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Neoadjuvant Darovasertib in Primary Uveal Melanoma: Follow-Up Data from the Phase 2 OptimUM-09 Study

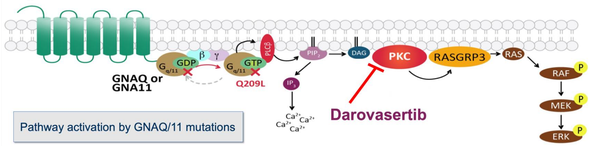
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Introduction

- Primary uveal melanoma (UM) treatment may require enucleation or vision-threatening plaque brachytherapy (PB)[1]
- Neoadjuvant darovasertib, a selective PKC inhibitor, has shown evidence of tumor shrinkage, eye preservation, reduced risk of severe vision loss and improved visual acuity during neoadjuvant treatment (**Figure** 1)[2]

Figure 1. Darovasertib Mechanism of Action

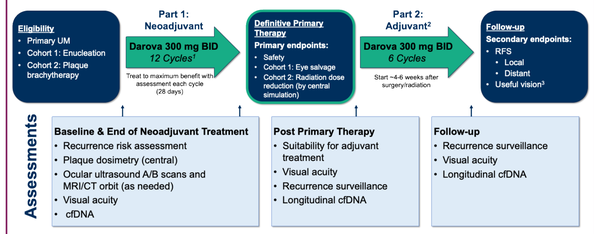


- Here, we present follow up results from subjects on the OptimUM-09 (NCT05907954) study evaluating neoadjuvant darovasertib in subjects requiring enucleation (cohort 1 [C1]) or PB (cohort 2 [C2])

Methods

- OptimUM-09 is a phase 2, single-arm neoadjuvant study in subjects with primary UM (**Figure 2**)

Figure 2. OptimUM-09 Study Design



Treatment to maximum benefit (no further tumor shrinkage or tumor growth noted on 2 consecutive assessments) or a maximum of 12 cycles

- Eligible primary UM subjects received darovasertib 300 mg BID in 28-day cycles
- Primary endpoints were eye preservation rate (C1) and projected radiation dose reduction to fovea and/or optic disc (C2)
- Secondary endpoints included tumor shrinkage (C1/2), and early treatment diabetic retinopathy study best-corrected visual acuity loss of ≥15 letters loss 1-year post-PB (C2)
- Exploratory endpoints included predicted risk of ≤20/200 vision (C2 only), metastatic-free survival (MFS)(C1/2), and local recurrence rate (C1/2)
- Safety was assessed in all subjects and tumor reduction was assessed in subjects with ≥1 post baseline tumor assessment
- Eye preservation rate was assessed in those who had undergone primary local therapy; radiation reduction was assessed in those with pre and post neoadjuvant centrally-simulated dosimetry data

Results

- As of June 15, 2026, 119 subjects (C1: 67; C2: 52) had received darovasertib (**Table 1**)

Table 1. Baseline Characteristics

	Cohort 1: Enucleation N=67	Cohort 2: Plaque Brachytherapy N=52
Age, median, years (range)	58 (23-82)	57.5 (31-85)
Male, n (%)	43 (64.2)	28 (53.8)
ECOG performance score, n (%)		
0	54 (80.6)	40 (76.9)
1	13 (19.4)	12 (23.1)
Tumor, mean (SD) mm		
Thickness - apex height	10.6 (2.9)	7.4 (2.8)
Largest basal diameter	16.0 (3.0)	13.8 (3.0)
Distance to fovea	5.9 (4.1)	6.2 (4.2)
Distance to optic nerve	5.5 (4.4)	5.3 (4.0)
VAS affected eye, mean (SD)	33.5 (33.2)	63.7 (28.8)
T Category, n (%)		
T1	1 (1.5)	6 (11.5)
T2	4 (6.0)	10 (19.2)
T3	32 (47.8)	32 (61.5)
T4	26 (38.8)	3 (5.8)
Not available	4 (6.0)	1 (1.9)
Molecular high risk, n (%)		
Monosomy 3 or Class 2 by GEP	19/50 (38.0)	14/42 (33.3)
PRAME positive	10/21 (47.6)	5/16 (31.3)

ECOG, Eastern Cooperative Oncology Group. GEP, gene expression profiling. PRAME, preferentially expressed antigen of melanoma. SD, standard deviation. VAS, visual acuity score.

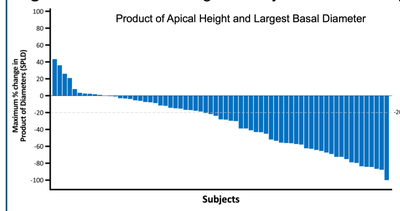
Safety

- Common adverse events (AEs) ≥20% included diarrhea (68.1%), nausea (62.2%), fatigue (35.3%), and vomiting (30.3%)
- Serious AEs (SAEs) occurred in 10% of subjects; the most common SAE was hypotension (3.4%)
- Drug interruption, reduction, or discontinuation due to AEs occurred in 27%, 9.2%, and 9.2%, respectively

Efficacy

- Overall, 85.7% had tumor shrinkage from baseline and 63.9% had ≥20% tumor shrinkage (C1: 55.2%; C2: 75.0%) (**Figure 3** and **Figure 4**)
- Eye preservation was achieved in 33 of 58 C1 subjects with primary local therapy (56.9%; 95% CI 43.2 to 69.8). Among subjects with at least 20% tumor reduction, 31 of 33 (93.9%) preserved their eye (**Figure 3**)

Figure 3. Tumor Shrinkage and Eye Preservation (C1)



Tumor Response

	Cohort 1 (N=67)
Tumor Reduction,* n (%)	56 (83.6)
≥20% Reduction	37 (55.2)
≥30% Reduction	31 (46.3)

Eye Preservation

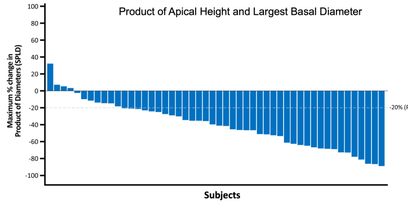
	Cohort 1 (N=58)
Eye Preservation Rate, n (%)**	33/58 (56.9)
In patients with 20% reduction*	31/33 (93.9)
Types of Primary Local Therapy, n (%)	
Enucleation	25/58 (43.1)
Plaque brachytherapy	24/58 (41.4)
External beam radiation	9/58 (15.5)

*Product of diameter measurements (i.e., product of apical height and largest basal diameter measurements), >20% tumor shrinkage required for partial response, based on endpoint definition utilized for upcoming OptimUM-10 study; **Eye preservation rate is the percentage of patients who avoided enucleation in Cohort 1. This analysis was conducted in the 58 patients who had primary local therapy; ^out of 33 subjects with actual primary local therapy and at least 20% tumor reduction. Per protocol efficacy evaluable population (N=67) for Cohort 1 was defined as all subjects who received at least one dose of study drug and have at least one post-baseline tumor assessment.

Results

- In Cohort 2, projected radiation dose reductions were observed in 76.7%, 79.1%, and 74.4% of subjects for the fovea, disc center, and lens, respectively (**Figure 4**)
- Reduction in predicted risk of severe vision loss at 3 years following PB was predicted in 60% (24/40) of the subjects[3]

Figure 4. Tumor Shrinkage and Radiation Reduction (C2)



Tumor Response

	Cohort 2 (N=52)
% Tumor Reduction, n (%)**	46 (88.5)
≥20% Reduction	39 (75.0)
≥30% Reduction	31 (59.6)

Projected Radiation Reduction to Key Eye Structures (N=43)*

Eye Structure	Subjects with Dose Reduction	Subjects with ≥20% Reduction
Fovea, n (%)	33 (76.7)	17 (39.5)
Disc Center	34 (79.1)	19 (44.2)
Lens	32 (74.4)	21 (48.8)

**Product of diameter measurements, >20% tumor shrinkage required for partial response, based on endpoint definition utilized for upcoming OptimUM-10 study. *Subjects with baseline and at least one post-baseline dosimetry assessment.
One patient was not evaluable and therefore not included in the efficacy evaluable population.

- Visual acuity score gain during neoadjuvant darovasertib - visual acuity score improvement was demonstrated across both cohorts: 54.7% and 60.5% subjects in C1 and 2, respectively
- Subjects with 5 or more letters gained at 2 consecutive visits: 36.5% and 24.2% in Cohort 1 and 2, respectively

Local and Metastatic Events

- Median local recurrence time was not reached; local treatment failure occurred in 7.5% (5/67) subjects in C1 (4 post eye-preserving treatment, 1 with >20% growth from nadir during neoadjuvant treatment) and 5.8% (3/52) subjects in C2 (**Table 3**)
- In C1 subjects treated with PB as eye preserving treatment, local recurrence occurred in 3 (4.5%) subjects at a median follow-up of 19 months, which is similar to historical rates from the COMS I-125 PB cohort (4.3-7.9%) at 18 months-3 years post PB[4]
  - Plaque sizing based on post-neoadjuvant LBD led to inadequate coverage of the baseline LBD + 2 mm margin in all 3 subjects; protocol amended to use baseline or largest recorded LBD
- Median time to metastatic recurrence was 30.7 months for C1 and not reached for C2; metastases developed in 23.9% of C1 (comparable to 1-year metastatic rate of 22.7% reported for a primary enucleation cohort)[5] and 13.5% of C2 subjects (**Table 3**)

Table 3. Local and Metastatic Events

	Cohort 1: N=67	Cohort 2: N=52	Total N=119
Local Recurrences			
Events, n (%)	5 (7.5)	3 (5.8)	8 (6.7)
Censored, n (%)	62 (92.5)	49 (94.2)	111 (93.3)
Median (95% CI), months[a]	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Q1, Q3 (months)	NE, NE	NE, NE	NE, NE
Min, Max (months)	1.5, 32.2	0.8, 31.4	0.8, 32.2
Metastatic Recurrences			
Events, n (%)	16 (23.9)	7 (13.5)	23 (19.3)
Censored, n (%)	51 (76.1)	45 (86.5)	96 (80.7)
Median (95% CI), months[a]	30.7 (23.00, NE)	NE (NE, NE)	30.7 (30.7, NE)
Q1, Q3 (months)	18.9, NE	NE, NE	23, NE
Min, Max (months)	1.5, 32.2	0.8, 31.4	0.8, 32.2

CI = confidence interval; KM = Kaplan-Meier; Q1/Q3 = 25th/75th percentiles. a Median and 95% CI from the KM estimate (Brookmeyer-Crowley). Time in months = (first date of metastasis or death date – treatment start date + 1)/30.4375. Event: metastasis or death from any cause. Censoring at LSTALVDT (date last known alive).

Results

- The median time to metastases was favorable compared to ~2 years reported historically for clinical and/or molecular high-risk UM (16.5 months and 24.7 months for GEP class 2/PRAME positive and negative tumors respectively, 19 months post primary enucleation for T3/T4 tumors, and 25 months post PB for T4 tumors)[6-11]
- Subjects who developed metastasis predominantly had T3/T4 disease, larger tumor size (9/16 with baseline LBD ≥18 mm), and high-risk molecular features (Class 2 GEP or monosomy 3 with 8q, 6q, 6p copy number changes, PRAME positivity)
- MFS probabilities by T stage in OptimUM-09 are in range of those reported historically with immediate local therapy suggesting no detriment from neoadjuvant treatment (**Table 4**)[6-7]
  - OptimUM-09 has a greater proportion of T3 and T4 tumors than in the historical datasets: OptimUM-09: 53.8%/24.4%; Harbor et al: 22.8%/7.8%; Shields et al: 21.0%/6.0%[6-7]

Table 4. MFS by T Stage for OptimUM-09 and Historical Studies

T stage	OptimUM-09 N=114 (2-year MFS)	Harbour et al[6] N=1,577 (3-year MFS)	Shields et al[7] N=7,731 (3-year MFS)
T1	100%	96.8%	96%
T2	87.5%	88.6%	93%
T3	73.4%	76.4%	81%
T4	63.4%	52%	68%

Conclusions

- Follow-up results from OptimUM-09 showed that neoadjuvant darovasertib was well tolerated, led to tumor shrinkage enabling eye preservation in >50% of EN eligible subjects, reduced projected radiation to critical eye structures in PB subjects, and led to VAS improvement in both cohorts
- The observed local and systemic disease control rates are in line with historical outcomes for immediate enucleation or PB suggesting no detriment with neoadjuvant treatment
- Metastatic events predominantly occurred in subjects with adverse baseline features, including larger tumor size and high-risk clinical and/or molecular characteristics
- Two registrational studies (OptimUM-10, NCT07015190; OptimUM-11, NCT07804186) are further evaluating darovasertib in the neoadjuvant (monotherapy) and adjuvant (in combination with crizotinib) settings

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