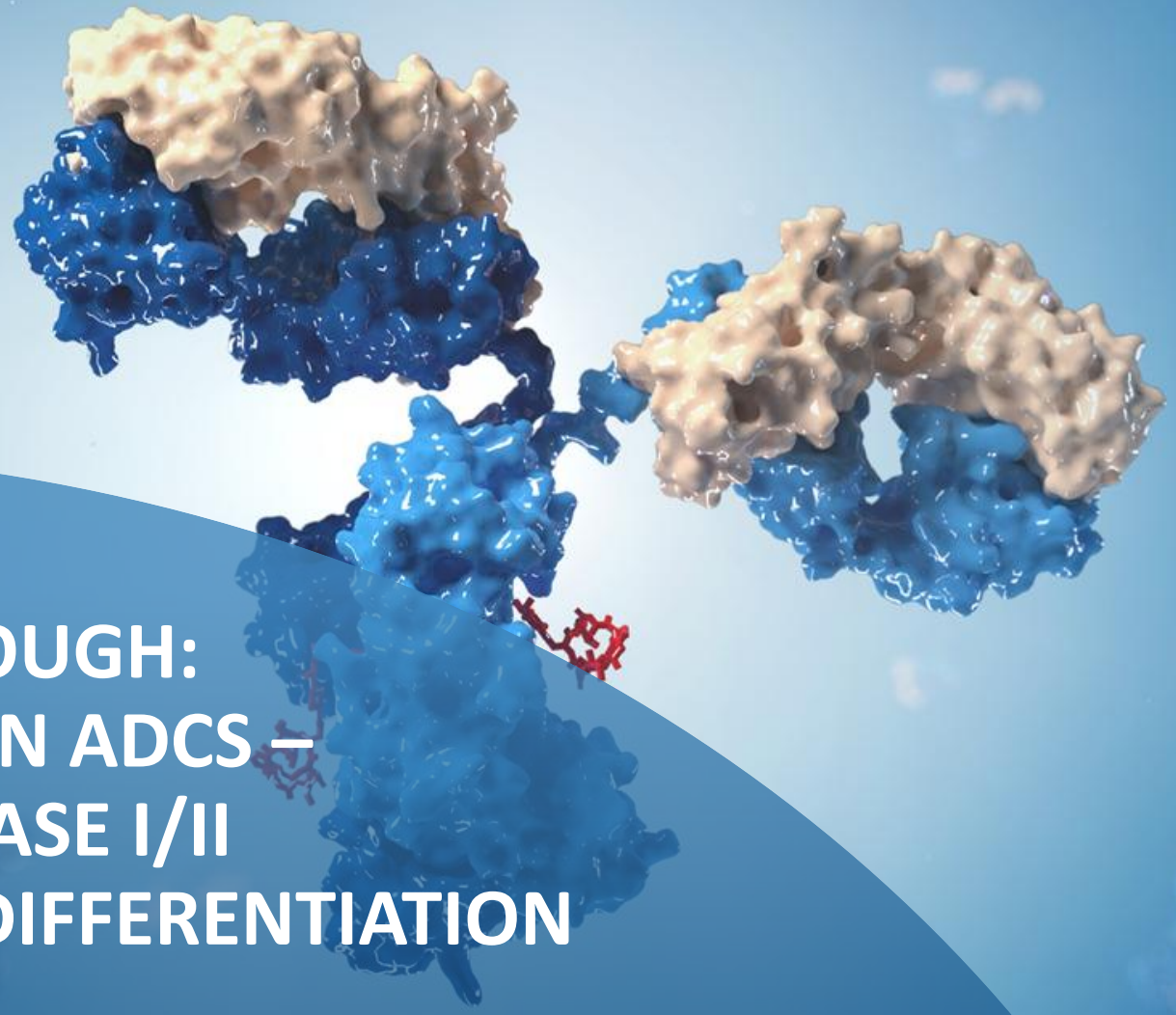
Heidelberg PHARMA



FROM BENCH TO BREAKTHROUGH: THE EVOLUTION OF AMANITIN ADCS – INSIGHTS FROM HDP-101 PHASE I/II & THE FUTURE OF PAYLOAD DIFFERENTIATION

Andreas Pahl, CEO Heidelberg Pharma

16th World ADC Conference – San Diego

Safe Harbor

FORWARD LOOKING STATEMENTS

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Such factors include, among others, the following: uncertainties related to results of our clinical trials, the uncertainty of regulatory approval and commercial uncertainty, reimbursement and drug price uncertainty, the absence of sales and marketing experience and limited manufacturing capabilities, attraction and retention of technologically skilled employees, dependence on licenses, patents and proprietary technology, dependence upon collaborators, future capital needs and the uncertainty of additional funding, risks of product liability and limitations of insurance, limitations of supplies, competition from other biopharmaceutical, chemical and pharmaceutical companies, environmental, health and safety matters, availability of licensing arrangements, currency fluctuations, adverse changes in governmental rules and fiscal policies, civil unrest, acts of God, acts of war, and other factors referenced in this communication.

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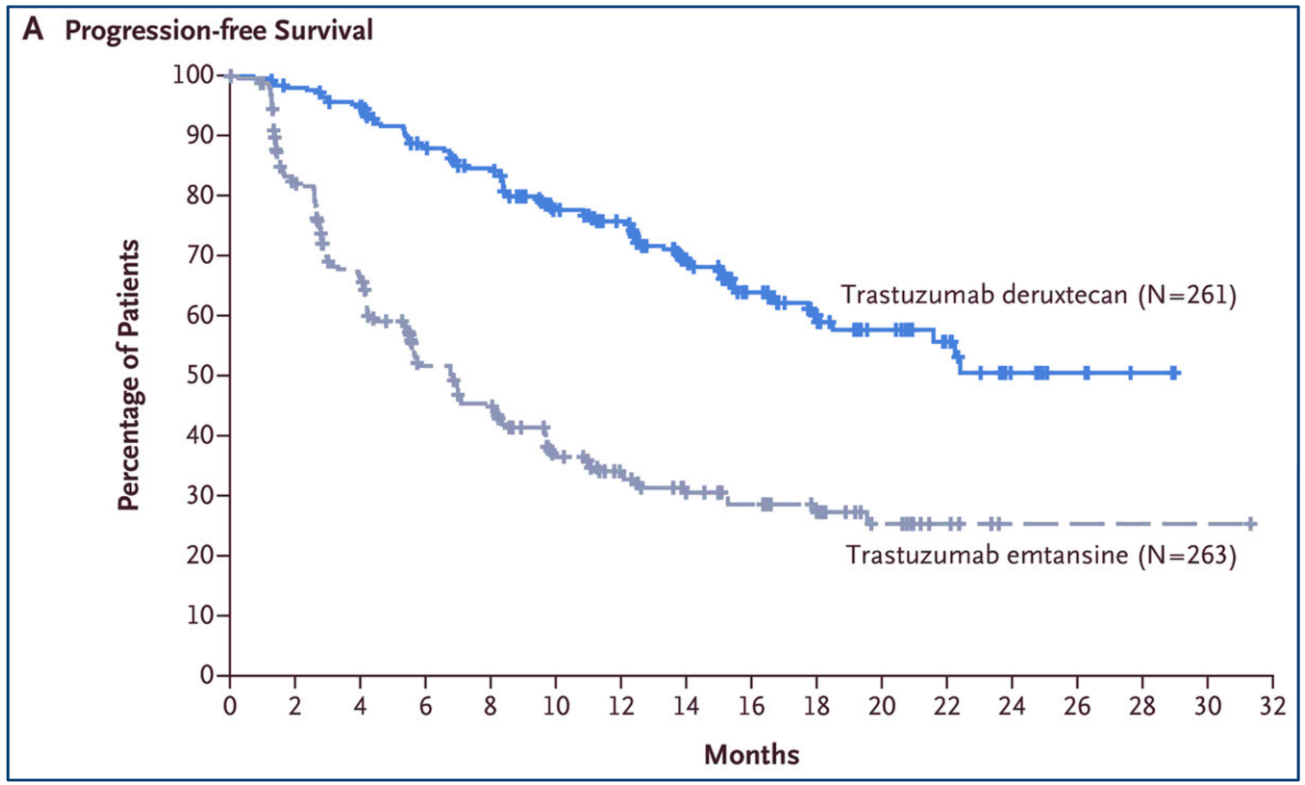
ATAC® is a registered trademark of Heidelberg Pharma Research GmbH.

The ADC Payload MOA Dramatically Impacts Tumor Response



Cortés, J. et al, N Engl J Med 2022; 386:1143-1154

— Enhertu®
Payload: deruxtecan (Topo 1 inhibitor)

— Kadcyla®
Payload: emtansine (Tubulin inhibitor)

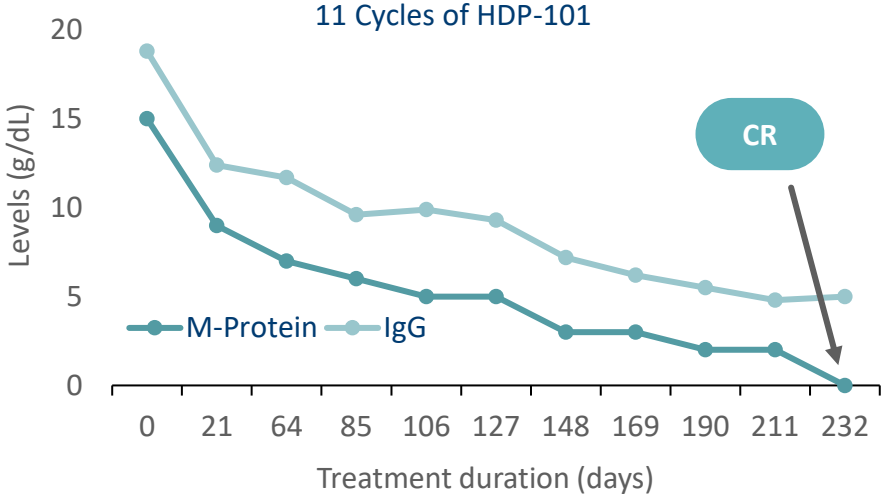
Same target (Her2), same antibody (Trastuzumab), in the same patient population

* MOA = mode of action

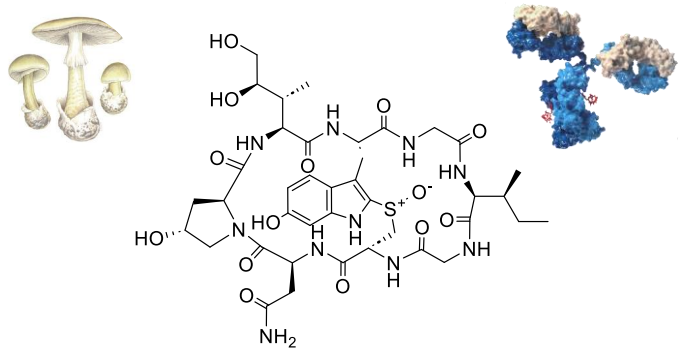
Heidelberg Pharma's Proprietary Amanitin Payload Technology to Generate a Disruptive New Class of ADCs

Novel MoA
Overcoming resistance

M-Protein & IgG Change Over
11 Cycles of HDP-101



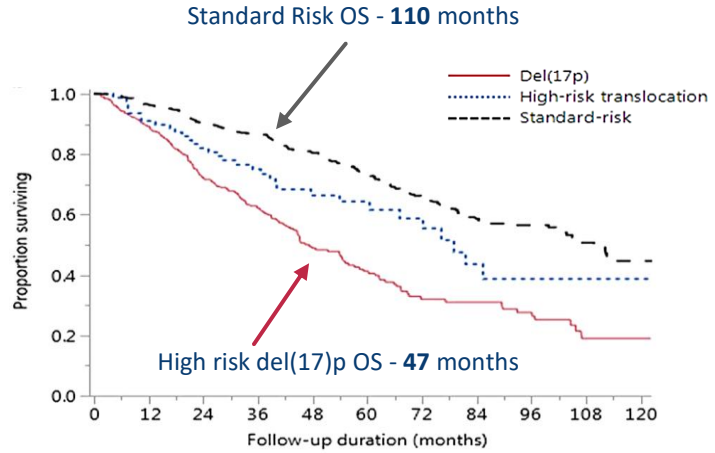
Single Player



26 Patent families

>500 Family members

Biomarker for Stratification of High-risk Patients



Lakshman et al., 2019; Blood Cancer J. PMID 30846679

First Amanitin-based ADC led to CR in 10th Line in a RRMM Patient

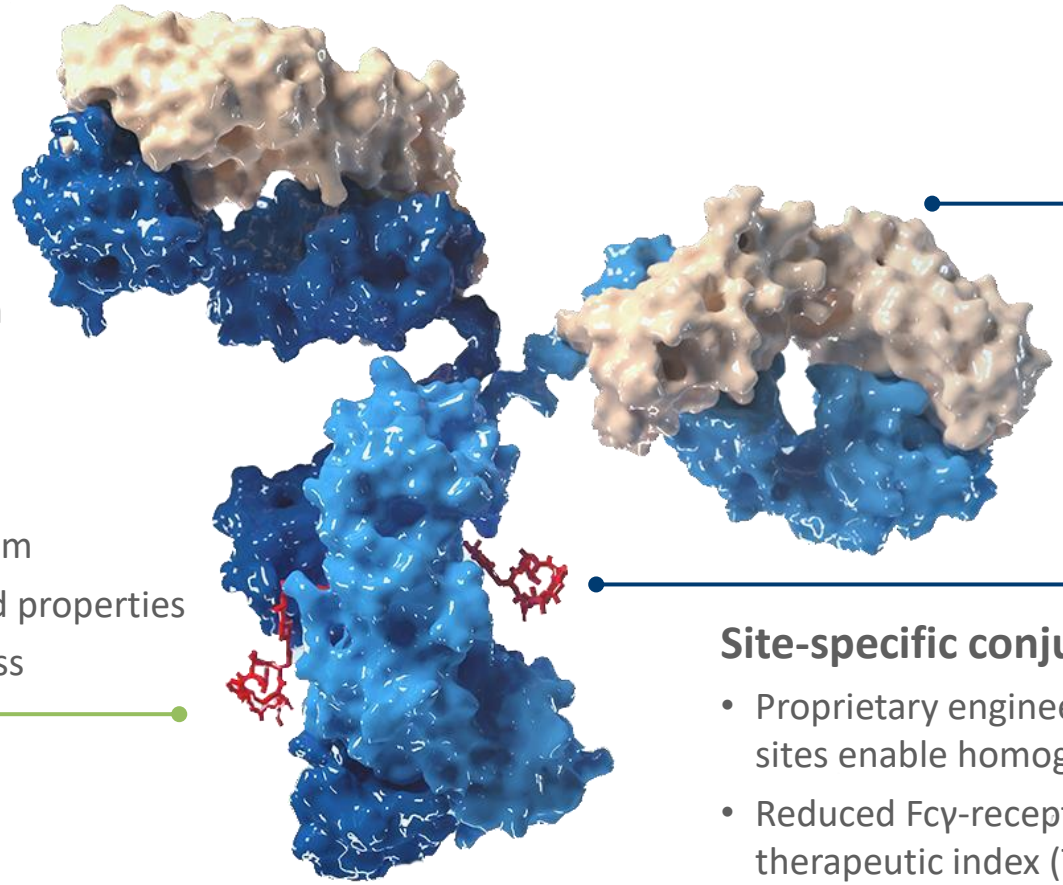
Exclusivity on Compound and Mode of Action

Amanitin is More Effective in del(17p) Patients

ATAC - Innovative ADCs With Amanitin Payload

Payload: α-Amanitin

- Identified in Amanita phalloides mushroom
- Completely novel MOA:
  - Inhibition of RNA Polymerase II
  - Kills dormant/non-dividing tumor cells
  - Circumvents resistance via new mechanism
- Synthetic amanitin derivatives with improved properties
- GMP manufacturing via fully synthetic process



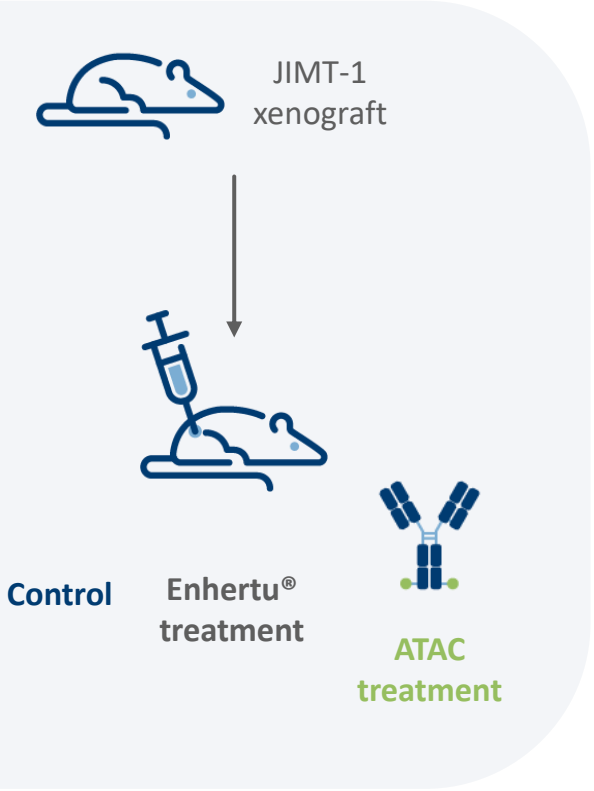
HDP-101 – anti-BCMA

Site-specific conjugation

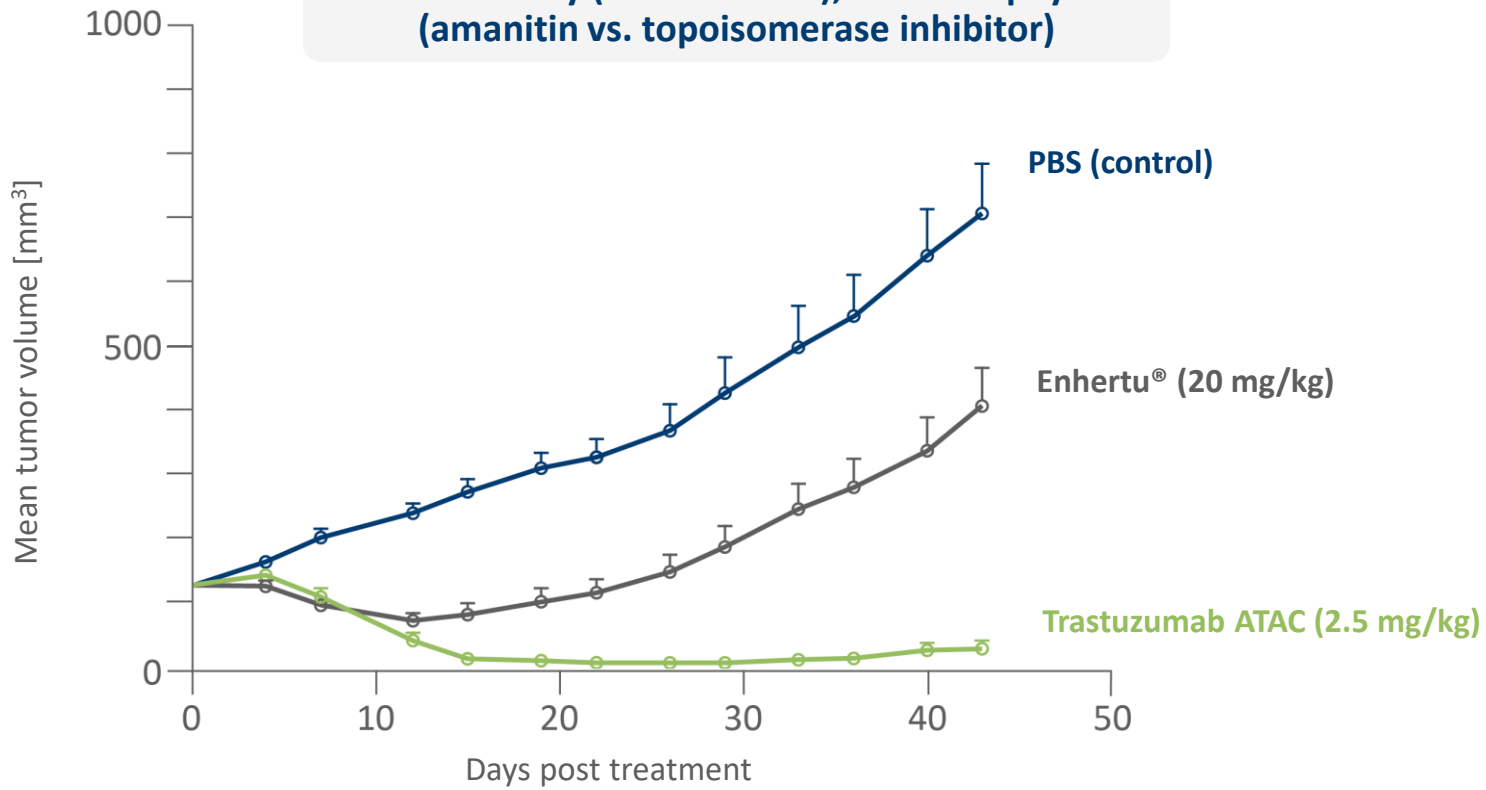
- Proprietary engineered cysteine conjugation sites enable homogenous ADC production
- Reduced Fcγ-receptor binding for improved therapeutic index (TI)
- Drug-Antibody Ratio (DAR) = 2.0

The Payload Makes the Difference

Breast Cancer Model (JIMT-1 Xenograft) is resistant to Kadcyla® and Enhertu®

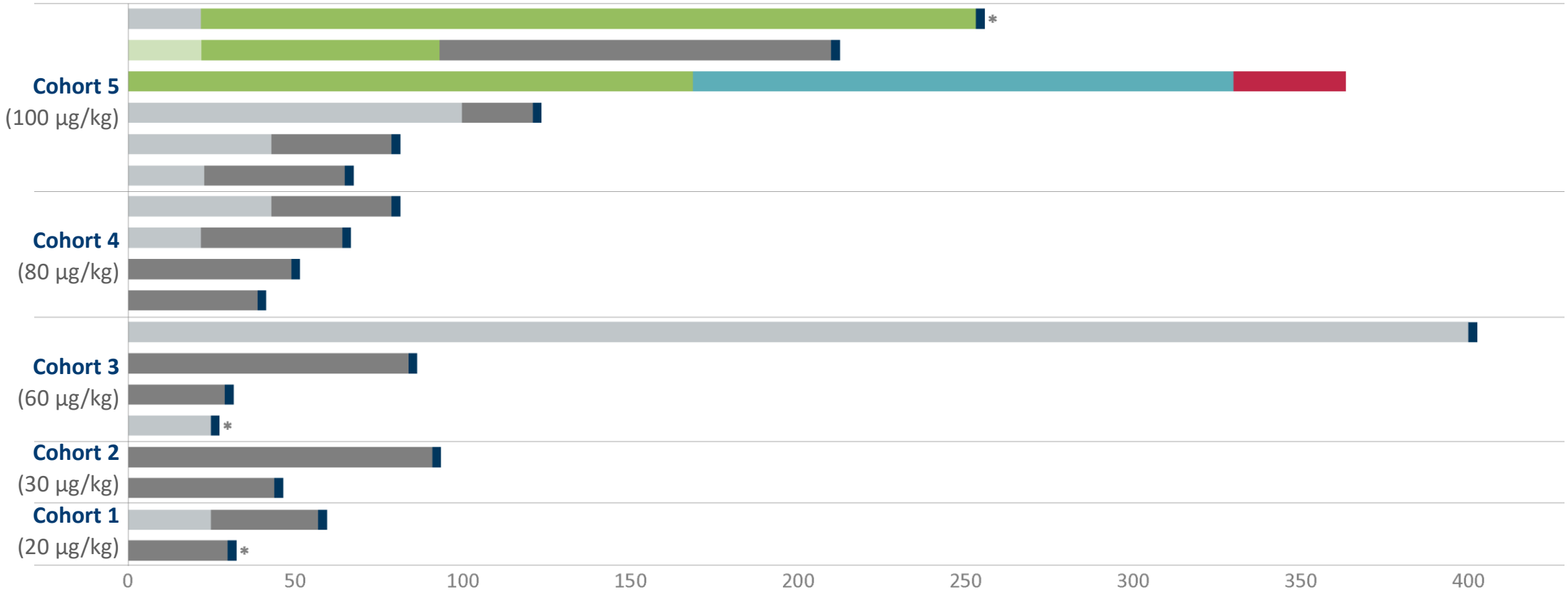


Same antibody (Trastuzumab), different payload (amanitin vs. topoisomerase inhibitor)



Trastuzumab ATAC leads to complete remission in resistant mouse model after single-dose

HDP-101-01 – Phase I Preliminary Efficacy Data (Cohort 1-5)



Readout: November 2024

Progressive disease (PD)
Stable disease (SD)
Minimal response (MR)
Partial response (PR)
Very good partial remission (VGPR)
Complete response (CR)
End of treatment
* Adverse Event, most likely myeloma related

Study Case: Cohort 5 Stringent Complete Response

70 Year Old Patient with Stage II IgG-Ķ Myeloma Since 2002

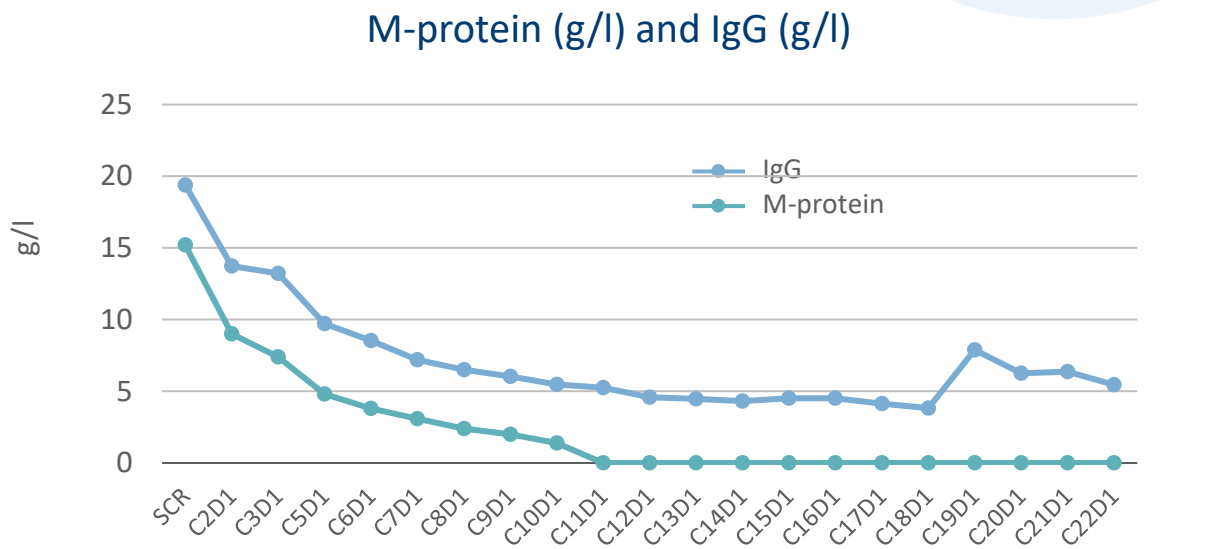
- 9 prior lines of therapies including transplant, IMiDs, PIs, and Daratumumab
- Last 3 treatment regimens & response:
  - **7th line**: BCMA CAR-T (Aug-2018) VGPR
  - **8th line**: GPRC5D/CD3 Bi-specific Antibody (Jul-2020) CR
  - **9th line**: Iber-Dex (Jan 2022) PR

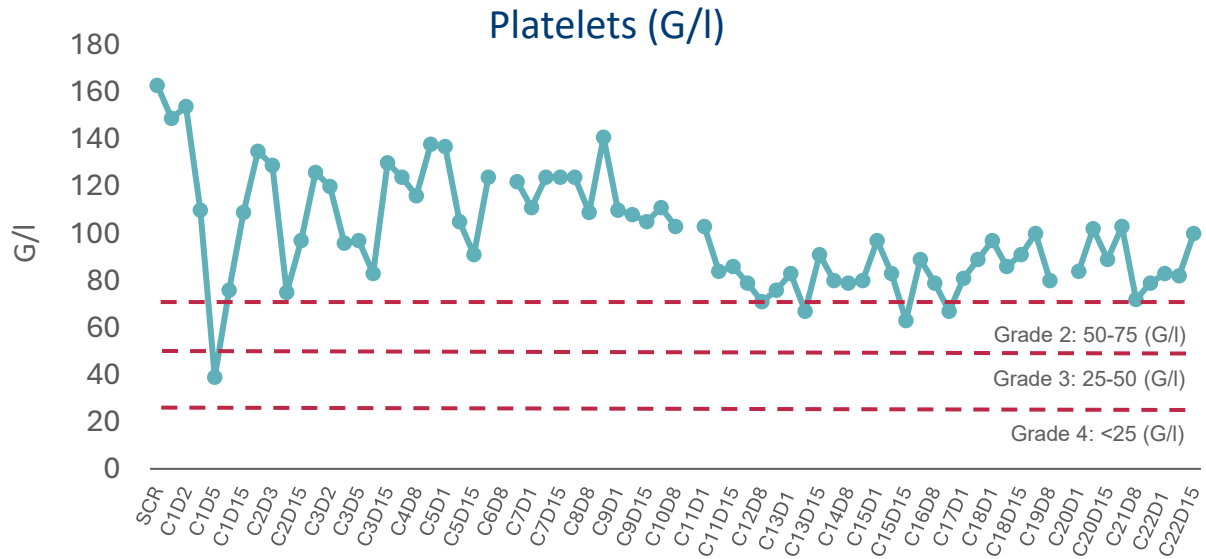
Started HDP-101 (100 µg/kg) in Oct 2023

- PR in cycle 2 (64 days of HDP-101)
- No detectable M-protein in blood from day 225
- sCR confirmed at day 344 (bone marrow biopsy)

Treatment well tolerated

- Overall mild AEs: No AESI, no DLT, no SAE
- No keratopathy, liver damage or lung toxicity
- No signs of ocular or renal toxicities
- Transient Grade 3 thrombocytopenia in cycle 1



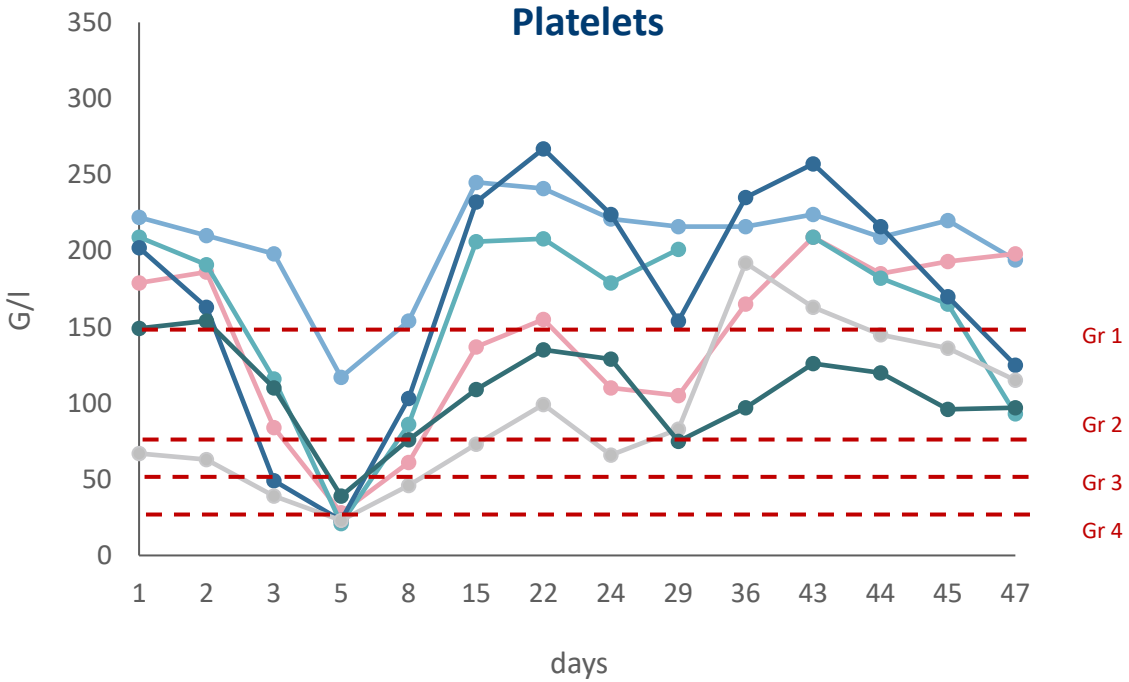


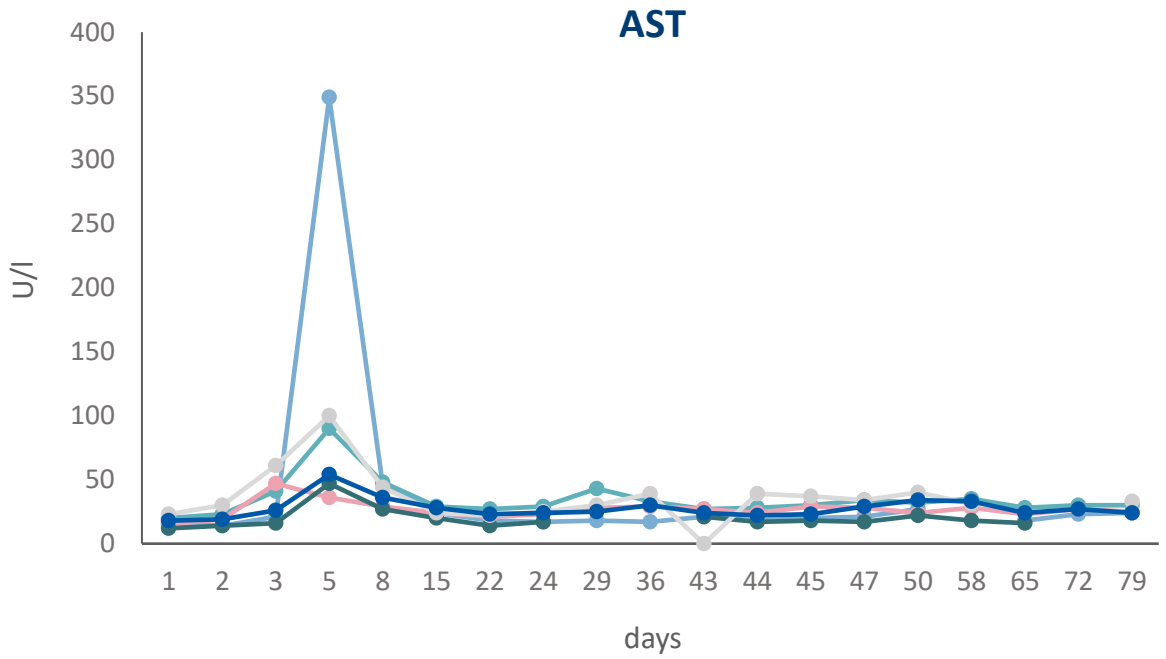
Readout: 15 May 2025

VGPR = very good partial response (>90% reduction from baseline of m-protein); IMiDs = immunomodulatory drugs; PIs = protease inhibitors; CR = complete response; PR = partial response; sCR = stringent complete response – absence of clonal plasma cells in bone marrow; AESI = adverse event of special interest; DLT = dose limiting toxicity; SAE = serious adverse events;

100 µg/kg Dosing Was Associated with Transient Thrombocytopenia and Liver Enzyme Elevation

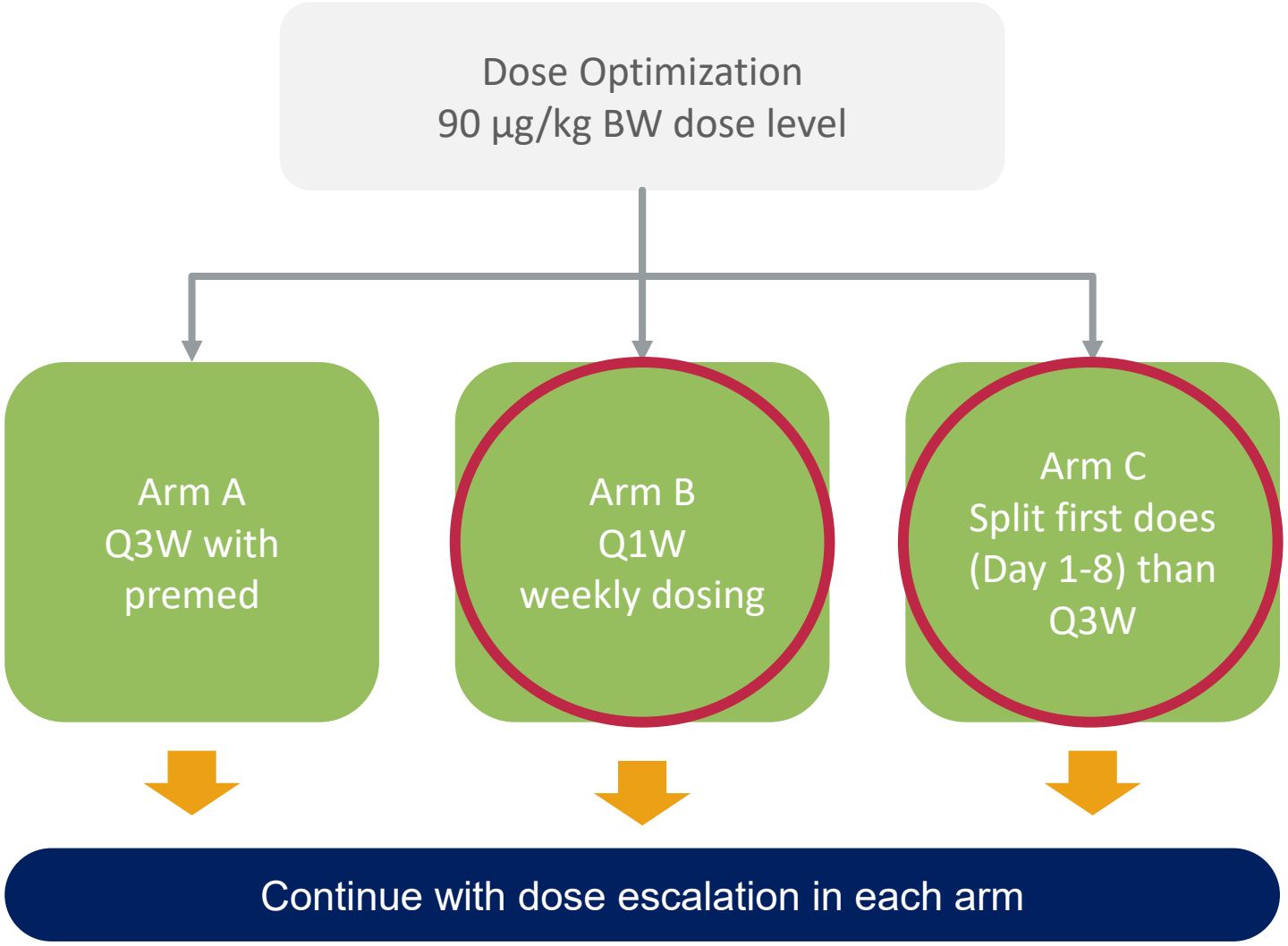
Cohort 5
(100 µg/kg)





Dose Optimization Strategies from Cohort 6

- Post-Cohort 5 Safety review: SRC recommended study continuation with mitigation strategies for transient thrombocytopenia
- Mitigation: corticosteroid/antihistamine premed, weekly dosing, split first-cycle dose, adjusted escalation and additional safety measures
- Cohorts 7-8: Arms B and C continued (Arm C with optional premed)
- One arm may be selected as the optimal Phase II dose for further development



HDP-101 Phase I/IIa Trial Design in Relapsed/Refractory Multiple Myeloma

Phase I: Dose Escalation

Q3W intravenous dosing, BLRM Design

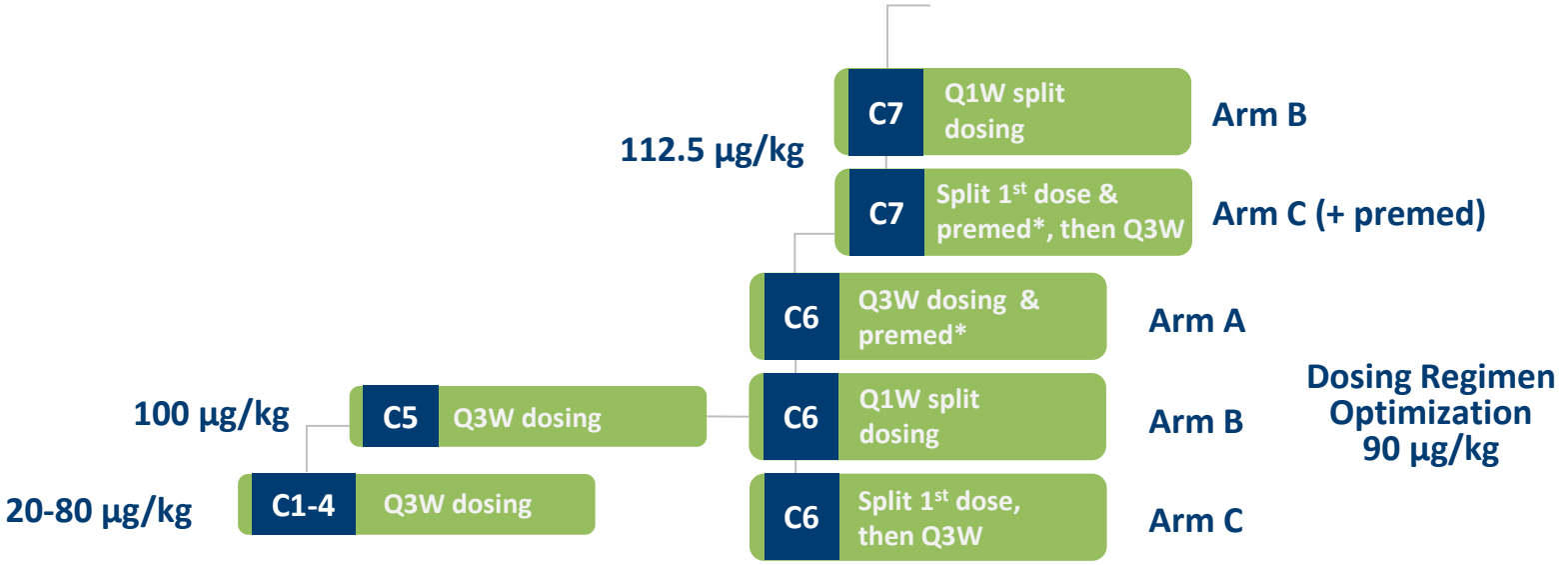
Objectives

Primary: MTD, RP2D

Secondary: Safety, Tolerability, PK, anti-tumor activity

RP2D Identification

Phase IIa: Dose Expansion



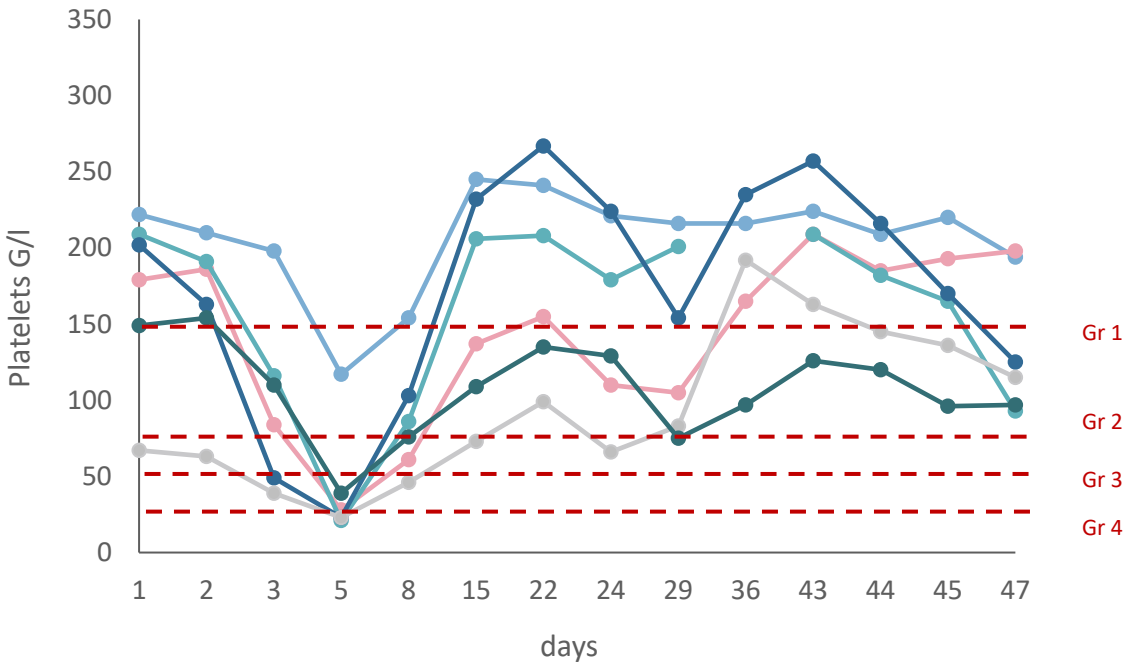
Key Eligibility Criteria

- Prior SCT or transplant ineligible
- Prior treatment with an immunomodulatory drug, proteasome inhibitor, and anti-CD38 treatment, alone or in combination
- Refractory or intolerant to any established standard of care therapy providing a meaningful clinical benefit for the patient

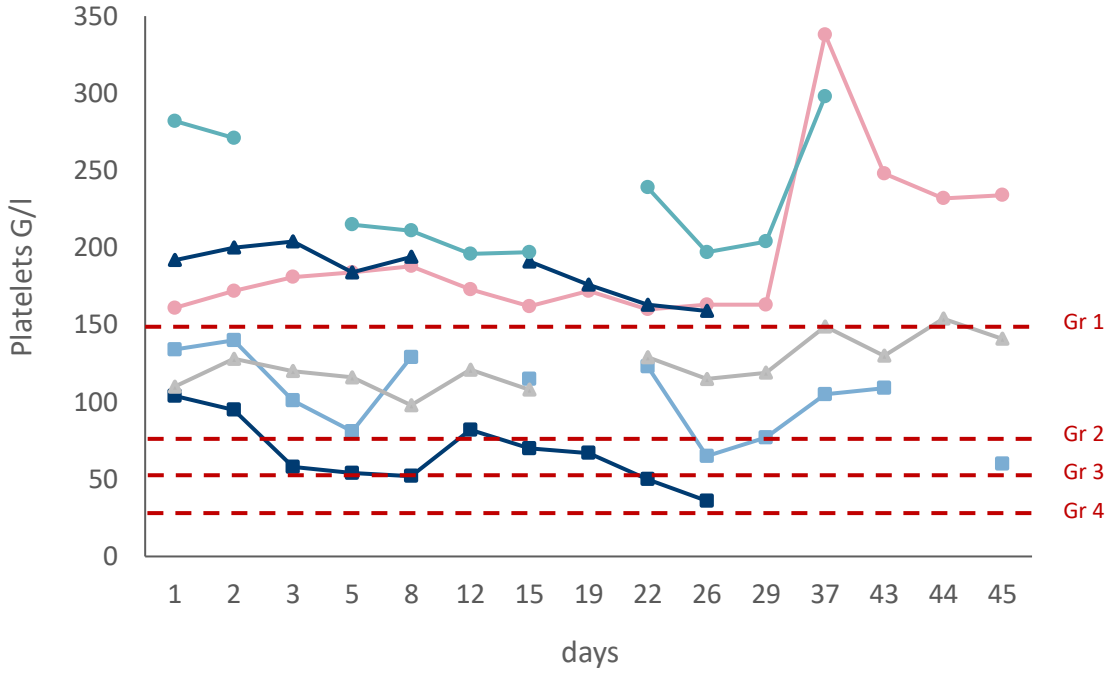
* NCT04879043; BLRM = Bayesian logistic regression model; DLT = dose-limiting toxicity; ORR = Objective response rate; PFS = progression free survival; OS = overall survival

New Treatment Strategies Had a Positive Effect on Thrombocytopenia

Cohort 5
(100 µg/kg)

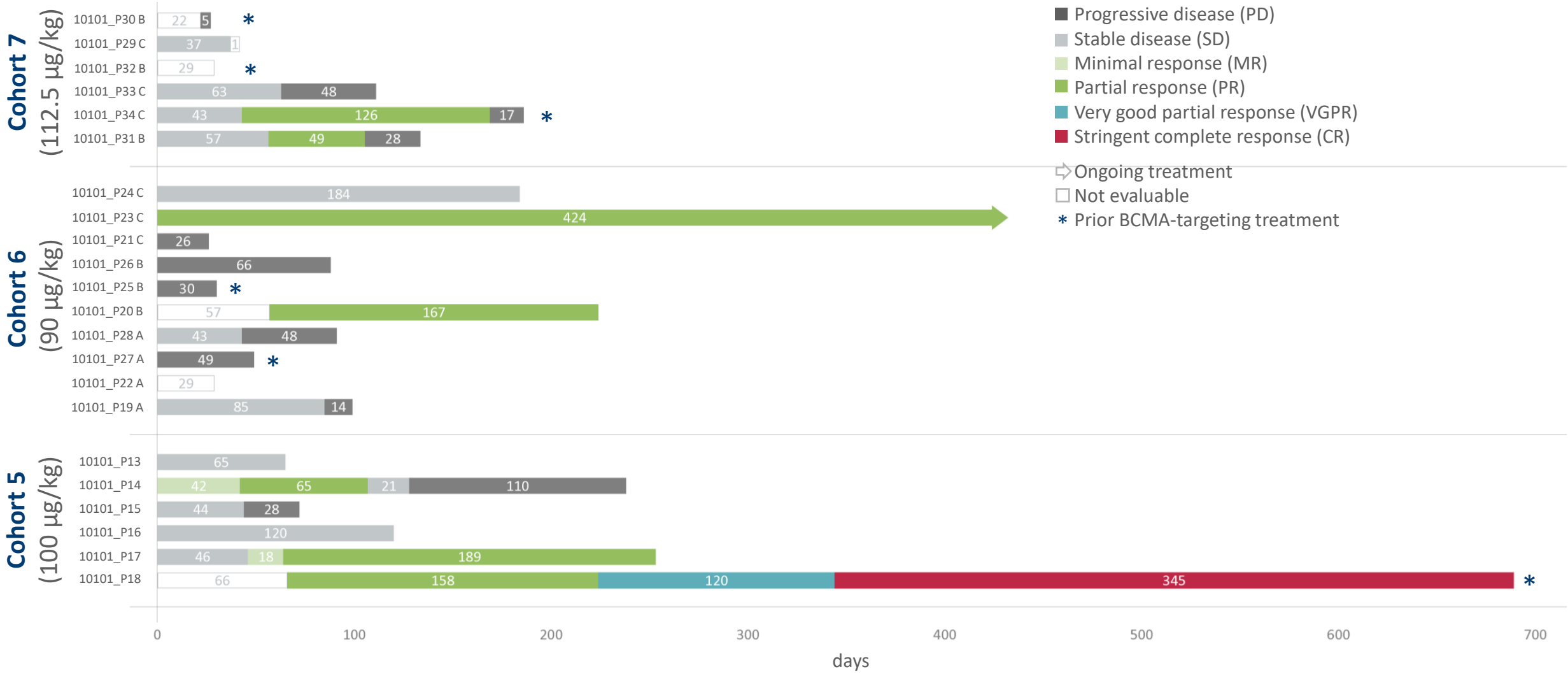


Cohort 7
(112.5 µg/kg)



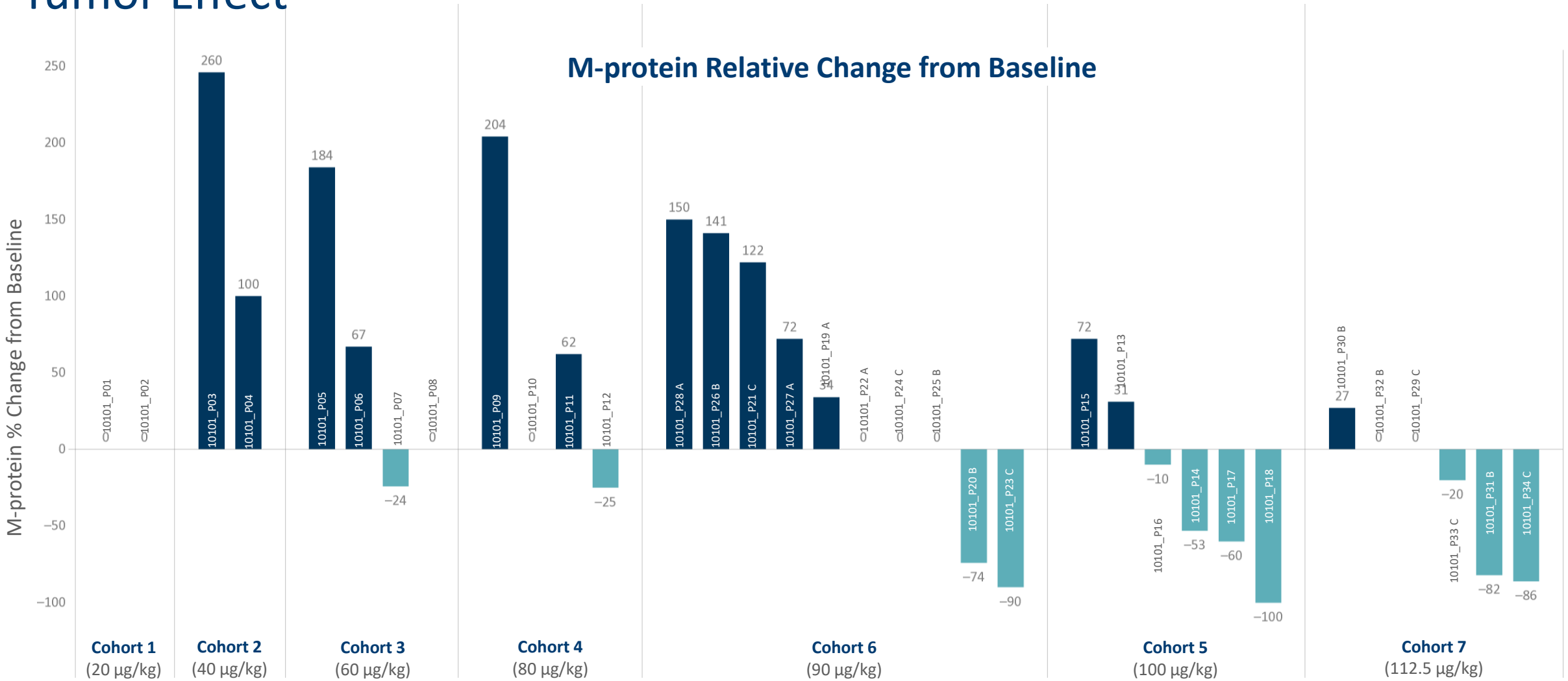
Dose Optimization from Cohort 6 to overcome transient thrombocytopenia after Cycle 1 and continue dose escalation

HDP-101 – Phase I Efficacy Data Cohort 5-7



Readout: 3 November 2025

Changes in the Dose Distribution Maintained the Anti-Tumor Effect



Note: Patients displayed with '0%' were not evaluable or not measurable for M-protein but had evidence of progressive disease and discontinued the study for progressive disease

Readout: 02 September 2025

HDP-101 Phase I/IIa Trial Design in Relapsed/Refractory Multiple Myeloma

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Q3W intravenous dosing, BLRM Design

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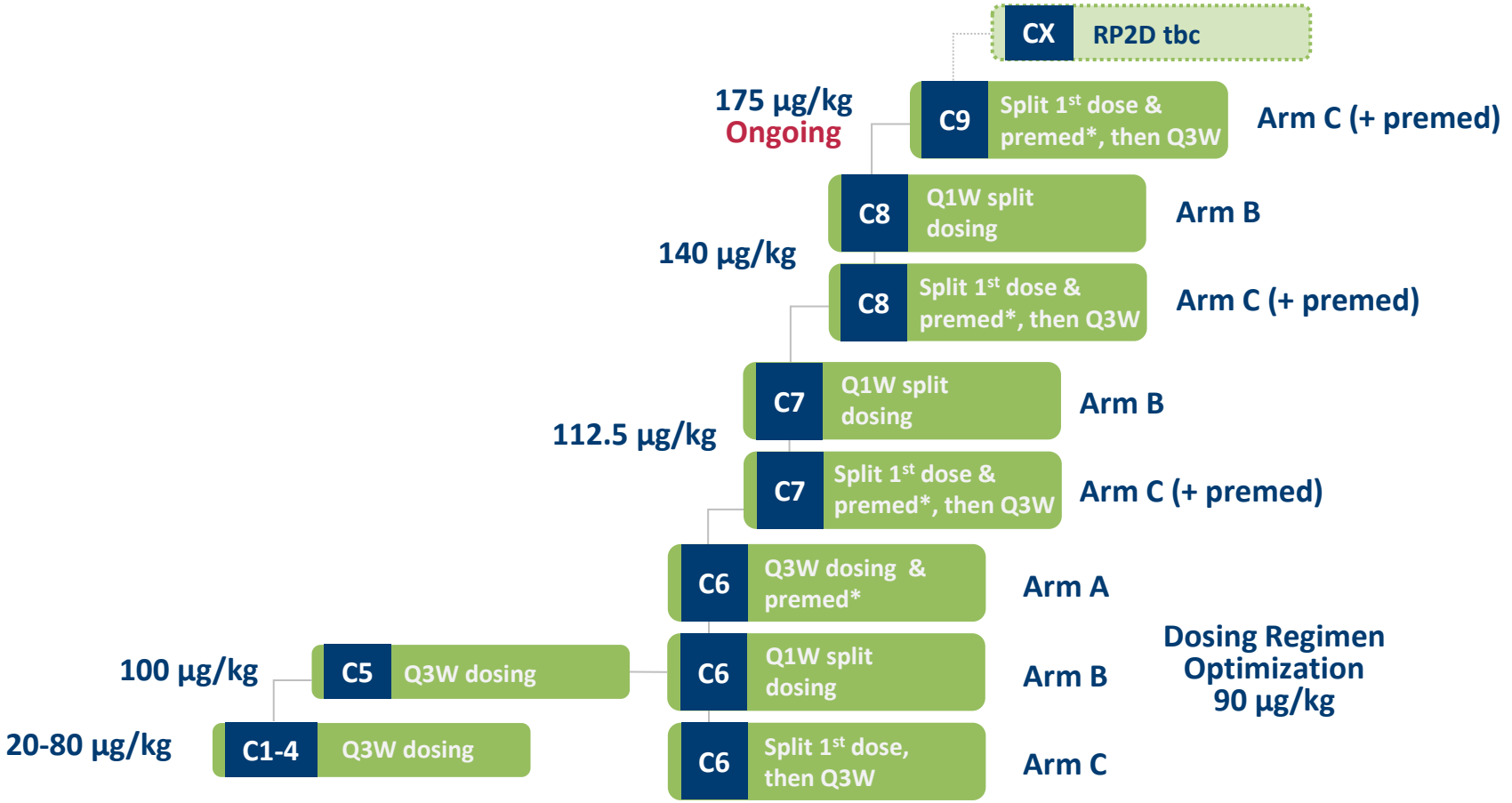
RP2D Identification

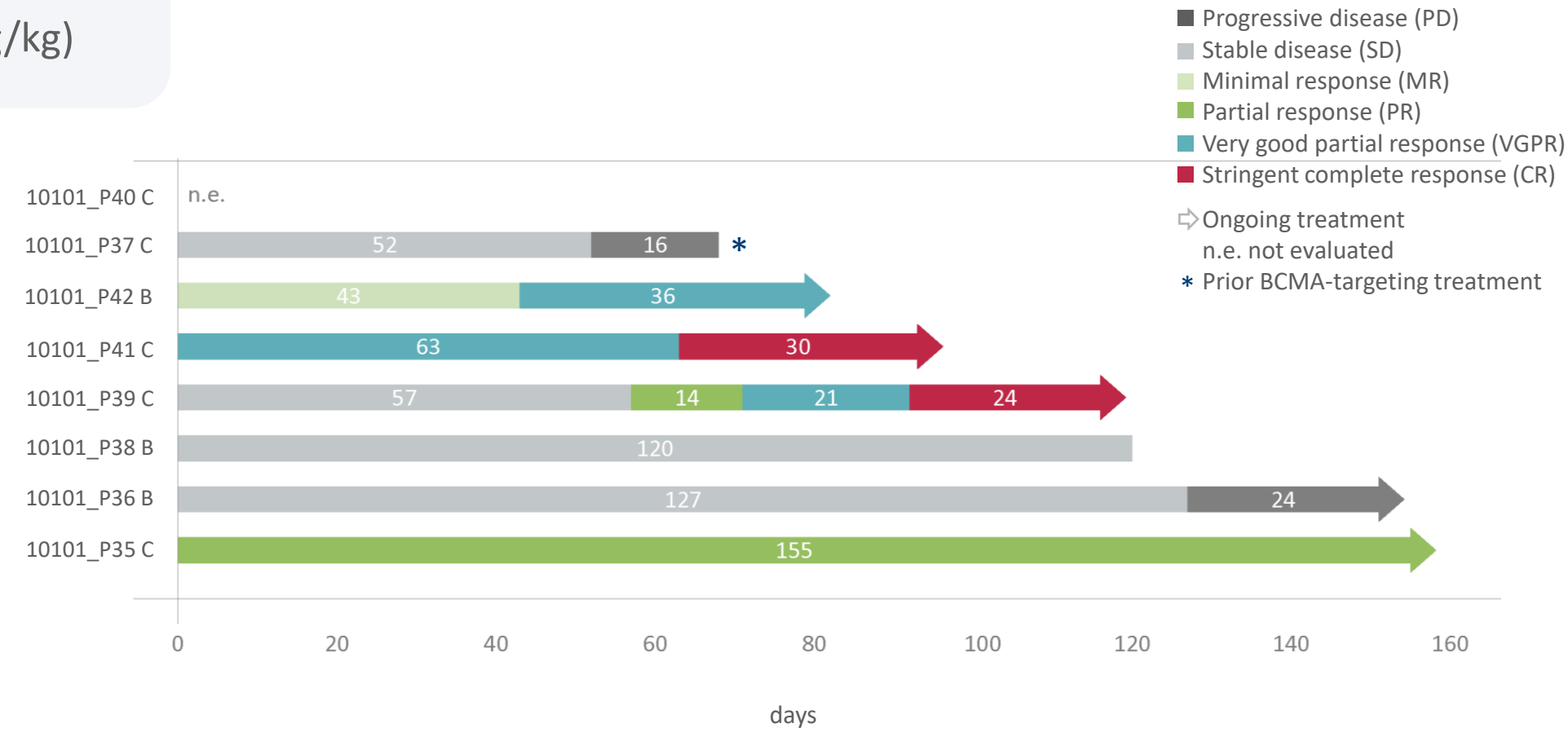
Phase IIa: Dose Expansion



* NCT04879043; BLRM = Bayesian logistic regression model; DLT = dose-limiting toxicity; ORR = Objective response rate; PFS = progression free survival; OS = overall survival

HDP-101 – Phase I Preliminary Efficacy Data (Cohort 8)

Cohort 8
(140 µg/kg)

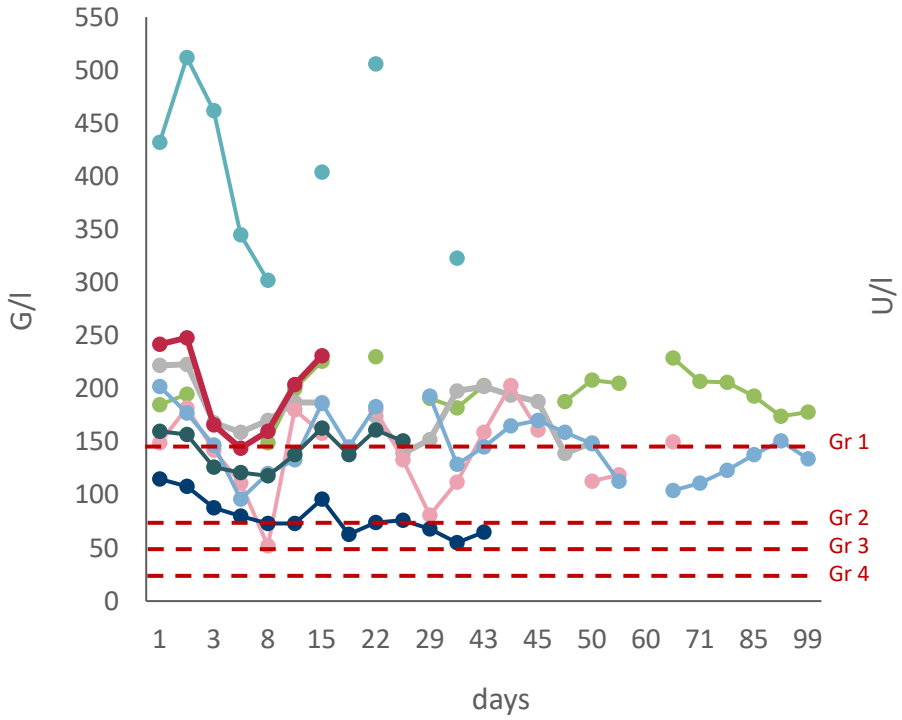


Readout: 3 November 2025

No Signs of Thrombocytopenia or Liver Damage

Cohort 8
(140 µg/kg)

Platelets



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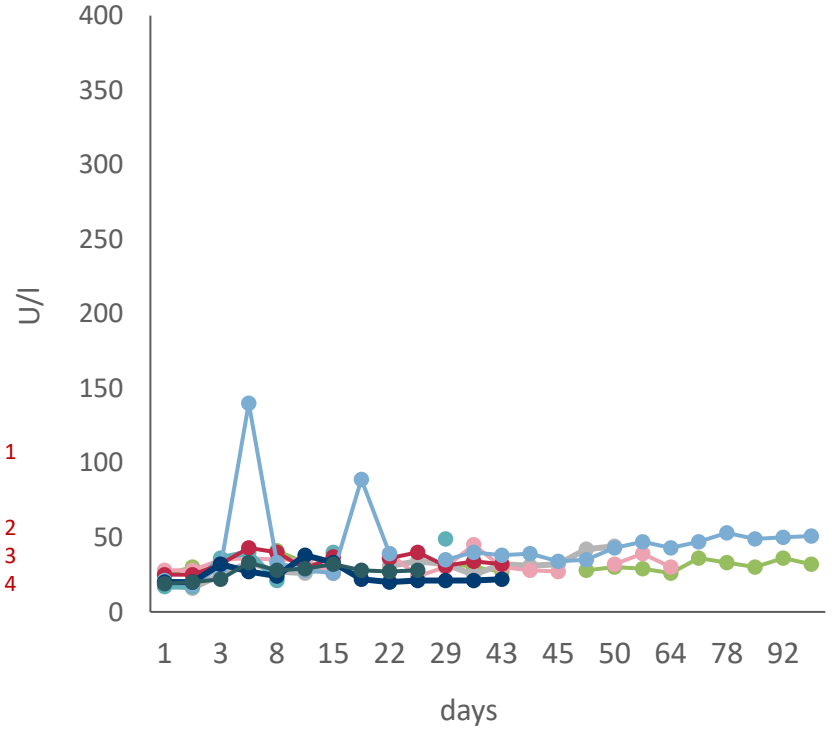

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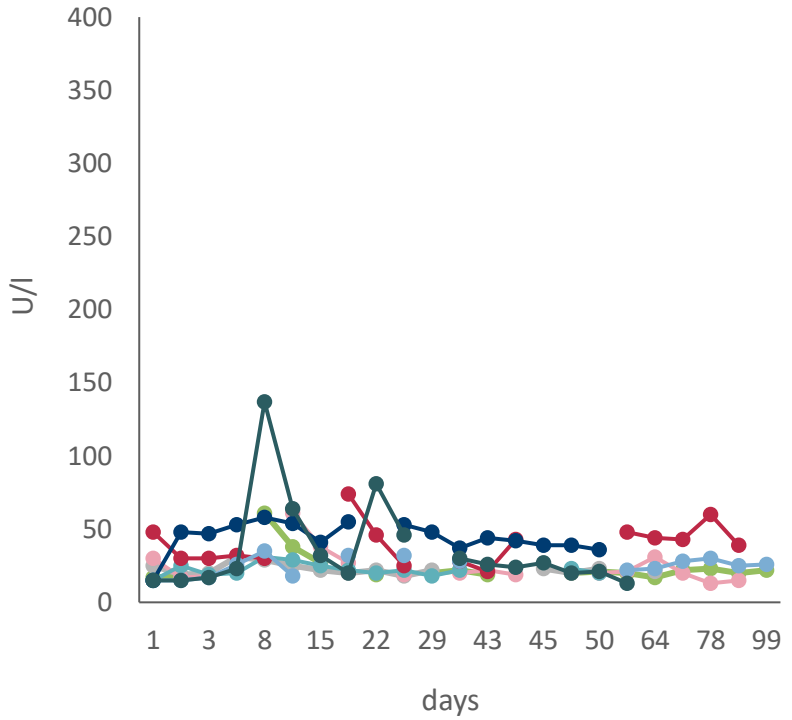


Readout: 02 September 2025

Most Common Treatment-Emergent AEs - Cohort 8 only

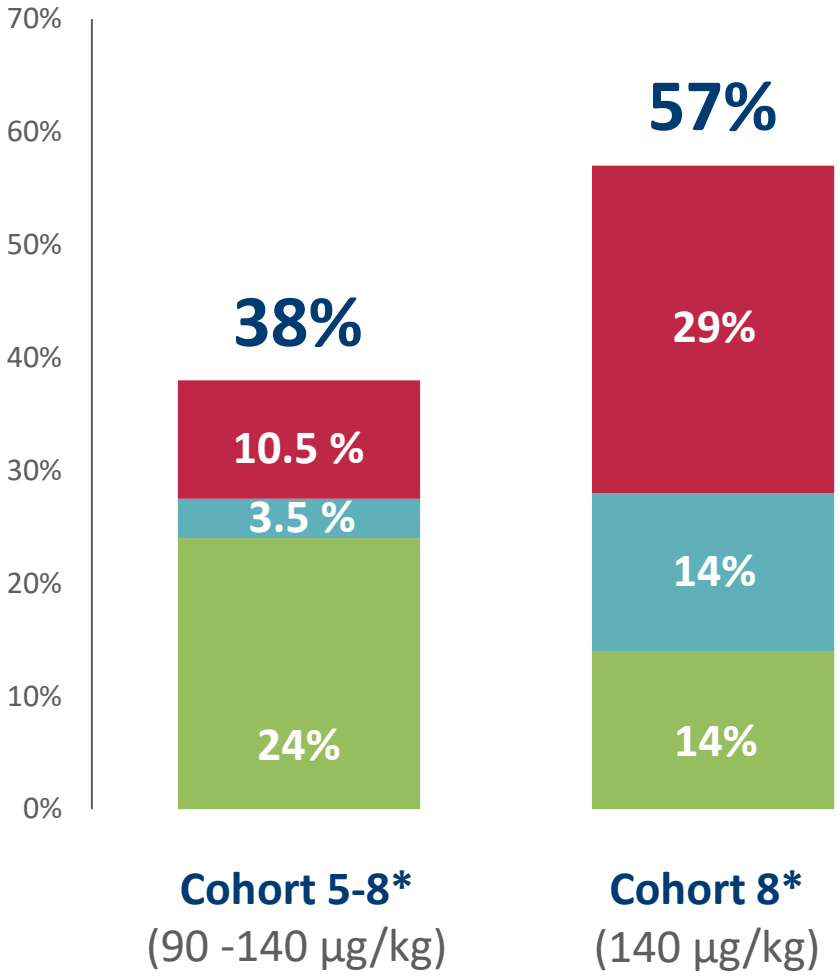
Preferred Term (N=8)	Any CTCAE	Grade 3-4
Thrombocytopenia	2	0
Anaemia	1	0
Arthralgia	0	0
Fatigue	1	0
Nausea	1	0
Aspartate aminotransferase increased	1	0
C-reactive protein increased	1	0
Platelet count decreased	2	0
Back pain	1	0
Diarrhoea	1	0
Urinary tract infection	0	0
Neutropenia	0	0
Hypophosphataemia	2	0
Leukopenia	1	0
Upper respiratory tract infection	0	0
Neutrophil count decreased	1	0
Constipation	1	0
White blood cell count decreased	1	0
Cough	0	0
Lymphocyte count decreased	1	0
Alanine aminotransferase increased	0	0
Decreased appetite	1	0
Headache	1	0

FAVORABLE SAFETY OF HDP-101

- Overall **mild AEs**: **no signs of ocular or renal tox, myelosuppression or liver damage**
- The implementation of new treatment optimization from Cohort 6 **mitigated thrombocytopenia** observed in Cohort 5 after initial dose
- **No cumulative or delayed toxicity** in three long-term treated patients (12+ months)
- No lung toxicity (at higher doses than MGTA-117)

Most common treatment-emergent AEs in Cohort 1-8 (occured at least in 10% of the patients)
Data are preliminary and not yet fully cleaned.

Objective Response Rates (ORR)



PRELIMINARY EFFICACY

- Multiple responses were seen (from 90 µg/kg) across different dosing arms, confirming that changes in the dose distribution **maintained the anti-tumor effect** while improving drug tolerability
- We observed **38% ORR in Cohort 5 to 8** with 11 responders out of 29 patients (7 PR, 1 VGPR and 3 sCR)
- At the current **highest dose of 140 µg/kg**, we observed **57% ORR**, with 4 responders out of 7 patients (1 PR, 1 VGPR, 2 sCR)

Partial response (PR)
Very good partial response (VGPR)
Stringent complete response (sCR)

* Response data from Cohort 8 remain immature. Current follow-up is too limited to draw definitive conclusions on efficacy in Cohort 8 and additional data collection is ongoing.

HDP-101 Phase I/IIa Trial Design in Relapsed/Refractory Multiple Myeloma

Phase I: Dose Escalation

Q3W intravenous dosing, BLRM Design

Objectives

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Secondary: Safety, Tolerability, PK, anti-tumor activity

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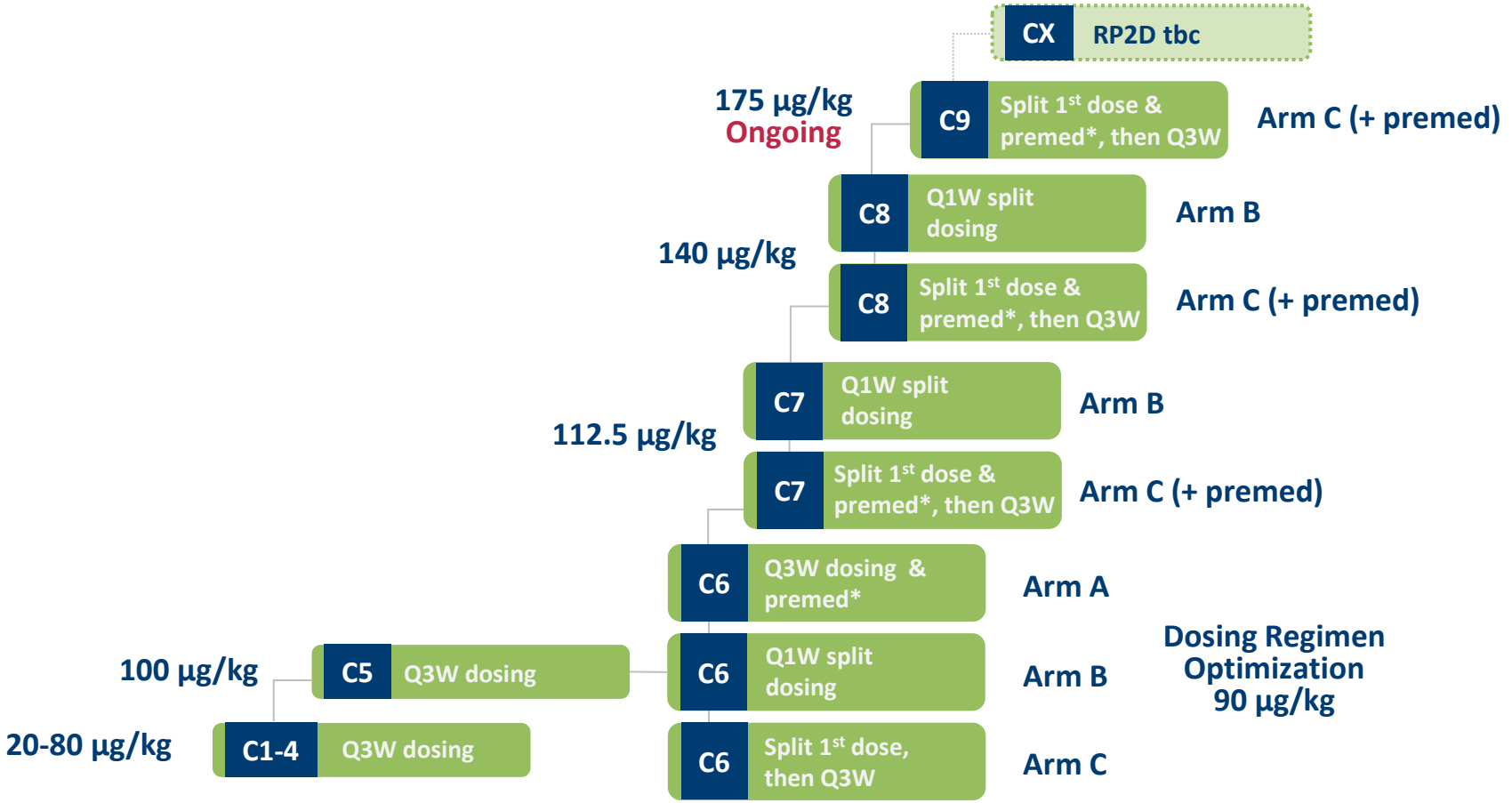
Phase IIa: Dose Expansion



* NCT04879043; BLRM = Bayesian logistic regression model; DLT = dose-limiting toxicity; ORR = Objective response rate; PFS = progression free survival; OS = overall survival

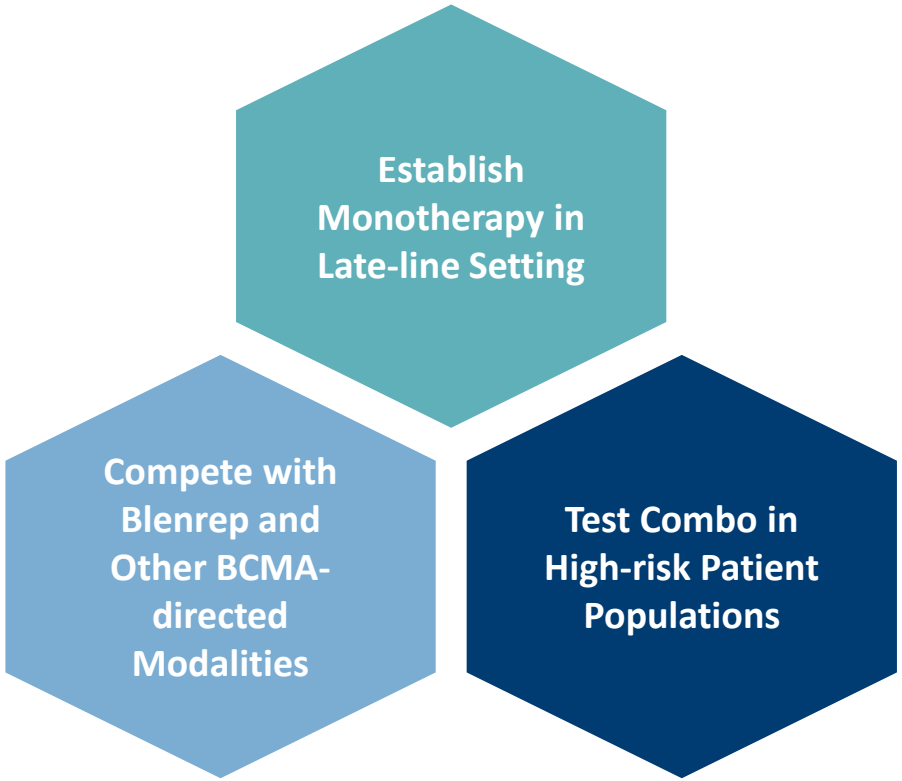
High Tolerability and Good Efficacy at Doses below MTD

A Comparative Analysis with Multiple Myeloma Approved Therapies

	HDP-101	Blenrep	Tecvayli	Carvykti
ORR	57%	30-35%	63%	90%
Dose	0.140 mg/kg Q3W	2.5/3.4 mg/kg Q3W	1.5 mg/kg QW (opt. Q2W)	2.5/3.4 mg/kg
TEAEs	Cohort 8 – Phase I TEAEs –grade 3 or higher • **No grade 3 or higher TEAEs** • **No ocular tox**	DREAMM-2[1] TEAEs –grade 3 or higher • Keratopathy 27% • Anemia 25% • Thrombocytopenia 24% AE-related dose reduction 40% AE-related dose delays 58% AE related permanet discontinuation 7% TAES any grade[3] Keratopathy 73%	MajesTEC-1[2] TEAEs –grade 3 or higher • Neutropenia 65% • Anemia 38% • thrombocytopenia 22% • Lymphopenia 33% • Infections 52% Additional TEAEs CRS occurred in 72% of pts (0.6% gr 3; no gr 4/5); 5 (3%) pts reported 9 ICANS events (all gr 1/2; all resolved)	CARTITUDE-2 (Cohort A and B)[3] TEAEs –grade 3 or higher • Neutropenia 18% • Lymphopenia 65% • Thrombocytopenia 33% • Anemia 46% • Leukopenia 45% AESI (gr1-2/gr3-4) • CRS 89%/7.5% • ICANS 10%/- • Other neurotoxicities 20%/5%

1: https://ashpublications.org/blood/article/140/Supplement%201/7301/488005/Single-Agent-Belantamab-Mafodotin-in-Patients-with
2: https://ascopubs.org/doi/pdfdirect/10.1200/JCO.2023.41.16_suppl.8011
3: https://ashpublications.org/blood/article/142/Supplement%201/1021/499006/The-Phase-2-CARTITUDE-2-Trial-Updated-Efficacy-and

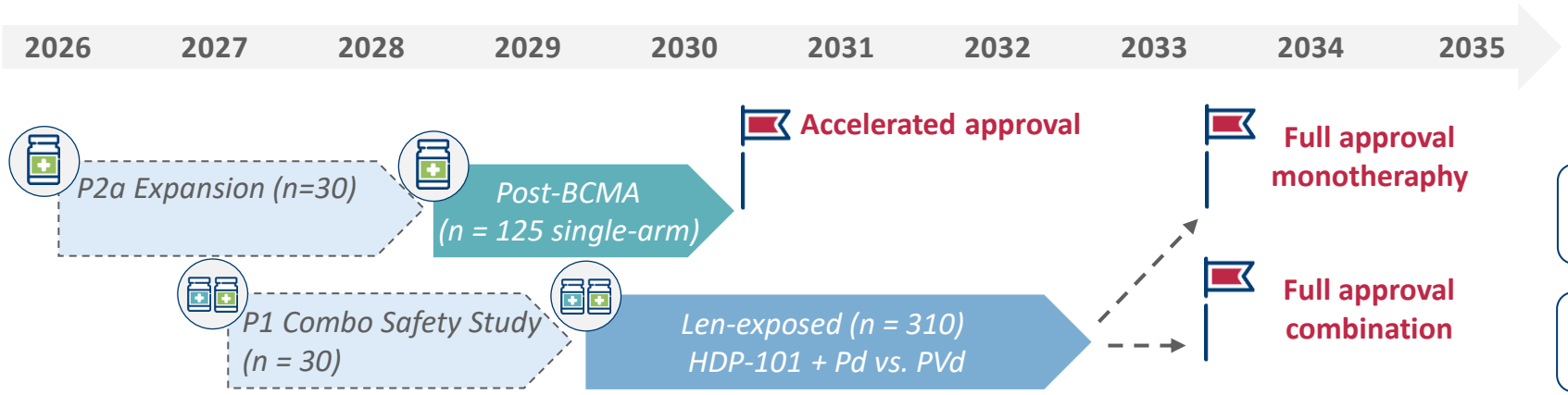
HDP-101 Relevant Throughout the Spectrum of Treatment in Early Relapse with Combination Regimens



Potential Study Populations	HDP-101 Regimens
Near Term Priority	
Post-BCMA	Monotherapy
Len-exposed *(similar to DREAMM-8)*	Combination (IMiD + dex)
Alternative Combinations	Combination (Kd + KPd)
High-risk (or del17p) RRMM	Combination
High-risk (or del17p) NDMM	Combination

dex: dexamethasone; IMiD: Immunomodulatory Drug; Len: Lenalidomide; Kd: Carfilzomib, dexamethasone; KPd: carfilzomib, pomalidomide, and dexamethasone; LoT: Line of Therapy; NDMM: Newly Diagnosed Multiple Myeloma; PI: Proteasome Inhibitor; RRMM: Relapse Refractory Multiple Myeloma.
Source: ClearView Analysis.

Planned Studies Tap into Large, Growing Patient Populations, with High Unmet Need to Prolong Survival



	Treatment Duration	Total Addressab. Population Size (U.S.)	Range of Analog Shares (%, WW)	Annual Peak Addressab. US Market[1]
Post-BCMA (n = 125 single-arm)	0.67 – 1 year	~13 K	25 – 33%[2]	$3.9 bn
Len-exposed (n = 310) HDP-101 + Pd vs. PVd	2 years	~25 K	5 – 15%[3]	$7.5 bn
Alternative Combinations (e.g. Kd, KPd) (n = 300)	2 years	~25 K	5 – 15%[3]	$1.1 – 3.4 bn
High-risk RRMM / NDMM (n = 250)	4 years[5]	2 – 8 K *del(17p) – high-risk*	30%[4]	$720 M – 2.8 bn

Late-line
Early Relapse
High-risk
Estimated Approval
Monotherapy
Combination

Other Study Options, Contingent on Combination Efficacy/Safety Readouts

[1] Calculated using the price of Blenrep as reference (~$300k per year); Assumes similar market penetration as projections for other BCMA modalities (Tecvayli, Carvykti). [2] Assumes HDP-101 launches into post-BCMA setting competing with GPRC5D, FcRH5, XPO1 and secures 1/4 to 1/3 of market. [3] Assumes similar market penetration as projections for other BCMA modalities (Tecvayli, Carvykti). [4] Assumes 50% of Darzalex share in NDMM setting, an entrenched regimen and a treat-to-progression regimen. [5] Assumes a treat-to-progression regimen.
NDMM: Newly Diagnosed Multiple Myeloma; RRMM: Relapse Refractory Multiple Myeloma.
Source: Clarivate DRG; ClearView Analysis.

Amanitin-ADC Shows Deep Responses Below MTD

- Phase I dose escalation data demonstrates **therapeutic window** in patients
- HDP-101 data provide **clinical validation** for the Amanitin platform

- **Promising safety profile**: no ocular tox, no renal tox, no myelosuppression, no liver damage
- **Overcome resistance**: complete response in patients refractory to other therapies against the same target
- HDP-101 received **Fast Track Designation** by FDA

- MTD not reached yet, dose escalation continuing
- **Therapeutic potential** of the drug likely to increase
- Delivery of **RP2D** is expected in early 2026

Heidelberg PHARMA

THANK YOU

Heidelberg Pharma AG
Ladenburg, Germany
Tel.: +49 6203 10090
investors@hdpharma.com
www.heidelberg-pharma.com