

# Phase 2 study of ganetespib (STA-9090) single agent in patients with metastatic and/or unresectable GIST

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## BACKGROUND

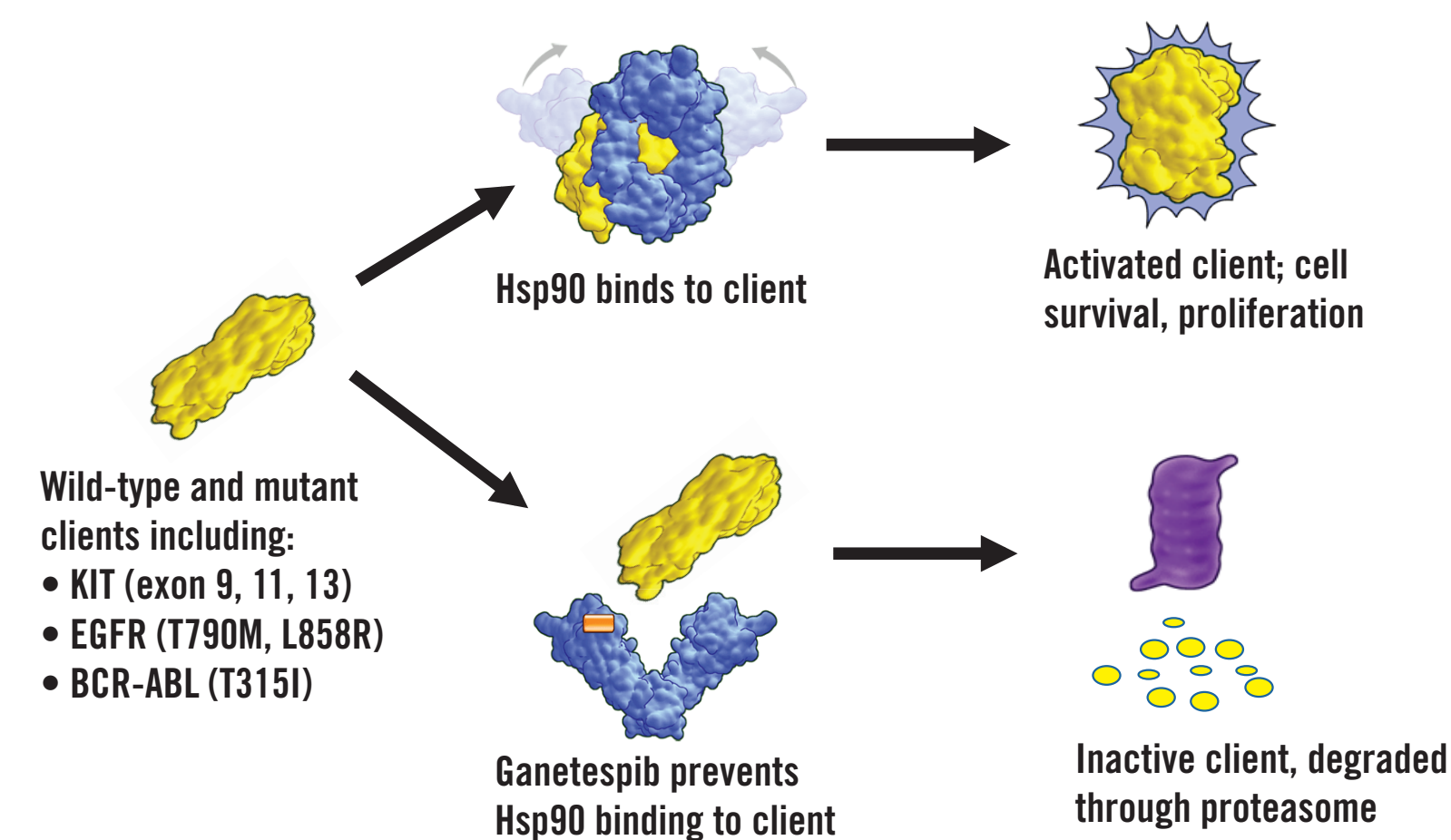
### Hsp90 Inhibition

- Hsp90 is a chaperone protein that controls the folding and processing of proteins that drive tumor development and progression
- Hsp90 clients include many proteins that play a critical role in tumor pathophysiology such as EGFR, HER2, c-MET, AKT, BCR-ABL, RAF, CDK4, KIT, FLT3, and VEGFR
- Degradation of client proteins allows for simultaneous targeting of multiple oncogenic signaling pathways
- Kinase client proteins are generally dependent on Hsp90 regardless of mutational status - wild type, TKI-sensitive, TKI-resistant - which creates potential for use in multiple settings

### Ganetespib (STA-9090) Background

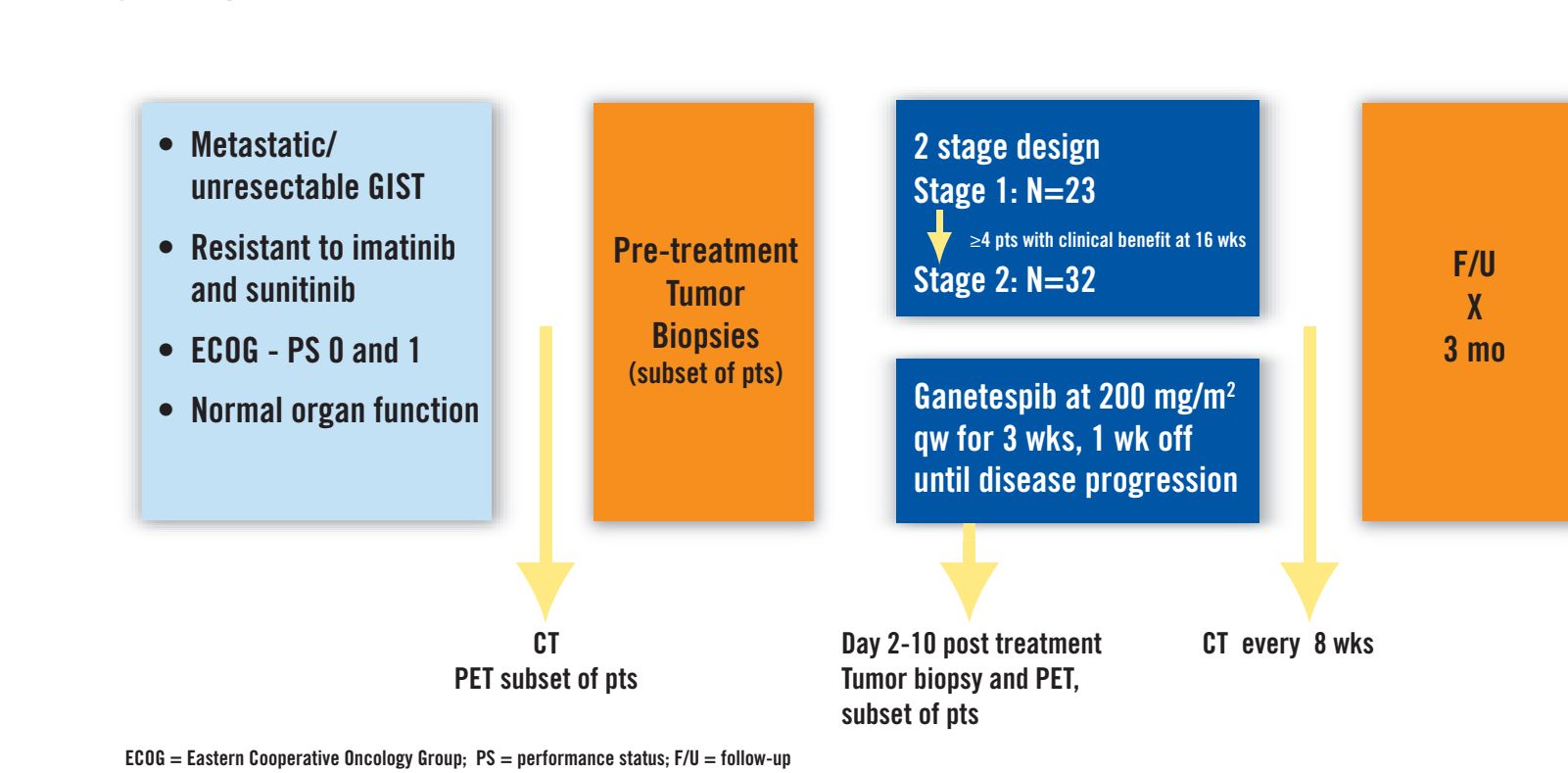
- Potent fully-synthetic Hsp90 inhibitor, structurally unrelated to first-generation natural-product-based ansamycin class of Hsp90 inhibitors
  - Superior activity to other Hsp90 inhibitors in preclinical studies
  - Potent activity against KIT and PDGFRA in preclinical models
- Promising signals of single-agent antitumor activity seen in early clinical trials in different types of cancers
- Good safety profile in >350 patients treated
  - Most common AE: diarrhea; generally Grade 1 and 2, manageable with supportive care
- Absence of serious liver or ocular toxicities seen with other Hsp90 inhibitors

### Ganetespib is Capable of Destabilizing Multiple Drug-Resistant Mutations



## METHODS

### Study Design



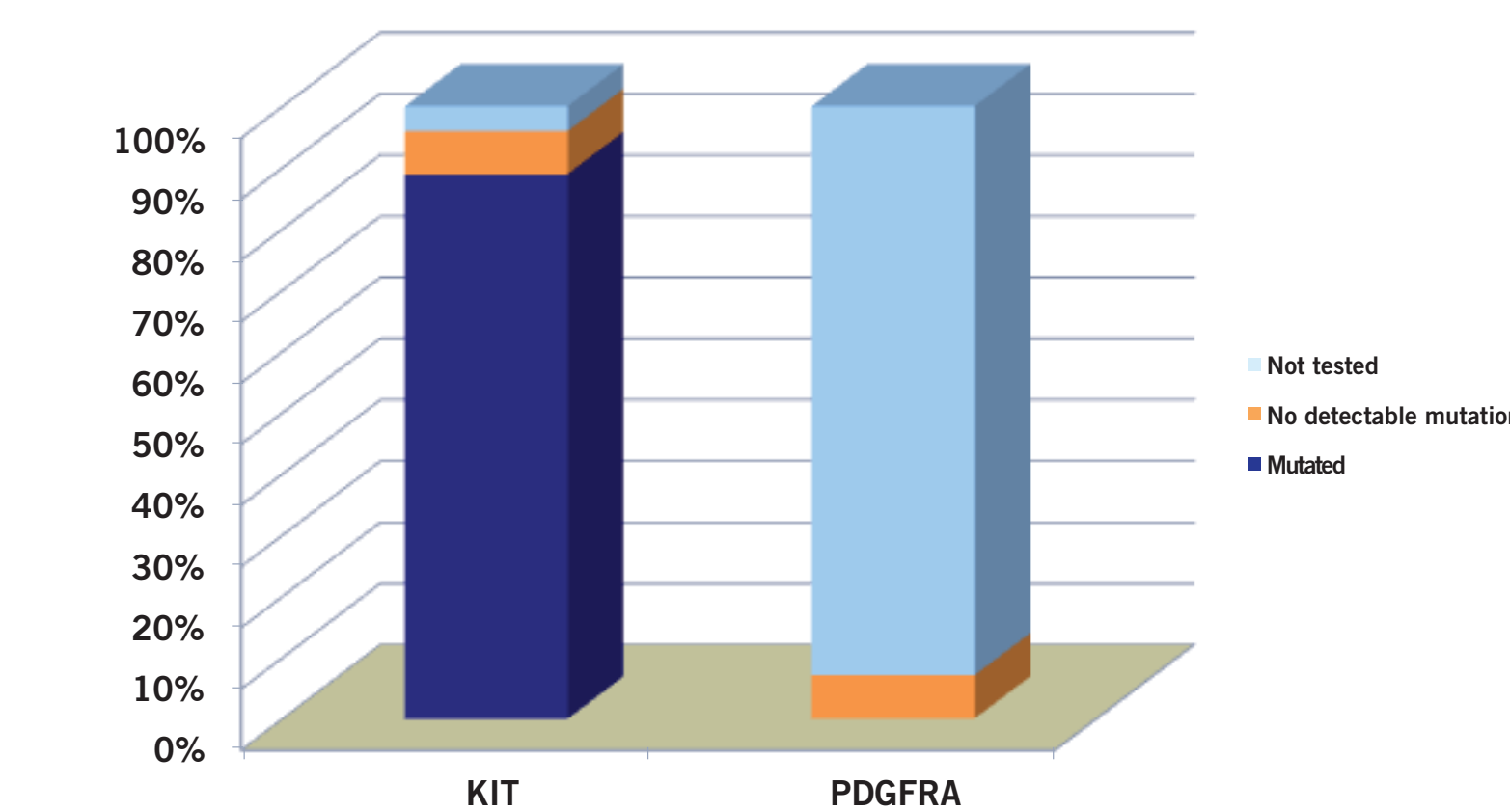
### Study Endpoints

- Primary endpoint:
  - Clinical benefit rate
    - Defined as CR/PR/SD (per RECIST) for at least 16 wks
- Secondary endpoints:
  - ORR
  - PFS
  - OS
  - Impact on tumor metabolic activity by functional imaging (<sup>18</sup>FDG-PET)
  - Safety and tolerability

### Demographics and Baseline Status

	Stage 1 (N=26)
Age (yrs) Median (Range)	53 (33, 67)
Sex (N, %)	
Male	15 (58)
Female	11 (42)
ECOG Status (N, %)	
0	14 (54)
1	12 (46)
# Prior Treatments	
Mean	6
Median	5
(Range)	(3, 11)

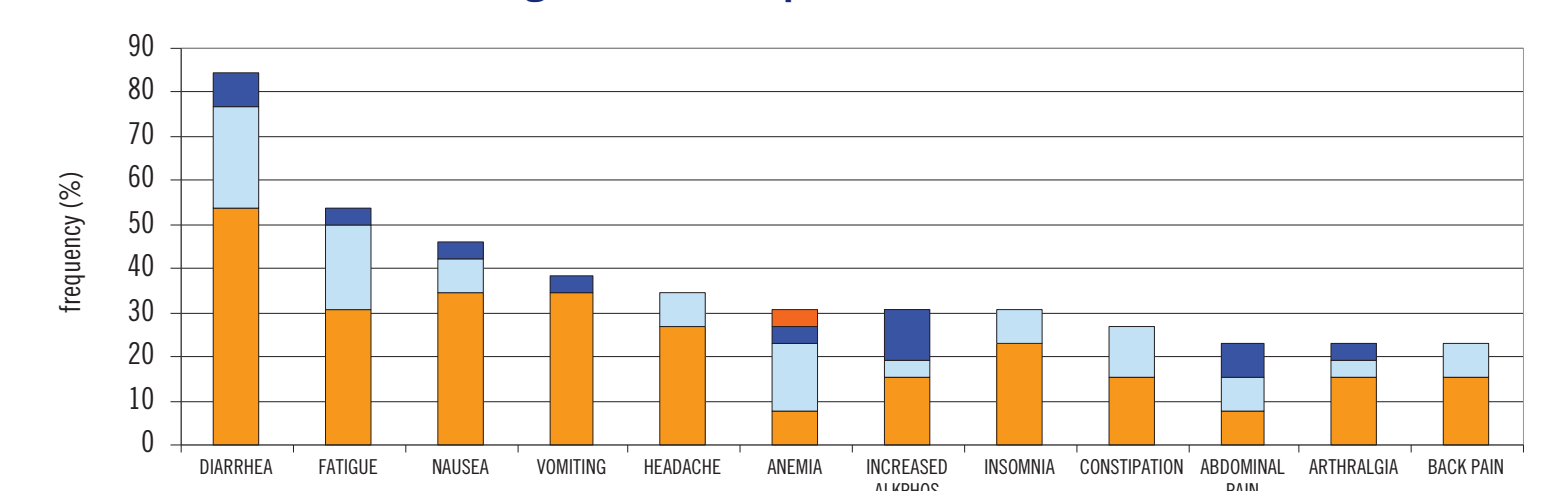
### Mutational Characterization Of All Patients



### Patient's Disposition: Reasons for Treatment Termination

	Stage 1 (N=23)
ITT/Safety population	26 (100)
Disease progression	18 (69)
Treatment failure	2 (8)
Adverse Event	3 (12)
Investigator Decision	2 (8)
Evaluable population	23 (100)
Disease progression	18 (78)
Treatment failure	2 (9)
Investigator Decision	2 (9)

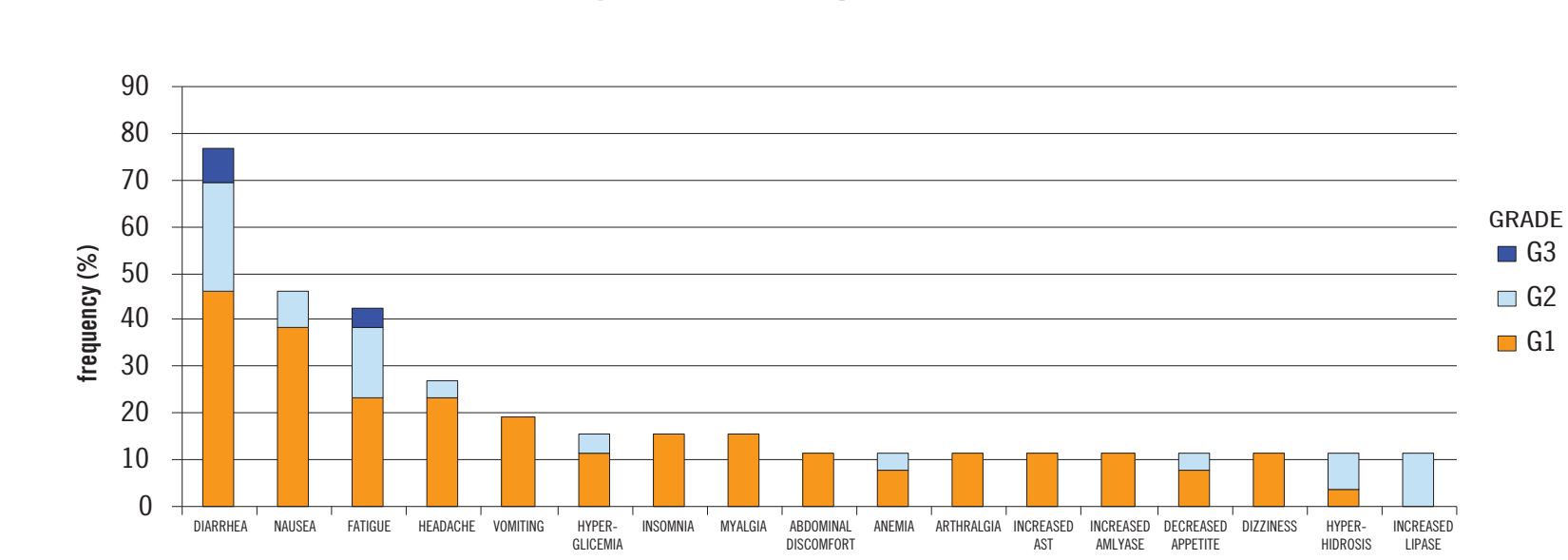
### Most Common AEs occurring in ≥ 20 % of patients



- Adverse Events regardless of relationship

## RESULTS

### Treatment Related AEs occurring in ≥ 10 % of patients

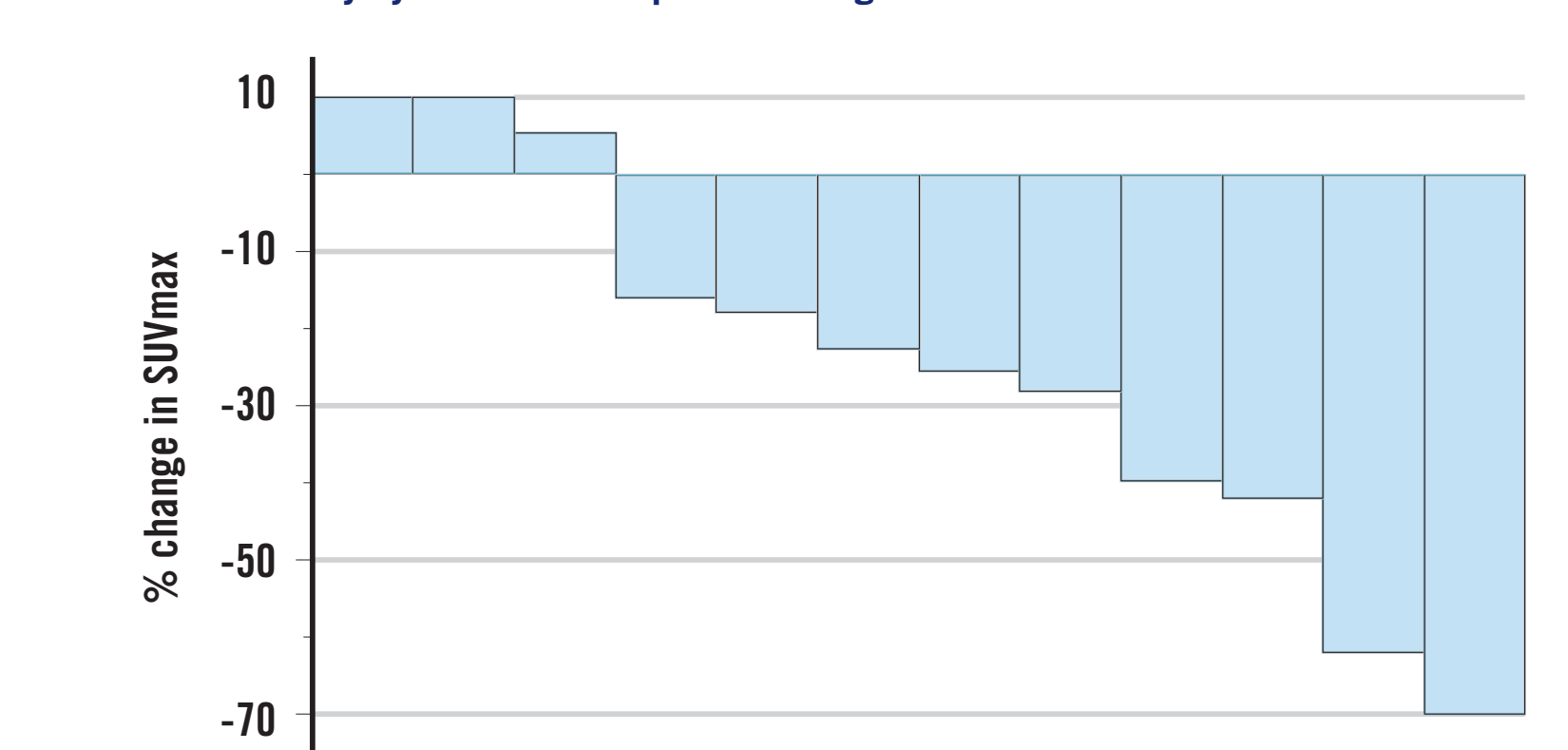


- Adverse Events judged at least possibly related to ganetespib

### Response in Evaluable Population (Investigator Review)

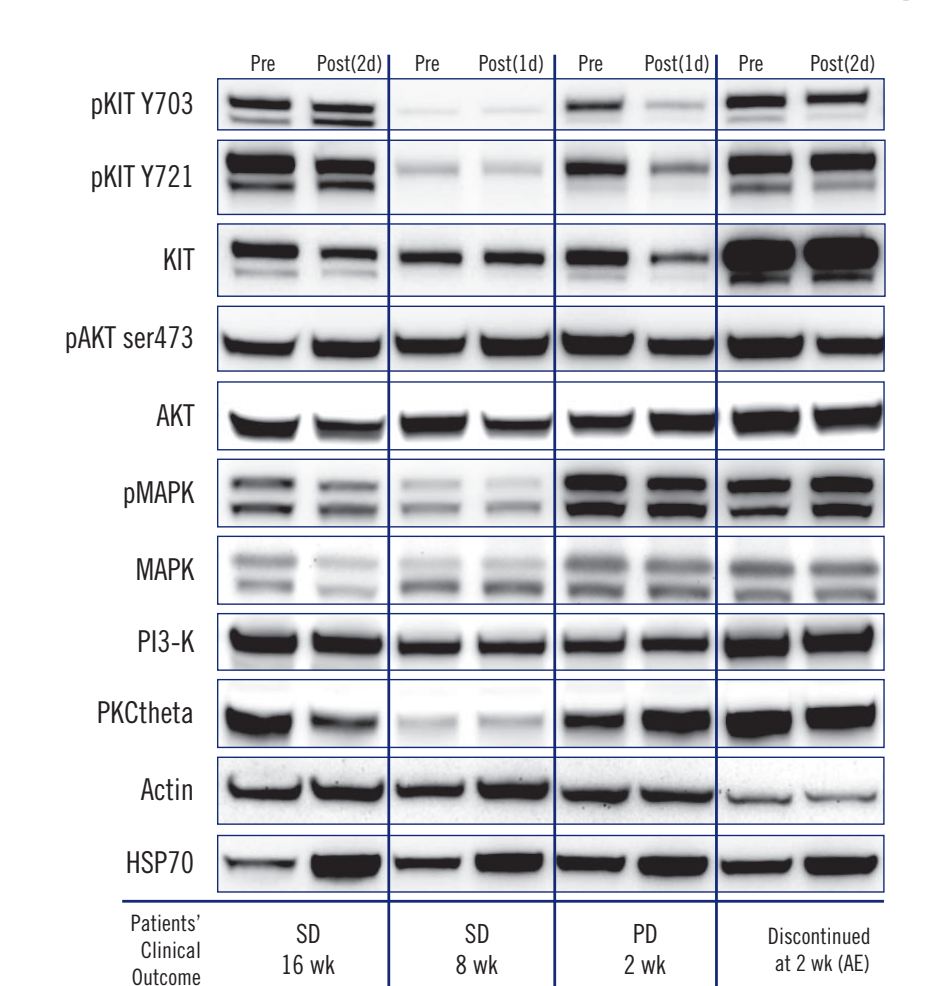
	Stage 1 (N=23)
Clinical benefit rate N (%) (CR+PR+SD ≥ 16 wks)	5 (22)
Objective response rate CR+PR	0
Non Evaluable (N, %)	1 (4)

### Antitumor Activity by Metabolic Response: Change from Baseline



- PET imaging performed 2-10 days post first treatment in a subset of patients
- 12 patients evaluated
- 7 (58%) reported >20% decrease in Standardized Uptake Value (SUV)

### Client Protein Evaluation in Patients Pre- and Post-Treatment Tumor Biopsies (Four Patients)



- Paired pre- and post-ganetespib (24 to 48h) tumor biopsies were analyzed
- Increased levels of Hsp70 indicates tumor exposure to ganetespib
- Levels of total KIT and phospho-KIT are downregulated, but only transiently
- Other signaling proteins downstream from KIT are also downregulated transiently

## CONCLUSIONS

- Ganetespib given once weekly is well-tolerated in heavily pretreated GIST patients
  - Most common AE: diarrhea; generally Grade 1 and 2, manageable with supportive care
- Decrease of tumor metabolic activity of >20% in half of the evaluated patients as measured by PET after first dose administration
- Single agent activity may be limited by duration and level of suppression of KIT client protein and other downstream pathways
  - Alternative schedule of drug administration to prolong suppression of KIT may be necessary to increase activity of this mechanistically rational agent with this mutant client protein

### Acknowledgements

- The authors would like to thank the study participants and their families, as well as all of the study investigators and study team members.

### Disclosures

- J. A. Morgan, S. George, W. D. Tap: nothing to disclose
- M. C. Heinrich, B. Chmielowski, J. A. Fletcher, M. von Mehren: research funding from Synta Pharmaceuticals, Corp.
- G. D. Demetri: Consultant or Advisory role GlaxoSmithKline, Novartis, Pfizer, Infinity Pharmaceuticals, Genentech/Roche and Kolltan Pharmaceuticals; stock ownership Kolltan Pharmaceuticals; research funding from Synta Pharmaceuticals, Corp.