2026 ASCO® ANNUAL MEETING

Darovasertib Plus Crizotinib vs Investigator's Choice as First-Line Treatment for Patients with HLA-A2 Negative Metastatic Uveal Melanoma: Primary Results from the OptimUM-02 Trial

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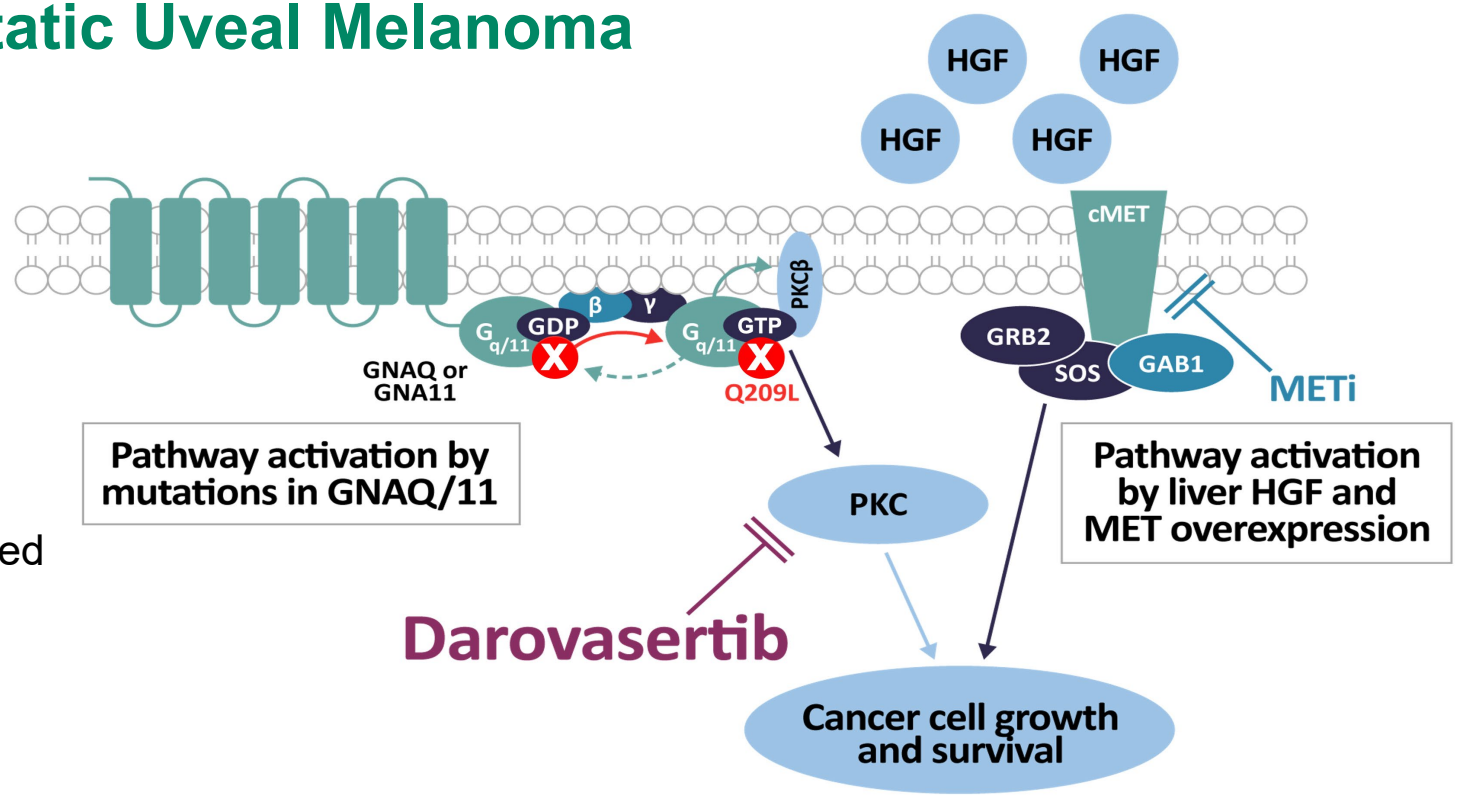
Darovasertib: First-in-Class, Oral Targeted PKC Inhibitor

Targeting PKC and MET in Metastatic Uveal Melanoma

- Uveal melanoma (UM) is the most common ocular cancer in adults
- Despite effective primary tumor treatment up to 50% of patients develop metastases
- Metastatic UM (mUM) has a poor prognosis with mPFS of 2.8 months and mOS of 10-12 months[1-2]
- Mutations in GNAQ/11 that activate PKC are detected in >95% of uveal melanoma tumors[3-4]
- Currently no FDA-approved treatments for HLA-A*02:01 negative mUM patients
- **OptimUM-01:** encouraging activity across both HLA-A*02:01-positive and negative mUM with darovasertib + crizotinib[5-6]
- **OptimUM-02:** evaluated darovasertib in combination with crizotinib as first-line therapy in patients with HLA-A*02:01–negative mUM



- **Darovasertib:** first-in-class, oral, PKC inhibitor with clinical activity in HLA-A*02:01-positive and negative mUM[5]
- **Crizotinib:** oral MET inhibitor, has shown complementary activity with darovasertib preclinically and clinically[6]

HLA, human leukocyte antigen. mOS, median overall survival. mPFS, median progression free survival. PKC, protein kinase C.

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;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. Presented at 2025 SMR Congress. Erlangen, Germany [abstract 209].

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OptimUM-02 Study Design

Phase 2/3, multi-center, multi-arm, multi-stage, open-label study

Patients:

Treatment naïve
HLA-A*02:01
negative mUM

Phase 2a*

2:2:1
R#

- **Darovasertib (300 mg BID)** + Crizotinib (200 mg BID)**
- **Darovasertib (200 mg BID)** + Crizotinib (200 mg BID)**
- **Investigator's Choice (control):** 1. Pembrolizumab 2. Ipilimumab + Nivolumab 3. Dacarbazine

Phase 2b and Phase 3*

2:1
R#

- **Darovasertib (300 mg BID)** + Crizotinib (200 mg BID)**
- **Investigator's Choice (control):** 1. Pembrolizumab 2. Ipilimumab + Nivolumab 3. Dacarbazine

Phase 2b Endpoints

Primary:

- PFS by BICR

Secondary:

- PFS by Investigator
- ORR by BICR, Investigator
- Duration of response
- Disease Control Rate ≥ 12 weeks
- Safety

Phase 3 Endpoints

Primary:

- Overall Survival
  (to be presented at later date when data matures)

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 (ipilimumab + 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, ipilimumab (3 mg/kg) + nivolumab (1 mg/kg) for 4 cycles followed by nivolumab (1mg/kg). ORR, objective response rate. Pembro, pembrolizumab (200 mg Q3W). PFS, progression-free survival.

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Analysis Populations

Efficacy

- All patients in the ITT population setting (phase 2b portion of trial)
  - Darovasertib 300 mg + crizotinib 200 mg (n=210)
  - Investigator's Choice (control, n=103)
- Analysis based on both BICR and Investigator assessments

Safety

- Safety was evaluated in all patients (phase 2a and 2b) who received at least one dose of darovasertib 300 mg + crizotinib 200 mg or control
  - Darovasertib 300mg + crizotinib 200 mg (N=239)
  - Investigator's Choice (control, N=100)

BICR, blinded independent central reader. ITT, intent-to-treat.

Primary Endpoint Statistical Analysis

PFS per BICR

- 130 PFS events were required to detect a hazard ratio of 0.55 with 90% power
  - Stratified log-rank test at a 1-sided α of 2.5%
- The median PFS in the control arm was assumed to be 3 months
- The target HR of 0.55 represents a 45% reduction in the risk of disease progression or death
  - Translates to approximately 5.5 months median PFS in the darovasertib + crizotinib arm assuming exponential distributions

BICR, blinded independent central reader. HR, hazard ratio. ORR, objective response rate. PFS, progression-free survival.

Baseline Characteristics

Efficacy Analysis Population

	Darovasertib + Crizotinib (N=210)	Investigator's Choice (N=103)
Age, mean (range)	61.1 (22 - 85)	61.5 (29 - 85)
Female, n (%)	101 (48.1)	52 (50.5)
Race, n (%)		
White	177 (84.3)	83 (80.6)
non-White	4 (1.9)	4 (3.9)
Not reported	29 (13.8)	16 (15.5)
ECOG		
0	162 (77.1)	87 (84.5)
1	48 (22.9)	16 (15.5)
Stratification LDH at Baseline (IRT) , 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)
Stratification ICT at Baseline (IRT) , n (%)		
Ipilimumab + nivolumab		79 (76.7)
Pembrolizumab or dacarbazine*		24 (23.3)

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

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Baseline Tumor Characteristics

Efficacy Analysis Population

	Darovasertib + Crizotinib (N=210)	Investigator's Choice (N=103)
Time since First Metastatic Diagnosis (year)		
n	210	103
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)
≥ 8.1 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)

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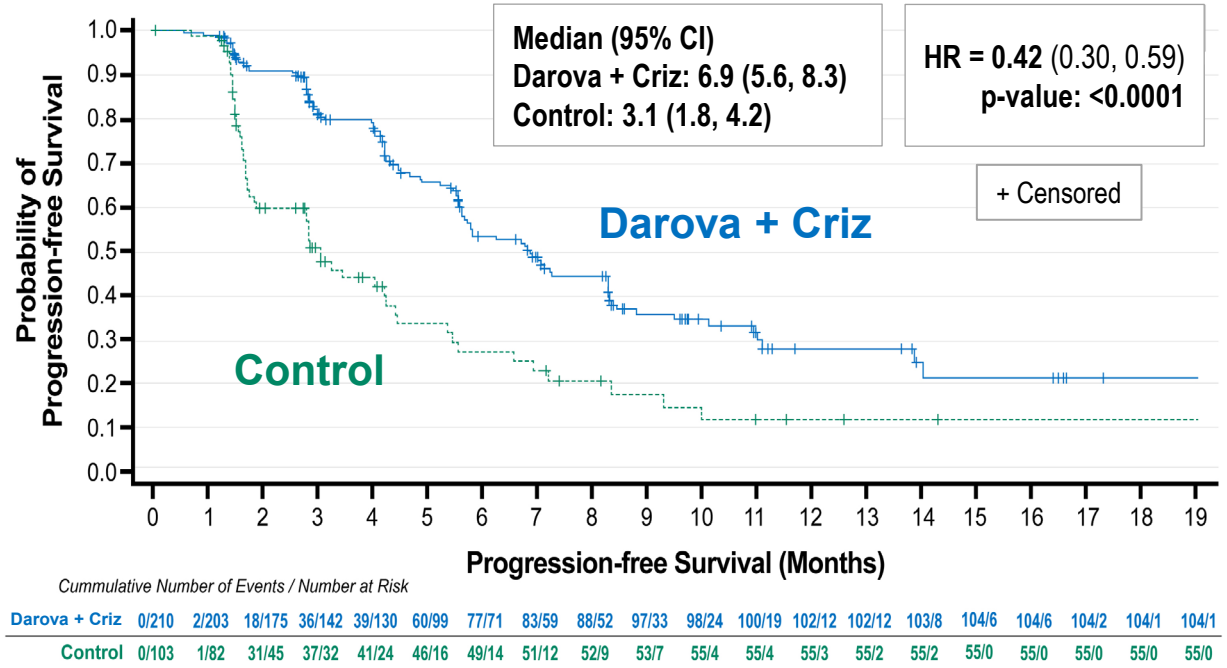
Primary Efficacy Endpoint Results

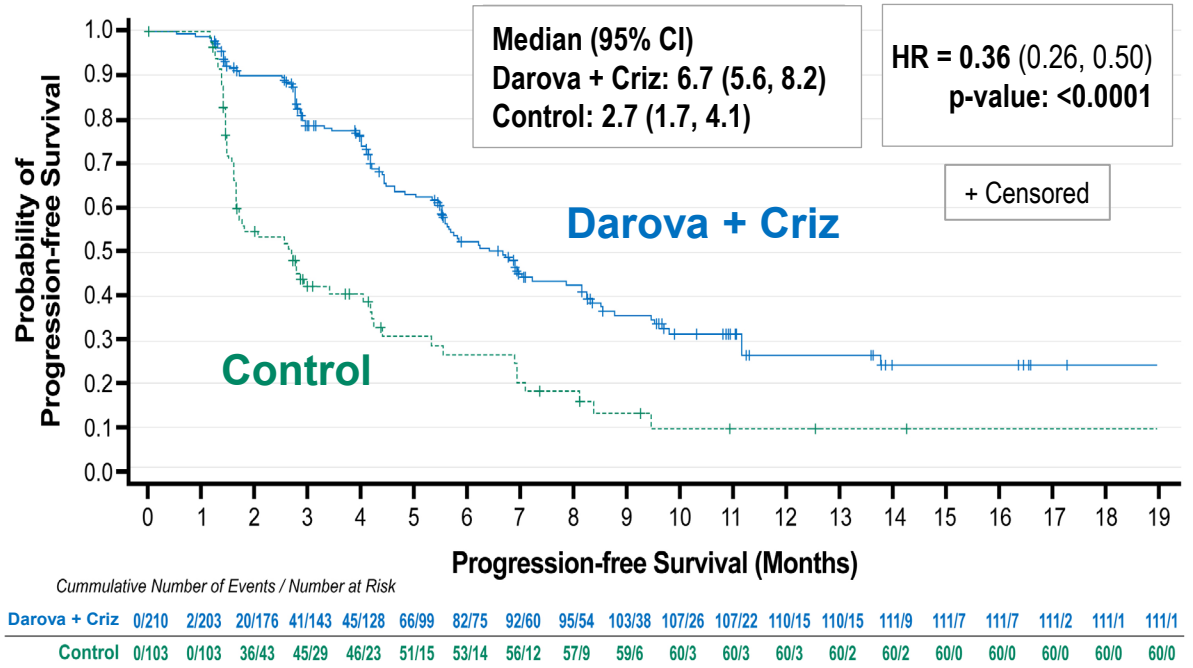
BICR Assessment



Cummulative Number of Events / Number at Risk

Darova + Criz	0/210	2/203	18/175	36/142	39/130	60/99	77/71	83/59	88/52	97/33	98/24	100/19	102/12	102/12	103/8	104/6	104/6	104/2	104/1	104/1
Control	0/103	1/82	31/45	37/32	41/24	46/16	49/14	51/12	52/9	53/7	55/4	55/4	55/3	55/2	55/2	55/0	55/0	55/0	55/0	55/0

Investigator Assessment



Cummulative Number of Events / Number at Risk

Darova + Criz	0/210	2/203	20/176	41/143	45/128	66/99	82/75	92/60	95/54	103/38	107/26	107/22	110/15	110/15	111/9	111/7	111/7	111/2	111/1	111/1
Control	0/103	0/103	36/43	45/29	46/23	51/15	53/14	56/12	57/9	59/6	60/3	60/3	60/3	60/2	60/2	60/0	60/0	60/0	60/0	60/0

- Clinically meaningful and statistically significant improvement in PFS with darova + criz vs control
- Reduction in the risk of progression or death:
  - 58% by BICR (HR: 0.42); 64% by investigator assessment (HR: 0.36), p < 0.0001

Median follow-up for the population was 7.4 months. Median duration of treatment for darovasertib and crizotinib was 6.31 months; for pembrolizumab, ipilimumab, and nivolumab, the median duration of treatment were 2.87, 2.56, and 2.79 months, respectively.
BICR, blinded independent central reader. Darova + criz, darovasertib + crizotinib. HR, hazard ratio. PFS, progression free survival.

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Secondary Efficacy Endpoint Results

	BICR Assessment		Investigator Assessment	
	Darovasertib + Crizotinib (N=210)	Investigator's Choice (N=103)	Darovasertib + Crizotinib (N=210)	Investigator's Choice (N=103)
Objective Response Rate				
Patients with a complete or partial response, n (%)	78 (37.1)	6 (5.8)	83 (39.5)	2 (1.9)
95% CI	30.6, 44.1	2.2, 12.3	32.9, 46.5	0.2, 6.8
Odds ratio (95% CI)	10.8 (4.4, 26.4)		34.6 (8.1, 146.9)	
p-value vs. control	<0.0001		<0.0001	
Duration of Response				
Median, months (95% CI)	6.8 (5.5, 11.3)	NE	6.8 (4.8, 9.7)	NE
Disease Control Rate				
Patients with a complete response, partial response, or stable disease for at least 12 weeks, n (%)	154 (73.3)	32 (31.1)	156 (74.3)	28 (27.2)
95% CI	66.8, 79.2	22.3, 40.9	67.8, 80.1	18.9, 36.8
Odds ratio (95% CI)	7.7 (4.3, 13.5)		9.5 (5.3, 17.0)	
p-value vs. control	<0.0001		<0.0001	

BICR, blinded independent central reader. CI, confidence interval.

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Best Overall Response

	BICR Assessment		Investigator Assessment	
	Darovasertib + Crizotinib (N=210)	Investigator's Choice (N=103)	Darovasertib + Crizotinib (N=210)	Investigator's Choice (N=103)
Best Overall Response, n (%)				
Complete Response	5 (2.4)	0	0	0
Partial Response	73 (34.8)	6 (5.8)	83 (39.5)	2 (1.9)
Stable Disease	107 (51.0)	43 (41.7)	99 (47.1)	39 (37.9)
Progressive Disease	13 (6.2)	29 (28.2)	15 (7.1)	34 (33.0)
Non-Evaluable by RECIST	0	1 (1.0)	1 (0.5)	4 (3.9)
Not Reported*	12 (5.7)	24 (23.3)	12 (5.7)	24 (23.3)

* Refers to the patients who did not have any post-baseline assessments. Investigator Choice Treatment: (24): withdrew consent before treatment (17), before 1st post-baseline scan (2); due to AE (1, G3 hypoxia), clinical progression (1) and death (2), scan not recoverable from outside facility (1). Darovasertib + crizotinib Treatment: (12); due to death (7), withdrew consent before 1st post-baseline scan (1); due to clinical progression (1), scans performed after clinical cutoff (1), scans not performed at EOT or during post-treatment period (2).

BICR, blinded independent central reader. CI, confidence interval.

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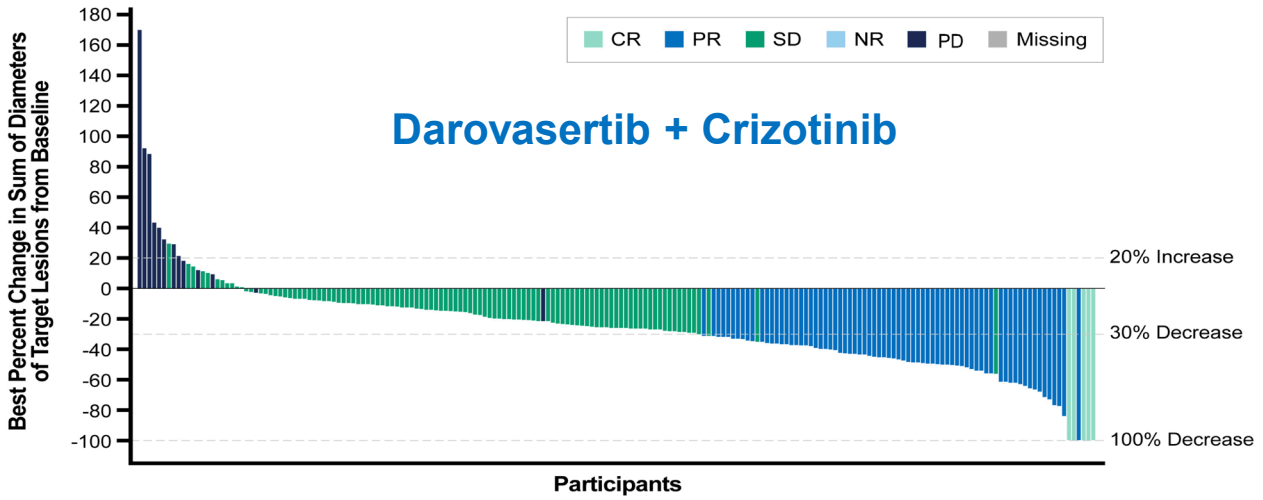
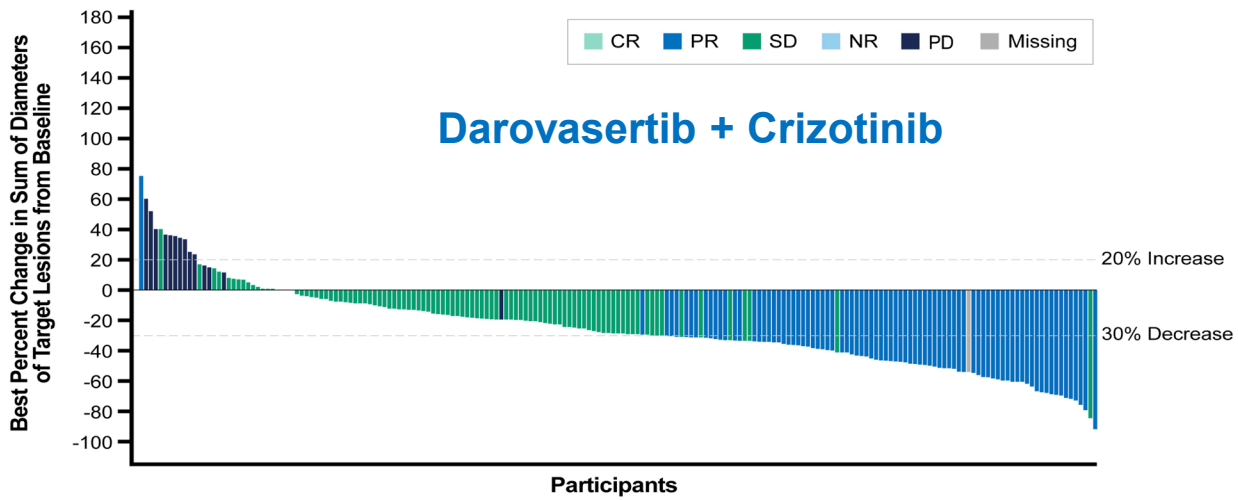
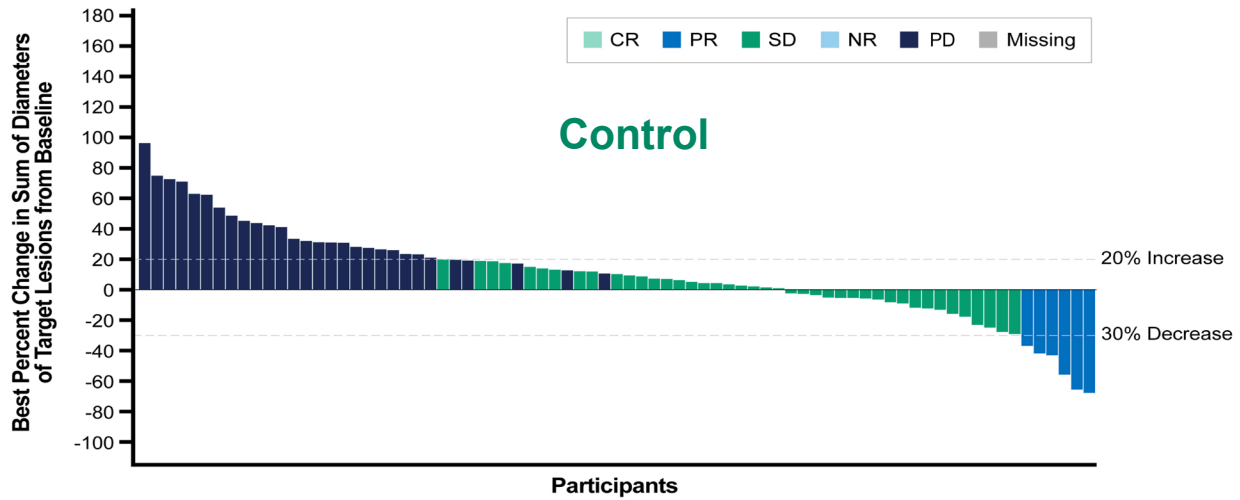
Best Overall Response

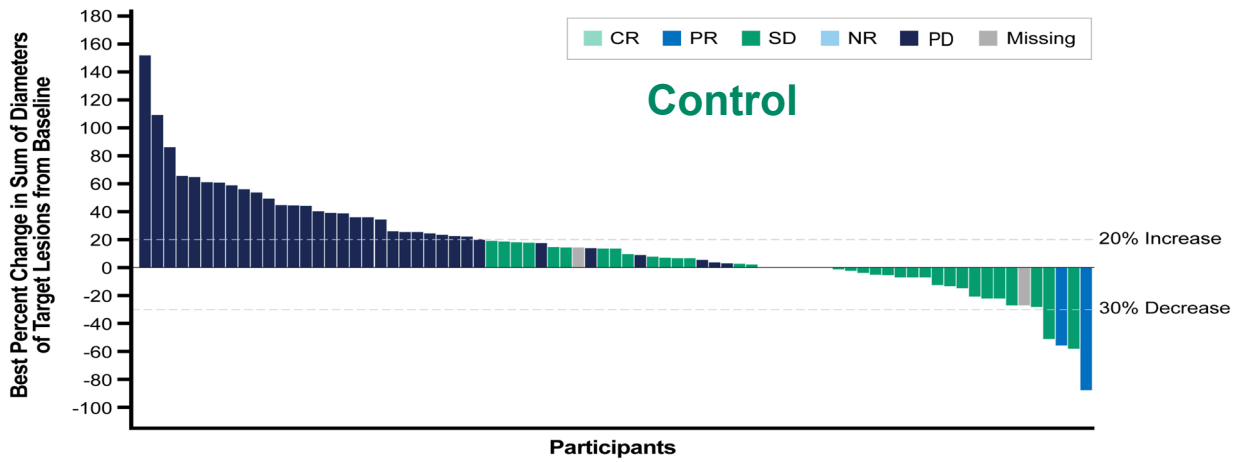
BICR Assessment



Investigator Assessment





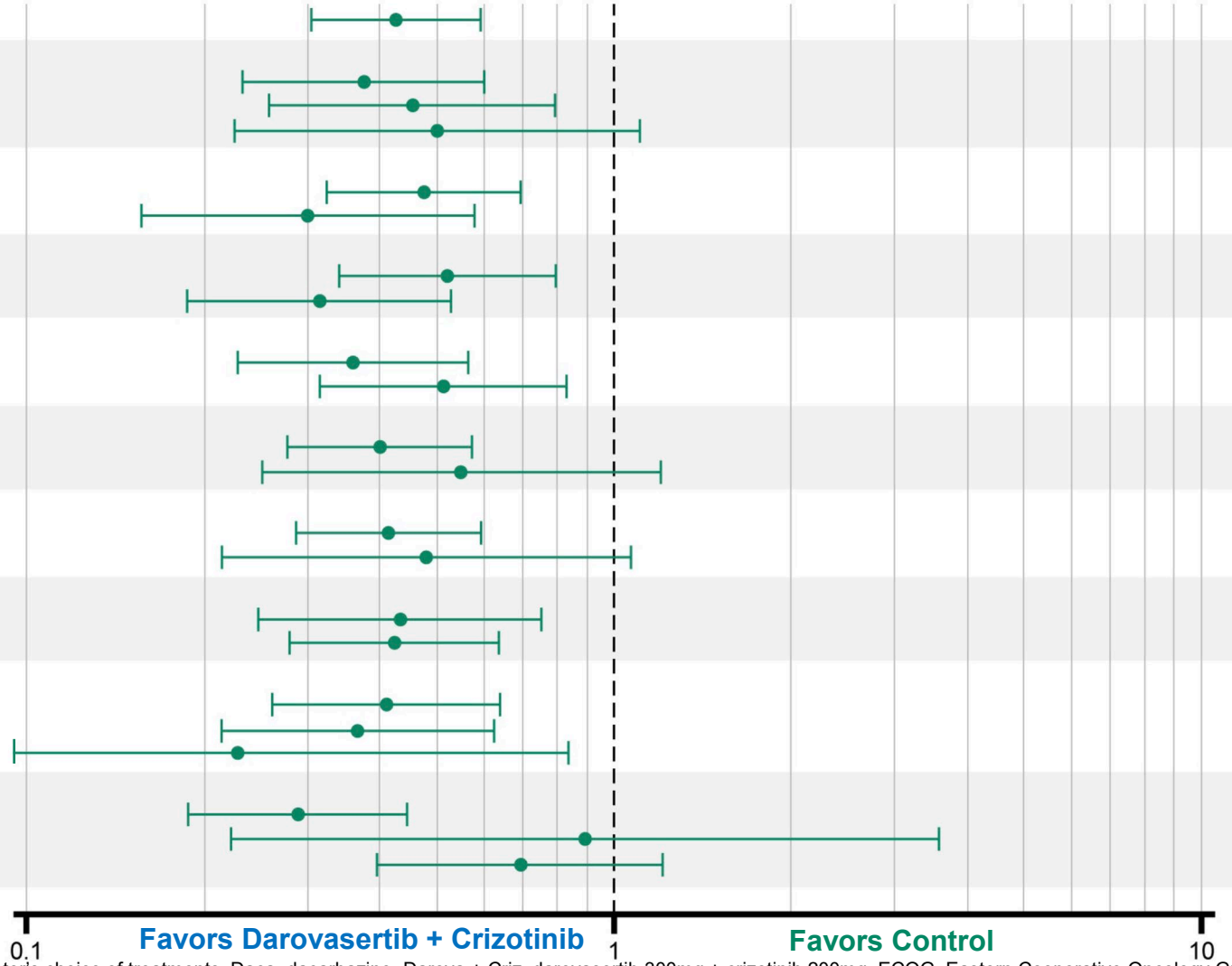


BICR, blinded independent central reader. CR, complete response. NR, not reported. PD, progressive disease. PR, partial response. SD, stable disease.

Primary Endpoint Results: PFS Subgroup Analysis

Results consistent across a broad range of patients

SUBGROUP	Participants Darova+Criz, Control	Hazard Ratio (95% CI) Darova+Criz – Control
All Participants	210, 103	0.42 (0.31, 0.59)
Strata by LDH		
≤ ULN	120, 62	0.37 (0.23, 0.60)
> ULN - < 2x ULN	65, 29	0.45 (0.26, 0.79)
≥ 2x ULN	25, 12	0.50 (0.23, 1.11)
Strata by ICT		
Ipi + Nivo	158, 79	0.47 (0.32, 0.69)
Pem or Daca	52, 24	0.30 (0.16, 0.58)
Age Group		
< 65 Years	118, 64	0.52 (0.34, 0.80)
≥ 65 Years	92, 39	0.31 (0.19, 0.53)
Gender		
Female	101, 52	0.36 (0.23, 0.56)
Male	109, 51	0.51 (0.31, 0.83)
Race		
White	177, 83	0.40 (0.28, 0.57)
Non-White	33, 20	0.55 (0.25, 1.20)
ECOG Status		
0	162, 87	0.41 (0.29, 0.59)
1	48, 16	0.48 (0.21, 1.07)
Geographic Region		
USA	74, 36	0.43 (0.25, 0.75)
Non-USA	136, 67	0.42 (0.28, 0.63)
Largest Single Target Lesion		
≤ 3 cm	119, 67	0.41 (0.26, 0.64)
3 cm - 8cm	73, 31	0.37 (0.21, 0.62)
≥ 8cm	18, 5	0.23 (0.06, 0.83)
Site of Metastates		
Hepatic Only	127, 65	0.29 (0.19, 0.44)
Extrahepatic Only	11, 7	0.89 (0.22, 3.58)
Hepatic and Extrahepatic	72, 31	0.69 (0.39, 1.21)



Results by BICR. Unstratified model.

BICR, blinded independent central reader. Control, investigator's choice of treatments. Daca, dacarbazine. Darova + Criz, 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.

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Overall Treatment Related Adverse Event

Summary

	Darovasertib + Crizotinib (N=239)	Investigator's Choice (N=100)
Median Relative Dose Intensity	91.0% for Darovasertib 77.1% for Crizotinib	100%
Any TRAE, n (%)	235 (98.3)	89 (89.0)
Grade 3 or 4	97 (40.6)	37 (37.0)
Grade 5*	1 (0.4)	1 (1.0)
Treatment related-SAE	22 (9.2)	25 (25.0)
Leading to withdrawn	2 (0.8)	5 (5.0)
Leading to darovasertib withdrawn	6 (2.5)	-
Leading to crizotinib withdrawn	24 (10.0)	-
Leading to IC withdrawn	-	19 (19.0)
Leading to darovasertib dose reduced	56 (23.4)	-
Leading to crizotinib dose reduced	63 (26.4)	-
Leading to IC dose reduced	-	0

* Grade 5 SAEs: Hepatic failure in the darovasertib + crizotinib arm in a subject with extensive bulky liver metastases in both lobes considered unrelated by Sponsor; gastrointestinal hemorrhage in ICT arm

IC, investigator's choice. SAE, serious adverse events. TRAE, treatment-related adverse events.

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Most Common Treatment Related Adverse Events

All Grades

	Darovasertib + Crizotinib (N=239)
Any TRAEs (≥20%), n (%)	235 (98.3)
Diarrhea	203 (84.9)
Nausea	179 (74.9)
Peripheral edema	160 (66.9)
Vomiting	119 (49.8)
Dermatitis acneiform	100 (41.8)
Fatigue	94 (39.3)
Hypotension	79 (33.1)
Hypoalbuminemia	61 (25.5)
Dysgeusia	61 (25.5)
Dizziness	61 (25.5)
Decreased appetite	57 (23.8)

	Investigator's Choice (N=100)
Any TRAEs (≥20%), n (%)	88 (88.0)
Diarrhea	29 (29.0)
Alanine aminotransferase increased	25 (25.0)
Aspartate aminotransferase increased	25 (25.0)
Fatigue	25 (25.0)
Nausea	25 (25.0)
Pruritus	24 (24.0)

TRAEs, treatment-related adverse events.

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Grade 3/4 Treatment Related Adverse Events

	Darovasertib + Crizotinib (N=239)
Any Grade 3/4 Adverse Events (≥2%), n (%)	97 (40.6)
Diarrhea	24 (10.0)
Syncope	17 (7.1)
Hypotension	9 (3.8)
Nausea	7 (2.9)
Peripheral edema	7 (2.9)
Anemia	6 (2.5)

	Investigator's Choice (N=100)
Any Grade 3/4 Adverse Events (≥2%), n (%)	37 (37.0)
Alanine aminotransferase increased	7 (7.0)
Aspartate aminotransferase increased	7 (7.0)
Diarrhea	6 (6.0)
Hepatitis	5 (5.0)
Colitis	4 (4.0)
Lipase increased	3 (3.0)
Autoimmune hepatitis	3 (3.0)
Amylase increased	3 (3.0)
Tubulointerstitial nephritis	2 (2.0)
Hypophysitis	2 (2.0)
Hyperthyroidism	2 (2.0)

TRAEs, treatment-related adverse events.

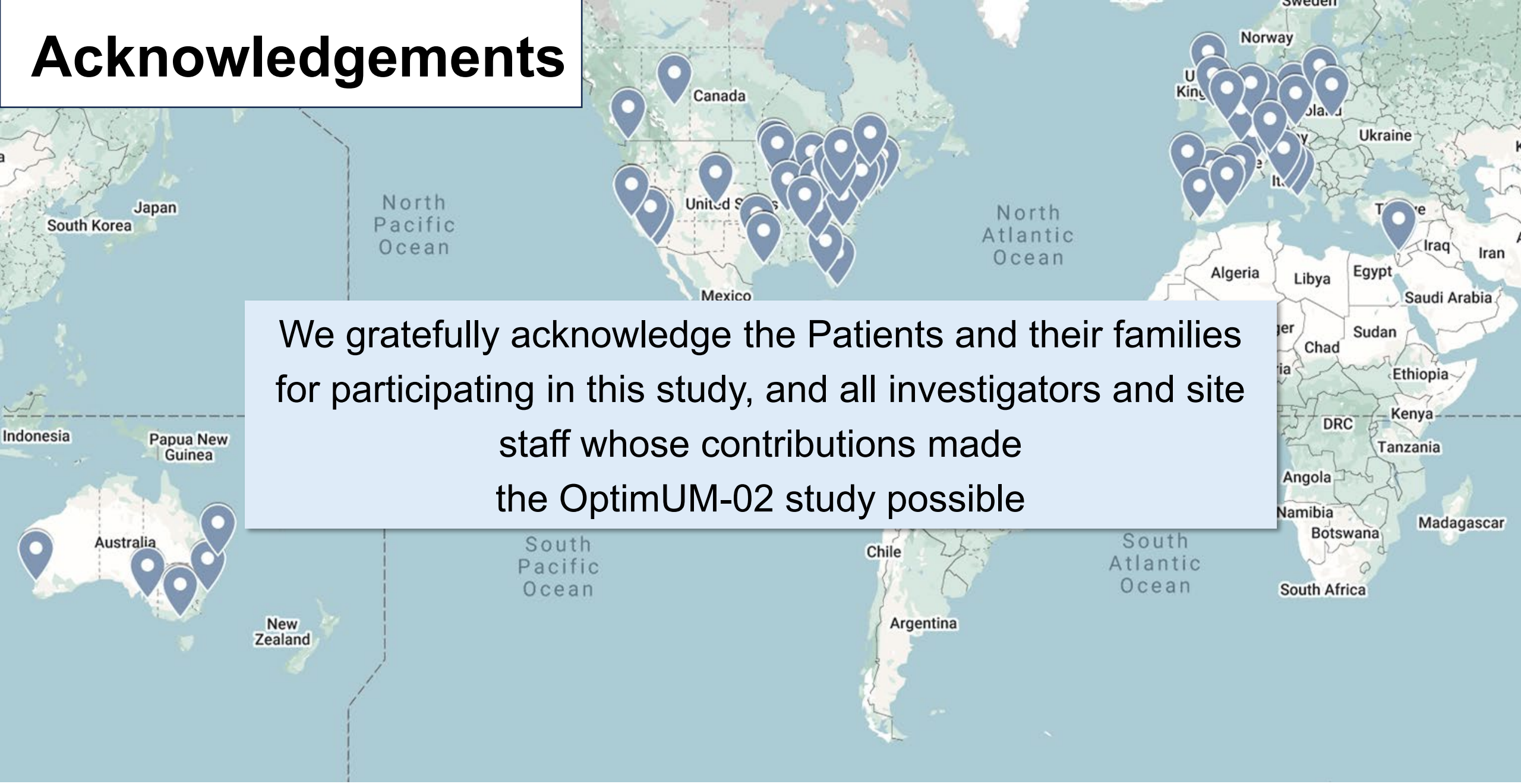
Summary

- In patients with HLA-A2-negative-mUM treated in the first-line setting, darovasertib +crizotinib demonstrated:
  - Clinically meaningful and significantly longer PFS vs investigator's choice (mPFS of 6.9 months vs 3.1 months, HR 0.42, indicating a 58% reduction in disease progression or death)
  - Significantly improved ORR (37.1% vs 5.8%) and DCR (73.3% vs. 31.1%) by BICR compared with the investigator's choice treatment, the majority (76.7%) were treated with ipilimumab + nivolumab
  - OS data is not yet mature; however, an early trend toward improved OS was observed with the darovasertib combination arm versus ICT. OS data will be presented at a future date
  - AEs consistent with prior safety profile, with low rate of TR-SAEs (9.2%) and discontinuations due to TRAEs for darovasertib and crizotinib (2.5 and 10% respectively)

The OptimUM-02 results support a potential new therapeutic standard for a disease with limited treatment options and poor prognosis

BICR, blinded independent central reader. IC, investigator's choice. DCR, disease control rate. HLA, human leukocyte antigen. HR, hazard ratio. mPFS, median progression free survival. mUM, metastatic uveal melanoma. ORR, objective response rate. TR-SAE, treatment-related serious adverse events. TRAE, treatment-related adverse events.

Acknowledgements



We gratefully acknowledge the Patients and their families for participating in this study, and all investigators and site staff whose contributions made the OptimUM-02 study possible

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