Activity of Cabozantinib (XL184) in Advanced Ovarian Cancer Patients: Results From a Phase 2 Randomized Discontinuation Trial (RDT)

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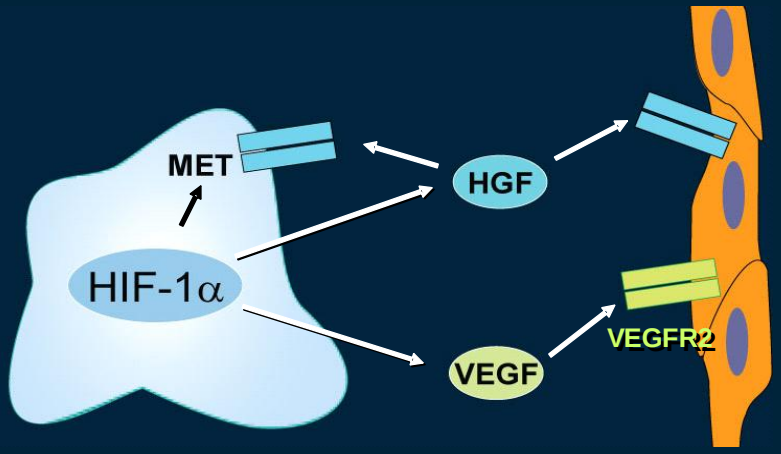
ASCO | Annual '11 Meeting

Cabozantinib: A Dual MET/VEGFR2 Inhibitor

- MET is activated in a wide range of malignancies
- MET drives genetic “invasion growth” pathway in tumor cell
- MET and VEGF signaling pathways act synergistically to drive angiogenesis



Proliferation (RAS-MAPK)
Increased invasiveness / EMT (RAS, FAK)
Inhibition of apoptosis (PI3 kinase)

↓

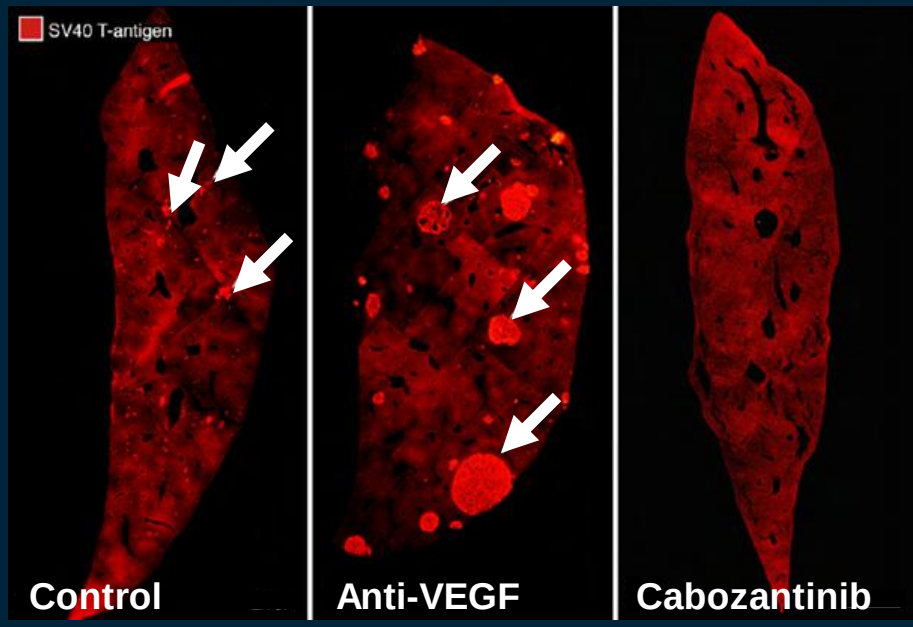
GROWTH-MOTILITY-INVASION

Increased MET
Increased VEGFR2
Decrease TSP-1

↓

ANGIOGENESIS

Anti-metastatic effect in liver



RIP-Tag2 mouse model (pancreatic neuroendocrine tumor)

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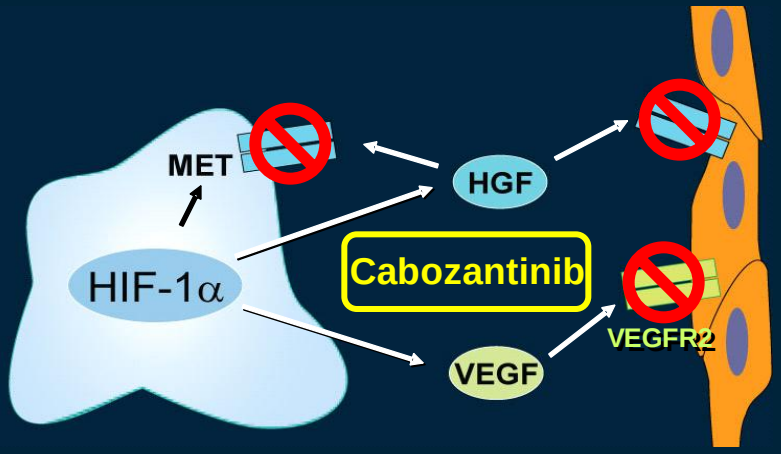

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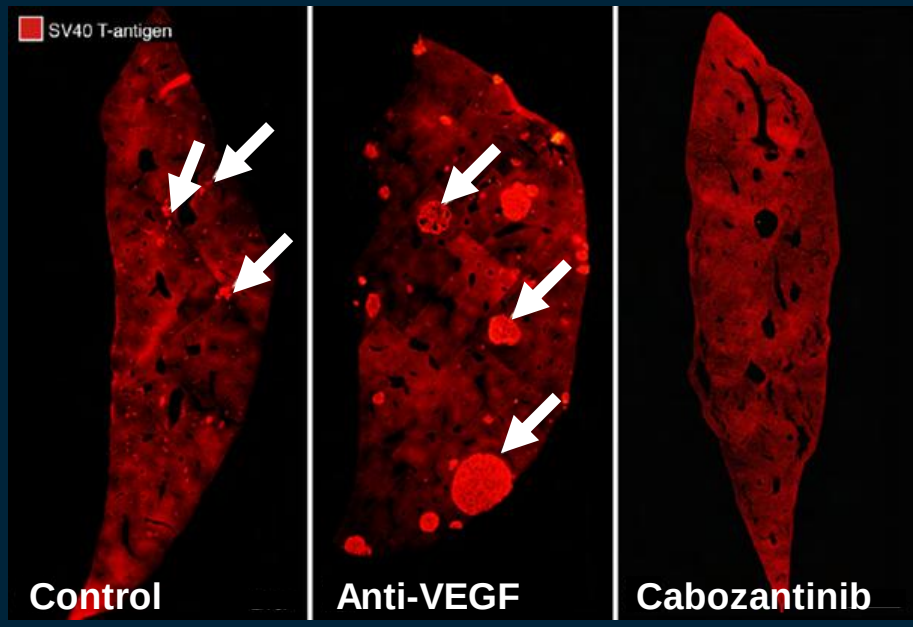

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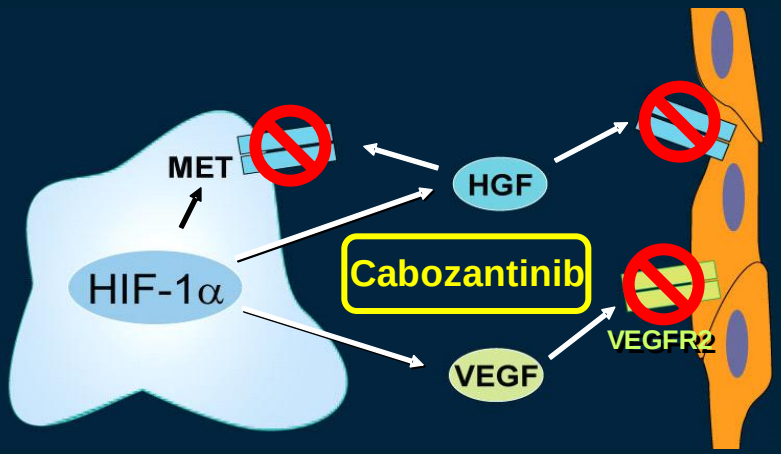

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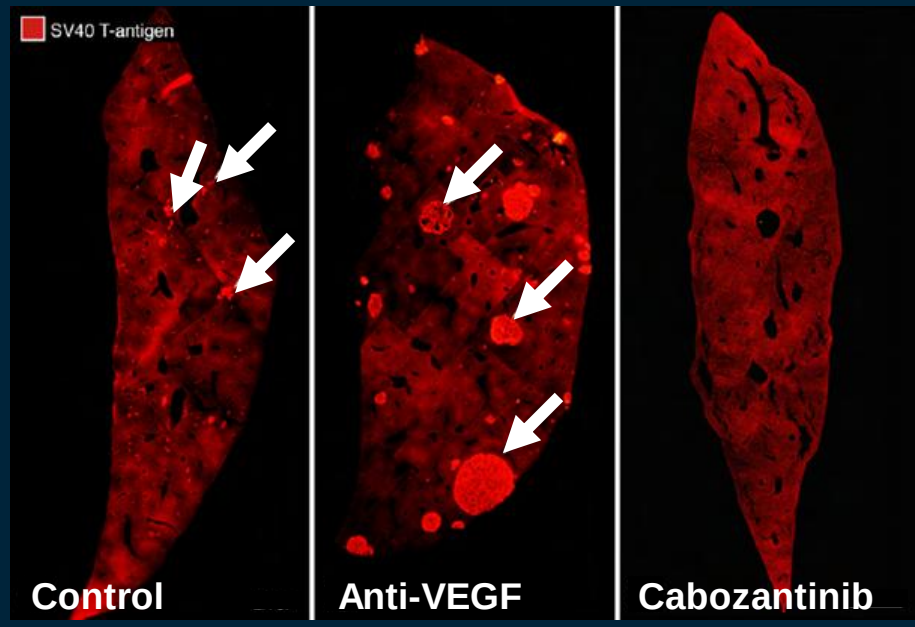

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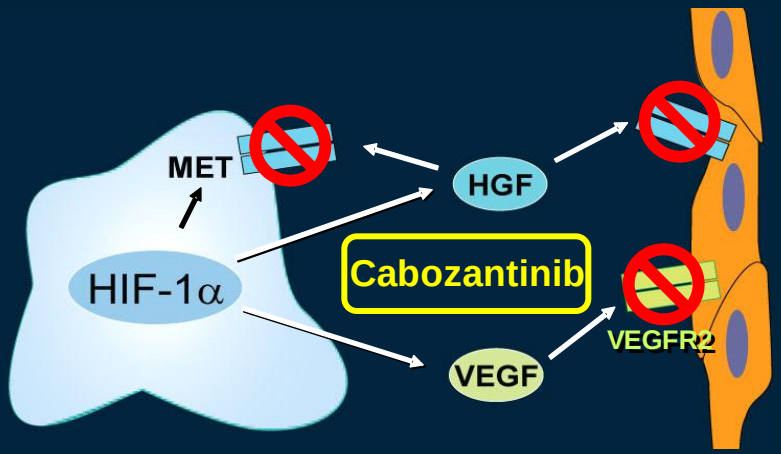

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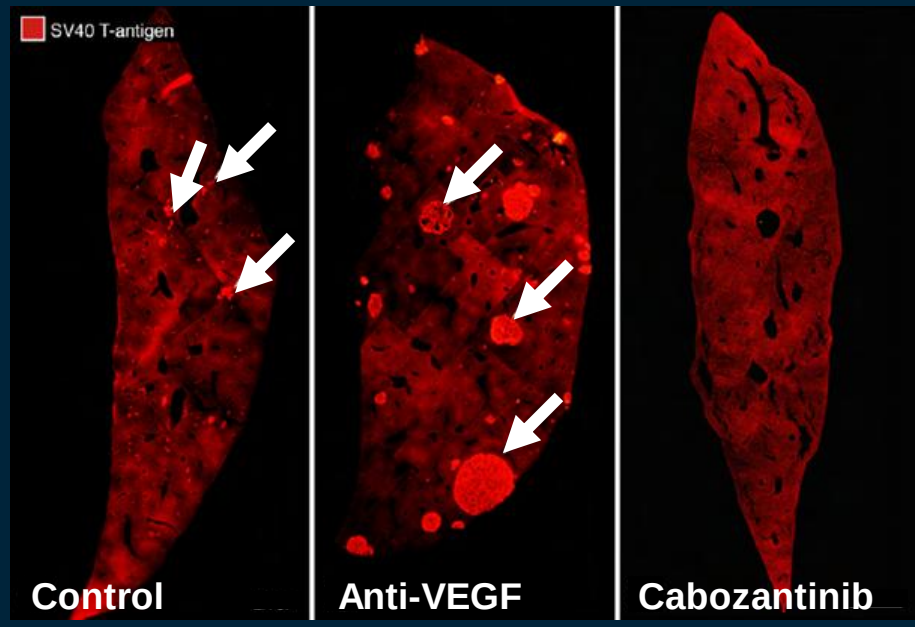

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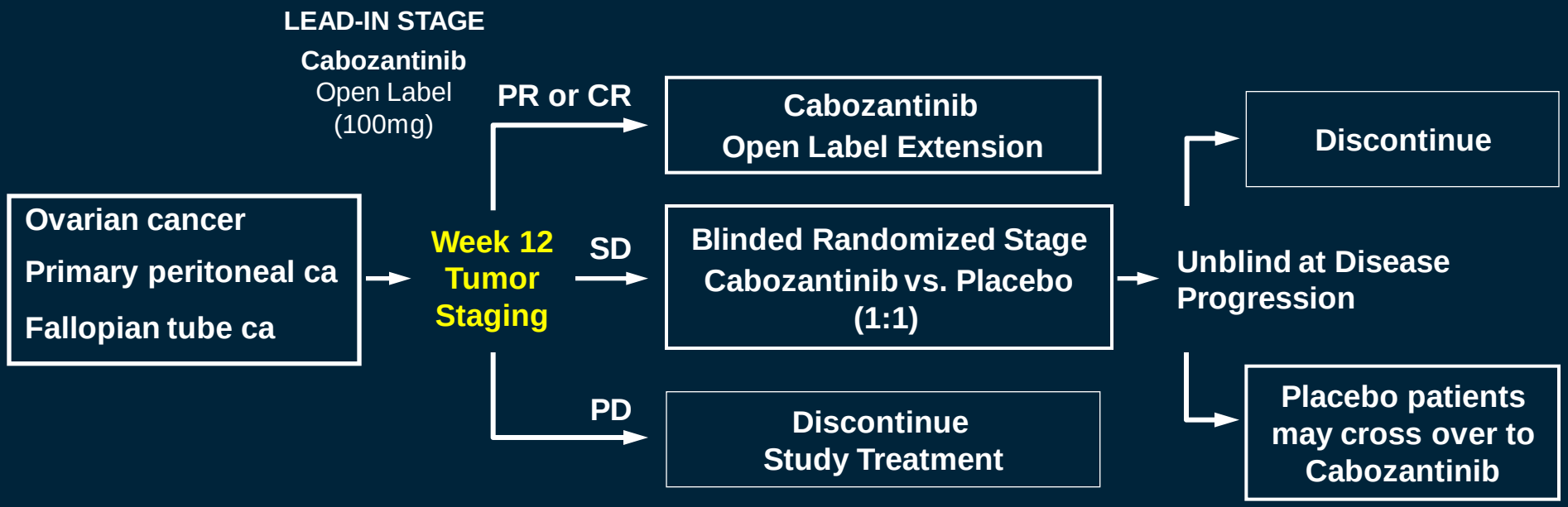
Study Design



Key Study Eligibility Criteria:

- Prior progressive disease and measurable target lesion(s) per mRECIST 1.0
  - Patients with PD per CA125 criteria alone *were excluded*
- Platinum refractory, resistant or sensitive
- ECOG performance status ≤ 1

Study Endpoints and Assessments

Study Endpoints:

- Efficacy
  - Lead-in Stage: Objective response per mRECIST 1.0
  - Randomized Stage: Progression-free survival
- Safety

Assessments:

- Tumor assessments by CT/MRI/bone scan at baseline and q6 weeks
- Pharmacodynamic assessments
  - Biomarkers, including CA-125

Baseline Characteristics

N = 70

Median Age, years (range)	61 (27 – 80)	Platinum-free Interval[b], n (%)	
Measurable disease, n (%)	70 (100)	Refractory/Resistant (≤ 6 months)	34 (49)
CA125 increased[a], n (%)	62 (89)	Sensitive (> 6 months)[c]	36 (51)
Primary disease site, n (%)		Prior lines of therapy, n (%)	
Ovary	65 (93)	0-1	12 (17)
Peritoneum	5 (7)	≥ 2	58 (83)
Metastatic disease, n (%)	69 (99)	Prior lines of platinum regimen, n (%)	
Histologic subtype, n (%)		0-1	30 (43)
Serous	55 (79)	≥ 2	40 (57)
Clear Cell	3 (4)	Prior lines: Agents of interest, n (%)	
Endometrioid	4 (6)	VEGF pathway inhibitor	7 (10)
Other	8 (11)	PLD / topotecan	22 (31)
Bone metastases, n (%)	6 (9)	Gemcitabine	20 (29)

PLD, pegylated liposomal doxorubicin

[a] Baseline CA125 ≥ ULN (upper limit of normal)

[b] Platinum-free interval: Progression during treatment with platinum or interval from the time of last dose of platinum to disease progression

[c] Includes 4 patients whose platinum-free interval could not be determined

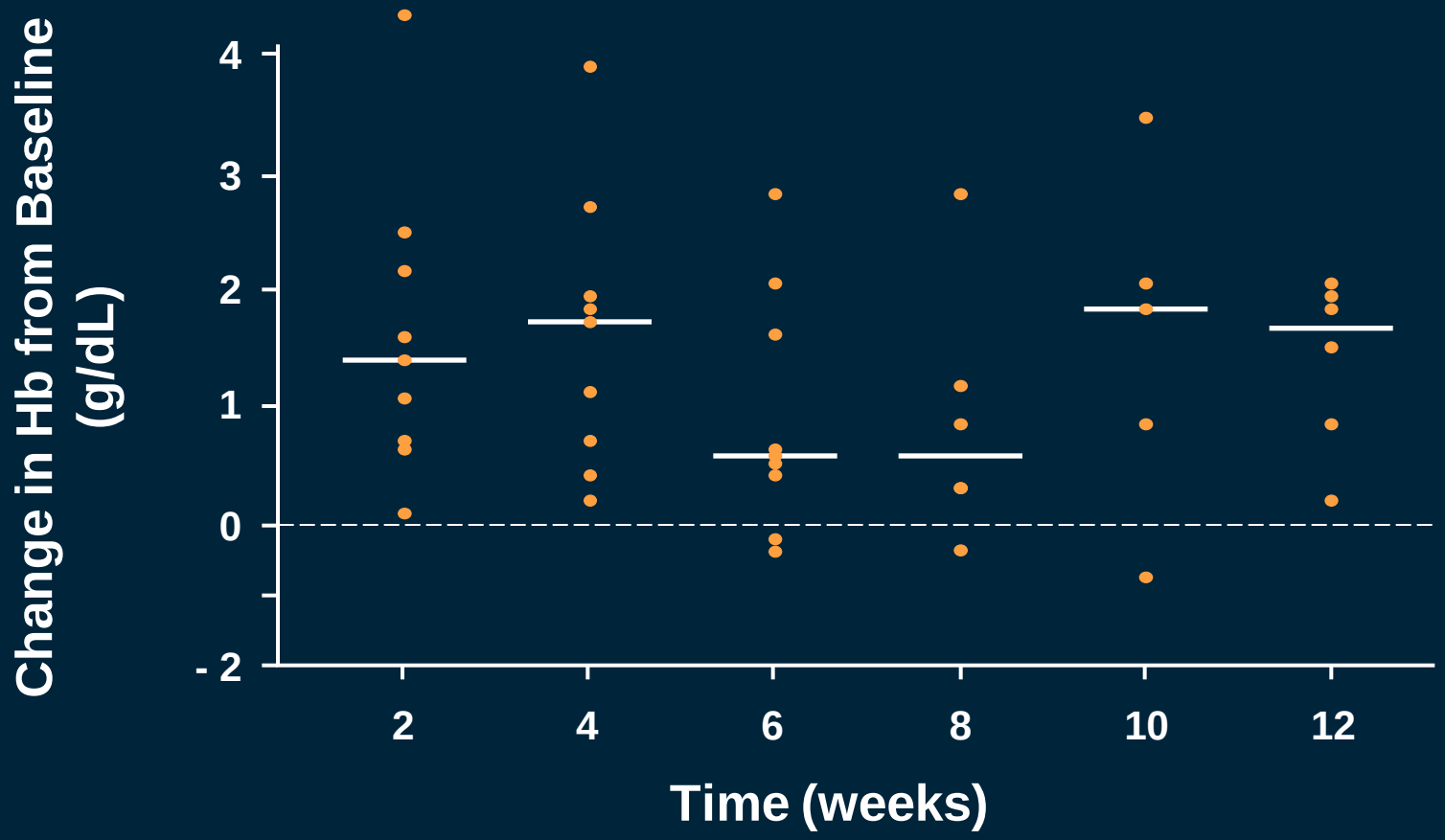
Most Frequently Reported Adverse Events During Lead-In Stage Regardless of Causality (N = 70)

Adverse Event[a]	All Grades, n (%)	Grade ≥ 3, n (%)
Fatigue[b]	51 (73)	6 (9)
Diarrhea	37 (53)	7 (10)
Nausea	36 (51)	1 (1)
Decreased appetite	26 (37)	-
PPE syndrome[b,c]	25 (36)	5 (7)
Vomiting	23 (33)	3 (4)
Dysgeusia	23 (33)	-
Constipation	20 (29)	1 (1)
Rash[b]	18 (26)	1 (1)
Transaminases increased[b]	17 (24)	1 (1)
Hypertension[b]	14 (20)	1 (1)
Dysphonia	14 (20)	-
Stomatitis	14 (20)	-
Abdominal pain	13 (19)	2 (3)
Dyspepsia	13 (19)	-
Hypomagnesemia	12 (17)	2 (3)
Less frequent but important medical events		
Hemorrhage[b]	8 (11)	-
Thrombosis venous[b]	4 (6)	3 (4)
Gastrointestinal perforation[b]	2 (3)	2 (3)

- 37% experiencing ≥ 1 dose reduction
- Two (3%) Related Grade 5 events overall (both after Lead-in Stage):
  - Enterocutaneous fistula
  - Intestinal perforation

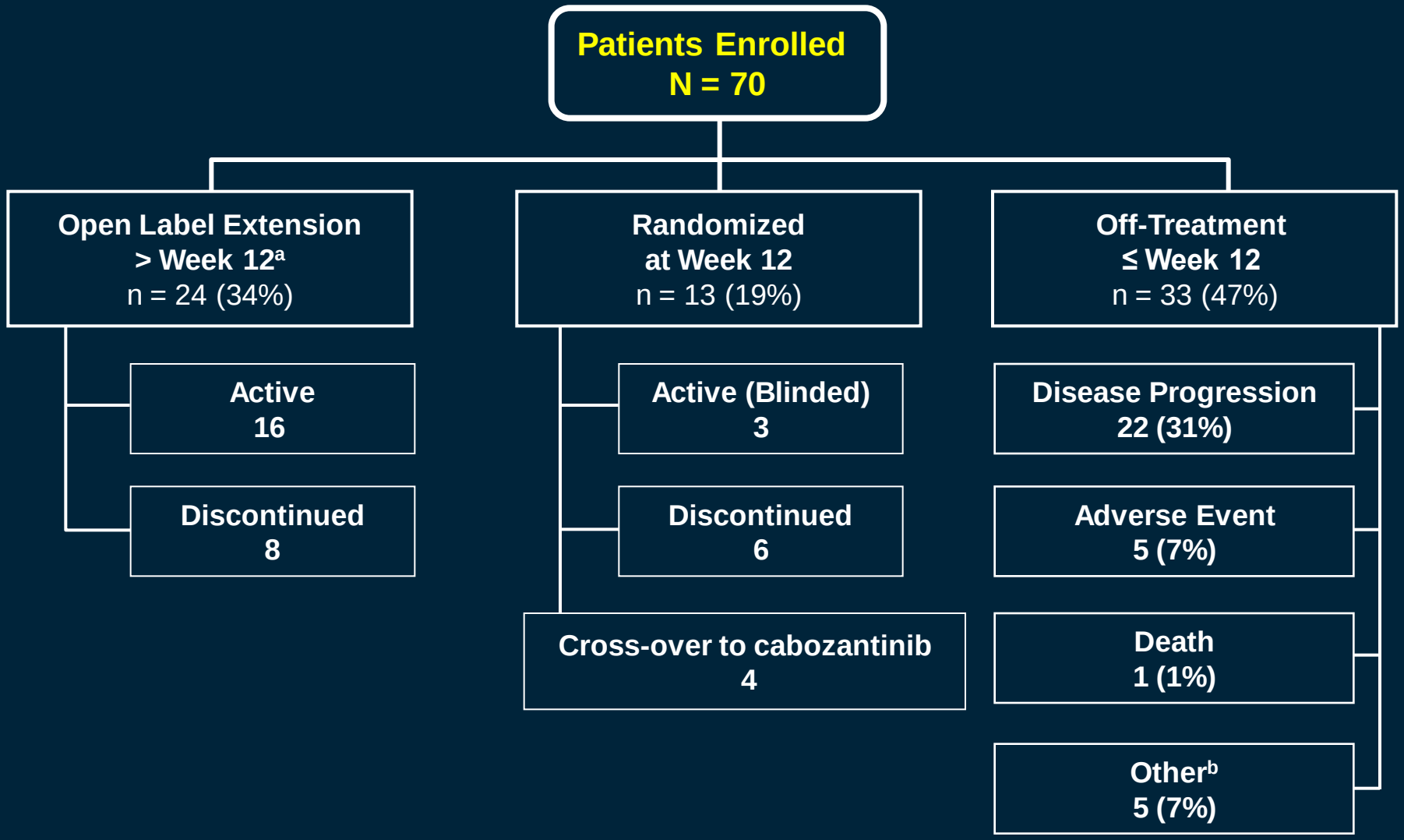
[a] CTCAE v.3.0 grading.
[b] Groupings of Preferred Terms related to a particular medical condition
[c] Palmar-Plantar Erythrodysesthesia syndrome.

Hemoglobin Changes Over Time in Patients With Hb <11 g/dL at Baseline (N = 9)



The median maximum rise in Hb was 2.3 g/dL (range 0.3 to 4)

Patient Disposition



[a] Includes 7 ovarian cancer patients converted to Open Label Extension of patients with SD in Lead-in Stage after approval of Protocol Amendment 1

[b] Other includes Patient Request 21 (4%), Lost to F/U 4 (1%), PI Decision 3 (1%) and "Other" 10 (2%)

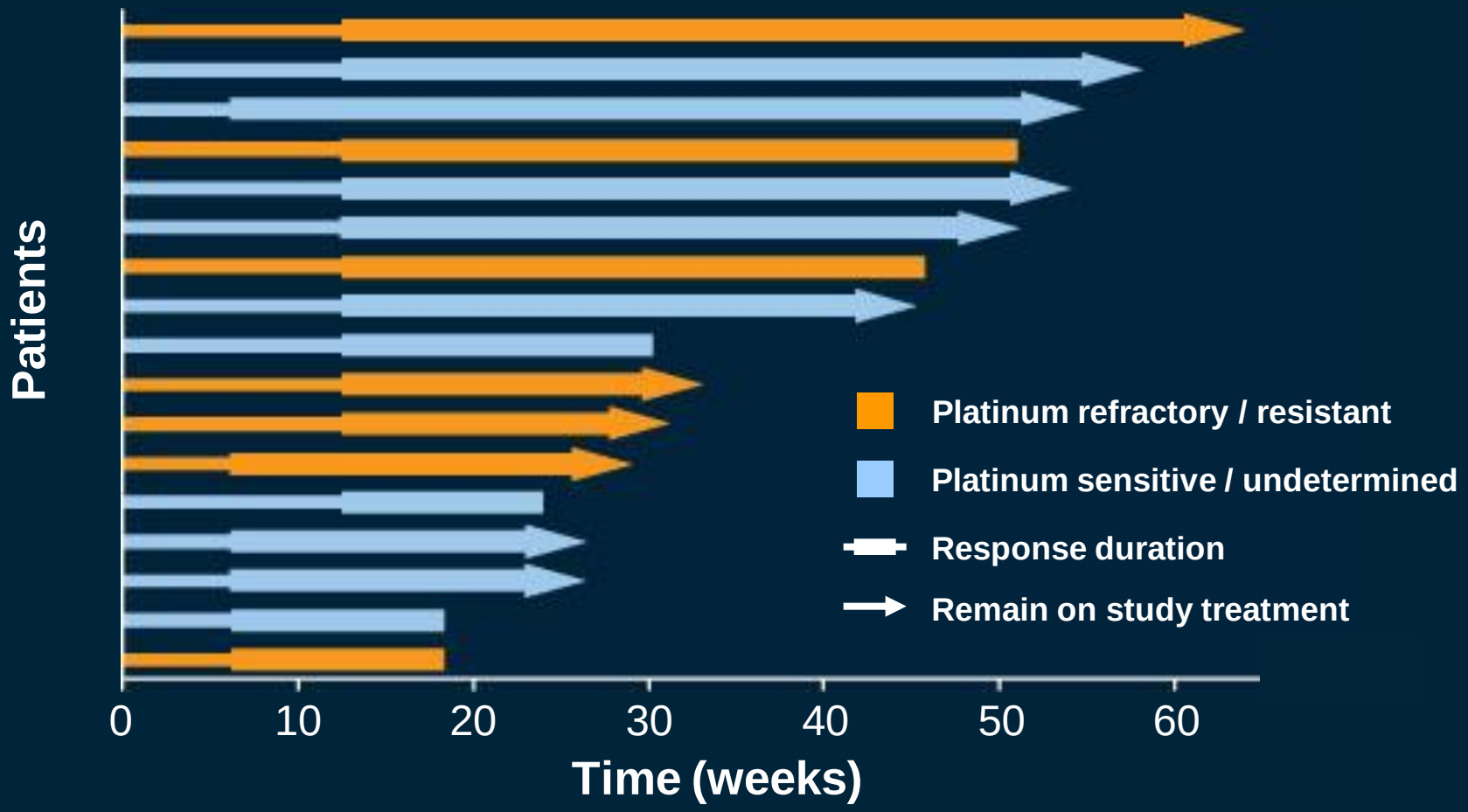
Summary of RECIST Response

Platinum Free Interval	Number Evaluable	PR N (%)	Week 12 DCR[a] (%)
< 1 month (refractory)	11	2 (18)[b]	36
1 – 6 months (resistant)	23	5 (22)	39
> 6 months (platinum sensitive)	36	10 (28)	67
Total	**70**	**17 (24)**	**53**

[a] Disease Control Rate (DCR) = (CR + PR + SD) at Week 12 / Response Evaluable

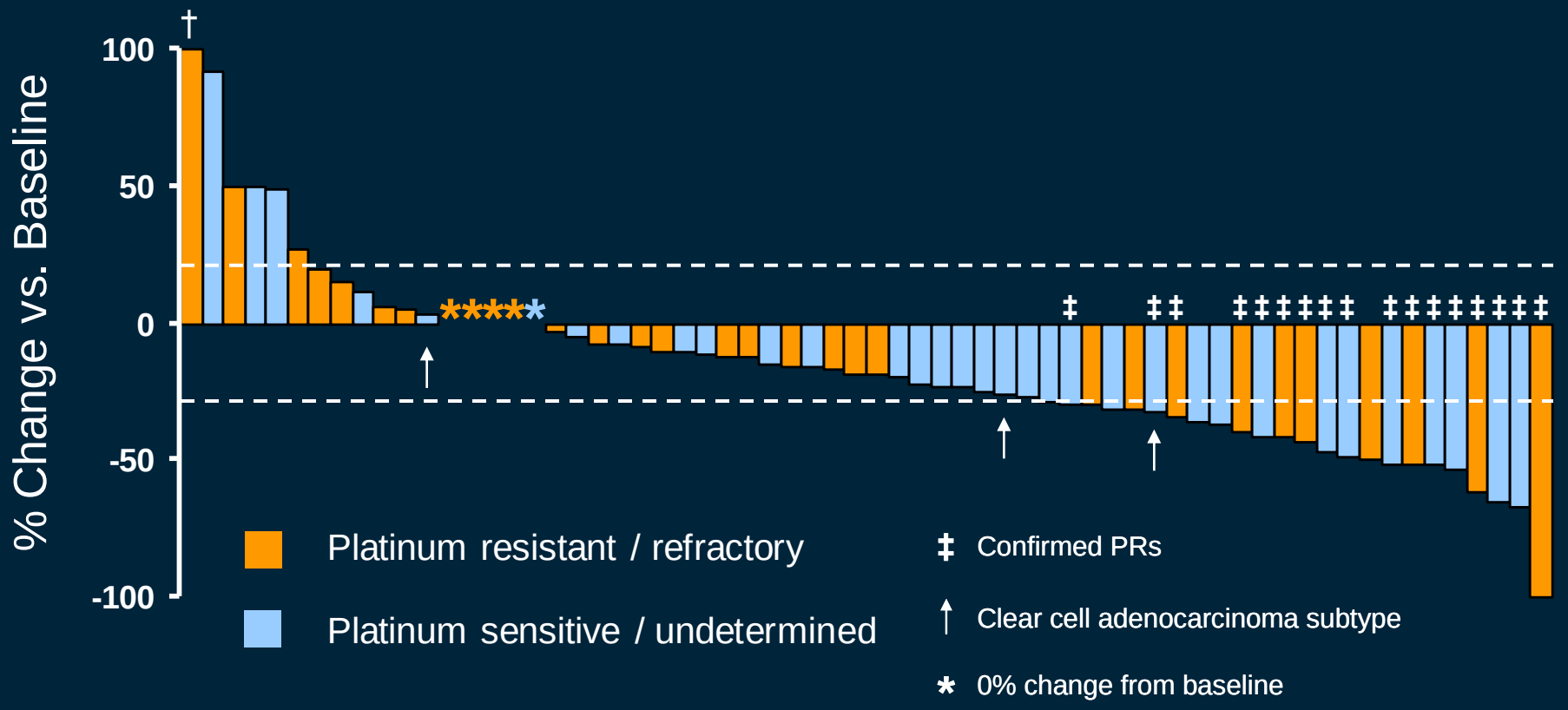
[b] Includes one complete response (CR)

Durability of Responses (N = 17)



With a median follow-up of 36 weeks, the median duration of response has not been reached

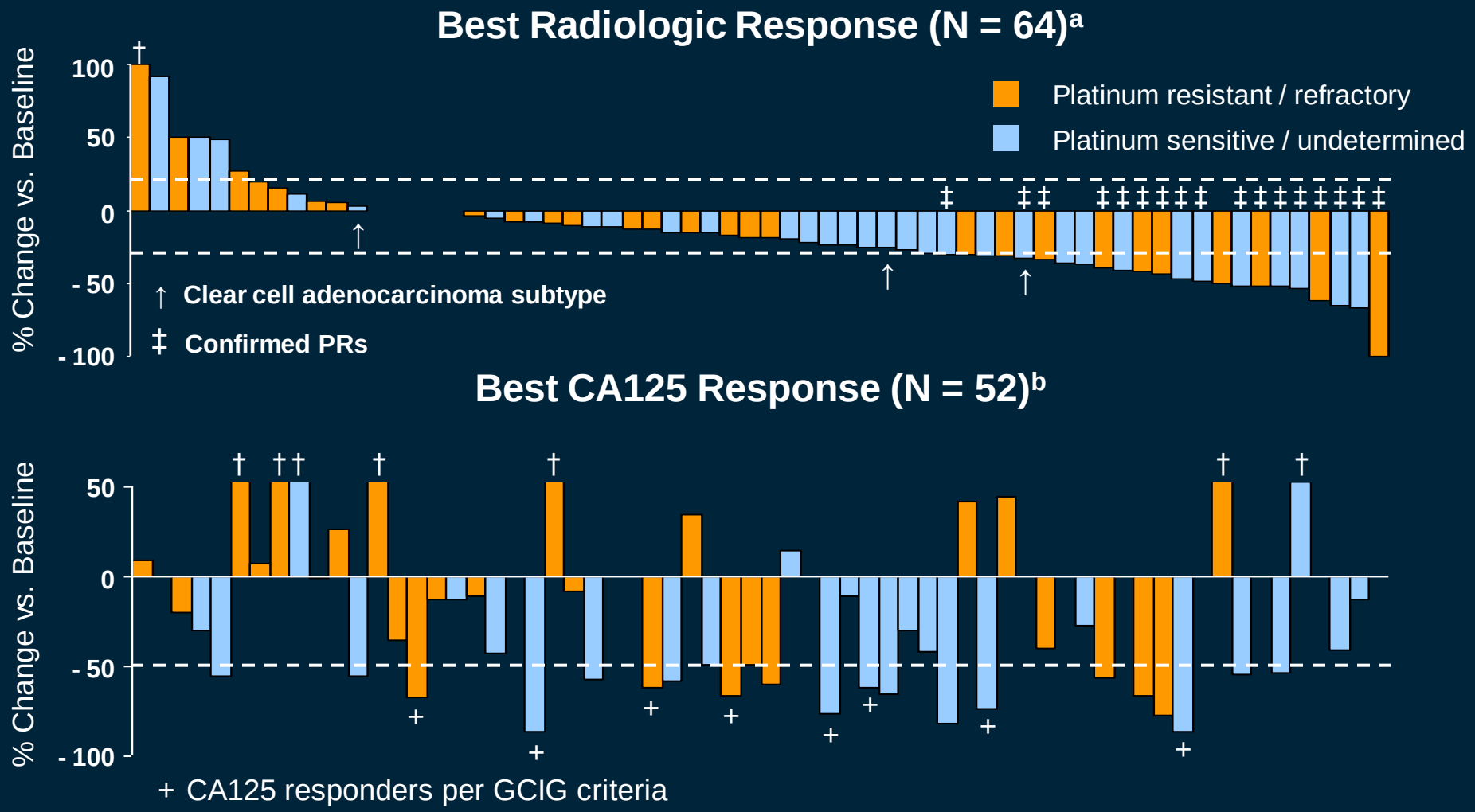
Effects on Measurable Lesions (N = 64)[a]



[a] Best Radiologic Response in Patients with ≥ 1 Post-Baseline Tumor Assessment

† Increase > 100% from baseline target lesion sum of longest diameters

Correlation of Response in Measurable Lesions and CA125

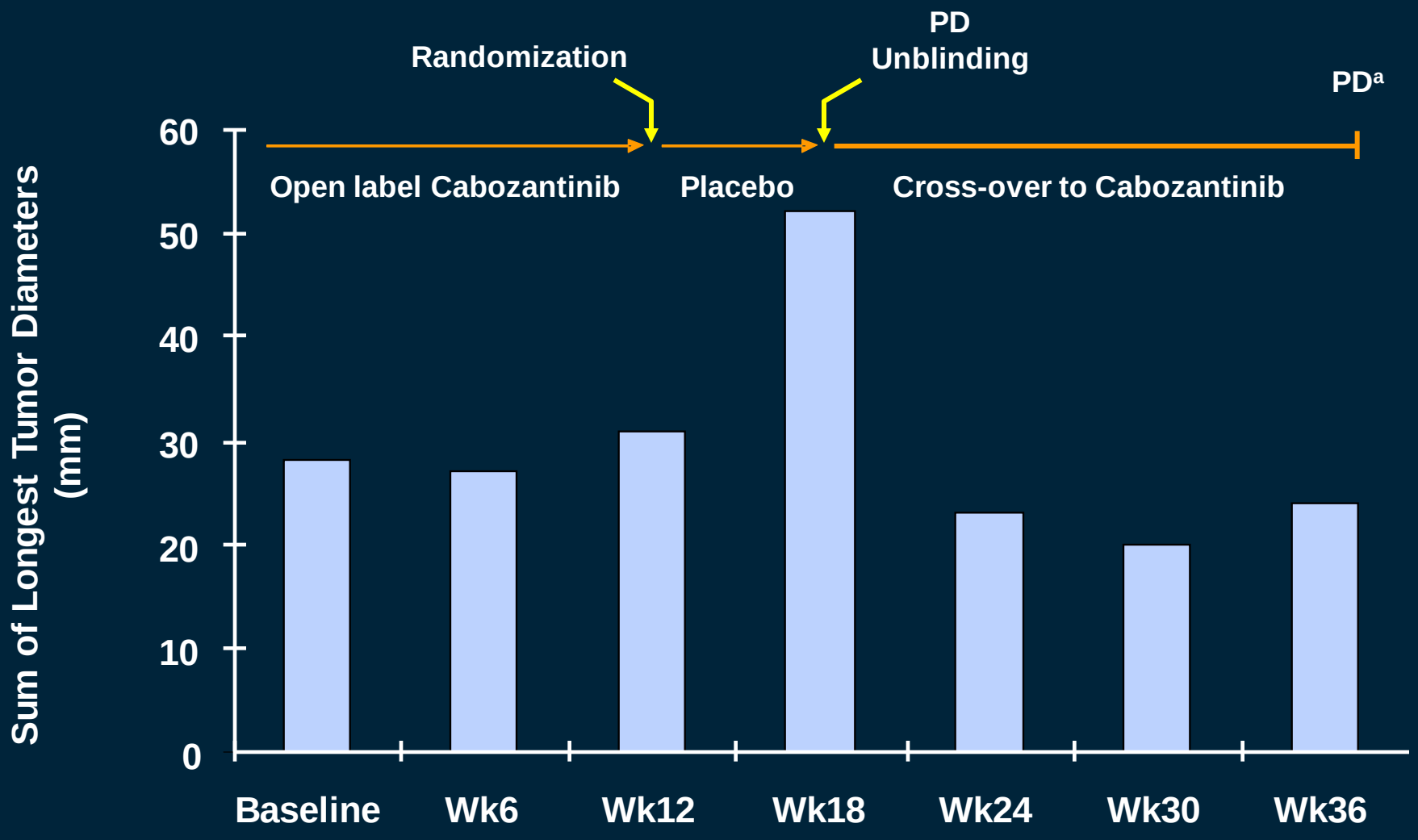


† Increase in % > upper limit of scale from baseline

[a] Patients with ≥ 1 Post-Baseline Tumor Assessment

[b] Only patients with CA125 ≥ 1 x ULN at baseline are shown; Patients with ≥ 1 Post-Baseline CA-125 Assessment Best response not necessarily from the same time point as the best radiological response.

Re-stabilization of PD after Crossing Over from Placebo to Cabozantinib



[a] Second PD due to unequivocal progression of nTL (ascites) and new lesion

Summary

- Cabozantinib demonstrates promising activity in both platinum-sensitive and platinum-resistant/refractory ovarian cancer
  - Week 12 overall disease control rate of 53%
  - Response rates of 18% in platinum-refractory, 22% in platinum-resistant and 28% in platinum-sensitive patients
- Cabozantinib shows encouraging duration of response
  - After 36 weeks of follow-up, median duration of response not reached
- Tolerability profile is consistent with that of other tyrosine kinase inhibitors
- Discordant effects observed between CA125 changes and clinical activity
- Simultaneous targeting of MET and VEGFR2 with cabozantinib results in robust effects in patients with advanced ovarian cancer
- Non-randomized expansion cohort is currently accruing in platinum-resistant/refractory ovarian cancer

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- **Israel:**

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  CC Lin (National Taiwan University Hospital), WC Su (National Cheng Kung University Hospital), CJ Tsao (Chi Mei Hospital), TS Yang (Chang Gung Memorial Hospital)
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