Cabozantinib (XL184) at 40mg in Patients with Metastatic Castration Resistant Prostate Cancer (mCRPC): Results of a Phase 2 Non-Randomized Expansion Cohort (NRE)

JS de Bono, MR Smith, D Rathkopf, PG Corn, D Mukherji, AL Harzstark, AO Sartor, DC Smith, N Tunariu, C Sweeney

Royal Marsden Hospital & Institute of Cancer Research, Sutton, United Kingdom; Massachusetts General Hospital Cancer Center, Boston, MA; Sidney Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan-Kettering Cancer Center, New York, NY; The University of Texas MD Anderson Cancer Center, Houston, TX; University of California, San Francisco, San Francisco, CA; Tulane Cancer Center, New Orleans, LA; University of Michigan, Ann Arbor, MI; Dana-Farber Cancer Institute, Boston, MA

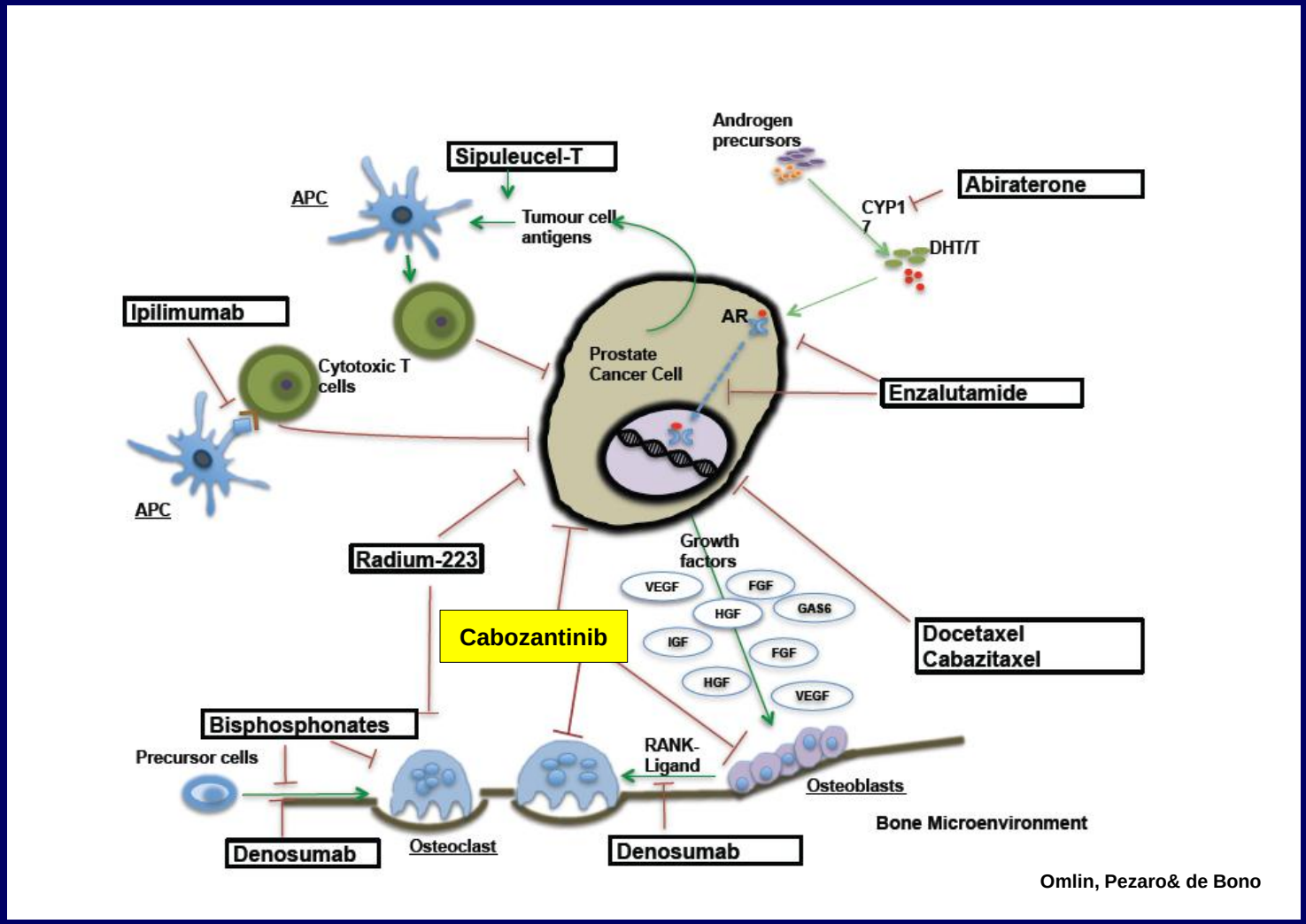
VIENNA 2012 ESMO congress

www.esmo2012.org

Disclosures

- JS de Bono: None
- MR Smith: Consultant Exelixis
- D Rathkopf: None
- PG Corn: None
- D Mukherji: None
- AL Harzstark: None
- AO Sartor: Consultant Exelixis
- DC Smith: Consultant Exelixis
- N Tunariu: None
- C Sweeney: None

Blocking Kinase Signaling by Cabozantinib

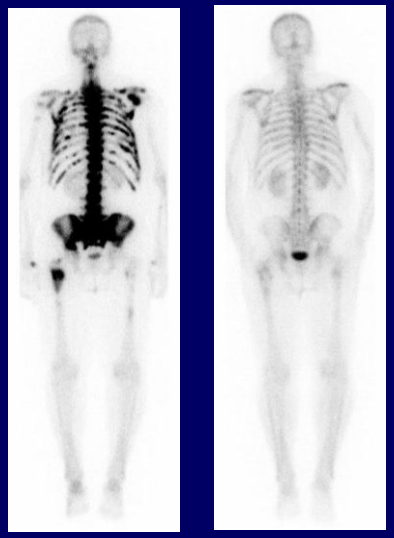


Inhibits VEGFR, MET, RET, AXL, KIT, FLT3

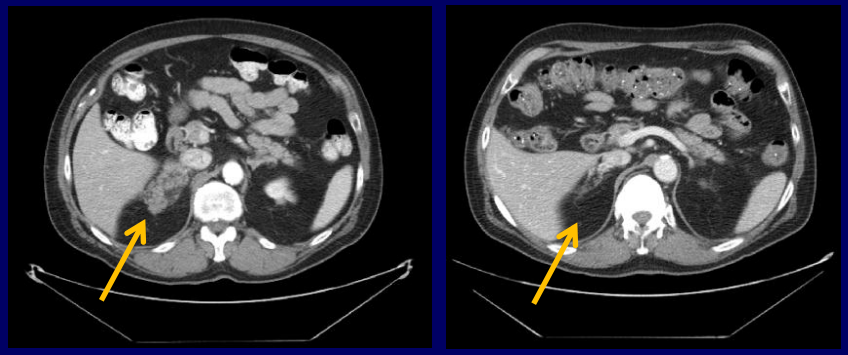
Cabozantinib at 100mg QD in mCRPC

- 67% demonstrated bone scan response
- 64% experienced pain reduction
- 80% showed soft tissue disease regression
- Median CTC change: 86% reduction
- Substantial reductions in bone markers
- Variable PSA changes
- **Dose reduction rate: 84%**

Bone



Soft tissue



MR Smith *et al*. ASCO 2012 (Abstract #4513)

Study Design

Single stage Phase 2 study sequentially enrolled two cohorts with doses of cabozantinib initially at 100mg and then at 40mg QD

Sample Size

- 51 patients were enrolled at 40mg to evaluate dose tolerability and determine antitumor activity to support dose selection for Phase 3

Key Eligibility Criteria

- Progressing CRPC with bone metastases on bone scan; prior docetaxel

Endpoints

- Primary: Bone scan response by CAD[1] and independent review
- Additional endpoints include:
  - Radiographic PFS, pain and narcotic use, CTCs, bone markers

[1] Computer assisted detection of bone scan lesion area (Brown *et al*. Nucl Med Commun 2012)

Baseline Characteristics 40mg Cohort (N=51)

Median age (range)	65 (43 – 84)
ECOG status, %	
0	35
1	65
Sites of disease, %	
Bone	100
Visceral	31
Measurable disease, %	41
Pain score ≥ 4, %	53
Pain ≥ 4 & narcotics, %	45
Fatigue any grade, %	55
≥ 2 prior regimens for CRPC, %	71

Prior therapies, %	
Docetaxel	100
Abiraterone	63
Enzalutamide	4
Cabazitaxel	25
Radionuclide	6
Bisphosphonate	45
Denosumab	41
PD from last taxane dose[1], %	
Less than 1 month	49
1-6 months	49
Median values	
PSA, ng/mL (range)	146 (9 – 2428)
CTC count (range)	25 (0– 3959)

[1] Not applicable for one patient

Patient Disposition

Summary of treatment status (40mg, N=51)	n (%)
Active	21 (41)
Treatment discontinued	30 (59)
Reason for discontinuation	
Progressive disease	20 (39)
Adverse event	8 (16)
Subject request/ lost to follow-up	2 (4)

Median treatment duration (range): 4.7 months (0.3 – 8.8+)

Time since first/ last patient enrolled: 9.2 / 4.9 months

Discontinuation rate for adverse events similar to other agents in late line CRPC

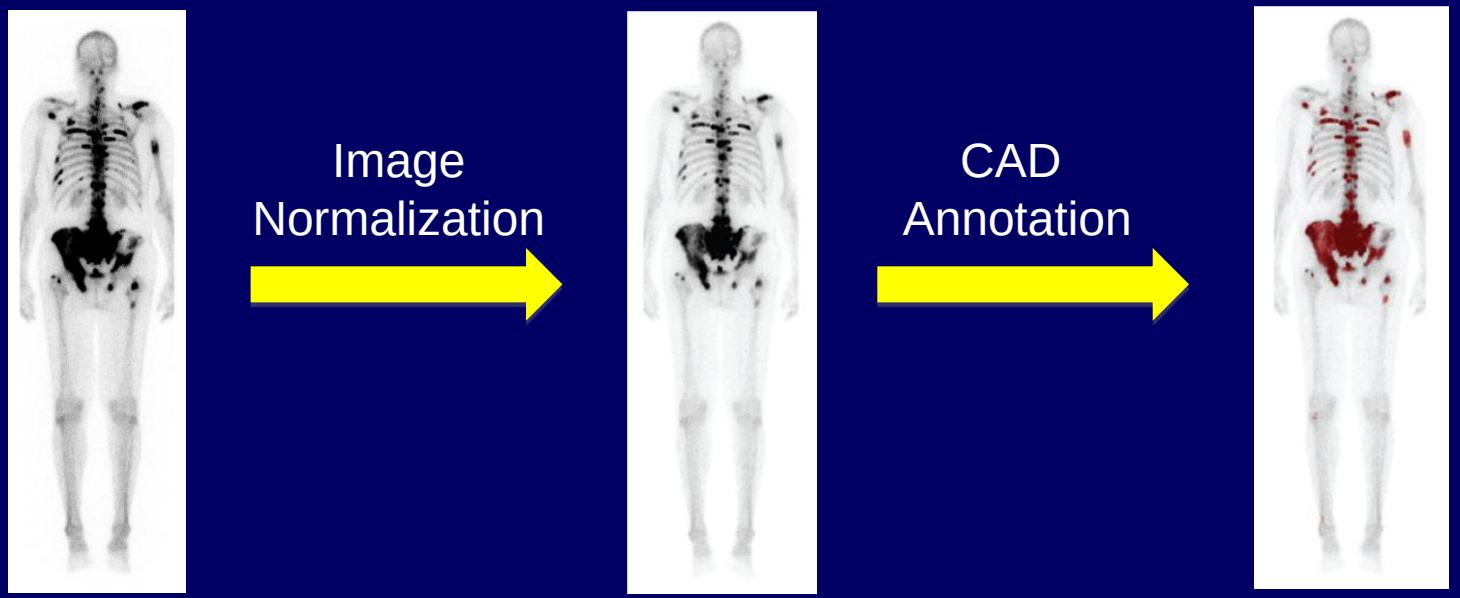
Most Frequently Reported Adverse Events

- 25% of patients experienced a dose reduction due to AE

Adverse Event (40mg, N=51)	All Grades, n (%)	Grade 3, n (%)	Grade 4, n (%)
Fatigue	31 (61)	6 (12)	–
Decreased Appetite	20 (39)	4 (8)	–
Diarrhea	18 (35)	–	–
Nausea	18 (35)	–	–
Vomiting	16 (31)	–	–
Back Pain	12 (24)	1 (2)	1 (2)
Weight Decreased	12 (24)	–	–
Dysgeusia	11 (22)	–	–
Hypertension	10 (20)	7 (14)	–
Dyspnea	10 (20)	–	–
Adverse Events of Interest			
Hand-foot syndrome	9 (18)	–	–
Thrombosis venous	7 (14)	1 (2)	6 (12)

Assessment of Bone Scan 'Response'

- Images normalized to reference atlas - radiotracer uptake annotated by CAD[1]
- Readers rejected non-tumor annotation (eg fracture, arthritis)
- Bone scan lesion area (BSLA), which represented the number of pixels with radiotracer uptake above the threshold for normal bone, was calculated
- Discordance between readers required adjudication
- Bone scan response defined as ≥30% decrease in BSLA



[1] Computer assisted detection of BSLA (Brown *et al*. Nucl Med Commun 2012)

Bone Scan 'Response' By CAD and Independent Radiology Review

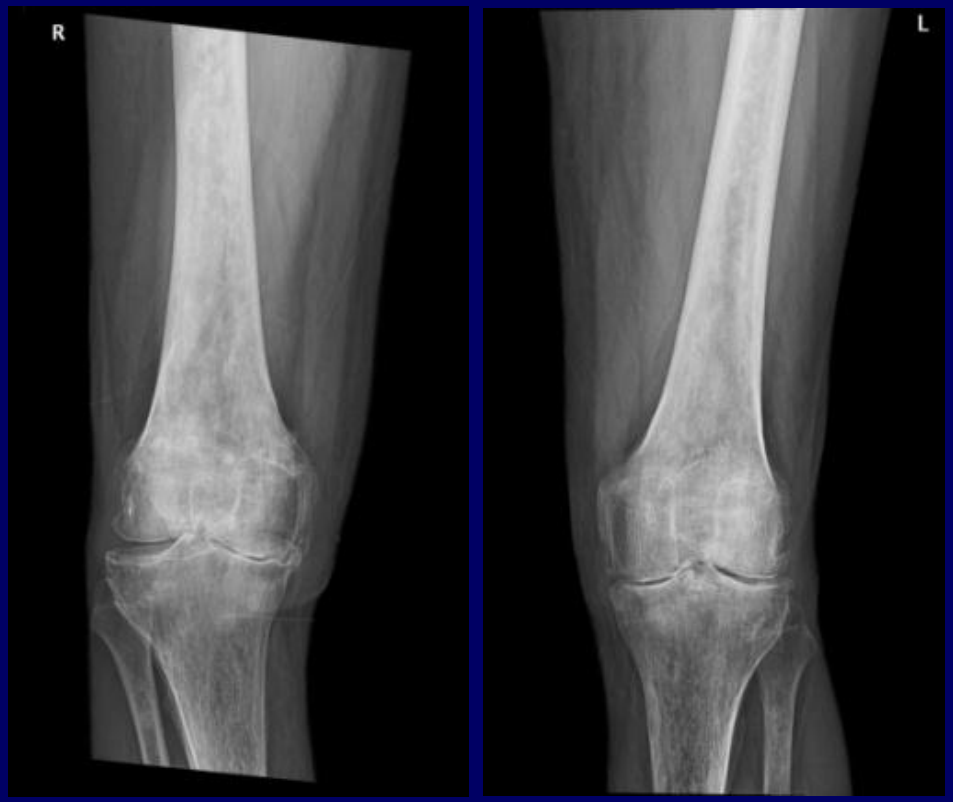
Bone scan evaluable (40mg, N=51)[1]	n (%)
Bone scan 'response'	25 (49)
Complete (100% reduction of BSLA)	1 (2)
Partial (≥30% reduction of BSLA)	24 (47)
Stable	15 (29)
Progressive disease[2]	7 (14)

BSLA, bone scan lesion area

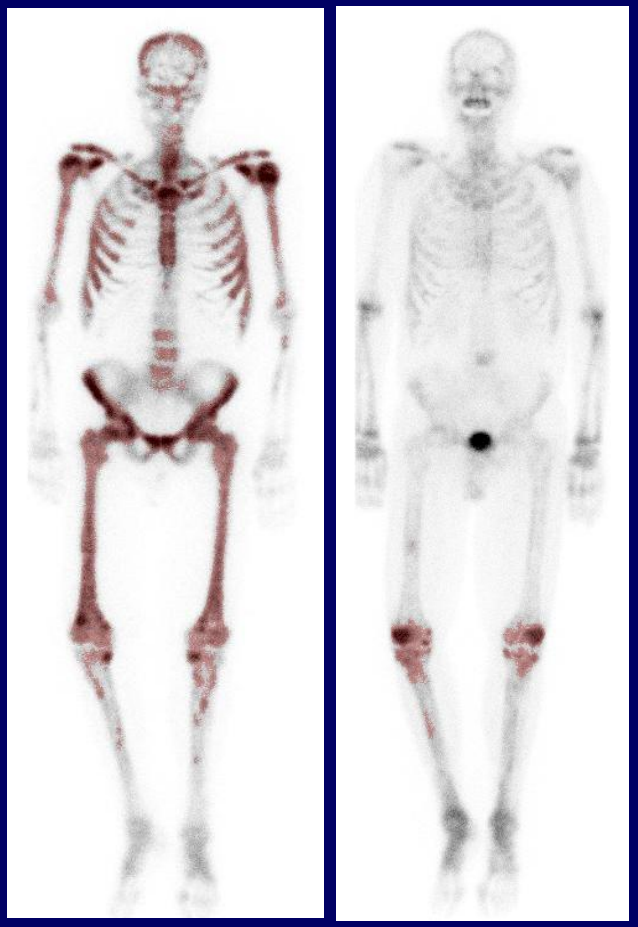
[1]Bone metastases at baseline and ≥1 post-baseline scan available for 47 patients

[2] Two or more new areas of uptake or unequivocal increase of uptake at metastatic sites

Cabozantinib Effects on Bone Scan Appear to be Tumor-Selective



Baseline X-Rays: Osteoarthritis (knees)



Baseline Week 18

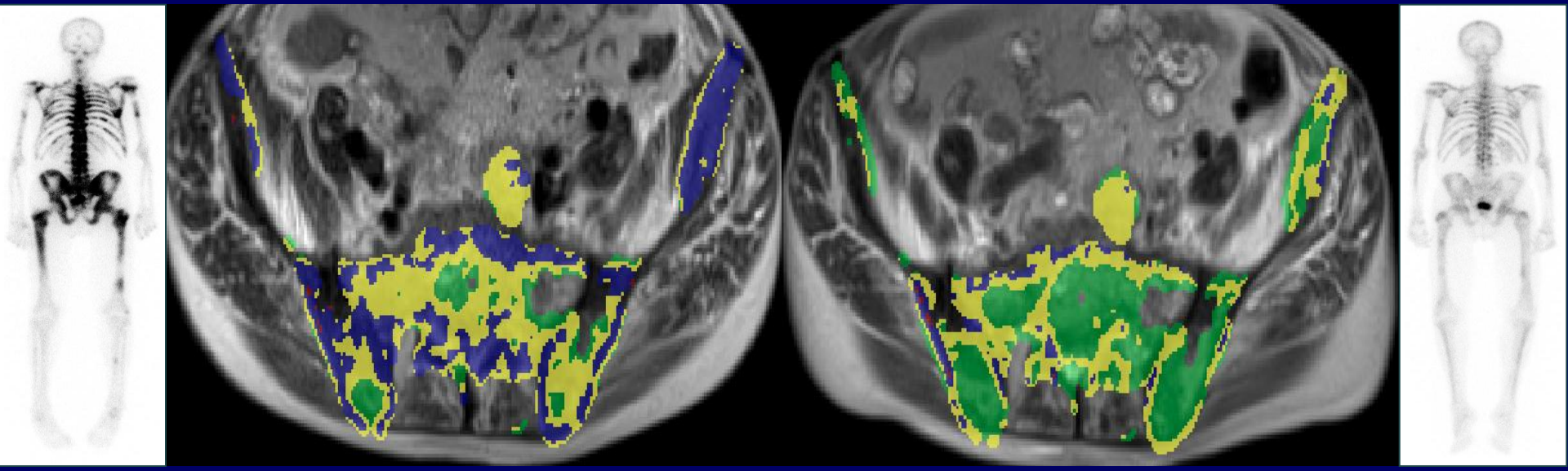
Resolution at sites of bone metastases with residual uptake at sites of osteoarthritis

Images from 100mg NRE cohort; courtesy of Dr. P. Corn (MD Anderson)

Cabozantinib Induces Tumor Cell Death at Sites of Bone Metastases as Reflected by Diffusion Weighted - MRI Findings

Baseline

Week 6

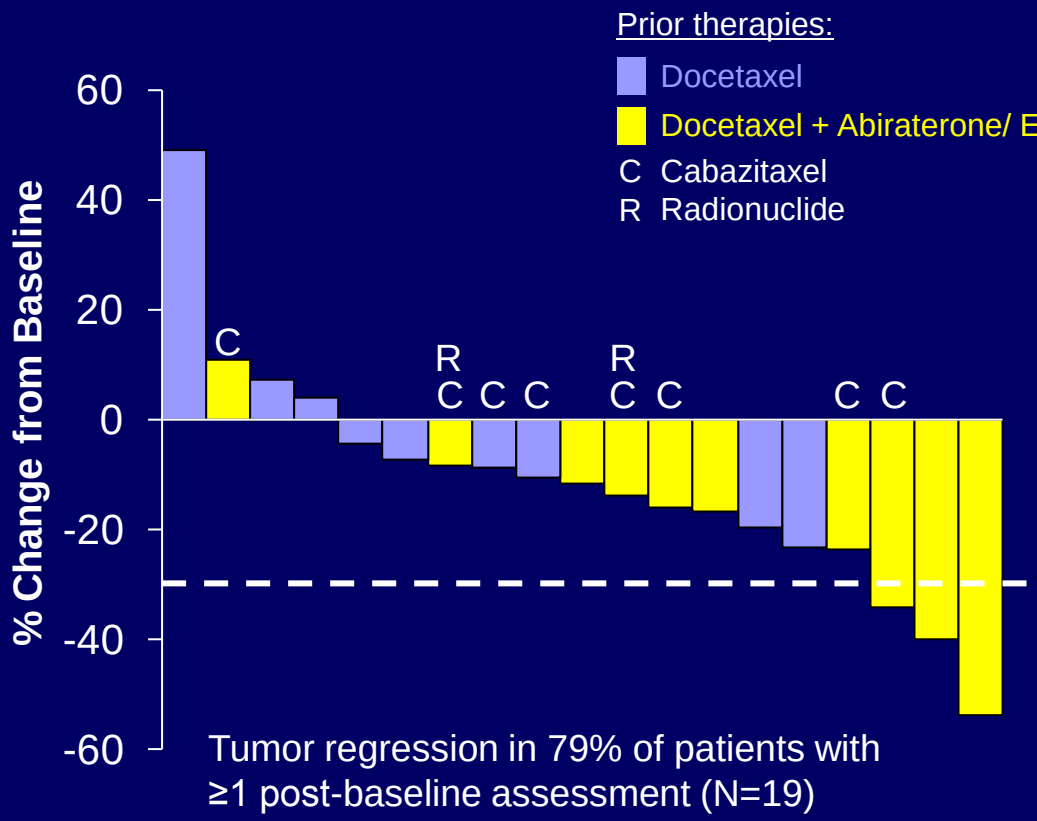


38% increase in mean Apparent Diffusion Coefficient at Week 6

High Cellularity Tumor **Low Cellularity Tumor** **Tumor Necrosis**

Images courtesy of Dr Nina Tunariu, Royal Marsden

Change in Measurable Soft Tissue Lesions



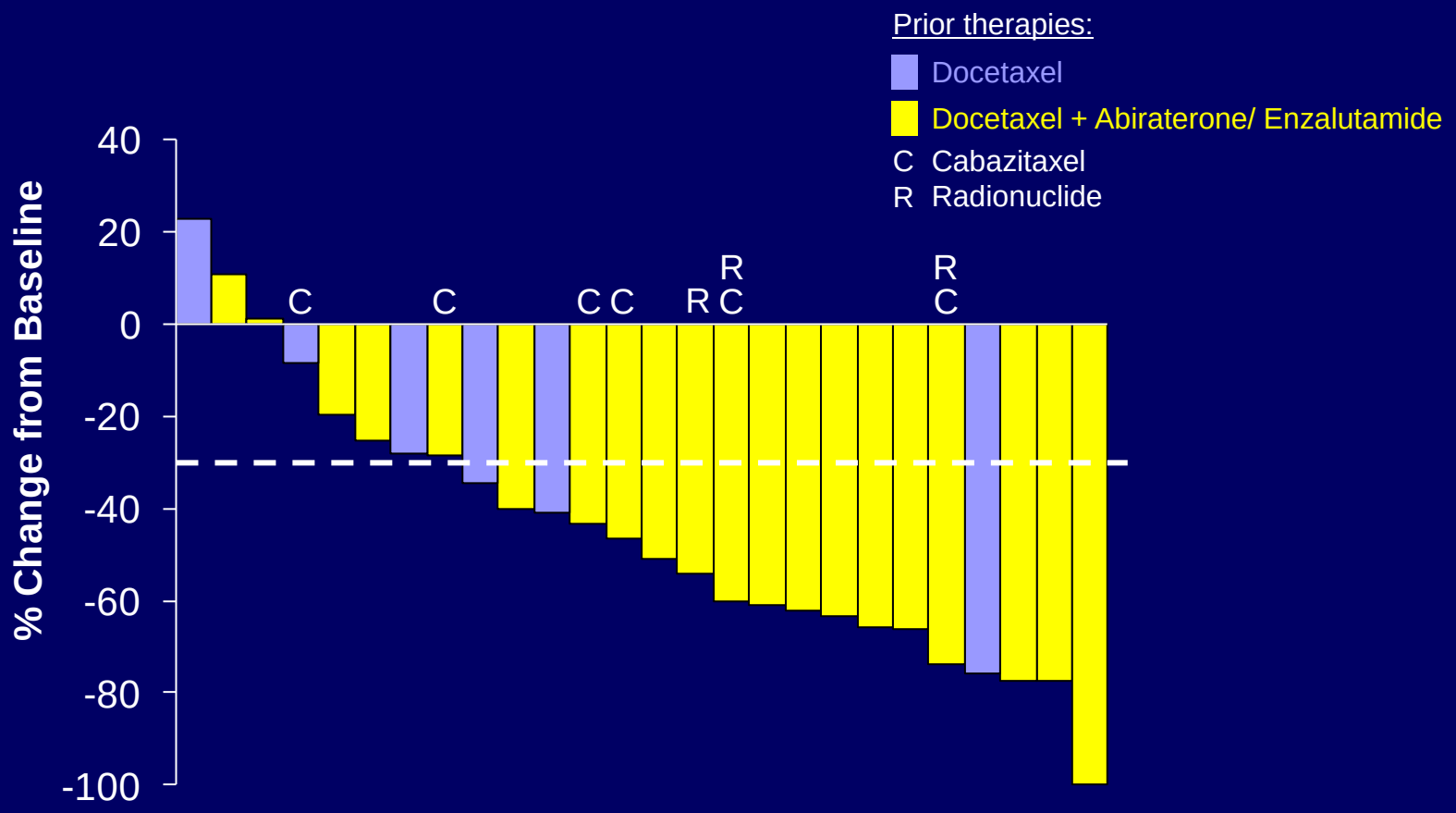
RECIST response [1]	%
PR	10
SD	71
PD	10

[1]N=21 with at least baseline data

Radiographic Progression-Free Survival of 4.1 months regardless of prior treatment with Abiraterone

Change in Pain Scores

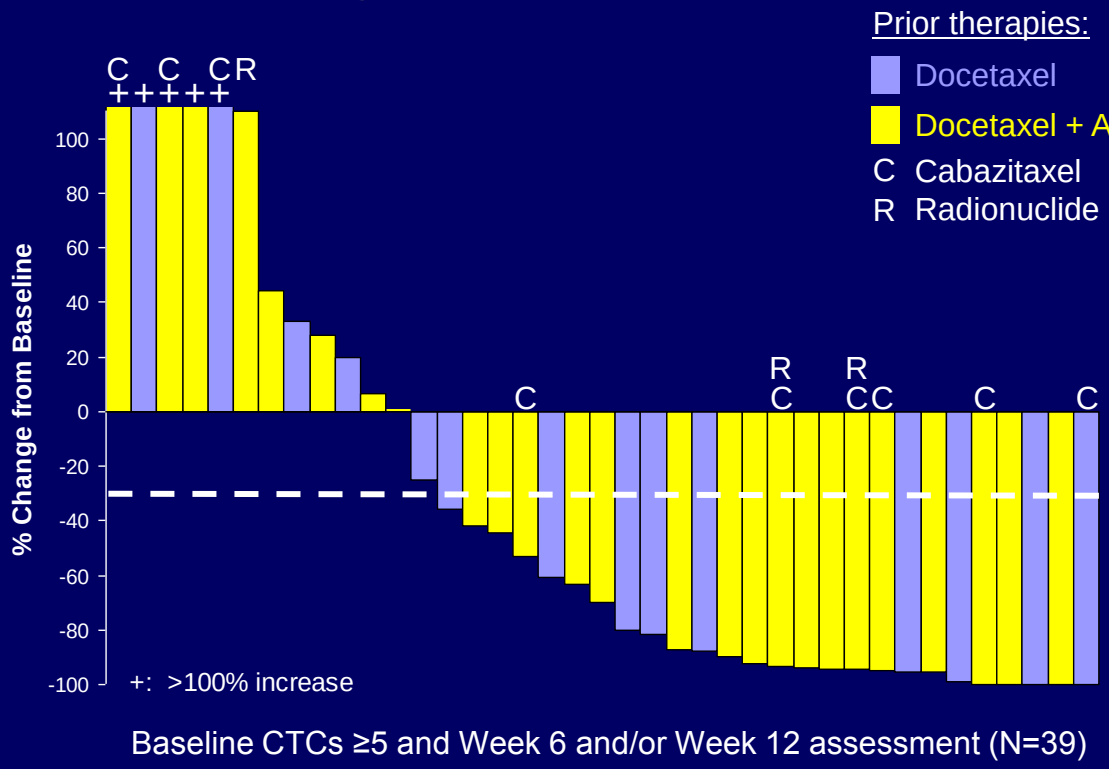
Patients with baseline score ≥4 (N=26)



- **69% had a pain decrease ≥30%**
- **Median change in pain: 49% reduction**
- **54% decreased narcotics use (1 patient discontinued narcotics)**

Changes in Biomarkers

Circulating Tumor Cells



Baseline CTCs ≥5 and Week 6 and/or Week 12 assessment (N=39)

- **67% demonstrated CTC decrease ≥30%**
- **Median CTC change: 70% decrease**
- **Conversion to <5 CTCs: 22% at Week 6**

Serum Bone Biomarkers

- Median change in CTx at Week 12: 31% reduction
- 50% of evaluable patients exhibited a decrease in BSAP at week 12 or later

Summary

- Cabozantinib at 40mg QD shows promising **single agent antitumor activity** with **improved tolerability** in advanced mCRPC
  - Regression of measurable disease and resolution of bone scans
  - Pain relief associated with decreased narcotic use
  - Reductions in CTCs and bone biomarkers
  - Fewer dose reductions compared to 100mg QD
- Phase 3 studies (COMET-1/ -2) now recruiting mCRPC patients

Acknowledgments

- We thank the Patients and their Families
- XL184-203 Investigators / Staff
- Study supported by Exelixis, Inc.