

Activity of Cabozantinib (XL184) in Metastatic NSCLC: Results From a Phase 2 Randomized Discontinuation Trial (RDT)

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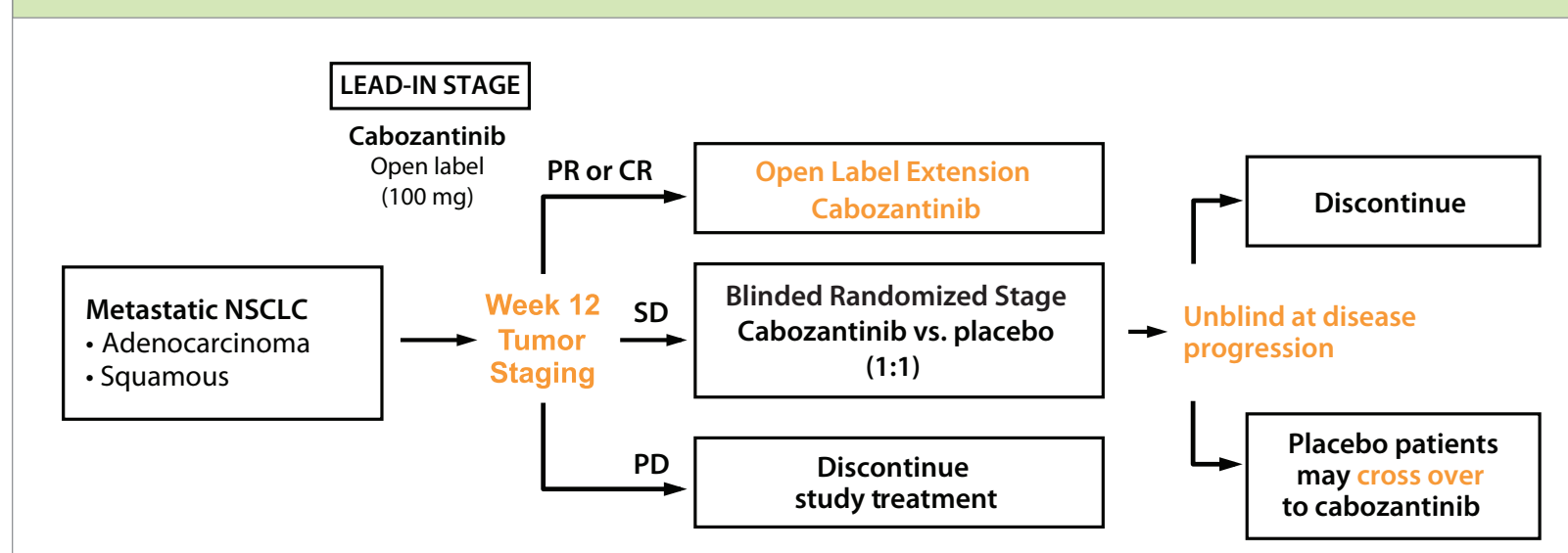
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INTRODUCTION

- Cabozantinib is a potent targeted therapy that inhibits MET, VEGFR2, and RET¹
- MET and VEGF signaling pathways:
 - Act synergistically to drive tumor angiogenesis²
 - Are implicated in tumor–bone interactions^{2–5}
- MET and HGF expression are frequently observed in non-small cell lung cancer (NSCLC)^{6,7}
 - MET–positive status as assessed by IHC is a negative prognostic indicator
- Molecular alterations affecting MET are relatively common in NSCLC
 - Activating mutations in MET found in ~3% of patients⁸
 - High (≥5) MET copy number detected in ~11% of primary tumors (independent negative prognostic factor)⁹
 - Amplification of MET is a mechanism of acquired resistance to EGFR inhibitors⁸
- KIF5B-RET gene fusions resulting in RET activation detected in 1–2% of lung adenocarcinomas^{10,11}
- Cabozantinib has resulted in resolution of bone metastases on bone scan and regression of soft tissue lesions in multiple tumor types^{12,13}
- This cohort was investigated as part of a Phase 2 RDT

METHODS

Figure 1. Study Design



Study Endpoints

- Efficacy
 - Lead-In Stage: objective response per RECIST 1.0
 - Randomized Stage: progression-free survival
- Safety

Key Eligibility Criteria

- Prior progressive disease and measurable target lesion by RECIST 1.0
- Histologies included squamous cell
- Maximum of three prior systemic anticancer treatment regimens (excluding investigational agents)
- ECOG performance status ≤1

Assessments

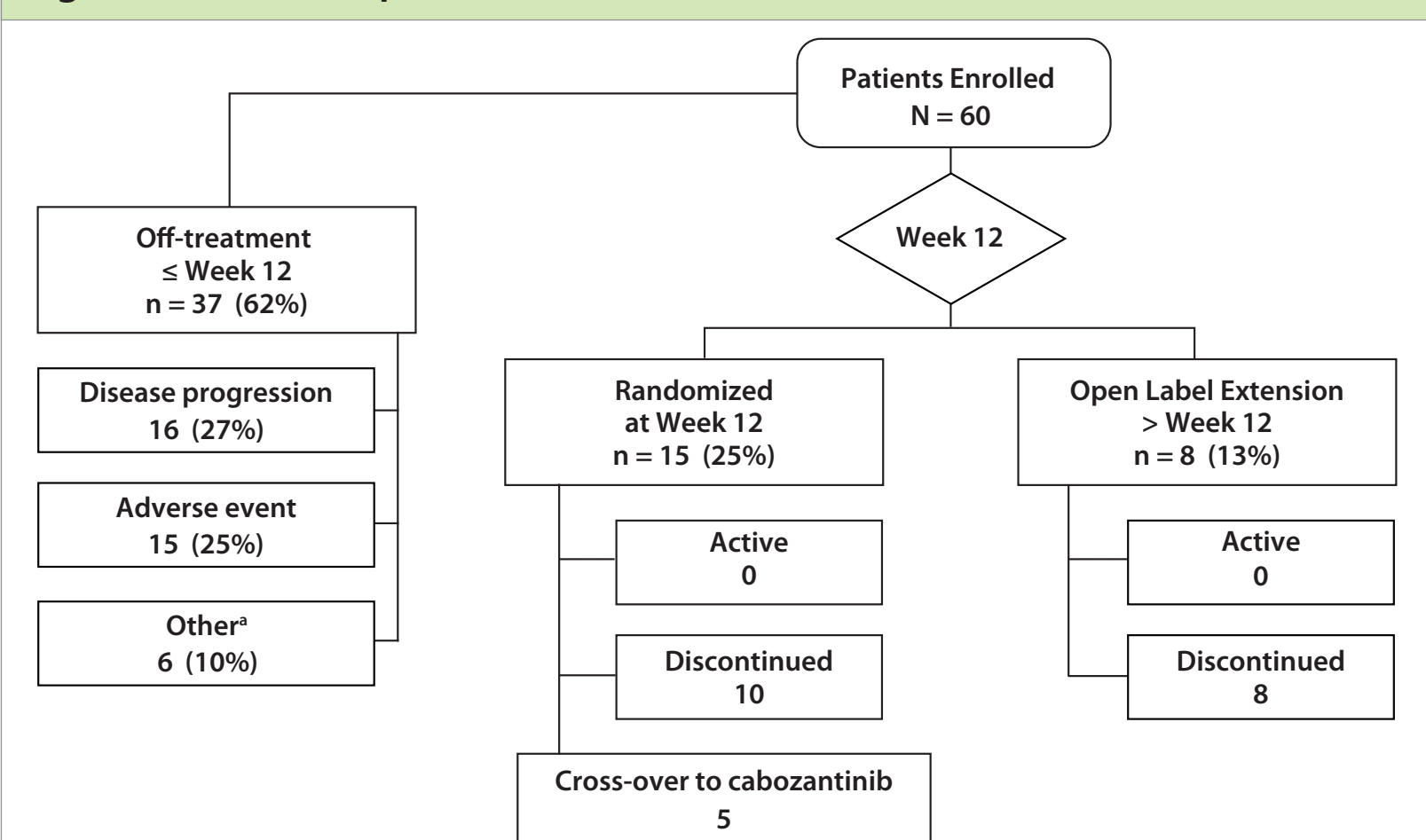
- Tumor assessments per RECIST using CT/MRI at baseline and every 6 weeks thereafter
- EGFR and KRAS mutational analysis (on available tumor tissue)

RESULTS

Table 1. Baseline Characteristics (N = 60)

Median age, years (range)	67 (37–88)
Gender, n (%)	
Male	33 (55)
Female	27 (45)
Ethnicity, n (%)	
Asian	2 (3)
Other	58 (97)
Stage at diagnosis, n (%)	
Stage IIIa	2 (3)
Stage IIIb	2 (3)
Stage IV	56 (93)
Histologic subtype, n (%)	
Squamous cell	17 (28)
Adenocarcinoma/other	43 (72)
Bone metastases, n (%)	13 (22)
Never smokers, n (%)	13 (22)
EGFR status, n (%)	
Mutation detected	6 (10)
No mutation detected	24 (40)
Unknown	30 (50)
KRAS status, n (%)	
Mutation detected	5 (8)
No mutation detected	21 (35)
Unknown	34 (57)
Prior lines of therapy, n (%)	
0–2	31 (52)
≥3	29 (48)
Prior anti-VEGF pathway therapy, n (%)	19 (32)
Prior anti-EGFR therapy, n (%)	29 (48)

Figure 2. Patient Disposition



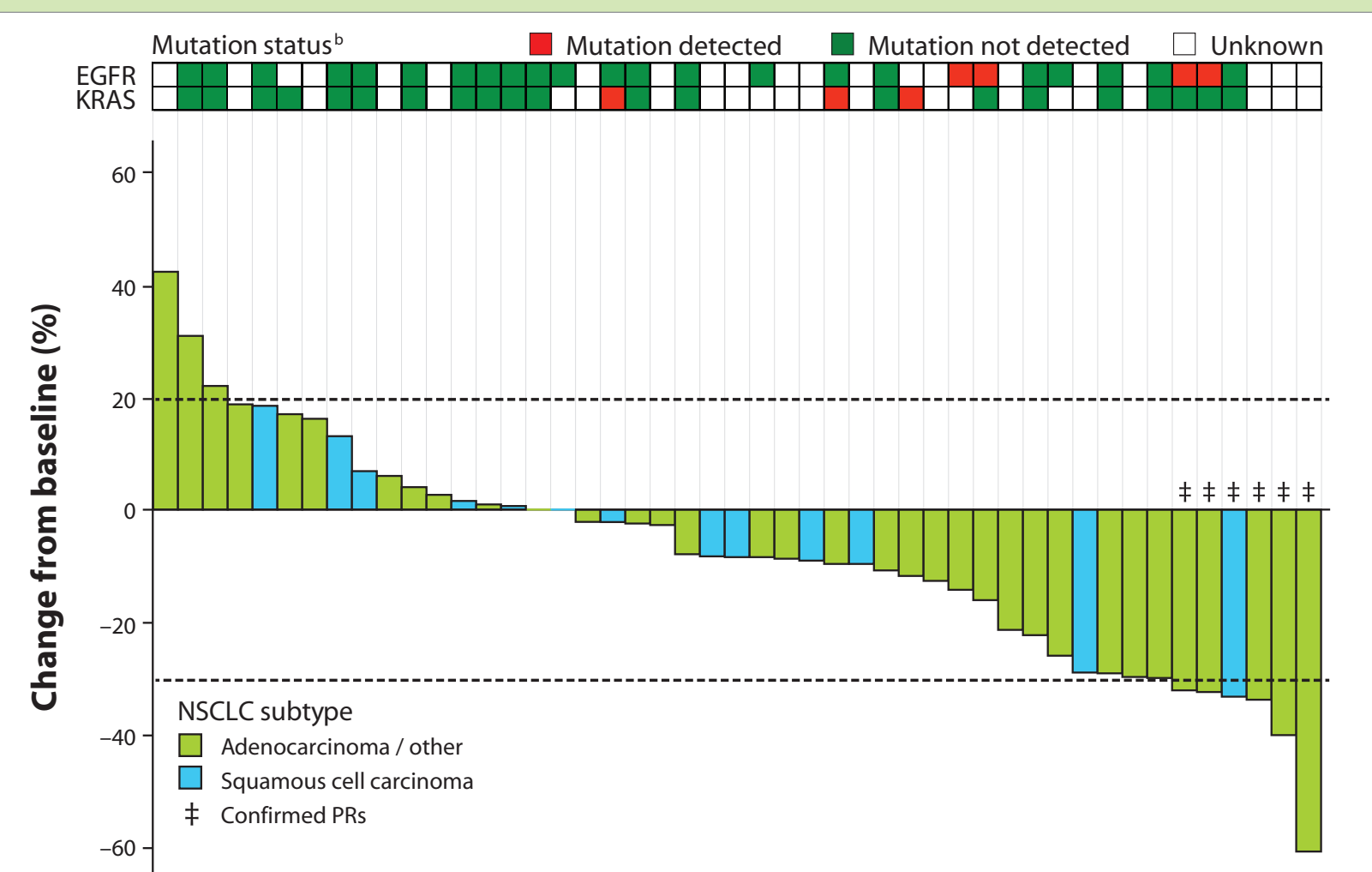
*Patient request other than AE (n = 5); patient decision for hospice (n = 1).

Table 2. Summary of RECIST Response

RECIST response evaluable, N	60 ^a
Objective response rate ^b , n (%)	
Confirmed partial response	6 (10)
Stable disease	29 (48)
Progressive disease	12 (20)
Week 12 DCR ^c , n (%)	23 (38)

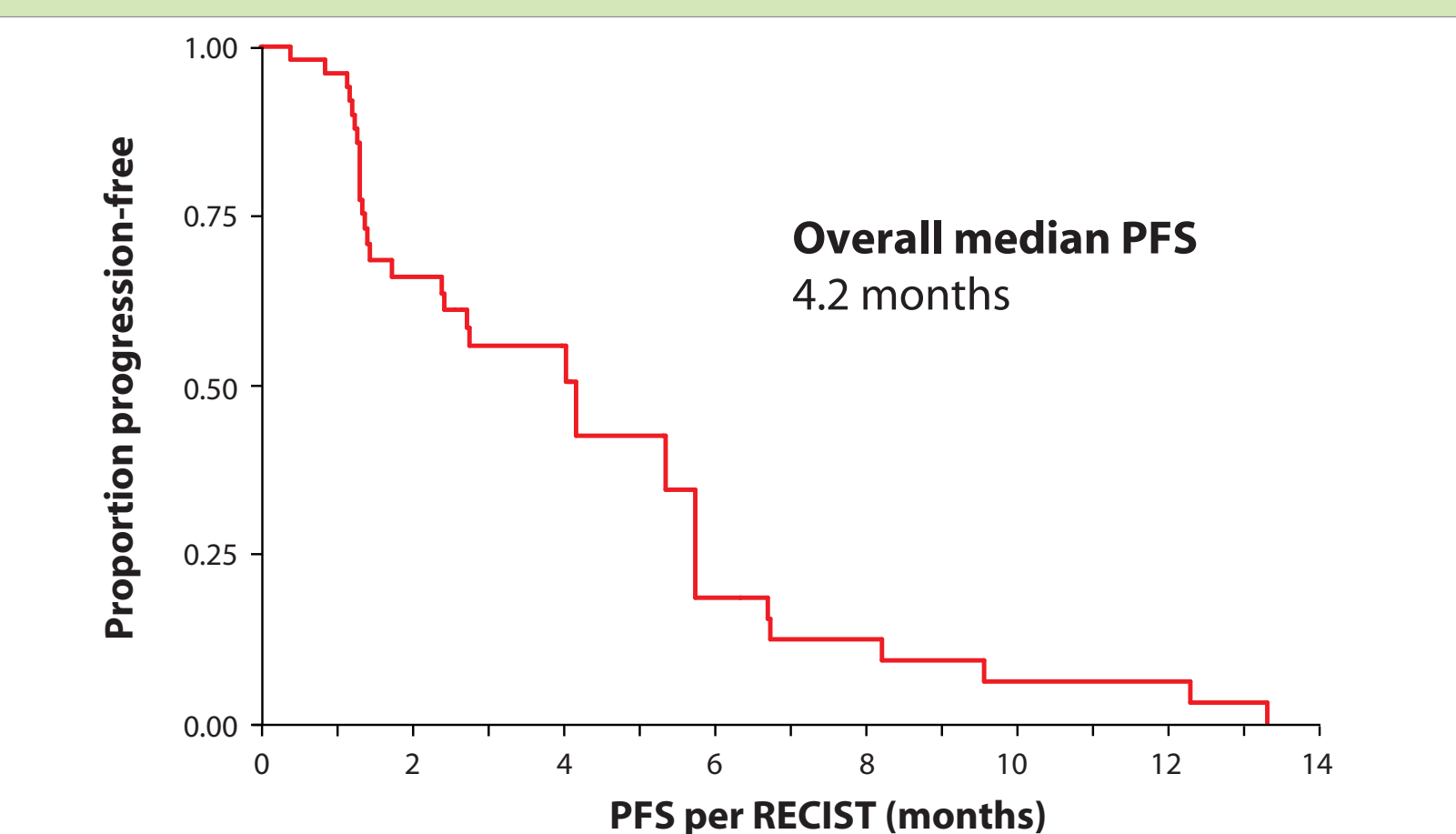
^a13 patients were not evaluable for post-baseline response assessments.
^bAll responses confirmed within 18 weeks.
^cDisease control rate (DCR) defined as PR + SD at week 12.

Figure 3. Best Change in Target Lesions^a (n = 47)



^aBest time point response by RECIST 1.0 in patients with ≥1 post-baseline tumor assessment.
^bMutation data based on in-house analyses of archival tumor tissue and investigator reporting.
• 38% of all NSCLC patients were on study treatment for >3 months (N = 60)

Figure 4. Overall Progression-Free Survival^a (N = 60)

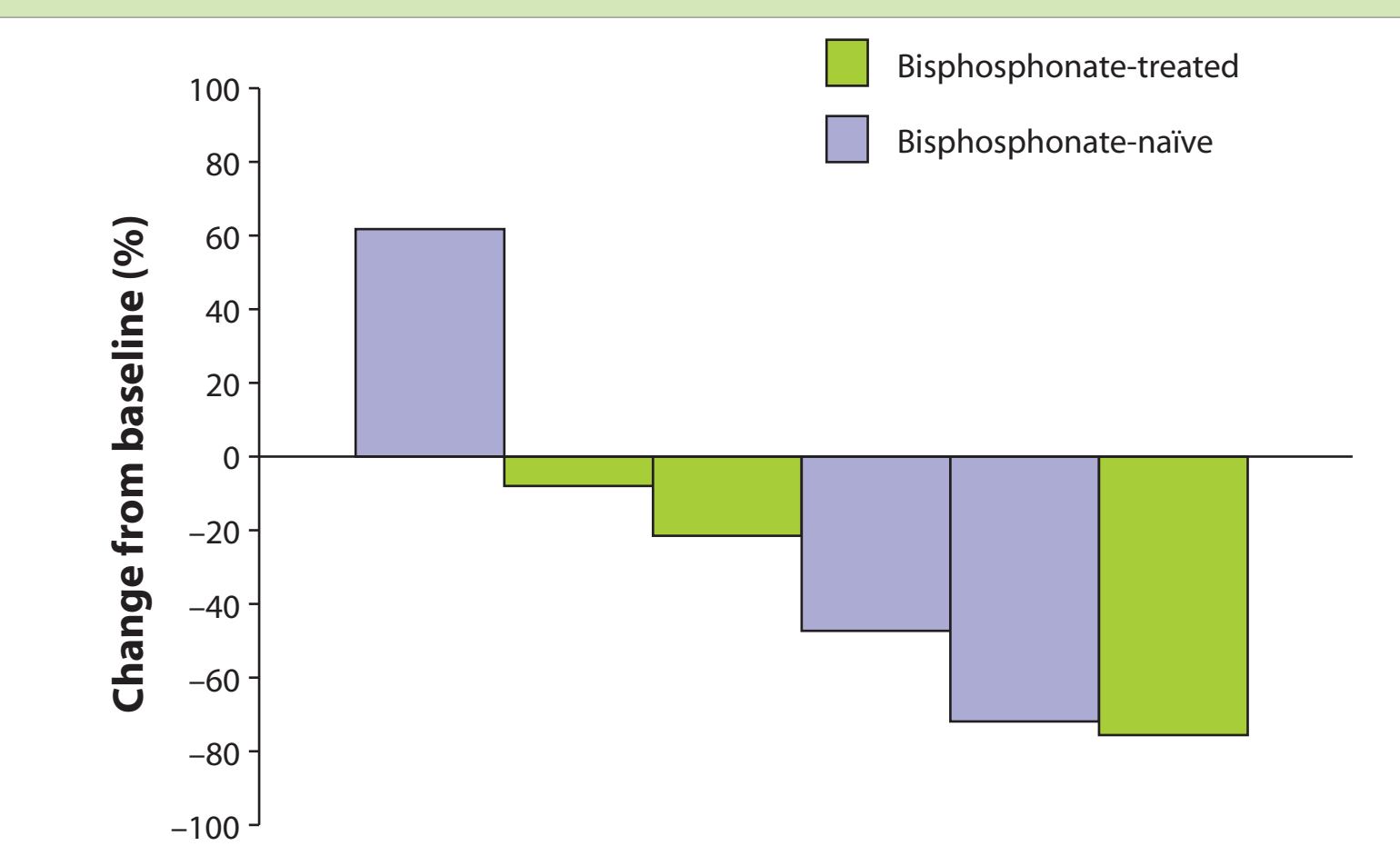


^aMethod described by Ratain et al.¹⁴

PFS Randomized Stage (n = 15)

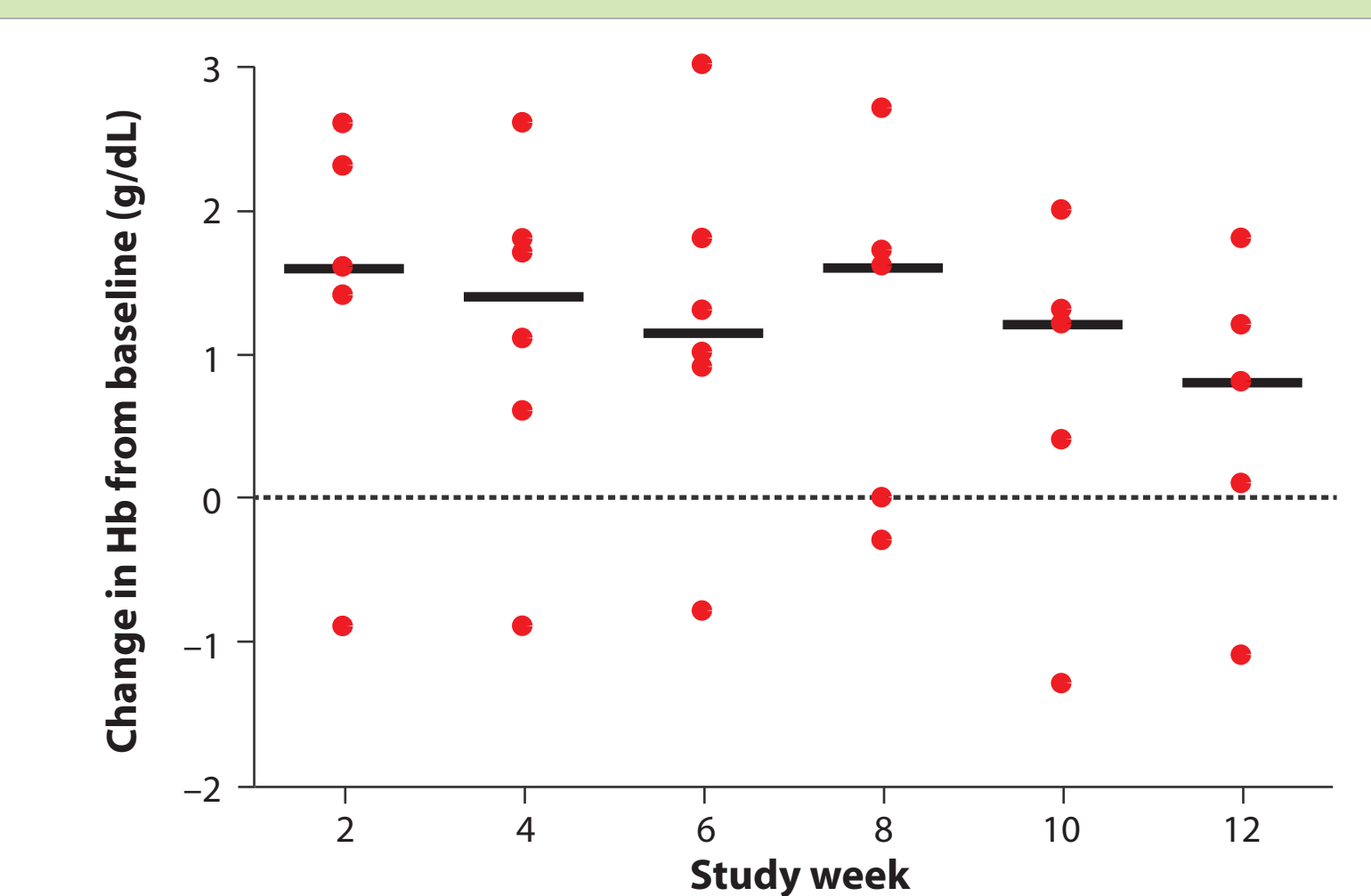
- At the time of data cut off and with median follow up of 2.0 months, the median PFS after randomization was 2.3 months for cabozantinib-treated patients (n = 8) versus 2.4 months for placebo patients (n = 7)

Figure 5. Effects on Plasma CTx, a Marker of Bone Resorption, in Patients With Bone Metastases^a (N = 6)



^aLimited to a subset of patients with at least one post-baseline CTx assessment (week 6 and/or week 12).

Figure 6. Hemoglobin Changes Over Time in Patients With Hb <11 g/dL at Baseline (N = 6)



- The median maximum rise in Hb was 1.8 g/dL (range 0 to 3)

REFERENCES

- Yakes FM, et al. *Mol Cancer Ther*. 2011;10(12):2298–308.
- Aftab DT and McDonald DM. *Clin Transl Oncol*. 2011;13:703–9.
- Knudsen BS, et al. *Urology*. 2002;60:1113–7.
- Zhang S, et al. *Mol Cancer*. 2010;9:9.
- Schimmoller F, et al. *Mol Cancer Ther*. 2011;10 (suppl):abstr A233.
- Ma PC, et al. *Genes Chromosomes Cancer*. 2008;47(12):1025–37.
- Masuya D, et al. *Br J Cancer*. 2004;90(8):1555–62.
- Pao W and Girard N. *Lancet Oncol*. 2011;12(2):175–80.
- Cappuzzo F, et al. *J Clin Oncol*. 2009;27(10):1667–74.
- Kohno T, et al. *Nat Med*. 2012;18(3):375–7.
- Takeuchi K et al. *Nat Med*. 2012;18(3):378–81.
- Gordon MS, et al. *J Clin Oncol*. 2011;29(suppl):abstr 3010.
- Hussain M, et al. *J Clin Oncol*. 2011;29(suppl):abstr 4516.
- Ratain MJ, et al. *J Clin Oncol*. 2006;24(16):2505–12.

Table 3. Most Frequently Reported Adverse Events During Lead-In Stage Regardless of Causality (N = 60)

Adverse Event ^a	All Grades, n (%)	Grade ≥3 ^b , n (%)
Fatigue	34 (57)	8 (13)
Diarrhea	34 (57)	4 (7)
Decreased appetite	27 (45)	2 (3)
Nausea	22 (37)	1 (2)
Constipation	18 (30)	0
Dysphonia	18 (30)	0
Vomiting	16 (27)	2 (3)
Hypertension	15 (25)	4 (7)
Dysgeusia	15 (25)	0
Hand-foot syndrome	13 (22)	5 (8)
Decreased weight	13 (22)	0
Asthenia	12 (20)	4 (7)

^aMedDRA v. 14.1 Preferred Terms (converted to US spelling), CTCAE v. 3.0 grading; n = number of patients with event.
^bOne related Grade 5 event of hemorrhage was reported during Lead-In Stage. Baseline tumor assessment showed a tumor mass infiltrating the pulmonary artery.

SUMMARY

- Cabozantinib demonstrates encouraging activity in this heavily pretreated NSCLC population
 - Median PFS of 4.2 months
 - 10% of patients (6/60) with confirmed PRs
 - 65% of patients (31/48) with ≥1 post-baseline scan experienced tumor regression
 - Effect observed regardless of KRAS or EGFR mutational status
- Safety profile similar to other TKIs with manageable AEs
- Further Phase 2 evaluation at 60 mg in NSCLC is planned:
 - Randomized Phase 2 trial of cabozantinib in EGFR wild-type, erlotinib–naïve population
 - Single-arm Phase 2 trial in patients with KIF5B-RET or related variant RET fusions

ACKNOWLEDGEMENTS

We thank the patients for their participation in XL184-203. We also thank the following additional investigators:

Belgium
J De Gève (Université Ziekenhuis Brussel)
S Holbrechts (Center Hospitalier Universitaire Ambroise)
G Jerusalem (Centre Hospitalier Saint Timon Liège)
K Buckerts (University Hospitals Leuven, Leuven Cancer Institute)
E Van Cutsem (University Hospitals Leuven, Leuven Cancer Institute)
Vergote (University Hospitals Leuven, Leuven Cancer Institute)
Israel
A Sella (Assaf Harodif Medical Center)
Taiwan
CC Lin (National Taiwan University Hospital)
WC Su (National Cheng Kung University Hospital)
CJ Tsao (Chi Mei Hospital, Yung-Kang City)
TS Yang (Chang Gung Memorial Hospital Linkou)
US
A Cohn (Rocky Mountain Cancer Centers)
A Daud (University of California San Francisco)
G Edelman (Mary Crowley Medical Research Center)

US, continued
S Gadgil (Karmaros Cancer Institute)
M Galsky (Comprehensive Cancer Center of Nevada)
M Gordon (Pinnacle Oncology/Hematology)
N Haas (University of Pennsylvania)
L Hart (Florida Cancer Specialists)
B Hellerstedt (Texas Oncology Cancer Center – Austin Central)
N Kluger (Yale University)
P Lara Jr (University of California Davis Medical Center)
J Lutsky (Mount Sinai Comprehensive Cancer Center)
A Mousa (Cancer Care Associates)
A Patrick (New York University)
M Perry (University of Missouri)
T Reardon (Hematology Oncology Consultants, Inc.)
D Richards (Texas Oncology/Tyler Cancer Center)
T Samuel (Medical College of Georgia)
M Sgrol (Central Indiana Cancer Center)
G Shapiro (Dana Farber Cancer Institute)
B Slik (Stanford University)

US, continued
D Smith (University of Michigan)
A Spira (Fairfax Northern Virginia Hematology Oncology)
J Stephenson Jr (Cancer Center of the Carolinas)
N Vogelzang (Comprehensive Cancer Centers of Nevada)

Editorial assistance was provided by KnowledgePoint360 LLC, and funded by Exelixis.

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