

# A Phase 1/2 study of AT13387, a heat shock protein 90 (Hsp90) inhibitor in combination with abiraterone acetate (AA) and prednisone (P) in patients with castration-resistant prostate cancer (mCRPC) no longer responding to AA

R. Ferraldeschi<sup>1</sup>, S. Slovin<sup>2</sup>, S.A. Hussain<sup>3</sup>, F. Saad<sup>4</sup>, J. Garcia<sup>5</sup>, F.F. Kabbinavar<sup>6</sup>, N. Uppal<sup>7</sup>, N.J. Vogelzang<sup>8</sup>, B.J. Poiesz<sup>9</sup>, E. Gelmann<sup>2</sup>, J. Picus<sup>10</sup>, D. Mahadevan<sup>11</sup>, S. Sundar<sup>12</sup>, A. Nikapota<sup>13</sup>, S. Pacey<sup>14</sup>, J. Lyons<sup>14</sup>, A. Oganessian<sup>15</sup>, L. Manlapaz-Espiritu<sup>15</sup>, Y. Hao<sup>15</sup>, H. Keer<sup>15</sup>, J. De Bono<sup>1</sup>;

<sup>1</sup>Sutton/UK, <sup>2</sup>New York, NY/US, <sup>3</sup>Liverpool/UK, <sup>4</sup>Montreal, QC/CA, <sup>5</sup>Cleveland, OH/US, <sup>6</sup>Los Angeles, CA/US, <sup>7</sup>Lake Success, NY/US, <sup>8</sup>Las Vegas, NV/US, <sup>9</sup>Syracuse, NY/US, <sup>10</sup>St Louis, MO/US, <sup>11</sup>Memphis, TN/US, <sup>12</sup>Nottingham/UK, <sup>13</sup>Brighton/UK, <sup>14</sup>Cambridge/UK, <sup>15</sup>Dublin, CA/US

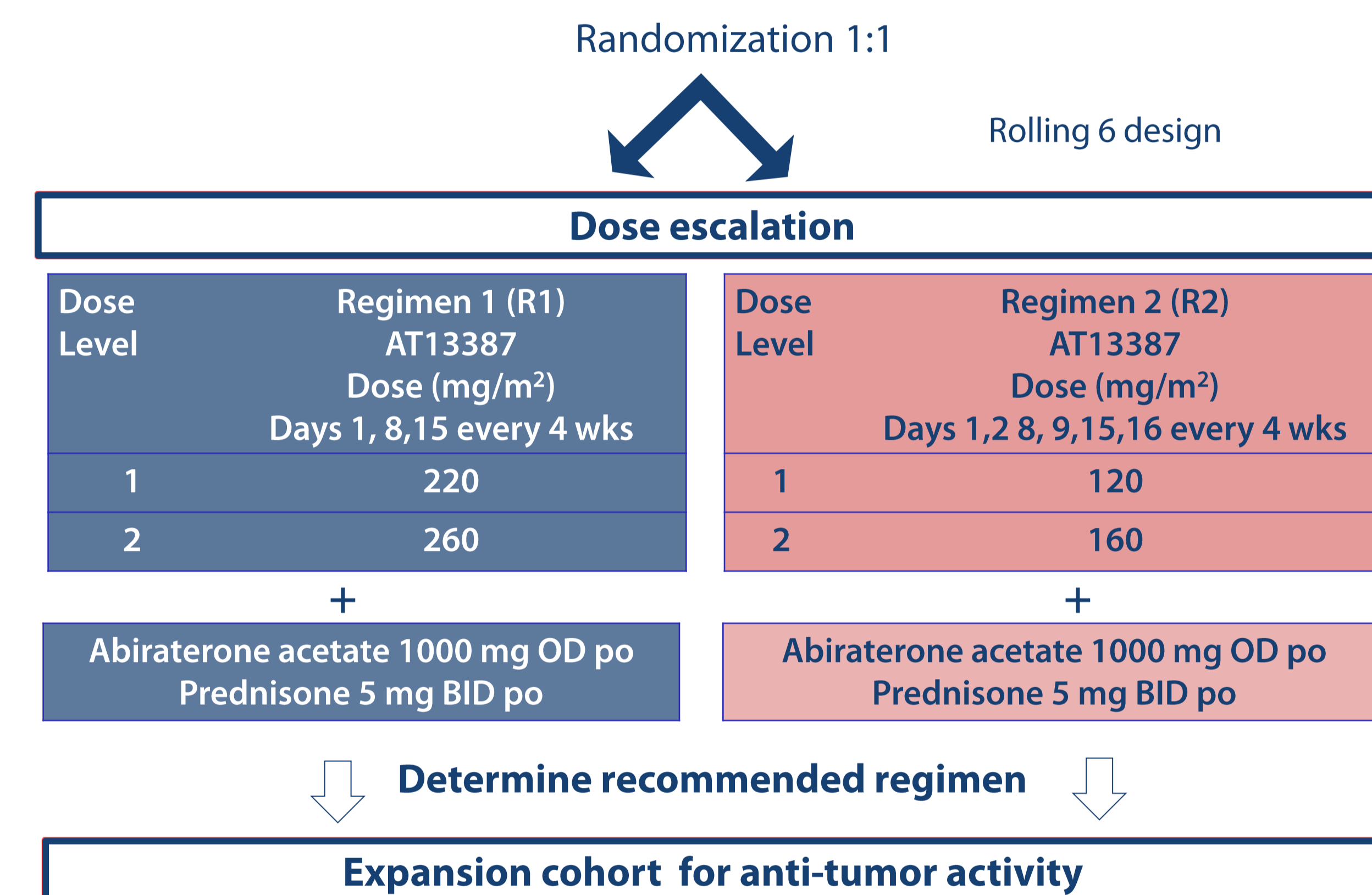
## Background

- Heat Shock Protein 90 (HSP90) is an ATP-dependent molecular chaperone that assists in correct folding of a wide variety of 'client' proteins (Androgen Receptor [AR], AKT, HER2 and CDK4).
- AT13387 (AT) is a fragment derived, second-generation novel potent non-ansamycin HSP90 inhibitor (Kd=0.71 nM)<sup>1</sup> with good tissue distribution, excellent in vivo anti-tumor activity and long tumor half life in preclinical models (65-78 hours).
- AT13387 demonstrated anti-tumor activity in preclinical castration-resistant prostate cancer (CRPC) models<sup>2</sup> and holds promise as a therapeutic agent by simultaneously down-regulating multiple aberrant signalling pathways.

## Study Design

A 2-part, Phase 1/2, open-label, parallel-group, randomized study in CRPC patients, with PSA progression, on abiraterone acetate (AA) and prednisone (P). Only the first part of the study was completed. Main eligibility criteria included:

- Disease progression on AA/P by PWGC2 criteria<sup>3</sup>
- Detectable circulating tumor cells (CTCs)



Evaluation of safety, activity, pharmacokinetics and pharmacodynamics

## Results

Enrolment is complete, although one subject is still on treatment. The results are based on data extracted from the database in August 2014.

### Patient Characteristics

	Regimen 1	Regimen 2
Number of Subjects Enrolled	23	25
Median Age (range)	70 (57, 90)	67.0 (55, 84)
ECOG PS		
0	7 (30%)	12 (48%)
1	14 (61%)	12 (48%)
2	2 (9%)	1 (4%)
Prior Chemotherapy	18 (78%)	20 (80%)
Time since diagnosis (month) median, range	77.5 (10.5, 210.5)	71.4 (18.4, 213.5)

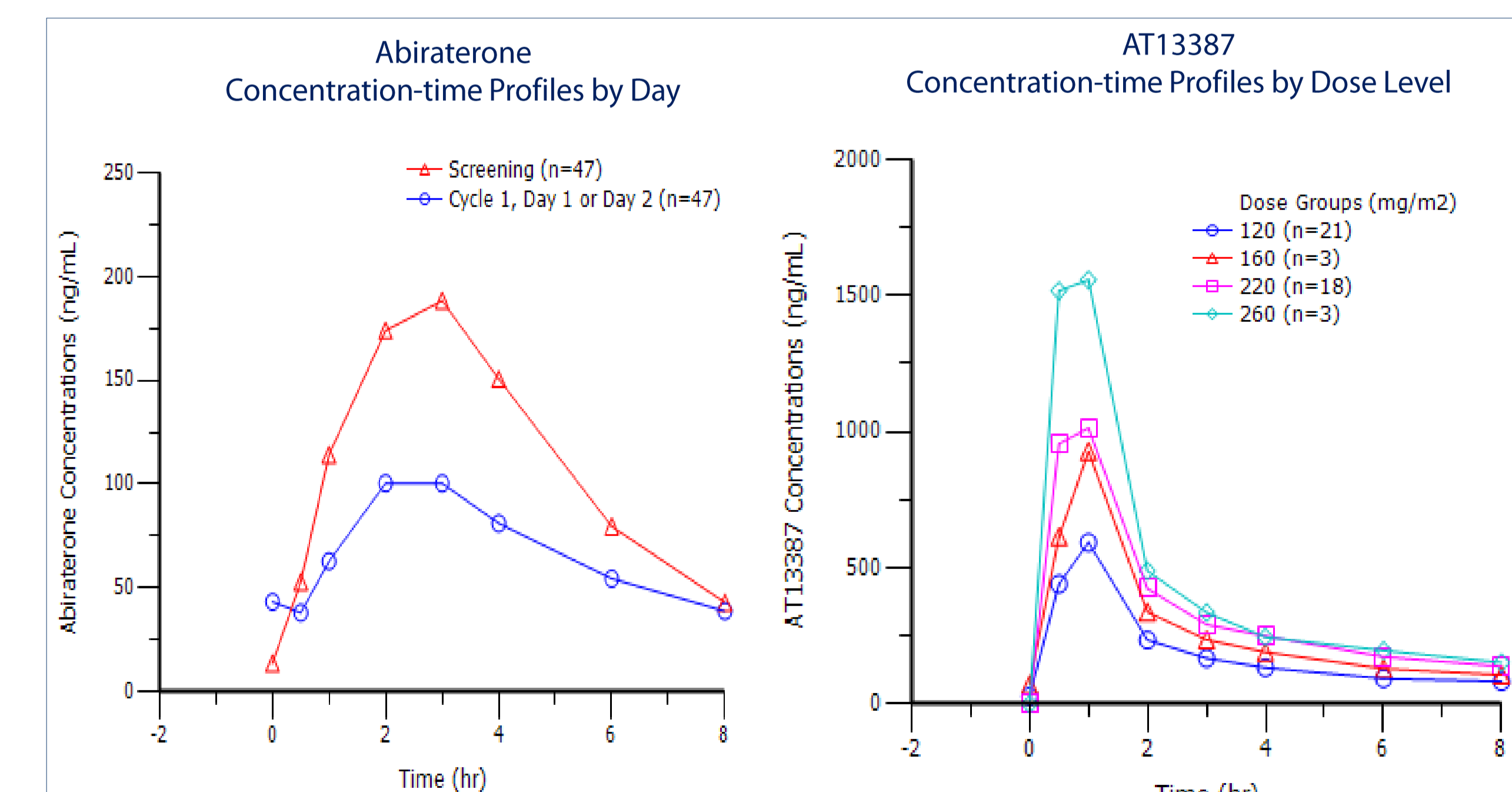
## Exposure and Safety Data

- In R1 the median number of cycles of treatment administered was 3.0 (range 1 to 12) and in R2 the median number of cycles of treatment was 2 (range 1 to 4). Nineteen (83%) and 17 (68%) of subjects received 100% of the planned dose in each cycle for R1 and R2, respectively.
- Grade 3 diarrhea was dose-limiting at 260 mg/m<sup>2</sup> and 160 mg/m<sup>2</sup> for R1 and R2, respectively.
- Although no DLTs were seen at doses of 220mg/m<sup>2</sup> in R1 or 120mg/m<sup>2</sup> in R2 combination treatment was not as well tolerated following multiple cycles of treatment. Seven (30.4%) and 4 (16%) subjects discontinued treatment as a result of toxicity in R1 and R2, respectively. The dose of AT13387 was reduced in 4 (6.1%) and 11 (18.6%) of all cycles for R1 and R2.
- The most common treatment related toxicities in R1 and R2 were diarrhea (91% and 96% of subjects in R1 and R2, respectively) and fatigue (65%, and 60% of subjects in R1 and R2, respectively).

### Related Adverse Events that occurred in ≥ 15% of subjects

Adverse Event	Regimen 1 No. of Subjects (%)	Regimen 2 No. of Subjects (%)
Number of subjects who reported at least one related TEAE	23 (100%)	25 (100%)
Anemia	3 (13%)	4 (16%)
Diarrhea	21 (91%)	24 (96%)
Nausea	10 (43%)	14 (56%)
Dry mouth	5 (22%)	5 (20%)
Vomiting	5 (22%)	10 (40%)
Fatigue	15 (65%)	15 (60%)
Infusion site pain	4 (17%)	3 (12%)
Weight decreased	2 (9%)	4 (16%)
Decreased appetite	11 (48%)	14 (56%)
Hypokalaemia	4 (17%)	0
Dizziness	3 (13%)	5 (20%)

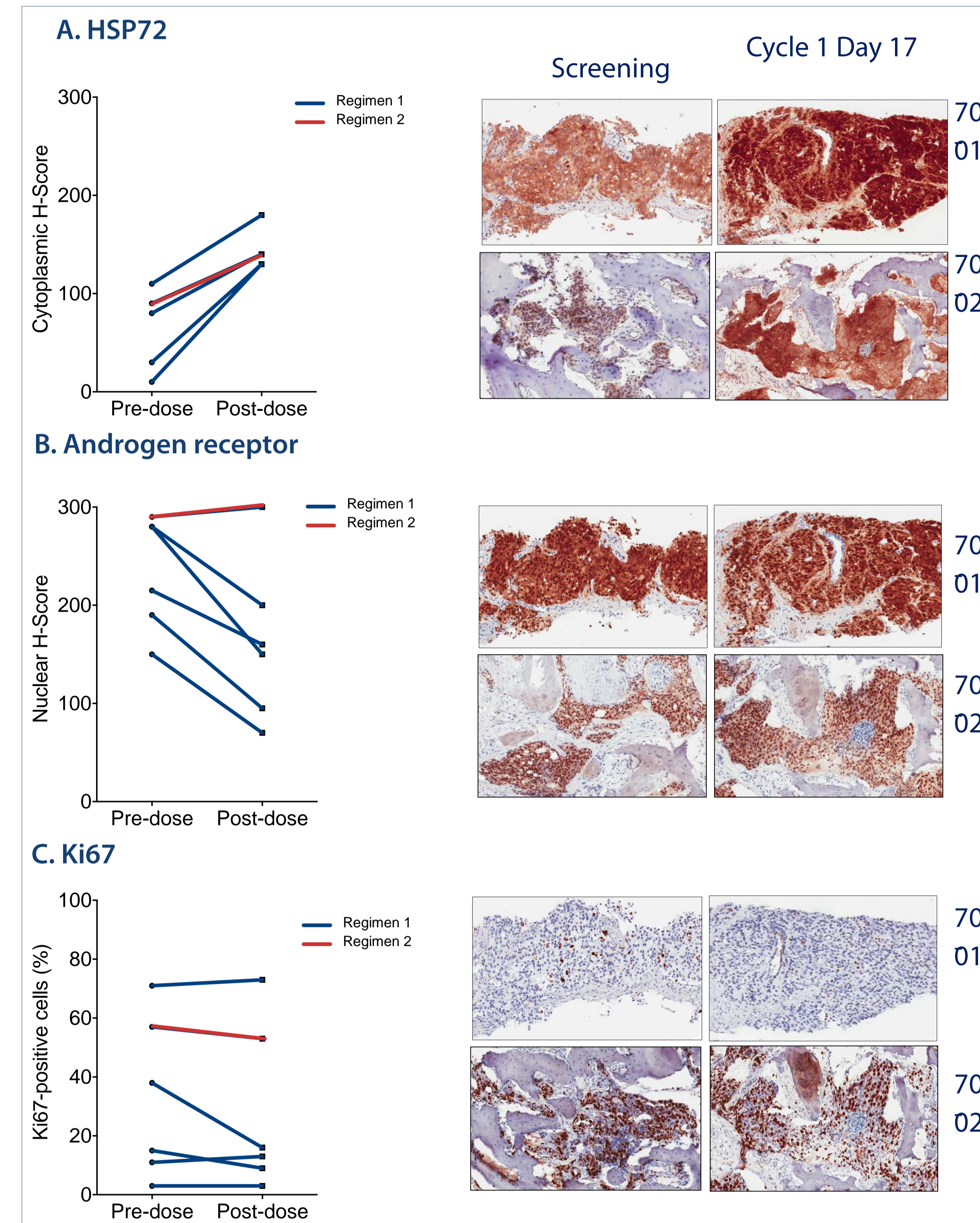
### Pharmacokinetic profile (PK)



- AT13387 exposures increased in a dose-proportional manner and were similar to those observed in a single agent AT Phase 1 dose escalation study (AT13387-01), suggesting no interaction from abiraterone on AT13387 PK.
- Abiraterone exposures appeared to be lower when co-administered with AT13387 (Cycle 1 Day 1/Day 2) vs screening. No direct metabolic drug-drug interactions were expected. The reason for this effect is unknown but possibly due to reduced GI transit time as a result of GI AEs (diarrhea) observed on days of dosing with AT13387.

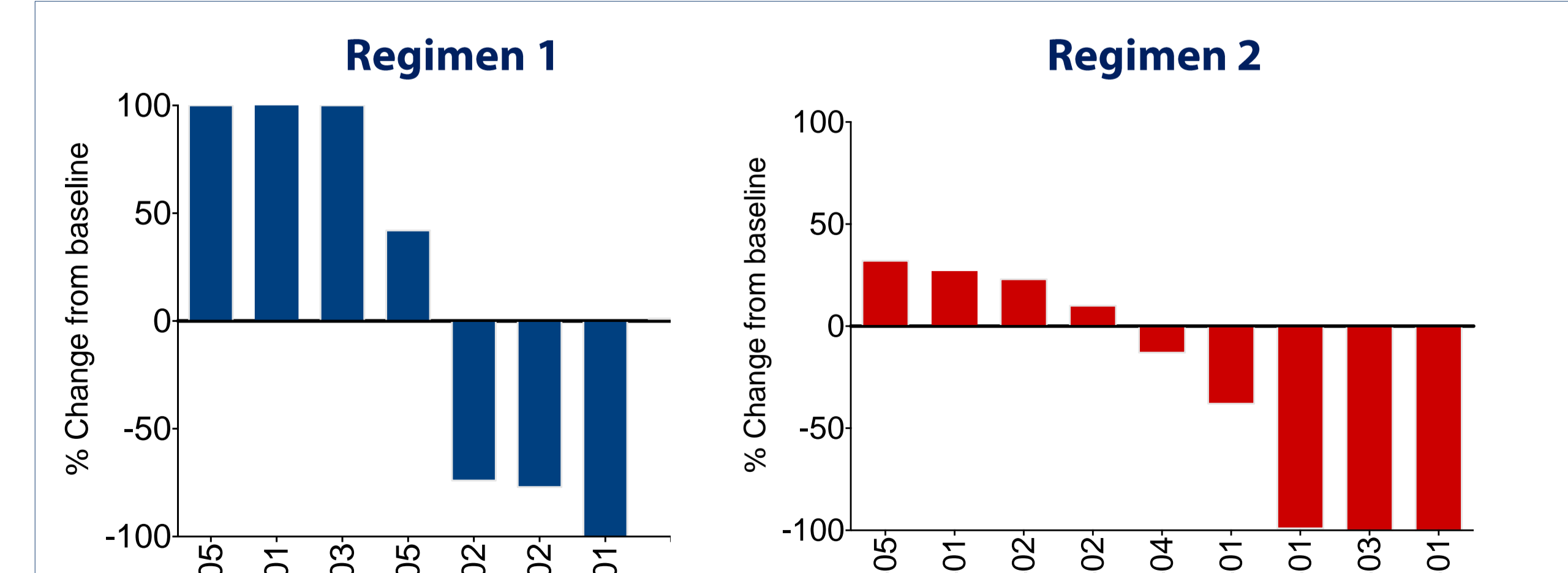
## Results

### Pharmacodynamics (PD)



Changes in HSP72 (A) and AR (B) expression in paired pre- and post-AT13387 biopsies in individual subjects. Immunostaining was assessed using a quasi-continuous H score, calculated by multiplying each intensity level (0 for absent, 1 for weak stain, 2 for moderate, and 3 for intense stain) by the corresponding percentage of positive cancer cells, and then summing the results to obtain a maximum H-score of 300.

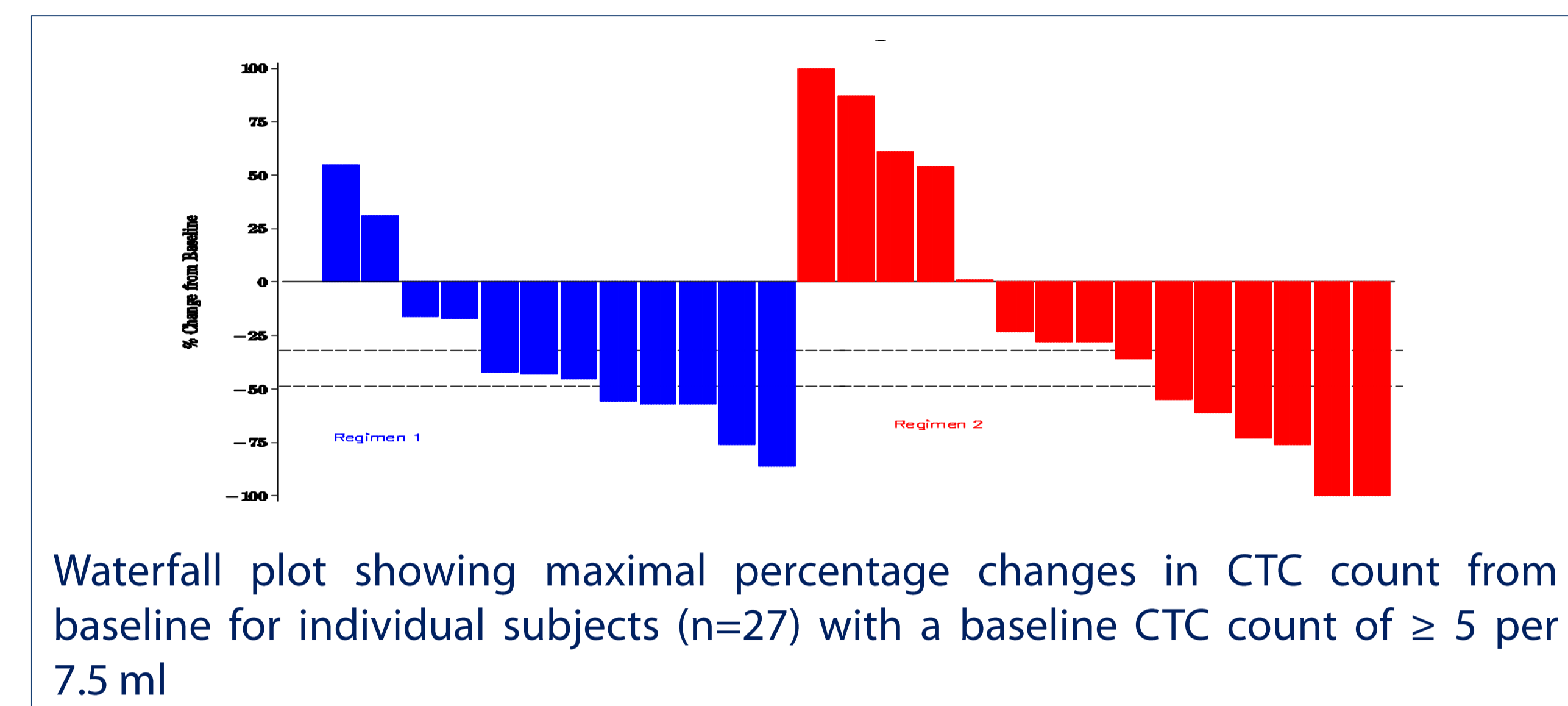
Changes in Ki67(C); results were recorded as the percentage of immunoreactive cells over at least 100 cancer cells.



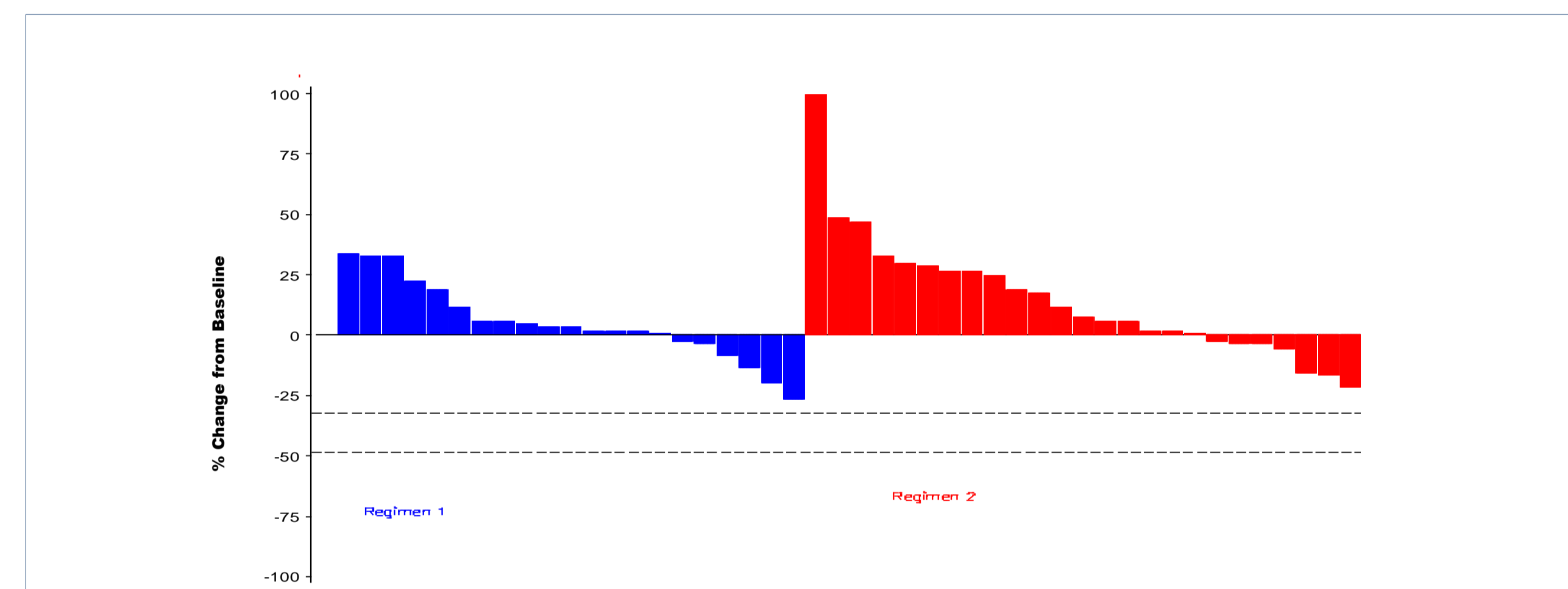
Waterfall plot showing changes in proportion of AR-positive CTCs from baseline for 16 evaluable subjects with a baseline CTC count of ≥ 5 per 7.5 ml and a Cycle 1 Day 17 CTC/AR count. AR positivity was evaluated by immunofluorescence on the CellSearch® System in samples collected at baseline (Screening and Cycle 1 Day 1) and post-AT13387 treatment (Cycle 1 Day 17)

### Anti-tumor activity

- No subjects had a objective tumor response per RECIST 1.1 and no PSA responses (≥ 50% decrease in PSA at week 12 per PCWG2) were observed.
- Eight subjects (35%) in R1 and 7 (29%) subjects in R2 had baseline CTCs ≥ 5 cells/7.5ml and either a conversion of CTCs from ≥ 5 cells/7.5ml of blood to < 5 cells/7.5ml or a decrease of more than 30% from the baseline CTC value on treatment. However, these declines in CTC values were transient and no CTC conversion from ≥ 5 to < 5 CTCs was observed at week 12.



Waterfall plot showing maximal percentage changes in CTC count from baseline for individual subjects (n=27) with a baseline CTC count of ≥ 5 per 7.5 ml



Waterfall plot showing the maximum decline in PSA (a negative % change) for subjects with PSA decline or the minimum increase (a positive % change) for subjects without PSA decline (n=46). Increases were capped at 100%.

- The median progression free survival was 80 days (95% CI of median value 71 to 85) and 85 days (95% CI of median value 78 – 147) for R1 and R2, respectively.

## Conclusions

- This study represents the first clinical trial of a HSP90 inhibitor in combination with AA/P. The MTDs were reached for once-weekly (220 mg/m<sup>2</sup>) and twice-weekly (120 mg/m<sup>2</sup>) regimens.
- Repeated cycles of combination AT/AA/P treatment at the MTDs were not as well tolerated and managed with AT dose reduction.
- Although the PD data showed evidence of target engagement (HSP72 induction) only modest depletion in the level of the AR was observed in paired tissue biopsies collected pre- and post-treatment.
- Although transient decreases in CTC levels were observed, AT and AA/P did not demonstrate adequate antitumor activity at the doses evaluated for the study to proceed to Part 2.

## References

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- Ferraldeschi R et al. *Cancer Research* 2013; 73: issue 8, supplement 1, abstract 2433 (Proceedings AACR 104th Annual Meeting 2013)
- Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol.* 2008; 26:1148-1159.