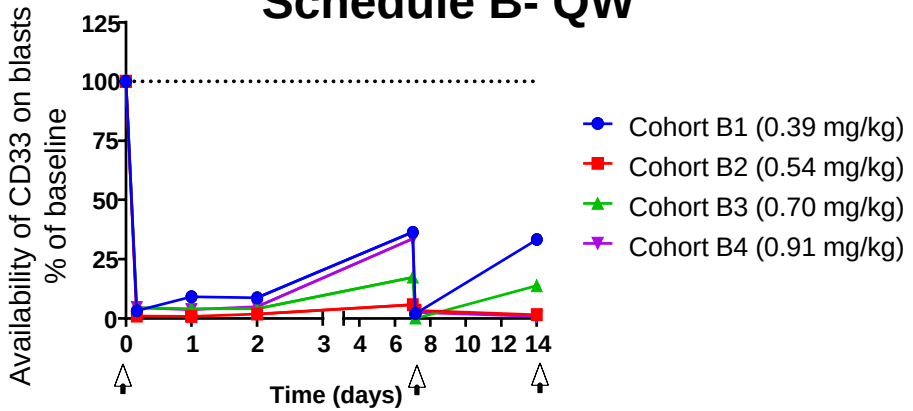
IMGN779 Phase 1 Study
Pharmacodynamics: CD33 saturation

Schedule A- Q2W



Schedule B- QW



Preliminary analyses

- **Q2W Schedule: Complete CD33 saturation is transient (<14 days)**
- **QW Schedule: More consistent saturation than Q2W schedule**

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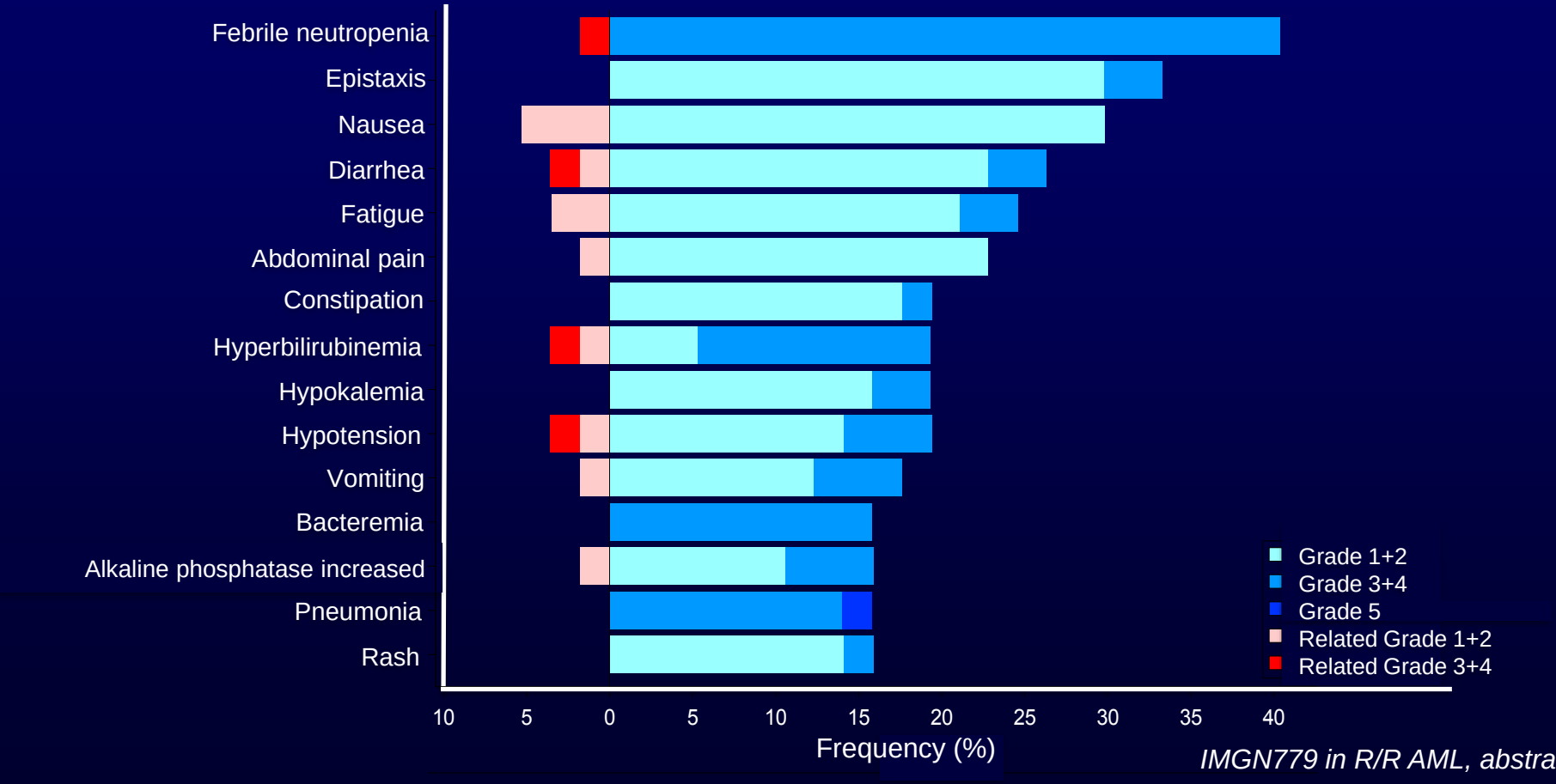
IMGN779 Phase 1 Study
Treatment-Emergent Adverse Events >15%



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IMGN779 Phase 1 Study
Safety Summary

- Median number of doses administered: 4 (range, 1-40)
- Most frequent SAEs infection-related: febrile neutropenia (37%), bacteremia (14%), and pneumonia (14%)
  - Three SAEs considered related to IMGN779: Grade 3 infusion-related reaction (n=2), and febrile neutropenia (n=1)
- No pattern of dose-dependent hepatotoxicity
  - Hyperbilirubinemia (19%), ALT elevation (14%)
  - One DLT (1.2 mg/kg QW): VOD with acute kidney injury (fatal)
- 10 deaths within 30 days of last dose: pneumonia / respiratory (n=6), sepsis / multi-organ (n=2), VOD (n=1) and myocardial infarction (n=1)

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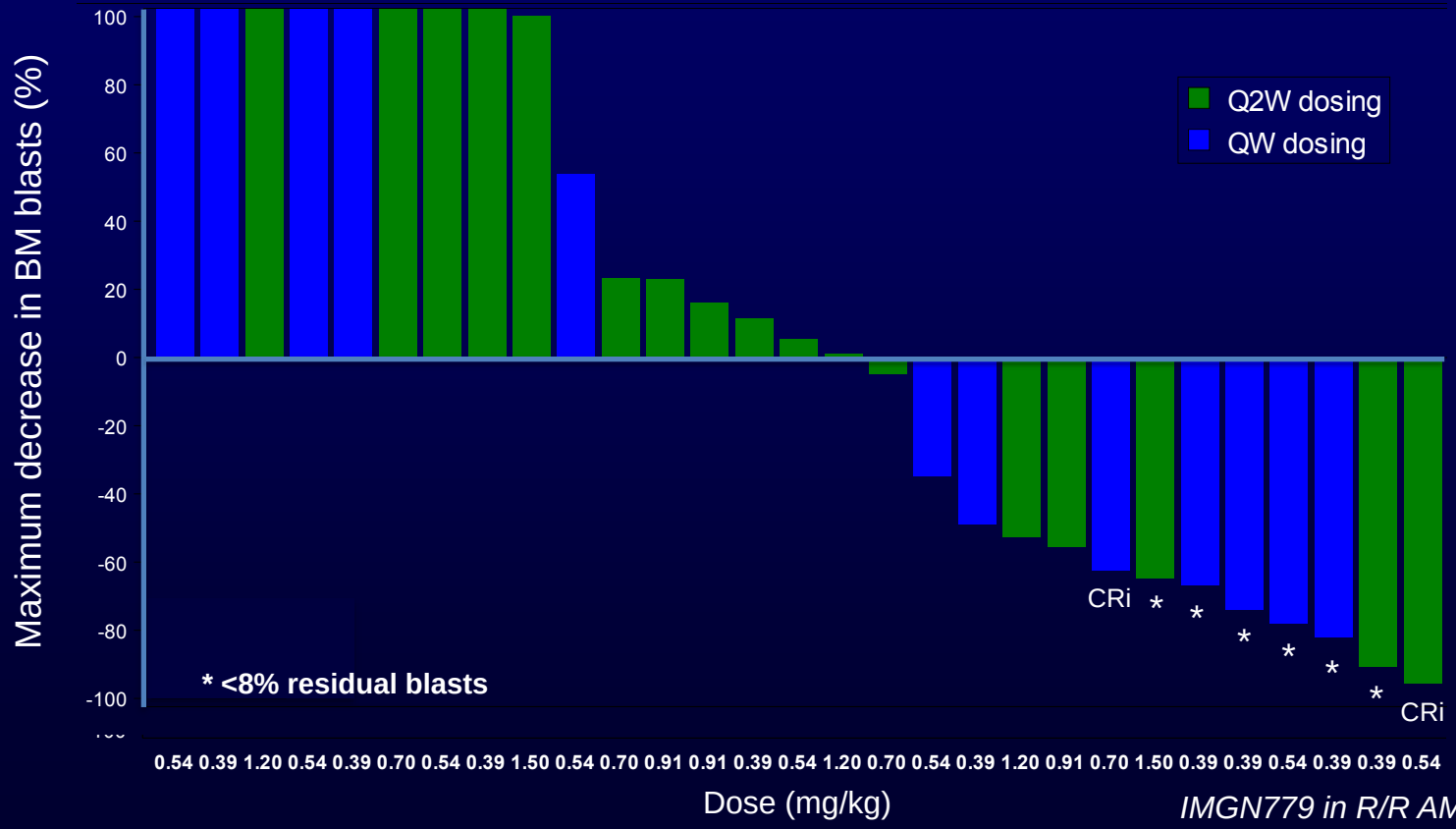
IMGN779 Phase 1 Study

Best Decrease in Bone Marrow Blasts

(Q2W and QW dosing, ≥0.39 mg/kg)



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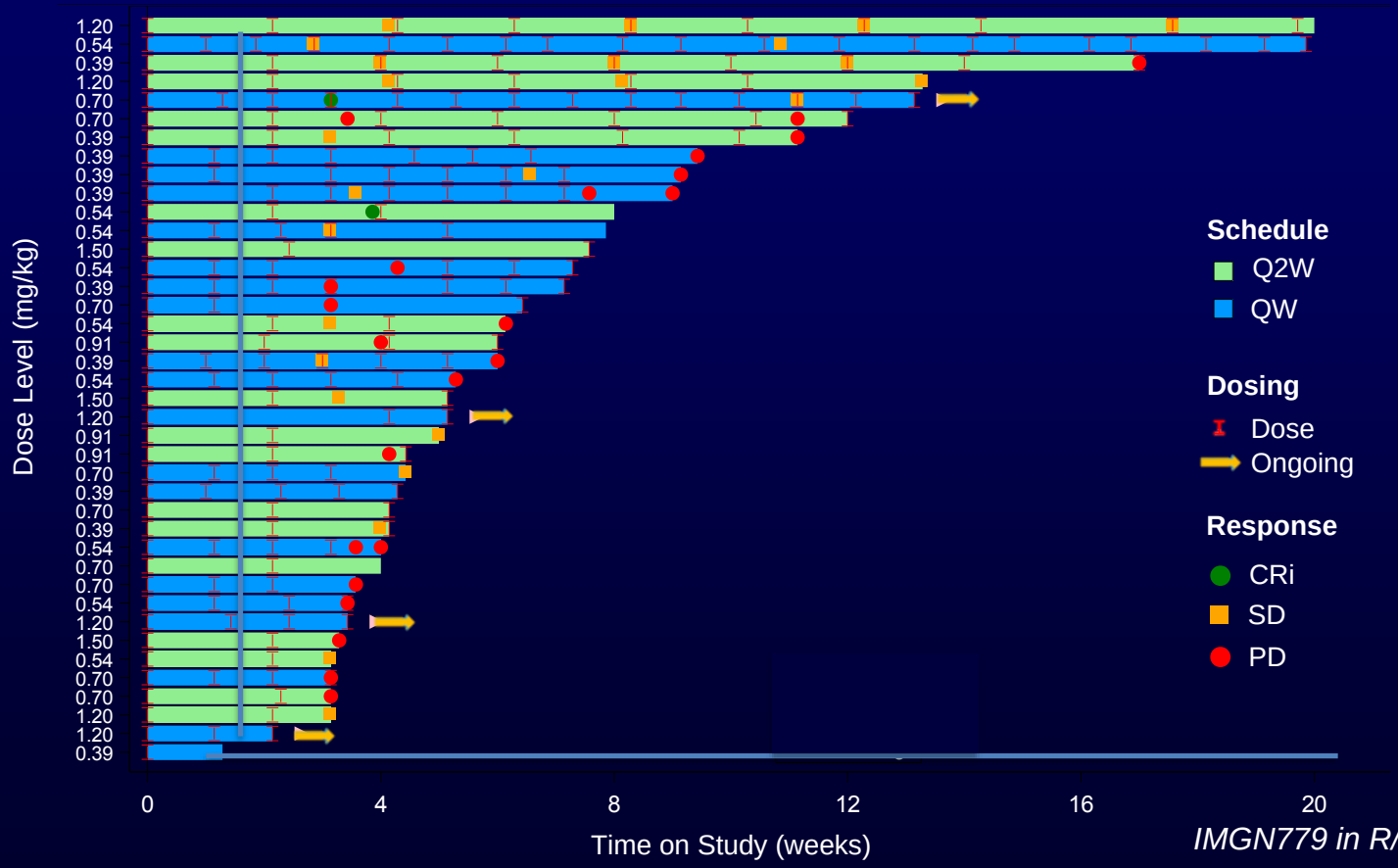
Time on Study (Q2W and QW dosing, ≥0.39 mg/kg)



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IMGN779 Phase 1 Study
Conclusions

- IMGN779 displays tolerability with repeat dosing across a wide range of doses in patients with relapsed AML
  - Limited cytopenias, one DLT reported
  - AEs consistent with underlying disease
  - No cumulative toxicity following multiple doses (up to 40 doses)
- IMGN779 demonstrates anti-leukemia activity in 41% (12 of 29) patients with evaluable bone marrows (≥0.39 mg/kg), although with limited CR/CRis at doses examined to date
- Enrollment continues to identify the RP2D and schedule, which may warrant further development as combination therapy in AML

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Thank you to the patients and families