Darovasertib with Crizotinib vs Investigator's Choice as First-Line Treatment for Patients with HLA-A2 Negative Metastatic Uveal Melanoma (OptimUM-02): A Subgroup Analysis

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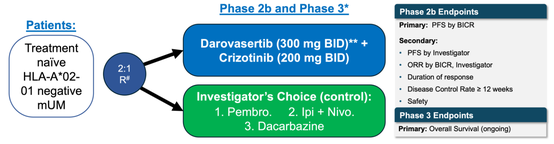
Introduction

- Metastatic uveal melanoma (mUM) is a rare disease with a poor prognosis
  - Historically, mUM has been associated with a median progression free survival (mPFS) of 2.8 months and a median overall survival (mOS) of ~12 months[1-2]
  - GNAQ/11 mutations, detected in >95% of UM tumors, activate downstream PKC signaling, which has emerged as a promising therapeutic target, particularly given the limited efficacy of standard melanoma treatments in mUM[3-4]
- Darovasertib, a first-in-class, oral, targeted PKC inhibitor, has shown promising results with the MET inhibitor crizotinib (darova+criz)[5-7]
  - Darova+criz demonstrated superior efficacy with manageable safety vs investigator's choice (control) agents in patients with HLA-A*02:01-negative mUM in OptimUM-02[8]
- Here, we present efficacy results from OptimUM-02 across subgroups defined by key baseline characteristics, including historically difficult to treat populations (e.g., high baseline LDH, extra-hepatic disease, or large lesions)

Methods

- OptimUM-02 is an open-label study of HLA-A*02:01 negative first-line mUM patients (**Figure 1**)

Figure 1. OptimUM-02 Study Design



#Patients will be stratified by baseline LDH (≤ULN vs >ULN, but less than 2-fold the ULN vs ≥ 2-fold the ULN) and investigator's choice of comparator. treatment (ipilumumab + nivolumab vs single-agent therapy). *Treatment will continue until disease progression, death (any cause), unacceptable toxicity or treatment discontinuation. **Treatment will commence with a 7-day run-in of darovasertib monotherapy (at dose corresponding to the treatment arm, and the run-in may be extended if clinically indicated) prior to starting crizotinib. BICR, blinded independent central reader. Dacarbazine, dacarbazine (1000 mg/m2 Q3W). Ipi+Nivo, ipilumumab (3 mg/kg) + nivolumab (1 mg/kg) for 4 cycles followed by nivolumab. ORR, objective response rate. Pembro, pembrolizumab (200 mg Q3W). PFS, progression-free survival.

- Eligible patients were randomized 2:1 to receive either darovasertib 300 mg BID + crizotinib 200 mg BID or investigator's choice (pembrolizumab, ipilimumab + nivolumab, or dacarbazine)
- Efficacy, including progression-free survival (PFS) and objective response rate (ORR), were evaluated by BICR across key subgroups
- Results were also compared with findings from the OptimUM-01 trial to assess consistency of response across studies

Results

- Overall, 313 patients (darova+criz: 210; control:103) were enrolled and included in the analyses (**Table 1**)
- Baseline characteristics were generally similar across both arms
- Key relevant prognostic factors included ECOG performance status, site of metastasis, tumor burden, and baseline LDH levels
- There were more ECOG 1 and bulky liver lesions in the darova+criz group
- Ipilimumab-nivolumab was selected for 79 patients and pembrolizumab was selected for 24 patients for the control; none selected dacarbazine

Results

Table 1. Baseline Characteristics

	Darovasertib 300 mg - Crizotinib 200 mg N=210	Investigator's Choice (control) N=103
Age, mean (range)	61.1 (22 - 85)	61.5 (29 - 85)
Female, n (%)	101 (48.1)	52 (50.5)
ECOG		
0	162 (77.1)	87 (84.5)
1	48 (22.9)	16 (15.5)
LDH at Baseline , n (%)		
≤ ULN	120 (57.1)	62 (60.2)
> ULN - < 2x ULN	65 (31.0)	29 (28.2)
≥ 2x ULN	25 (11.9)	12 (11.7)
Control at Baseline , n (%)		
Ipilimumab + Nivolumab	158 (75.2)	79 (76.7)
Pembrolizumab or Dacarbazine*	52 (24.8)	24 (23.3)
Time since First Metastatic Dx (year)		
Median (Range)	0.18 (0.0 – 8.1)	0.19 (0.0 – 4.6)
Size of Largest Metastatic Lesion Category		
≤ 3 cm	119 (56.7)	67 (65.0)
3.1 - 8.0 cm	73 (34.8)	31 (30.1)
≥ 8.0 cm	18 (8.6)	5 (4.9)
Metastatic Sites, n (%)		
Hepatic Disease Only	127 (60.5)	65 (63.1)
Extrahepatic Disease Only	11 (5.2)	7 (6.8)
Hepatic and Extrahepatic Disease	72 (34.3)	31 (30.1)
Prior Oligometastatic-directed Surgery, n (%)	5 (2.4)	6 (5.8)

Dx, diagnosis. ECOG PS, Eastern Cooperative Oncology Group performance status. LDH, lactate dehydrogenase, HLA, human leukocyte antigen. SD, standard deviation. ULN, upper limit of normal. *No patients received dacarbazine in the investigator's choice arm

- The median PFS by BICR was 6.9 months for darova+criz (5.6, 8.3) and 3.1 months for IC (1.8, 4.2); HR: 0.42, p<0.0001 (**Table 2**)
  - Results were generally consistent for stratified and unstratified analyses

Table 2. Subgroup Efficacy Results (BICR; stratified)

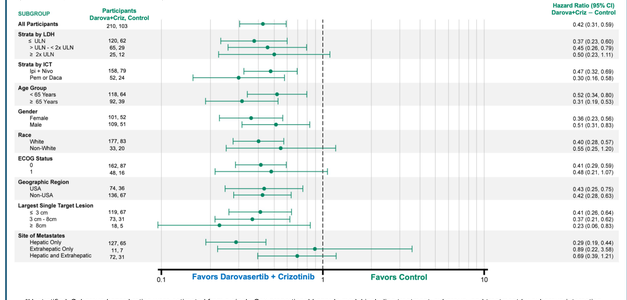
	ORR by BICR (%)		mPFS by BICR (months)	
	Darovasertib + Crizotinib (N=210)	Control (N=103)	Darovasertib + Crizotinib (N=210)	Control (N=103)
Overall, (n=darova+criz, IC)	37.1	5.8	6.9	3.1
Strata by LDH,				
Normal (n=120, 62)	46.7	8.1	8.4	4.2
>ULN- < 2x ULN (n=65, 29)	27.7	3.4	5.7	1.8
≥2X ULN (n=25, 12)	16.0	0	3.1	1.7
Sites of disease				
Hepatic (n=127, 65)	45.7	3.1	8.3	2.9
Extrahepatic only (n=11, 7)	27.3	0	6.7	8.3
Hepatic & extrahepatic (n=72, 31)	23.6	12.9	4.9	2.8
ECOG PS				
0 (n=162, 87)	38.3	5.8	6.8	3.1
1 (n=48, 16)	33.3	6.3	6.9	3.1
Largest lesion size				
<3cm (n=119, 67)	42.9	6.0	8.3	4.0
≥3-8 cm (n=73, 31)	34.3	6.5	5.6	1.6
≥8 cm (n=18, 5)	11.1	0	4.2	1.7
Strata by Control group				
Ipilimumab + nivolumab (n=158, 79)	37.3	5.1	6.9	3.1
Pembrolizumab or dacarbazine* (n=52, 24)	36.5	8.3	5.8	2.8

*No patients received dacarbazine in the investigator's choice arm

Results

- PFS results were generally consistent across key subgroups, with most favoring darova+criz over control (**Figure 2**)
- Stratified PFS subgroup analyses were broadly consistent with the unstratified analysis, with darova+criz generally favored in larger subgroups
- For select subgroup categories (i.e., LDH ≥2 × ULN, target lesion ≥8 cm, and extrahepatic-only metastases), the small number of participants resulted in wide 95% confidence intervals that included the null value, limiting the interpretation of treatment effect estimates in these categories

Figure 2. Forest Plot of PFS Results for Key Baseline Characteristics (BICR; unstratified*)[6]



*Unstratified: Subgroup hazard ratios were estimated from a single Cox proportional hazards model including treatment, subgroup, and treatment-by-subgroup interaction terms, with a common baseline hazard across subgroup levels. Stratified: The treatment hazard ratio was estimated using a Cox proportional hazards model stratified by prespecified factors, allowing each stratum to have its own baseline hazard while estimating a common treatment effect across strata. BICR, blinded independent central reader. Control, investigator's choice of treatments. Daca, dacarbazine. Darova, darovasertib 300mg - crizotinib 200mg. ECOG, Eastern Cooperative Oncology Group. Ipi, ipilimumab. LDH, lactate dehydrogenase. Nivo, nivolumab. Pem, pembrolizumab. PFS, progression-free survival. ULN, upper limit of normal.

- In the overall population, ORR by BICR was 37.1% vs. 5.8% (p< 0.0001) in the darova+criz and IC groups, respectively (**Table 2**)
- Tumor response, as assessed by ORR, generally favored darova+criz across subgroups (**Figure 3**)

Figure 3. Forest Plot of ORR Results for Key Baseline Characteristics (BICR; unstratified)

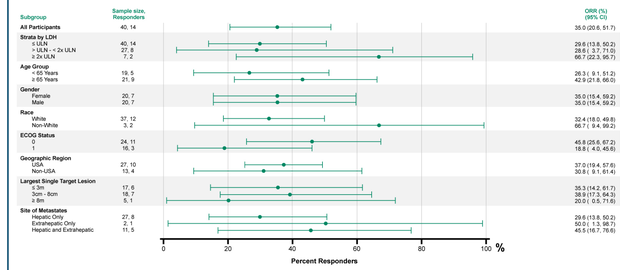
BICR, blinded independent central reader. Control, investigator's choice of treatments. Daca, dacarbazine. Darova, darovasertib 300mg - crizotinib 200mg. ECOG, Eastern Cooperative Oncology Group. Ipi, ipilimumab. LDH, lactate dehydrogenase. Nivo, nivolumab. Pem, pembrolizumab. PFS, progression-free survival. ULN, upper limit of normal.

- BICR results for PFS and ORR were generally consistent regardless of baseline LDH, location of metastases, ECOG PS, lesion size, or investigator's choice of therapy

Results

- ORR results in treatment-naïve patients from OptimUM-01 were similar to those observed in OptimUM-02 (**Figure 4**)

Figure 4. Forest Plot of ORR Results for Key Baseline Characteristics from OptimUM-01 in 1L HLA-A*02:01-agnostic patient population (BICR; unstratified)



ECOG, Eastern Cooperative Oncology Group. LDH, lactate dehydrogenase. ULN, upper limit of normal.

Conclusions

- Building on the positive overall results from OptimUM-02, ORR and PFS findings generally favored darova+criz across a broad range of mUM subgroups, supporting the consistency of the overall treatment benefit and aligning with findings from the broader metastatic OptimUM clinical program
- Collectively, these findings further support the potential of with darova+criz as a new oral standard of care for patients with HLA-A*02:01-negative mUM in the first-line setting

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