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ctDNA Reduction and Clinical Efficacy of the Darovasertib + Crizotinib Combination in Metastatic Uveal Melanoma

Abstract # 1081O - ctDNA Reduction and Clinical Efficacy of the Darovasertib + Crizotinib Combination in Metastatic Uveal Melanoma

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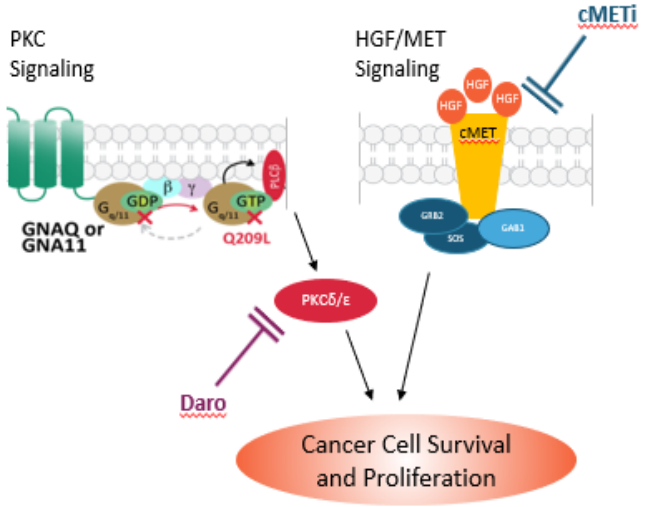
Targeting Two Critical Growth and Survival Pathways in Metastatic Uveal Melanoma (MUM)

Rationale for the Darovasertib + Crizotinib Combination

Uveal Melanoma (UM) Background

- **GNAQ/GNA11** and other upstream mutations are universally present in UM
- These mutations lead to **activation of PKC signaling** which serves as a key driver
- **MUM occurs in approximately 50% of UM patients**, for which there are no approved systemic therapies for HLA-A*02:01 negative disease
- **Darovasertib (Daro/IDE-196)** is an oral, potent and selective PKC inhibitor
- **First in human study** of single agent Daro in MUM observed clinical responses, a well tolerated safety profile, and RP2D of 300 mg bid[1]
- In the metastatic setting, **cMET is overexpressed** and can additionally drive cell growth and survival pathways
- **Crizotinib (Crizo)** is an oral, potent inhibitor of cMET

Interception of Two Key Growth and Survival Pathways in MUM



Synergy was Observed in Uveal Melanoma Cell Lines Treated with Darovasertib + Crizotinib (AACR 2021)

[1]Piperno-Neumann, S et al. "A phase I trial of LXS196, a protein kinase C (PKC) inhibitor, for metastatic uveal melanoma." *British Journal of Cancer* vol. 128,6 (2023): 1040-1051.

Phase 2 Expansion of Darovasertib + Crizotinib Combination in MUM

This Interim Analysis includes the Daro + Crizo Phase 2 Expansion Cohort: NCT03947385

Key Eligibility Criteria:
- Metastatic uveal melanoma
- Measurable disease by RECIST 1.1
- PS= 0-1
- Adequate organ function

Treatment:
- Daro + Crizo combination
  - 300 mg BID Darovasertib
  - 200 mg BID Crizotinib
- Treated to progression or toxicity
- Scans + ctDNA every 8 wks

Interim Analysis:
- Safety summary
- Efficacy per investigator
- Molecular response (ctDNA)
- Key subset analyses

- Analysis includes the first 68 patients treated in the expansion cohort = Any-Line of prior systemic therapies
- Efficacy evaluable population includes all patients with at least 1 evaluable post-baseline scan n=63
- First-Line (1L) evaluable patients (n=20) did not receive any prior systemic treatment for metastatic disease
- Median study follow-up of 19.1 months (time from first treatment to data extraction) including additional follow-up of ~6 months since abstract submission
- Dose optimization evaluation is on-going

Study Population was High Risk with Poor Prognostic Features

Baseline Characteristics

Baseline Characteristics		Any-Line* n=63 (%)	First-Line n=20 (%)
Age (yrs)	< 65	35 (56)	10 (50)
	≥ 65	28 (44)	10 (50)
Sex	Female	32 (51)	9 (45)
	Male	31 (49)	11 (55)
ECOG PS	0	43 (68)	14 (70)
	1	20 (32)	6 (30)
Baseline LDH	Normal	25 (40)	10 (50)
	> ULN	**38 (60)**	**10 (50)**
Largest metastatic lesion	≤ 3.0 cm	22 (35)	8 (40)
	3.1 to 8.0 cm	**35 (56)**	**9 (45)**
	≥ 8.1 cm	**6 (10)**	**3 (15)**
Location of metastases	Hepatic Only	19 (30)	10 (50)
	Extrahepatic Only	3 (5)	0
	Hepatic and Extrahepatic	**41 (65)**	**10 (50)**

*Pretreated patients had a median of 2 prior therapies
^ Efficacy evaluable population data extraction cut-off of 22 August, 2023 (based on preliminary analysis of unlocked database)

The Combination has a Manageable AE Profile: Low Rates of High-grade AEs and Discontinuations due to AEs

Darovasertib + Crizotinib Safety Summary

Drug-Related AE Summary*	
Safety Summary	**All treated n=68 (%)**
AEs	67 (99%)
Grade 3 AEs	21 (31%)
Grade 4/5 AEs	0 (0%) / 1 (2%)*
SAEs	7 (10.3%)
AEs leading to Discontinuation^	5 (7.4%)

Drug-Related AEs with >20% Total Prevalence*					
Adverse Event	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4/5**	**Total**
Diarrhea	50%	37%	4%	0%	91%
Nausea	40%	38%	2%	0%	79%
Edema peripheral	28%	27%	3%	0%	57%
Vomiting	38%	13%	1%	0%	53%
Dermatitis acneiform	34%	10%	0%	0%	44%
Fatigue	9%	24%	4%	0%	37%
Hypotension	15%	13%	6%	0%	34%
Hypoalbuminemia	9%	24%	0%	0%	32%
Dizziness	16%	10%	1%	0%	28%
Decreased Appetite	16%	4%	0%	0%	21%

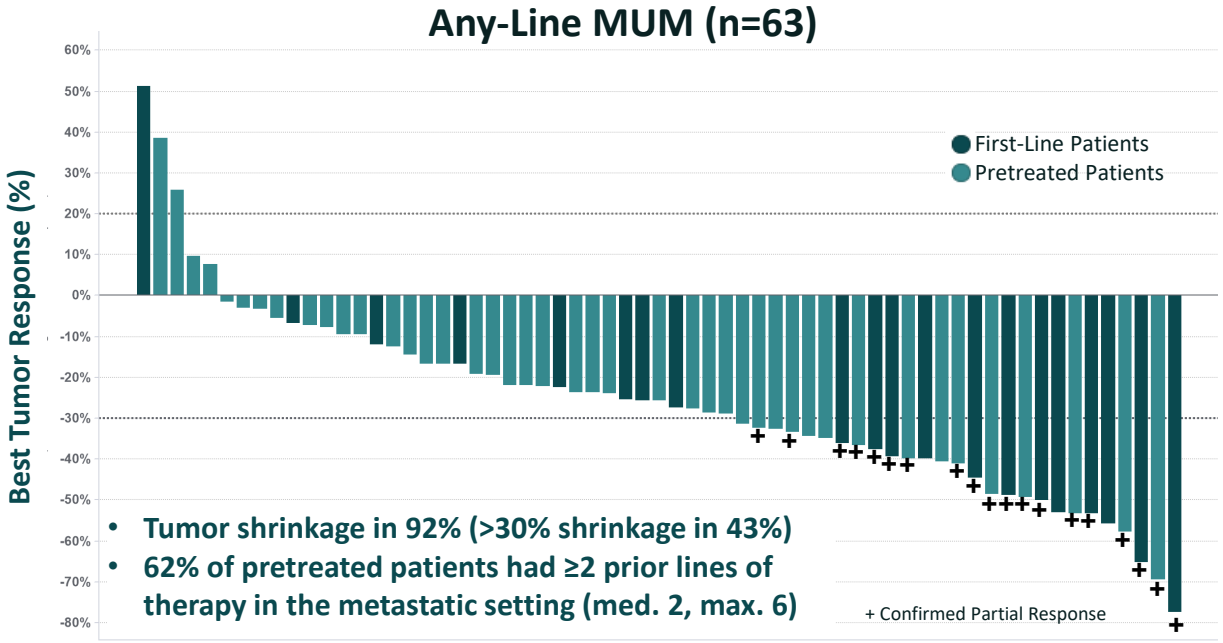
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Data extraction cut-off of 22 August, 2023 (based on preliminary analysis of unlocked database)

* One patient observed a Grade 5 SAE which the treating investigator assessed as most likely related to disease progression, and possibly related to the study therapies; principal investigators on the study reviewed the event and concluded this SAE was most likely due to disease progression, and Sponsor concluded it was most likely due to disease progression and not likely related to study therapies

^ AEs leading to discontinuation include reference to either darovasertib or crizotinib.

Overall Response & Disease Control Rates in Any-Line MUM Pts



- Tumor shrinkage in 92% (>30% shrinkage in 43%)
- 62% of pretreated patients had ≥2 prior lines of therapy in the metastatic setting (med. 2, max. 6)

Response by RECIST 1.1 Any-Line MUM	Evaluable (N=63)
Confirmed ORR (19/63)	30%
Best Overall Response (RECIST 1.1)	
cPR (19/63)	30%
SD (37/63)	59%
PD (7/63)	11%
DCR (56/63)	89%

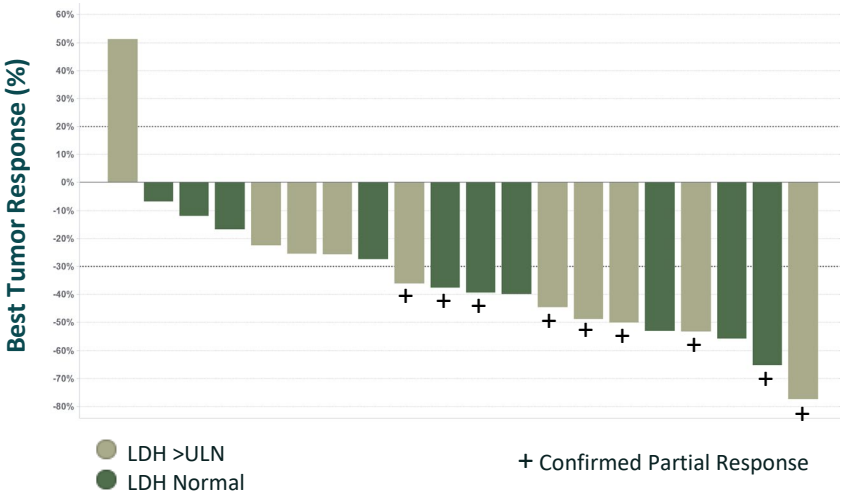
IDEAYA Data: preliminary analysis of unlocked database as of 08/22/2023 by investigator review; data cutoff based on treatment Day 1 of Cycle 1 (C1D1) as of 9/22/2022,
ORR = Overall Response Rate; DCR = Disease Control Rate; cPR = Confirmed Partial Response; SD = Stable Disease; PD = Progressive Disease

Overall Response Rates in First Line and Hepatic Only MUM

First-Line MUM (n=20)

ORR: 45%; **DCR:** 90%

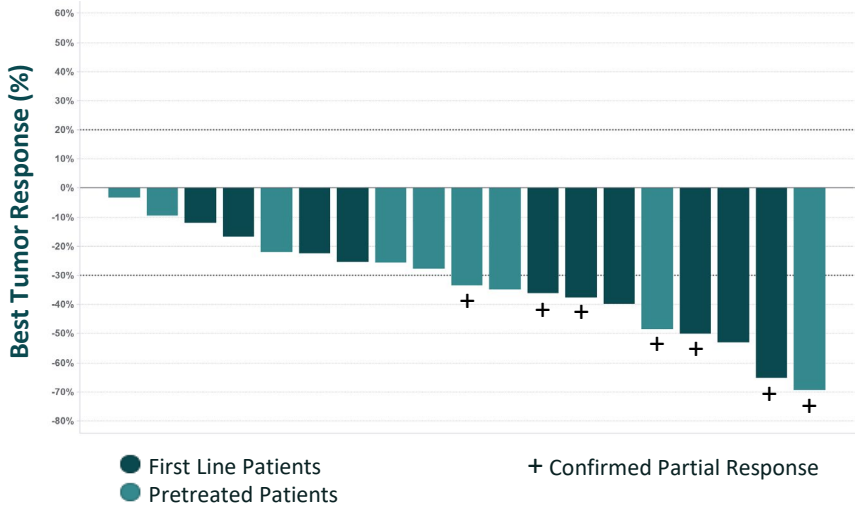
BOR: cPR 45%; SD 45%; PD 10%



Hepatic-Only MUM (n=19)

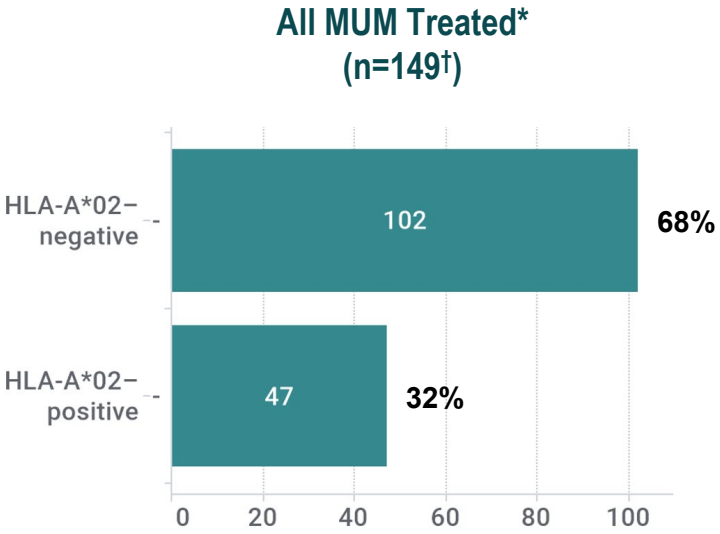
ORR: 37%; **DCR:** 100%

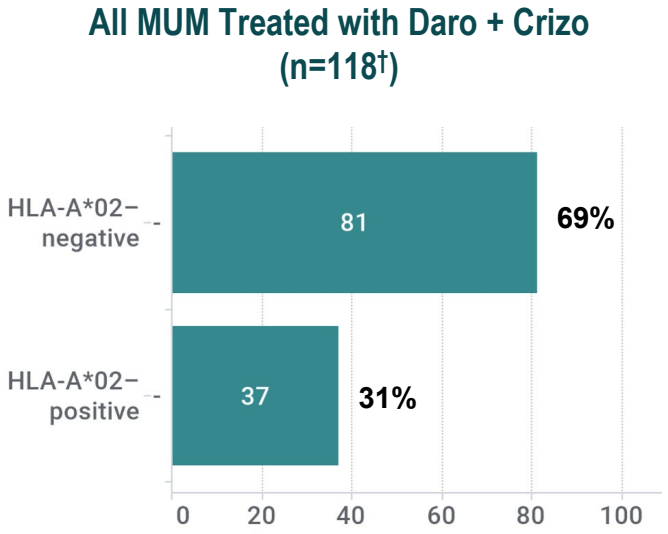
BOR: cPR 37%; SD 63%; PD 0%



IDEAYA Data: preliminary analysis of unlocked database as of 08/22/2023 by investigator review; data cutoff based on treatment Day 1 of Cycle 1 (C1D1) as of 9/22/2022

Approximately 70% of MUM Patients were HLA-A*02:01 Negative





†Includes all patients with known HLA status

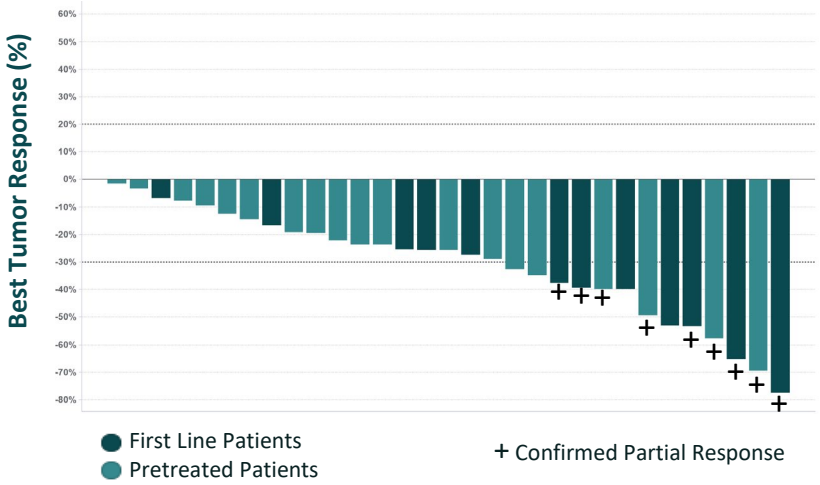
*Includes MUM patients treated with darovasertib in the clinical trial, including monotherapy and combination arms

IDEAYA Data: preliminary analysis of unlocked database as of 08/22/2023; data cutoff based on treatment Day 1 of Cycle 1 (C1D1) as of 9/22/2022

Darovasertib + Crizotinib Effective Regardless of HLA-A*02:01 Status

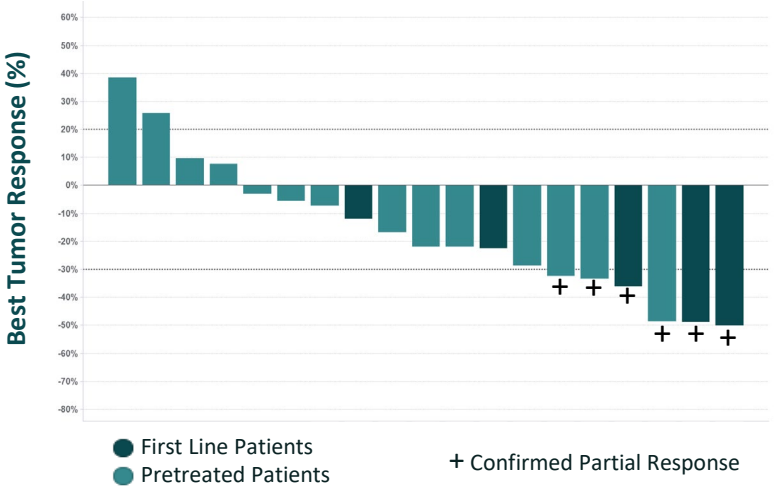
HLA-A*02:01 Negative (n=31)

Any-Line: 29% ORR; 94% DCR
First-Line: 42% ORR; 100% DCR



HLA-A*02:01 Positive (n=19)

Any-Line: 32% ORR; 84% DCR
First-Line: 60% ORR; 100% DCR

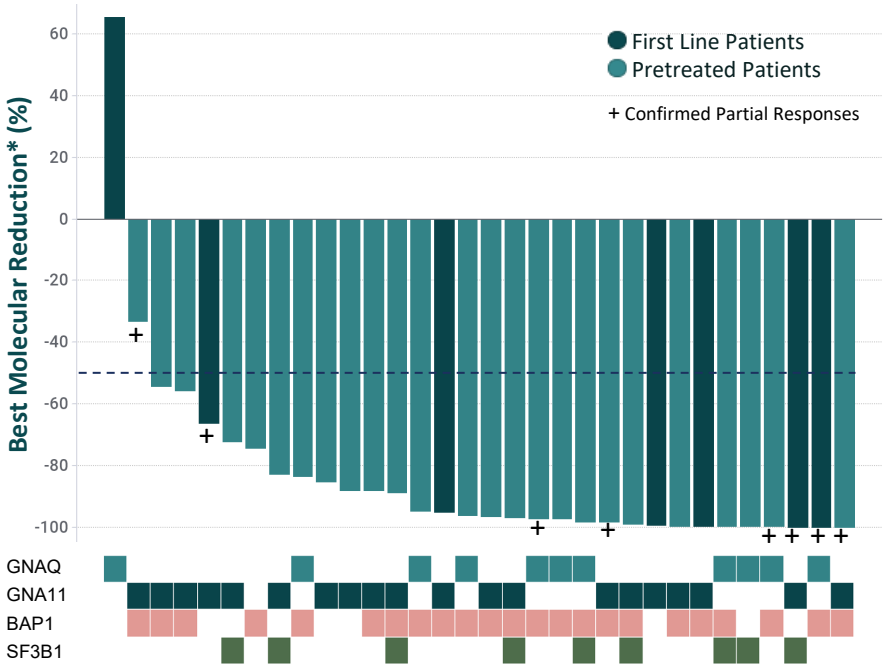


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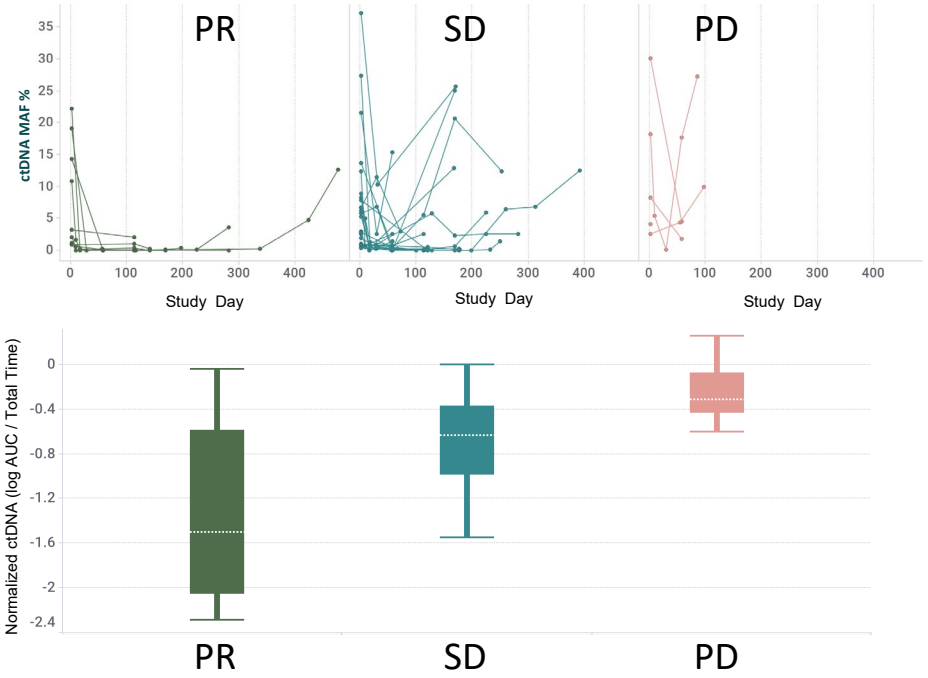
IDEAYA Data: preliminary analysis of unlocked database as of 08/22/2023 by investigator review; data cutoff based on treatment Day 1 of Cycle 1 (C1D1) as of 9/22/2022

94% Molecular Response* Rate was Observed in Any-Line MUM Patients Treated with the Darovasertib + Crizotinib Combination

Molecular Response Regardless of BAP1 Mutation



Molecular Response Correlates with RECIST BOR



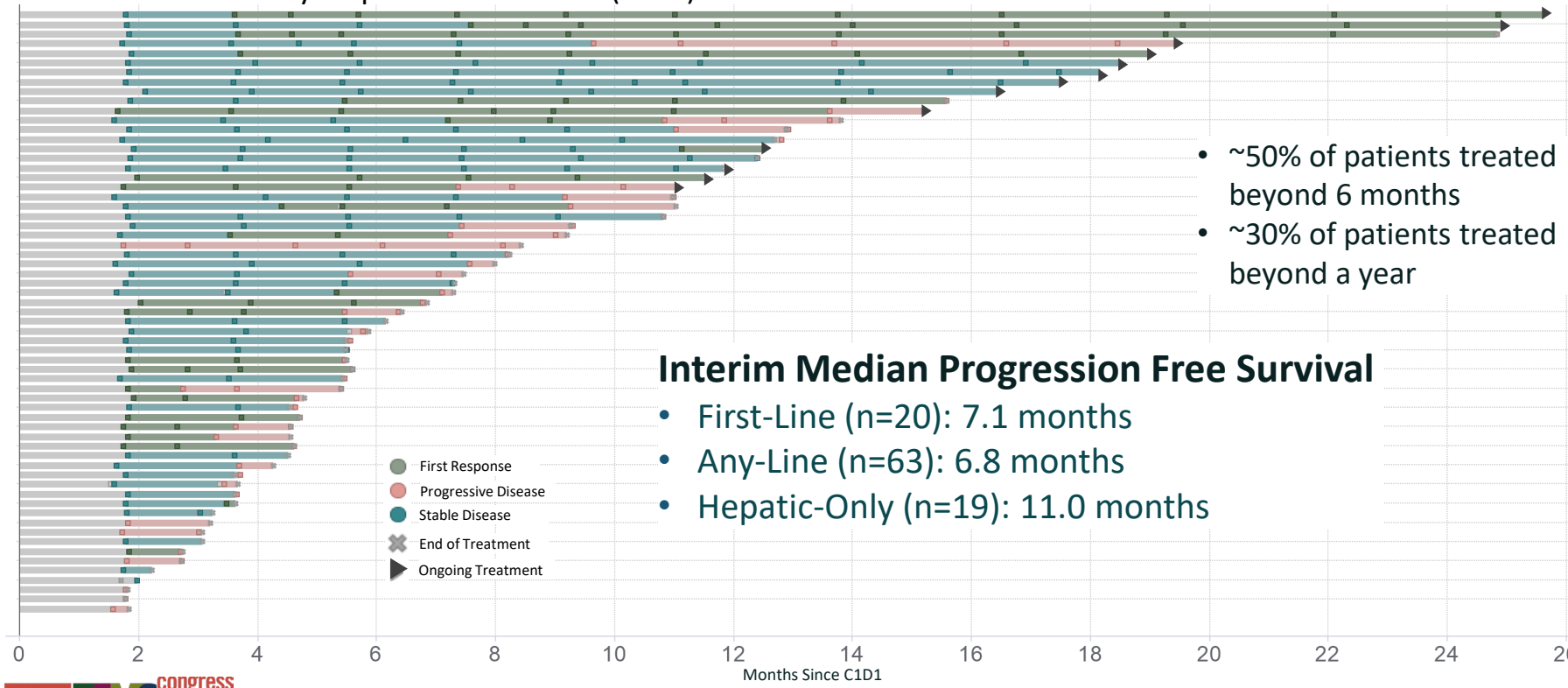
*Molecular response defined as at least 50% reduction in %MAF at any timepoint

IDEAYA Data: preliminary analysis of unlocked database as of 08/22/2023 by investigator review; data cutoff based on treatment Day 1 of Cycle 1 (C1D1) as of 9/22/2022

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Encouraging PFS with Darovasertib + Crizotinib Treatment in MUM Patients

Time on treatment by response assessment (n=63)



- ~50% of patients treated beyond 6 months
- ~30% of patients treated beyond a year

Interim Median Progression Free Survival

- First-Line (n=20): 7.1 months
- Any-Line (n=63): 6.8 months
- Hepatic-Only (n=19): 11.0 months

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IDEAYA Data: preliminary analysis of unlocked database as of 08/22/2023 by investigator review; data cutoff based on treatment Day 1 of Cycle 1 (C1D1) as of 9/22/2022

Conclusions

- The preliminary Darovasertib + Crizotinib combination ORR & mPFS suggests an emerging treatment advance even in high-risk poor prognosis MUM patients
  - ORR of 45% (First-Line) and 30% (Any-Line)
  - mPFS of 7.1 months (First-Line) and 6.8 months (Any-Line)
  - Durable disease control in a large proportion of the patients
- 94% molecular response rate that correlated with radiographic response
- Responses were independent of HLA-A*02:01 status
- Approximately 70% of MUM patients were HLA-A*02:01 negative phenotype
- The combination has a manageable safety profile
- The pronounced efficacy seen in First-Line and Hepatic-Only patients (early phase of the disease) supports the ongoing registration study in First-Line MUM (NCT05987332)
- Neoadjuvant/Adjuvant Darovasertib being evaluated concurrently in primary uveal melanoma (IDE196-009: NCT05907954 and NADOM: NCT05187884)

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- California Pacific Medical Center, San Francisco, CA
- University of Cincinnati, Cincinnati OH
- Columbia University, New York, NY
- Duke University, Raleigh, NC
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- Florida Cancer Specialists, Fort Myers, FL
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