

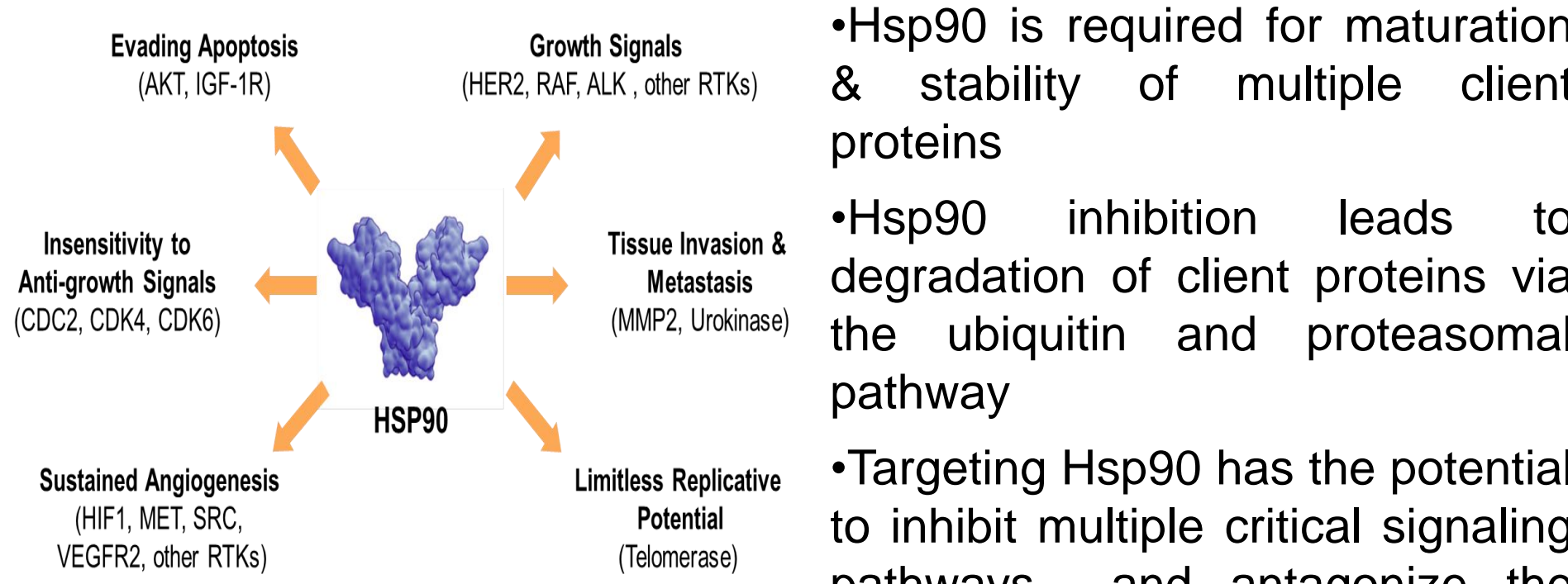
# A Phase II trial of Ganetespib: Efficacy and safety in patients (pts) with metastatic breast cancer (MBC)

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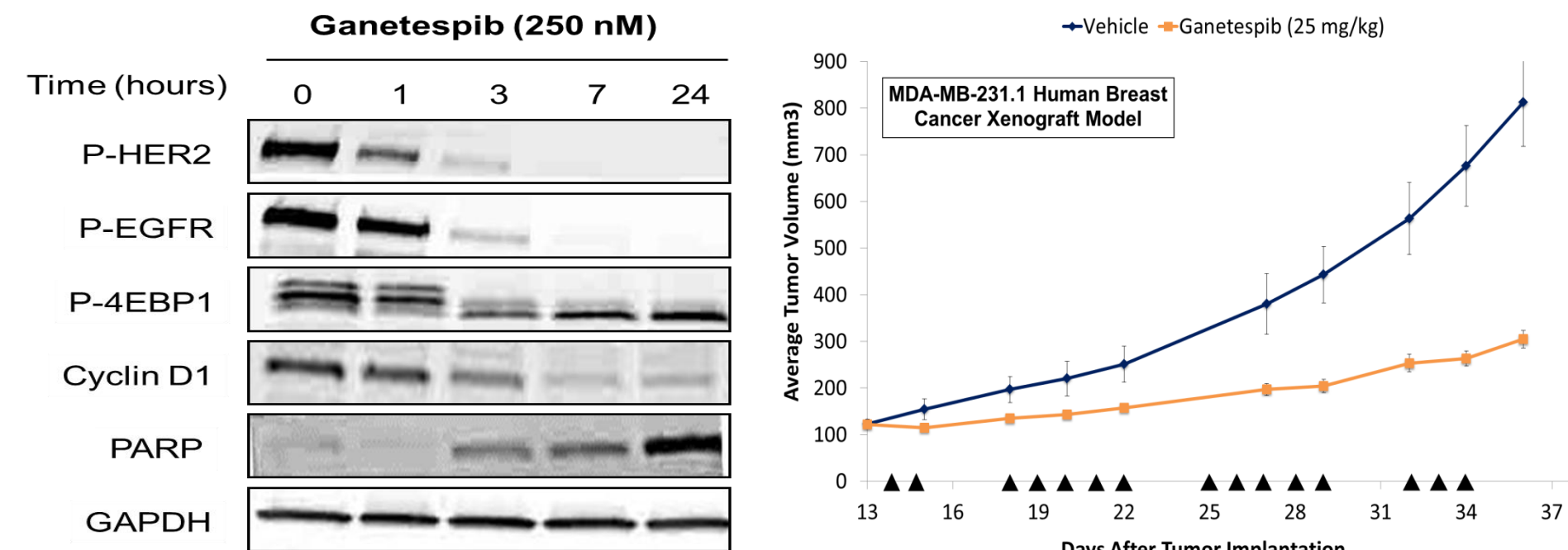
## Background and Rationale

Ganetespib is a synthetic, small molecule, non-geldanamycin Hsp90 inhibitor in clinical trials



Hanahan & Weinberg, Cell 2000, 100: 57-70

Ganetespib has broad inhibitory effects on oncoproteins and shows anti-tumor activity in different breast cancer subtypes including triple negative breast cancer



•BT-474 cells treated with ganetespib for 16 hours  
• Protein analysis-Western Blot

•Efficacy in MDA-MB-231 xenograft model

We therefore tested ganetespib in an unselected cohort of patients with advanced breast cancer

## Objectives

- Primary objective: Overall response rate (CR+PR) using RECIST 1.1
- Secondary objective: 1) Duration of response, clinical benefit rate, progression free survival, time to response and overall survival. 2) Further characterize the safety profile of ganetespib
- Exploratory Objective: To correlate response with tumor phenotype

## Study Design

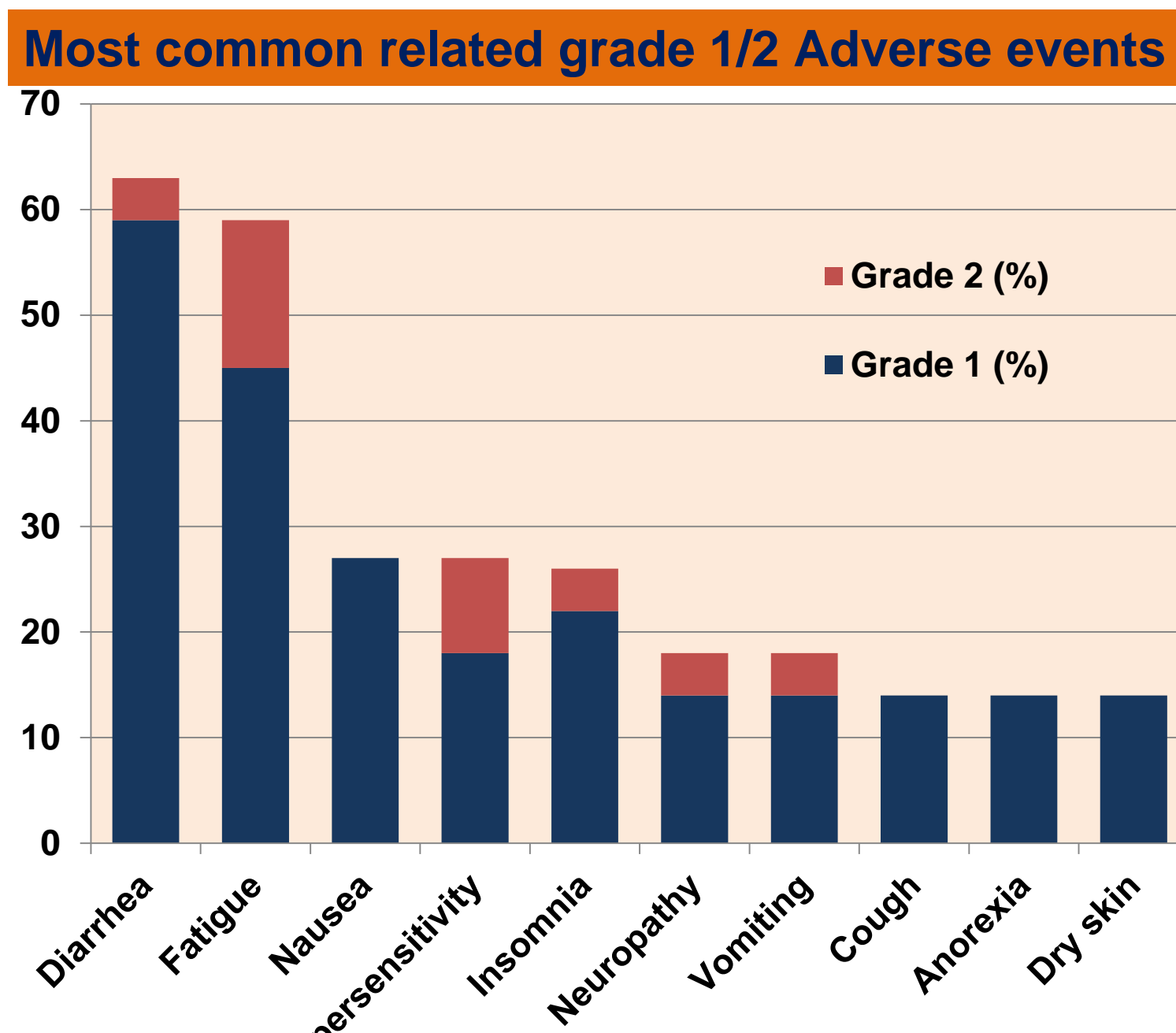
•Monotherapy, open-label, phase 2 study in MBC  
•Schema: 200mg/m<sup>2</sup> 1-hr IV 3 weeks/4

- Inclusion Criteria:
  - Measurable disease by RECIST 1.1
  - Up to 3 lines of chemotherapy in the metastatic setting
  - Patients with HER2+ disease must have received prior trastuzumab
  - No limit on prior lines of hormonal therapy
- Exclusion Criteria:
  - Prior Hsp90 inhibitor therapy
  - Untreated or active CNS disease
  - Ejection Fraction <50%
- Simon two-stage model:
  - First-stage: target accrual - 22 patients (if 3 responses then increase accrual to 40)

## Results

| Baseline Characteristics                          | N          |
|---|------------|
| Total Enrolled                                    | 22         |
| Median Age (years, range)                         | 51 (38-70) |
| Subtype   |            |
| ER+/HER2+   | 10         |
| ER-/HER2+   | 3          |
| ER+/HER2-TNBC                                     | 6          |
| ER-/HER2-TNBC                                     | 3          |
| Median ECOG                                       | 0 (0-1)    |
| Prior lines of chemotherapy in metastatic setting |            |
| 1   | 8          |
| 2   | 9          |
| 3   | 5          |
| Prior lines of trastuzumab in metastatic setting  |            |
| 0   | 9          |
| 1   | 6          |
| 2   | 6          |
| 3   | 1          |

## Results: Toxicity



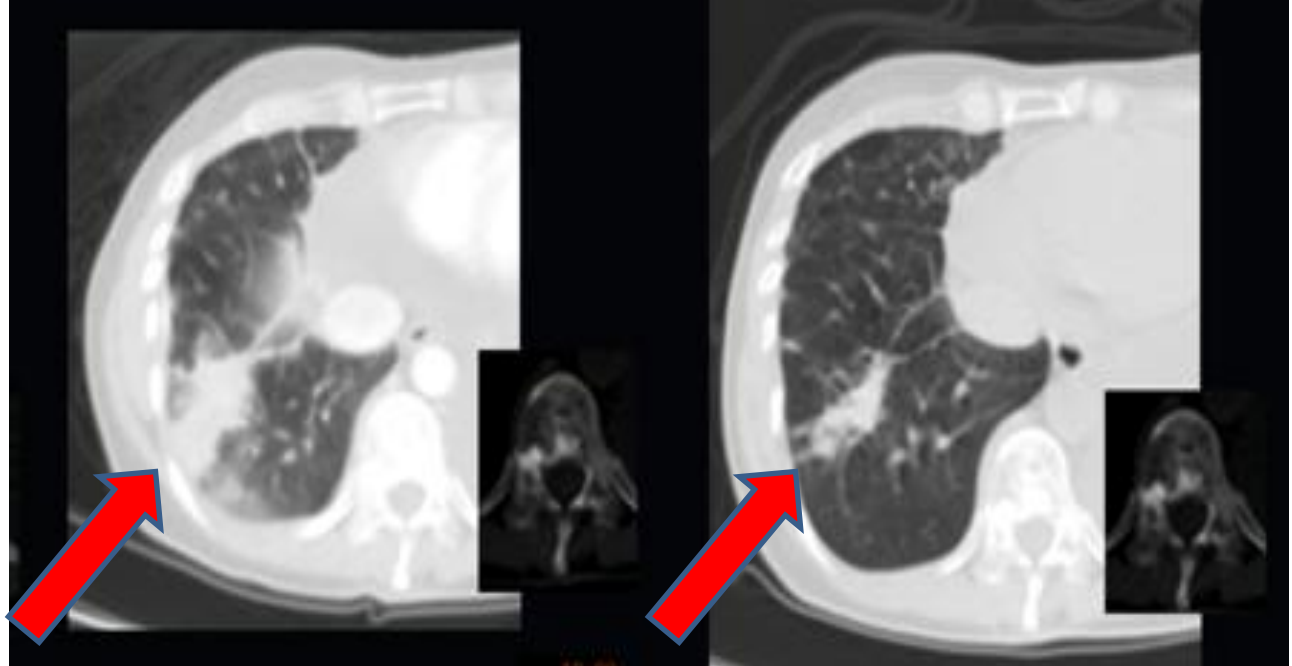
## Related grade 3/4 Adverse events

| N | Event  | Outcome  |
|---|--|--|
| 1 | Grade 3 Elevated Amylase   | Asymptomatic and reversible without any intervention   |
| 1 | Grade 3 Abdominal pain, grade 2 diarrhea, grade 2 vomiting         | Hospitalized and required dose-reduction in next cycle + pre-medication with anti-diarrheal medications with no further recurrence |
| 2 | Grade 3 Diarrhea   | Dose-reduction in one of the two patients + pre-medication with anti-diarrheal medications in both with resolution                 |
| 1 | Grade 3 asymptomatic decline in left ventricular ejection fraction | Patient was already off-study at this time, patient died of rapid disease progression  |

## Results: Efficacy

| Response  | Total (N=22)*     | ER+/HER2- (N=6)   | HER2+ (N = 13)* | TNBC (N=3) |
|---|-------------------|---|-----------------|------------|
| ORR   | 2 (9%)            | 0   | 2 (15%)         | 0          |
| CR  | 0                 | 0   | 0               | 0          |
| PR [duration, months]                             | 2 (9%) [5, 5#]    | 0   | 2               | 0          |
| SD [duration, months]                             | 7 (32%) [2 - 4.5] | 0   | 6 (46%)         | 1 (33%)§   |
| CBR (CR+PR+SD > 6mths)                            | 2 (9%)            | 0   | 2 (15%)         | 0          |
| Median PFS (weeks, range); N=19 **                | 7 (7-19)          | *2 patients were not evaluable due to elevated LFT's attributable to disease progression without follow-up imaging. # Patient actively continuing treatment on trial. § Patient had stable disease but was hospitalized due to a complicated pneumonia (unrelated to drug) and taken off study. |                 |            |
| Median OS amongst survivors (weeks); Deaths (N=6) | 28                |   |                 |            |

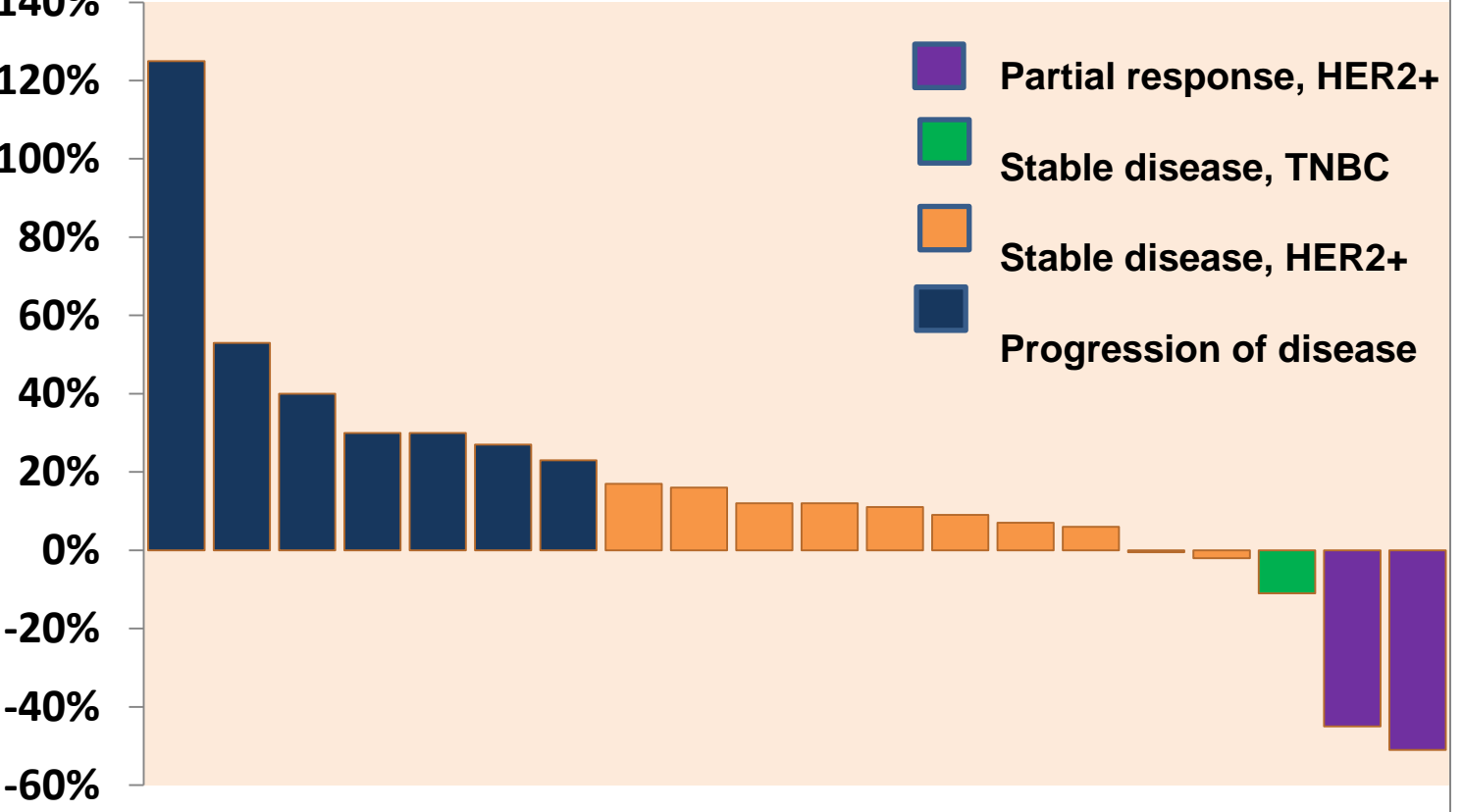
48 YO F with metastatic TNBC to the lungs and bone



Baseline FDG PET/CT Red arrow: Right lower lobe lung metastases

FDG PET/CT Day 19 after ganetespib therapy

## Best response N = 20\*



## Conclusion

- The study did not meet the pre-specified criteria for response rate in the first-stage in this heavily pre-treated group of patients.
- However, single agent ganetespib does show activity in trastuzumab-refractory HER2+ and triple negative breast cancer.
- Ganetespib is well tolerated at weekly schedule with expected gastrointestinal toxicity which was easily manageable with pre-medications.

## Future Directions

•Based on pre-clinical data that shows synergy for Hsp90 inhibitors with taxanes, a phase I/II trial of weekly ganetespib in combination with weekly paclitaxel with or without trastuzumab is planned in metastatic HER2+ and triple negative breast cancer respectively.