First Reported Overall Survival Results from a Phase 1/2 Study of Darovasertib Plus Crizotinib as First-line Treatment for Metastatic Uveal Melanoma (OptimUM-01)

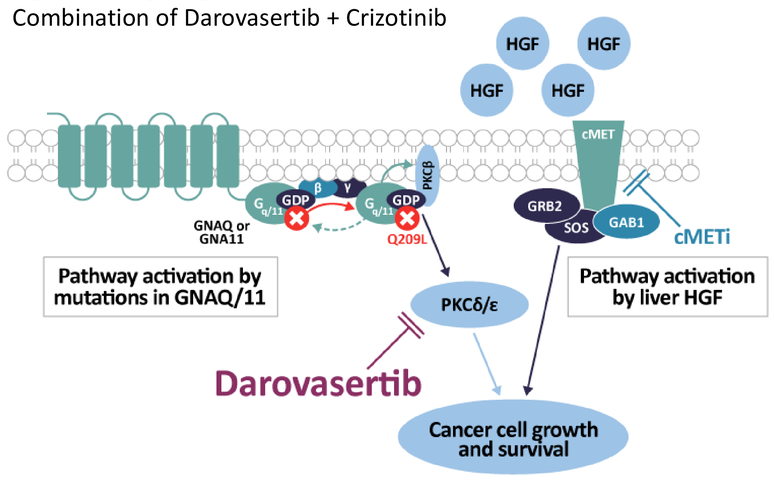
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Background

- 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 10-12 months[1-2]
- 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 (**Figure 1**)[5]
- Crizotinib, an oral c-MET inhibitor, has shown complementary activity with darovasertib preclinically[6]
- In this phase 1/2 clinical trial (OptimUM-01; NCT03947385), the combination of darovasertib plus crizotinib had promising efficacy in treatment-naïve and pretreated mUM irrespective of human leukocyte antigen (HLA) status, with a tolerable safety profile
- Presented are updated safety and efficacy results for patients treated with darovasertib 300 mg twice daily (BID) plus crizotinib 200 mg BID in the first-line setting

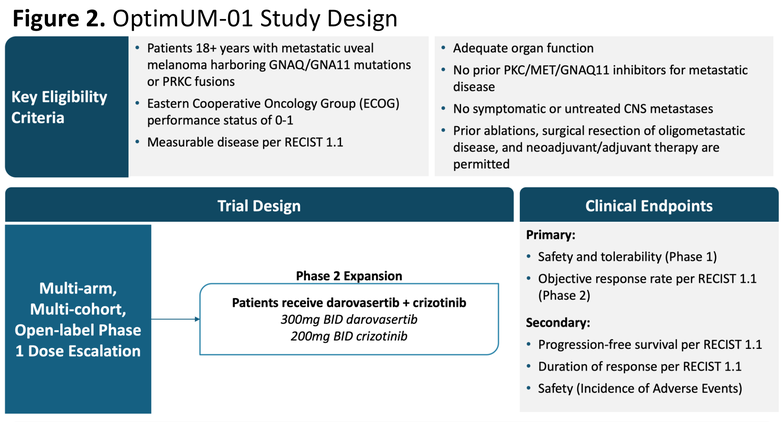
Figure 1. Targeting PKC and cMET in Metastatic Uveal Melanoma with Combination of Darovasertib + Crizotinib



Methods

- The OptimUM-01 study is a phase 1/2, multi-center, open-label, dose escalation and expansion study of darovasertib in patients with mUM or non-uveal melanoma (non-mUM) tumors (**Figure 2**)
  - This analysis focuses on the first-line patients in the phase 2 expansion of OptimUM-01, which evaluated the efficacy and safety of the combination of darovasertib 300 mg BID plus crizotinib 200 mg BID in mUM

Figure 2. OptimUM-01 Study Design



Results

- As of 28 May 2025, 44 pts with mUM and no prior systemic cancer therapy have received the recommended phase 2 dose of darovasertib 300 mg BID plus crizotinib 200 mg BID
- Baseline characteristics are as follows (**Table 1**)**:** median age 64.5 years; 47.7% women; 93.2% white; ECOG PS 1: 38.6%; 43.2% with metastatic lesions >3 cm; 40.9% with hepatic and extrahepatic disease; 4.5% with extrahepatic disease only; and 31.8% with elevated lactate dehydrogenase (15.9% >2x ULN)
  - HLA-A2*02:01 status was 68.2% negative, 27.3% positive, and 4.5% unknown

Table 1. Baseline Characteristics

	First-Line n=44
Age, median years	64.5
< 65, n (%)	22 (50.0)
≥ 65, n (%)	22 (50.0)
Sex, n (%)	
Female	21 (47.7)
Male	23 (52.3)
Race, n (%)	
White	41 (93.2%)
Asian	1 (2.3%)
Other/not reported	2 (4.5%)
ECOG PS, n (%)	
0	27 (61.4)
1	17 (38.6)
Baseline LDH, n (%)	
Normal	29 (65.9)
> ULN	14 (31.8)
Largest metastatic lesion, n (%)	
≤ 3.0 cm	24 (54.5)
3.1 to 8.0 cm	15 (34.1)
≥ 8.1 cm	4 (9.1)
Location of metastases, n (%)	
Hepatic Only	23 (52.3)
Extrahepatic Only	2 (4.5)
Hepatic and Extrahepatic	18 (40.9)
HLA-A2*02:01 Status, n (%)	
Negative	30 (68.2)
Positive	12 (27.3)
Unknown	2 (4.5)

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

Results *(continued)*

- The median dose intensity for darovasertib and crizotinib was 92.6% and 88.0%, respectively
- The mean duration of exposure to darovasertib was 10.0 months
- Adverse events are summarized in **Table 2**
  - Overall, 97.7% of patients experienced at least one treatment-related adverse event (TRAE), most of which were mild to moderate in severity.
  - All Grade TRAEs leading to permanent discontinuation and treatment-related serious adverse events (TRSAEs) occurred in 4.5% and 9.1% of patients, respectively
  - The most common TRAEs (>30%) were diarrhea, nausea, edema, vomiting, dermatitis, hypoalbuminemia, and fatigue
  - No Grade 3 or greater TRAEs >5%

Table 2. Treatment-Related Adverse Events

	First Line (N=44) All Grades n (%)	First Line (N=44) ≥ Grade 3 n (%)
TRAE	43 (97.7)	12 (27.3)
TRSAE	4 (9.1%)	3 (6.8%)
TRAE leading to discontinuation	2 (4.5%)	1 (2.3%)
TRAE that occurred in >30% for all grades		
Diarrhea	40 (90.9)	1 (2.3)
Nausea	35 (79.5)	0
Edema Peripheral	27 (61.4)	0
Vomiting	21 (47.7)	0
Dermatitis Acneiform	19 (43.2)	0
Hypoalbuminemia	19 (43.2)	1 (2.3)
Fatigue	17 (38.6)	0

TRAE, treatment-related adverse event. TRSAE, treatment-related serious adverse events.

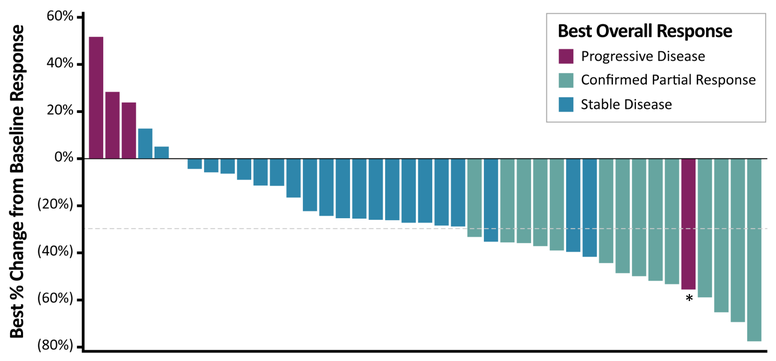
- The objective response rate (ORR) was 34.1% (14/41) with confirmed partial responses (**Table 3**)
- The disease control rate (DCR) at 8 weeks was 90.2%
- A waterfall plot displaying percent change from baseline in sum of longest diameter response is presented for first-line patients in **Figure 3**

Table 3. Objective Response Rate Summary (confirmed)

	First Line (N=41)
Objective Response Rate, n (%)	14 (34.1)
95% CI	20.1, 50.6
Best Overall Response, n (%)	
Complete Response	0 (0.0)
Partial Response	14 (34.1)
Stable Disease	23 (56.1)
Progressive Disease	4 (9.8)
Disease Control Rate, n (%)	37 (90.2)
95% (CI)	76.9, 97.3
Duration of Response, median months	9.0
95% (CI)	3.8, 12.0

CI, Confidence Interval. SD, standard deviation.
Confirmed Objective Tumor Response as Assessed by Investigator per RECIST 1.1.
Response summarized for all patients who had at least one dose of study drug and had at least 1 post-baseline tumor assessments. Three patients who discontinued treatment prior to post-baseline tumor assessments were excluded from this analysis.
Confidence interval is calculated using Clopper-Pearson method.

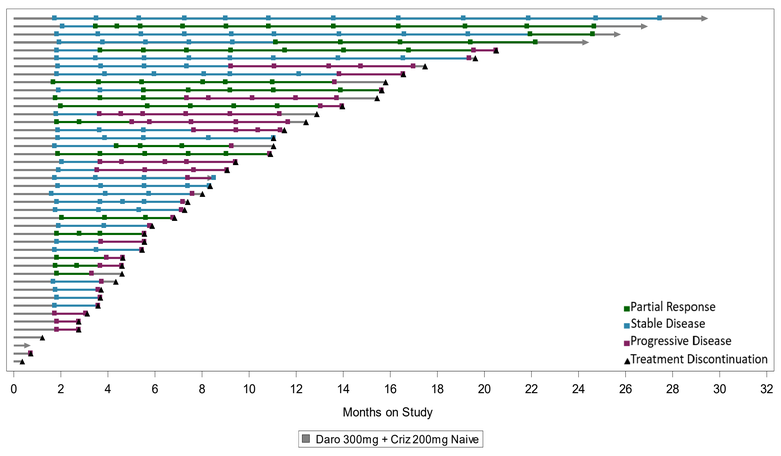
Figure 3. Best Percent Change from Baseline in Sum of Diameters



* By RECIST v1.1, patient had target lesion response, but progression detected with new lesions and non-target lesions.

- Median duration of response (DOR) was 9.0 months
  - A swimmer plot displaying months on study for each patient with best response is shown in **Figure 4**

Figure 4. Swimmer Plot of Tumor Response over Time



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References

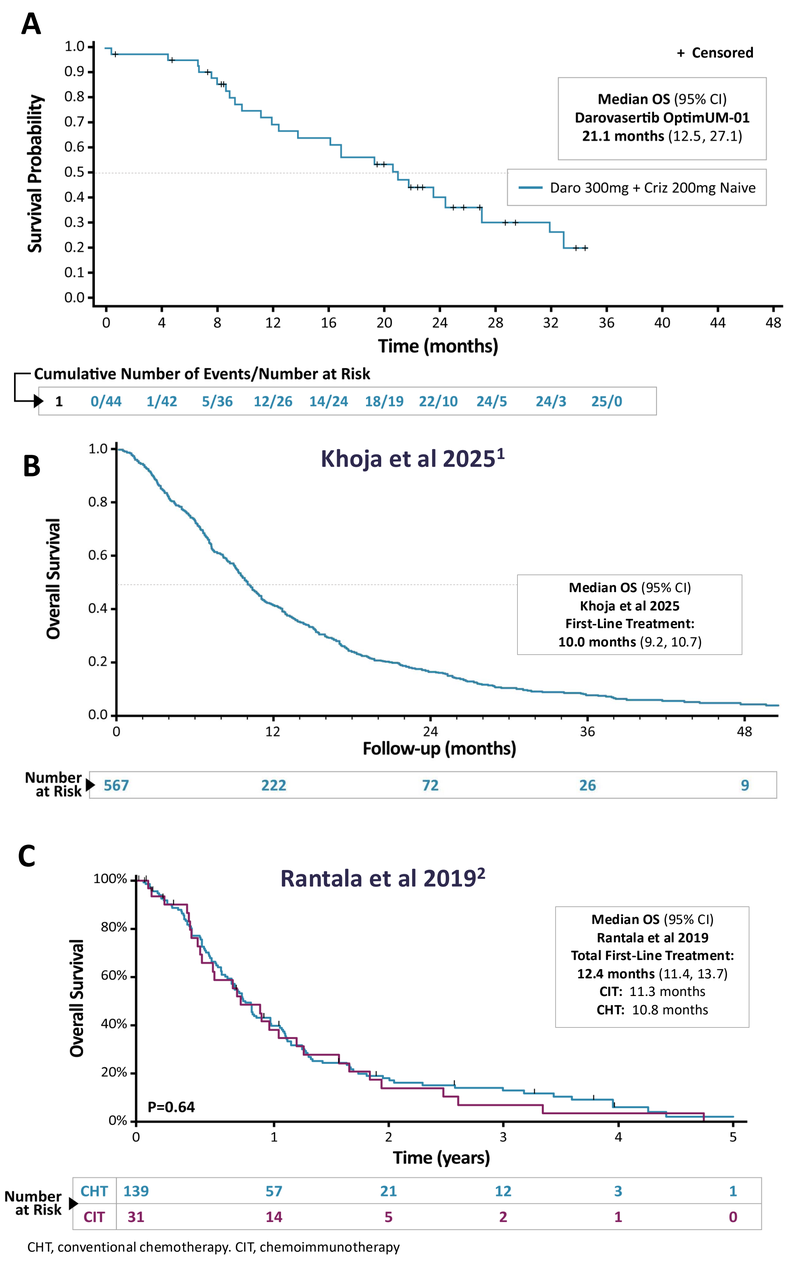
1. Khoja L, et al. J Clin Oncol. 2025;43:(suppl) Abstract 9539. 2. Rantala ES, et al. Melanoma Res. 2019;29:561-568. 3. Park JJ, et al. Oncogenesis. 2024;28:13-9.
4. Sullivan RJ, Shoushtari AN. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Available from: https://www.uptodate.com/contents/the-molecular-biology-of-melanoma (Accessed on May 21, 2025) 5. Piperno-Neumann S, et al. Br J Cancer. 2023;128:1040-1051. 6. McKean M et al. Ann of Oncol. 2023;34:S651.

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Results *(continued)*

- With a median follow-up time of 25 months, **mOS was 21.1 months** (95%CI: 12.5, 27.1) (**Figure 6**)
  - These results compared favorably to historical mOS of 10-12 months[1-2]

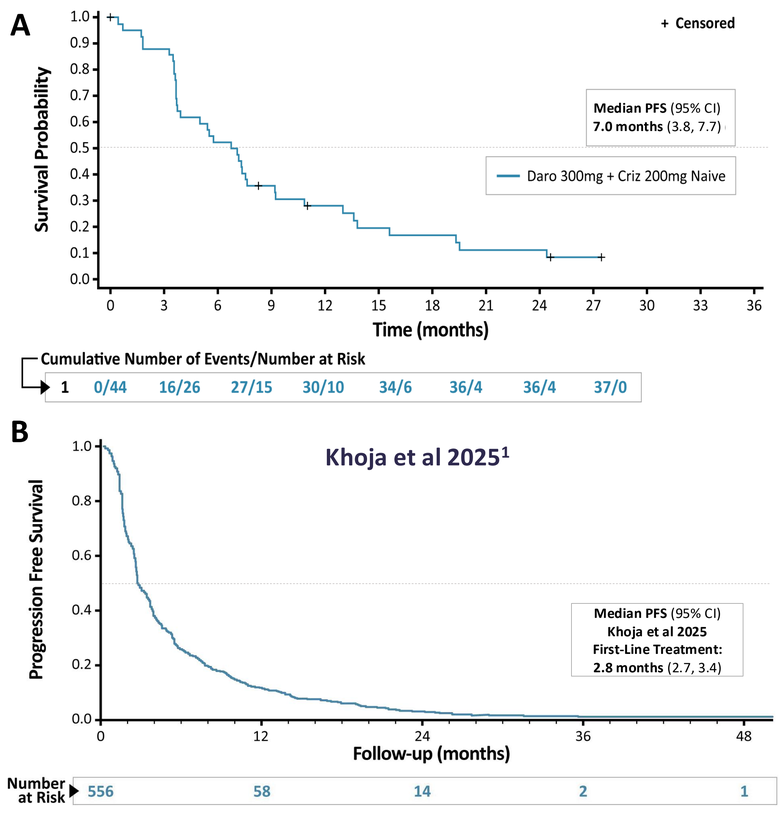
Figure 6. Kaplan Meier Plot Overall Survival for A.) Combination of Darovasertib plus Crizotinib and Historical Controls from B.) Khoja et al[1] and C.) Rantala et al[2]



CHT, conventional chemotherapy. CIT, chemoimmunotherapy

- The **mPFS was 7.0 months** (95% CI: 3.8, 7.7) in patients treated with darovasertib plus crizotinib combination (median follow-up 25 months; **Figure 7**)
  - These results compared favorably to historical mPFS of 2.8 months[1]

Figure 7. Kaplan Meier Plot Progression Free Survival for A.) Combination of Darovasertib plus Crizotinib and B.) Historical Control[1]



- Median OS was notable compared to historical controls at 21.1 months, despite 39% of patients having ECOG PS 1

Conclusions

- The mOS for darovasertib plus crizotinib in the first-line mUM setting was 21.1 months which compares favorably to historical mOS of 10-12 months[1-2]
- In addition, higher ORR as well as longer mPFS, and DOR were observed relative to standard of care treatments
- These findings suggest that darovasertib plus crizotinib may represent a novel first-line treatment option and support the ongoing registrational phase 2/3 trial in the first-line setting (OptimUM-02; NCT05987332)