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Darovasertib and Crizotinib for HLA-A*02:01–Positive Metastatic Uveal Melanoma: Results from the Phase 2 OptimUM-01 Study

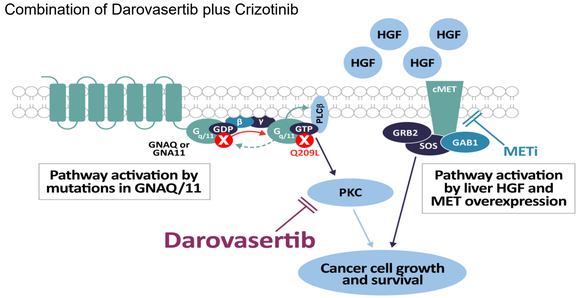
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Introduction

- Metastatic uveal melanoma (mUM) has a poor prognosis with median progression free survival (mPFS) of 2.8 months and a median overall survival (mOS) of ~12 months in the treatment-naïve setting[1-2]
  - Historical outcomes in second-line mUM are poor, with a mOS of ~8 months, a 1-year OS rate of ~37%, mPFS of ~2–3 months, and an ORR of ~5%[2]
- Mutations in GNAQ/11 that activate protein kinase C (PKC) are detected in >95% of uveal melanoma tumors[3-4]
- Darovasertib is a first-in-class, oral, targeted PKC inhibitor with clinical activity in mUM[5]
- Crizotinib, an oral MET inhibitor, has shown complementary activity with darovasertib preclinically (**Figure 1**)

Figure 1. Targeting PKC and MET in Metastatic Uveal Melanoma with Combination of Darovasertib plus Crizotinib



- The OptimUM-01 study demonstrated promising clinical activity with a manageable adverse event profile for darovasertib + crizotinib (darova+criz) in 44 first-line patients with mUM, irrespective of HLA-A02:01 status[7]
- Recent results from the phase 2b portion of the OptimUM-02 study demonstrated that first-line treatment with darova+criz resulted in significantly longer PFS (median 6.9 months) than investigator's choice of therapy (median 3.1 months)
  - Treatment with darova+criz had a manageable safety profile in 239 patients with mUM, with diarrhea (84.9%), nausea (74.9%), peripheral edema (66.0%), and vomiting (49.8%) as the most common adverse events[8]
- Herein, we evaluated darova+criz among HLA-A02:01-positive patients enrolled in the expansion phase of the OptimUM-01 study (Data extract date of March 23, 2026)
  - For comparison, we have also included the efficacy analyses of the HLA-A02:01-negative patients enrolled in the OptimUM-01 study

Methods

- OptimUM-01 is a phase 1/2, multi-center, open-label, dose escalation and expansion study including patients with solid tumors harboring GNAQ/11 mutations
  - This analysis focuses on the phase 2 expansion in HLA-A02:01-positive patients with mUM treated with darova+criz
- Eligibility criteria included RECIST v1.1 measurable disease, ECOG status 0-1, and adequate organ function
- Endpoints included PFS, OS, and safety as well as objective response rate (ORR), duration of response (DOR), and disease control rate (DCR)
- Safety was evaluated by ongoing monitoring of adverse events, clinical laboratory tests, EKGs, and changes in vital signs

Results

- Overall, 101 HLA-A02:01-positive patients were treated **(Table 1)**, with a median follow-up of 10.4 months for overall survival
- Most patients (88/101) had received prior systemic therapy for mUM: 13 patients had no prior systemic therapies , and 15 patients received darova+criz in the second line setting after prior tebentafusp as the first-line therapy
- Elevated baseline LDH level was present in 64.4%, with 21.8% of patients with an LDH level that was 2x upper limit of normal or higher
- At baseline, 37.6% of patients had hepatic and extrahepatic disease, 50.5% had hepatic disease only, and 11.9% had extrahepatic disease only

Table 1. Baseline Characteristics of HLA-A02:01-Positive Population from OptimUM-01

	Treatment-Naïve N=13	Overall N=101
Age, median years (range)	65.0 (21, 81)	66.0 (21, 81)
Sex, n (%)		
Female	7 (53.8)	44 (43.6)
Race, n (%)		
White	13 (100.0)	95 (94.1)
Asian	0 (0)	1 (1.0)
Not reported	0 (0)	5 (5.0)
ECOG PS, n (%)		
0	6 (46.2)	66 (65.3)
1	7 (53.8)	35 (34.7)
Baseline LDH, n (%)		
≤ ULN	7 (53.8)	36 (35.6)
> ULN and < 2xULN	4 (30.8)	43 (42.6)
≥ 2X ULN	2 (15.4)	22 (21.8)
Metastases location, n (%)		
Hepatic only	8 (61.5)	51 (50.5)
Extrahepatic only	2 (15.4)	12 (11.9)
Hepatic and extrahepatic	3 (23.1)	38 (37.6)
Prior lines of therapy, n (%)		
0	13 (100)	13 (12.9)
1	-	20 (19.8)
2+	-	67 (66.3)
Not recorded, previously treated	-	1 (1.0)

ECOG PS, Eastern Cooperative Oncology Group performance status. LDH, lactate dehydrogenase, HLA, human leukocyte antigen. ULN, upper limit of normal.

- The confirmed ORR was 36.4% in treatment-naïve patients and 22.1% in overall population (**Table 2**)
- The median PFS in treatment-naïve and overall population were 7.4 months (95%CI: 3.6-19.6) and 5.4 months (95%CI: 3.7-6.8), respectively (**Table 2; Figure 2**)
- The median OS was 27.1 months (95%CI: 8.9, not evaluable) and 13.4 months (95%CI: 9.8, 26.3) in treatment-naïve and overall populations, respectively (**Table 2; Figure 3**)

Table 2. Efficacy Results HLA-A02:01-Positive Population from OptimUM-01

	Treatment-Naïve N=13	Overall N=101
ORR, n/N (%)*	4/11 (36.4)	19/86 (22.1)
95% CI	10.9, 69.2	13.9, 32.3
Confirmed best overall response, n/N (%)*		
Complete response	0/11 (0.0)	0/86 (0.0)
Partial response	4/11 (36.4)	19/86 (22.1)
Stable disease	6/11 (54.5)	49/86 (57.0)
Progressive disease	0/11 (0.0)	9/86 (10.5)
Not evaluable	1/11 (9.1)	9/86 (10.5)
DCR, n/N (%)*	10/11 (90.9)	69/86 (80.2)
Median DOR, months*	10.2	7.4
Median PFS, months^	7.4	5.4
95% CI	3.6, 19.6	3.7, 6.8
Median OS, months^	27.1	13.4
95% CI	8.9, NE	9.8, 26.3

CI, Confidence Interval. NE, not evaluable. Confirmed Objective Tumor Response as Assessed by Investigator per RECIST 1.1. *Response assessments utilized the efficacy evaluable population which includes all patients had ≥3 post-baseline assessments or who discontinued treatment. ^PFS and OS assessments utilized the all enrolled Population which include all patients who had ≥1 dose of treatment.

Results

- In second-line patients following tebentafusp, the confirmed ORR, median PFS, and median OS was 35.7%, 5.7 months (95%CI: 3.7, not evaluable), and 12.1 months (95%CI: 9.8, not evaluable), respectively

Figure 2. Progression-Free Survival Results

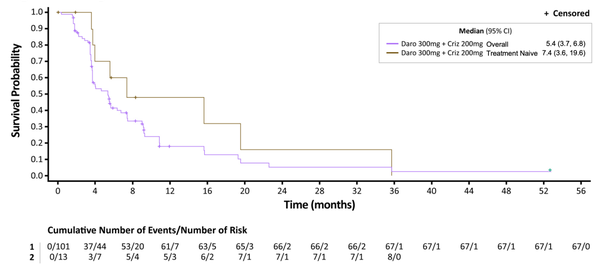
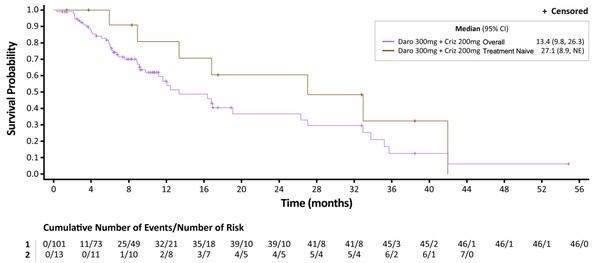


Figure 3. Overall Survival Results



- Efficacy results with darova+criz treatment among HLA-A02:01-positive patients was generally consistent to those for HLA-A02:01-negative patients enrolled in the OptimUM-01 study in both treatment-naïve patients and overall population (**Table 3**)

Table 3. Efficacy Results Comparison for HLA-A02:01-Positive and HLA-A02:01-Negative patients from the OptimUM-01 Study

	HLA-A02:01-Positive	HLA-A02:01-Negative
Treatment-Naïve	**N=13**	**N=29**
ORR, n/N (%)*	4/11 (36.4)	9/29 (31.0)
95% CI	10.9, 69.2	15.3, 50.8
DCR, n/N (%)*	10/11 (90.9)	25/29 (86.2)
Median DOR, months*	10.2	9.0
Median PFS, months^	7.4	7.1
95% CI	3.6, 19.6	3.7, 9.2
Median OS, months^	27.1	19.4
95% CI	8.9, NE	12.0, 23.8
Overall	**N=101**	**N=61**
ORR, n/N (%)*	19/86 (22.1)	16/61 (26.2)
95% CI	13.9, 32.3	15.8, 39.1
DCR, n/N (%)*	69/86 (80.2)	53/61 (86.9)
Median DOR, months*	7.4	7.3
Median PFS, months^	5.4	7.2
95% CI	3.7, 6.8	5.0, 7.8
Median OS, months^	13.4	15.0
95% CI	9.8, 26.3	11.7, 20.7

CI, Confidence Interval. NE, not evaluable. Confirmed Objective Tumor Response as Assessed by Investigator per RECIST 1.1. *Response assessments utilized the efficacy evaluable population which includes all patients had ≥3 post-baseline assessments or who discontinued treatment. ^PFS and OS assessments utilized the all enrolled Population which include all patients who had ≥1 dose of treatment.

Results

- The most common treatment-related adverse events (TRAEs) were diarrhea (82%), nausea (76%), peripheral edema (70%), and vomiting (57%)(**Table 4**)
- Grade ≥3 TRAEs included hypotension (5.9%), syncope (5.9%), and pulmonary embolism (5.0%); treatment discontinuations due to AEs occurred in 15 patients (14.9%), 9 of which were considered treatment-related

Table 4. Treatment-Related Adverse Event Summary (All Grades ≥20%) in HLA-A02:01-Positive Population from OptimUM-01

	Overall (N=101) n (%)
Related adverse event (AE)	101 (100)
Related serious AE	12 (11.9)
Related ≥ grade 3	38 (37.6)
Related AE leading to discontinuation	9 (8.9)
Related AEs leading to reduction	28 (27.7)
Related AE that occurred in ≥20% for all grades	
Diarrhea	83 (82.2)
Nausea	77 (76.2)
Edema Peripheral	71 (70.3)
Vomiting	58 (57.4)
Fatigue	55 (54.5)
Dizziness	38 (37.6)
Dermatitis Acneiform	35 (34.7)
Hypotension	33 (32.7)

Conclusions

- Darova + criz demonstrated encouraging and durable clinical activity in HLA-A*02:01-positive patients with mUM, supporting its potential as an additional treatment option for this population
- The combination has a manageable safety profile with a low discontinuation rate of 14.9% due to AEs
- Together with findings in HLA-A02:01-negative patients, these results support the clinical activity of darova+criz in mUM irrespective of HLA-A02:01 status

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