Correlation of ctDNA and Response in Patients with PDGFRα D842 GIST Treated with Avapritinib

1623P

Suzanne George,[1,*] Sebastian Bauer,[2] Robin L. Jones,[3] Cesar Serrano,[4] Margaret von Mehren,[5] Yoon-Koo Kang,[6] Patrick Schöffski,[7] Philippe Cassier,[8] Ferry A. Eskens,[9] Olivier Mir,[10] William D. Tap,[11] Sant P. Chawla,[12] Piotr Rutkowski,[13] Hongliang Shi,[14] Oleg Schmidt-Kittler,[14] Brenton Mar,[14] Michael Heinrich[15]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]University Hospital Essen, Essen, Germany; [3]Royal Marsden Hospital NHS Foundation Trust, London, UK; [4]Vall d'Hebron Institute of Oncology, Barcelona, Spain; [5]Fox Chase Cancer Center, Philadelphia, PA, USA; [6]Asan Medical Center, Seoul, South Korea; [7]University Hospitals Leuven, Leuven, Belgium; [8]Centre Léon Bérard, Lyon, France; [9]Erasmus MC Cancer Institute, Rotterdam, The Netherlands; [10]Institut Gustave Roussy, Villejuif, France; [11]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [12]Sarcoma Oncology Research Center, Santa Monica, CA, USA; [13]Maria Sklodowska-Curie Institute – Oncology Center, Warszawa, Poland; [14]Blueprint Medicines Corporation, Boston, MA, USA; [15]Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA.

*Presenting author.

INTRODUCTION

- Avapritinib, a potent and selective inhibitor of activated KIT and PDGFRA, has shown broad clinical activity in patients with gastrointestinal stromal tumors (GIST) in the phase 1 NAVIGATOR study (ClinicalTrials.gov Identifier: NCT02508532). Previously presented data from the NAVIGATOR study showed:
  - 71% objective response rate (ORR) and 100% disease control rate (DCR) for avapritinib in patients with PDGFRα D842-mutant GIST[1*]
  - 17% ORR and 77% DCR for avapritinib in patients with heavily pre-treated 3rd-line or later GIST (median 5th line)[1*]
  - Avapritinib was generally well tolerated and most adverse events were Grade 1 or 2[1]
- Based on data from the NAVIGATOR study, avapritinib was granted Breakthrough Therapy Designation by the U.S. Food and Drug Administration for the treatment of unresectable or metastatic PDGFRα D842V-mutant GIST
- Profiling of circulating tumor DNA (ctDNA) via liquid biopsy is an exploratory noninvasive method of detecting and monitoring GIST with the potential to inform prognosis and treatment[2,3]
- In the NAVIGATOR study, we evaluated baseline ctDNA levels and changes in ctDNA during treatment with avapritinib, as well as their relationship to clinical outcomes, to assess the potential utility of ctDNA in GIST treatment
- Here we describe ctDNA analyses in patients with PDGFRα D842V-mutant GIST treated with avapritinib in the NAVIGATOR study. Nearly all patients in this genomically similar population had tumor reductions, thus simplifying the interpretation of ctDNA data

*Data are based on a cut off date of October 11, 2017.

Objective

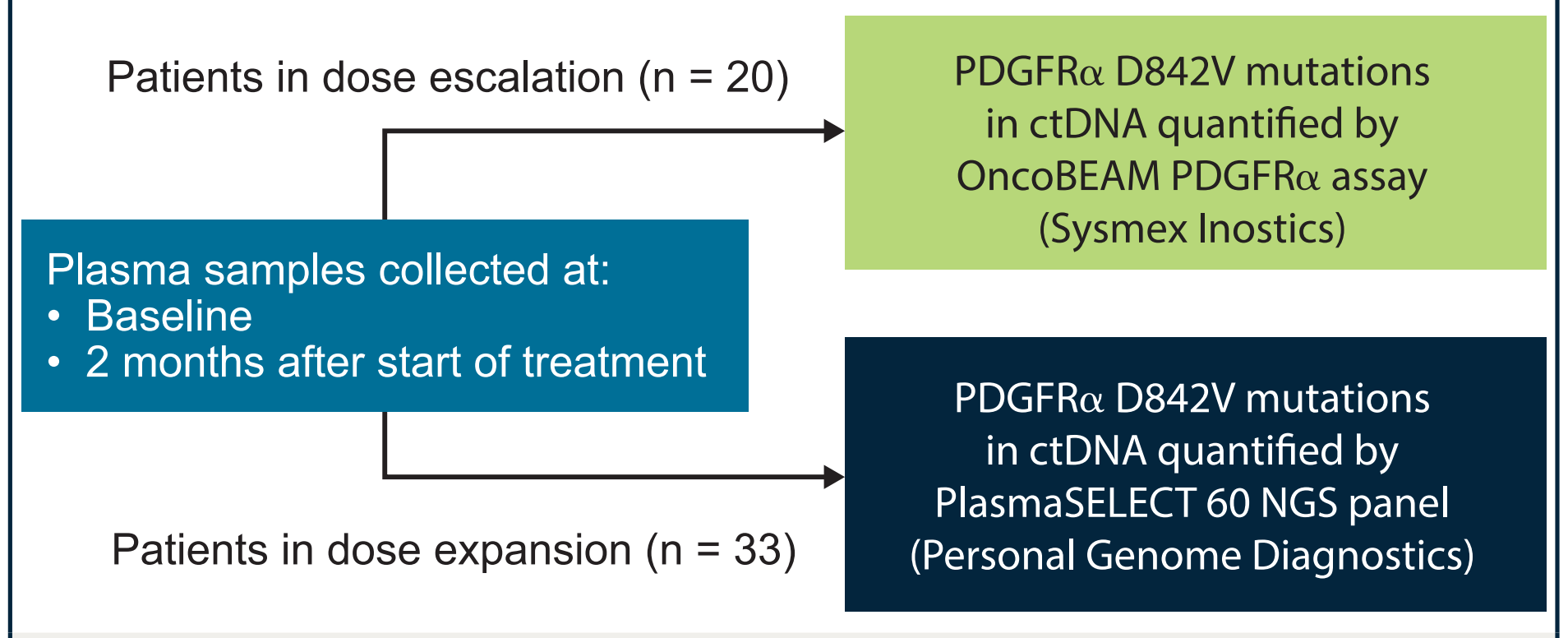
- The objective of this exploratory analysis from the NAVIGATOR study was to determine the utility of ctDNA levels at baseline and on therapy as an independent predictive biomarker in metastatic GIST in a genomically homogeneous population

METHODS

Study design

- NAVIGATOR is a phase 1, international, open-label, multicenter study evaluating the safety, tolerability, pharmacokinetics, pharmacodynamics, and anti-tumor activity of avapritinib in patients with unresectable or metastatic GIST
- In the dose-escalation and dose-expansion parts of the NAVIGATOR study, enrolled patients have been treated with avapritinib at doses of 30-600 mg orally (PO), once daily (QD). The recommended phase 2 dose (RP2D) was determined to be 300 mg PO QD
- NAVIGATOR is designed to enroll approximately 250 patients with advanced GIST, including approximately 50 patients with PDGFRα D842V-mutant GIST
- The data presented here are as of a data cutoff date of September 9, 2018

Figure 1. Analysis of ctDNA in GIST patients from the NAVIGATOR study.



Patients in dose escalation (n = 20)

Plasma samples collected at:
- Baseline
- 2 months after start of treatment

Patients in dose expansion (n = 33)

PDGFRα D842V mutations in ctDNA quantified by OncoBEAM PDGFRα assay (Sysmex Inostics)

PDGFRα D842V mutations in ctDNA quantified by PlasmaSELECT 60 NGS panel (Personal Genome Diagnostics)

Analysis of ctDNA

- This ctDNA–response correlation was limited to patients with PDGFRα D842V GIST treated with avapritinib at any dose (Figure 1)
- Progression free survival (PFS) was estimated by the Kaplan-Meier method
  - All scans were centrally read (BioTelemetry)
- Univariate and multivariate Cox regressions were calculated with coxph (Terry M. Therneau et. al., package 'survival', https://github.com/therneau/survival)
  - Variables achieving a significance of *P* <0.2 in univariate analysis were entered in the multivariate model
- Time-dependent receiver operating characteristics (ROC) were performed with a kernel-weighted Kaplan-Meier estimator cdROC (Sonia P. Fernandez et. al., package 'nsROC', https://CRAN.R-project.org/package=nsROC)

RESULTS

Patients and treatments

Table 1. Baseline patient demographics and characteristics.

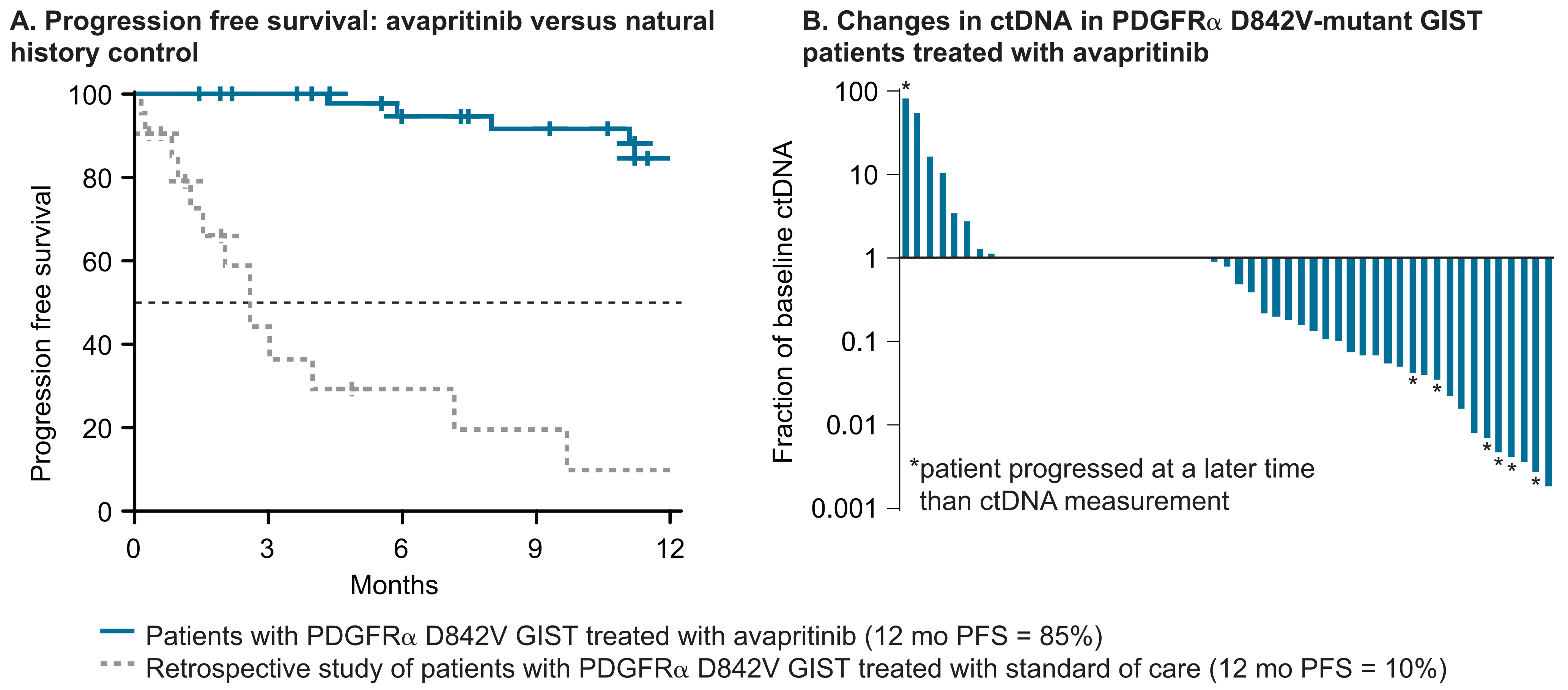
Characteristic	Patients (N = 53)
Median (range) age, years	63 (25-78)
Sex, n (%)	
Male	38 (71.7)
Female	15 (28.3)
Median (range) target lesion sum, mm	136 (15-459)
Prior therapies, n (%)	
0	11 (20.8)
1	19 (35.8)
2	9 (17.0)
>2	14 (26.4)
ECOG status, n (%)	
0	23 (43.4)
1	27 (50.9)
2	3 (5.7)
Dose, n (%)	
30-200 mg	17 (32.1)
300-400 mg	35 (66.0)
600 mg	1 (1.9)
Median (range) ctDNA MAF	
Baseline	0.32% (LOD-51)
On therapy	0.05% (LOD-7.7)
Fold change	0.45 (0.003-77)

LOD, limit-of-detection.
For the purpose of this analysis, we defined the LOD as being 0.05% (this may differ from assay vendor advertised sensitivity limit).

Avapritinib demonstrated robust clinical activity in PDGFRα D842V-mutant GIST

- Avapritinib demonstrated a 12-month PFS rate of 85% in patients with PDGFRα D842V-mutant GIST in comparision to a 12-month PFS rate of 10% for patients receiving standard of care in a retrospective chart review (Figure 2A)
- Unexpectedly, 6 of 7 patients that progressed did so despite having some of the deepest reductions in PDGFRα D842V allele burden in ctDNA in the cohort after 2 months of therapy (Figure 2B)

Figure 2. Progression free survival and changes in ctDNA on study.



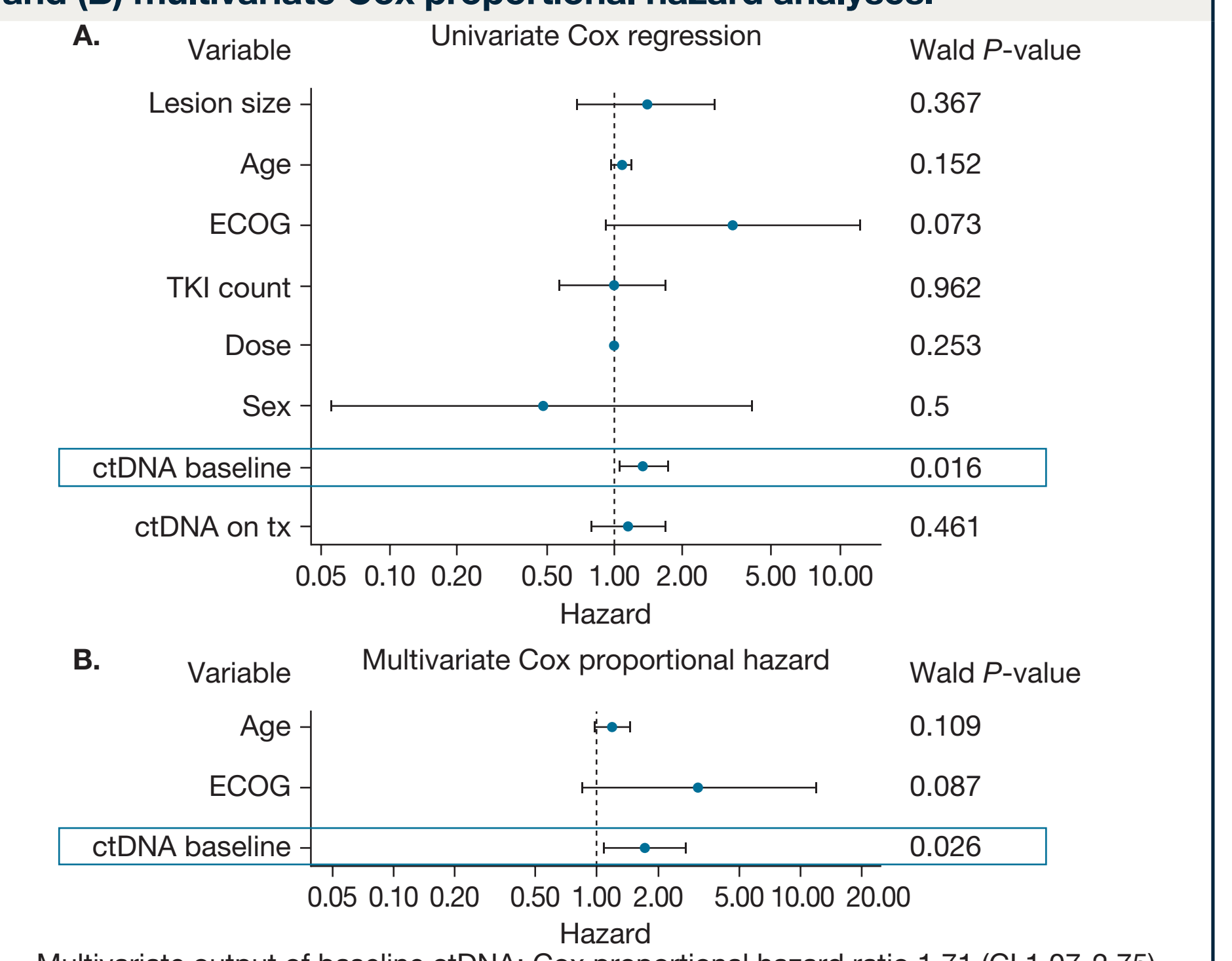
A. Progression free survival: avapritinib versus natural history control

B. Changes in ctDNA in PDGFRα D842V-mutant GIST patients treated with avapritinib

Baseline, not change in, ctDNA levels were predictive of progression free survival

- To explain this result, multiple potential variables were examined as potential confounders, including:
  - Sum of Response Evaluation Criteria in Solid Tumors (RECIST) target lesions (lesion size)
  - Age
  - Eastern Cooperative Oncology Group (ECOG) status
  - Number of prior tyrosine kinase inhibitor treatments (TKI count)
  - Avapritinib dose
  - Sex
  - Baseline ctDNA
  - Change in ctDNA on treatment
- Univariate analysis revealed that baseline, not change in, ctDNA level was the only statistically significant variable for predicting PFS (Figure 3A)
- Multivariate Cox proportional hazard ratios confirmed that ctDNA was the strongest independent baseline predictive indicator of PFS over established predictive indicators including ECOG performance status, lesion size, and age (Figure 3B)

Figure 3. Identification of baseline ctDNA as predictor of progression free survival by Cox regression analysis. (A) Univariate Cox regression and (B) multivariate Cox proportional hazard analyses.



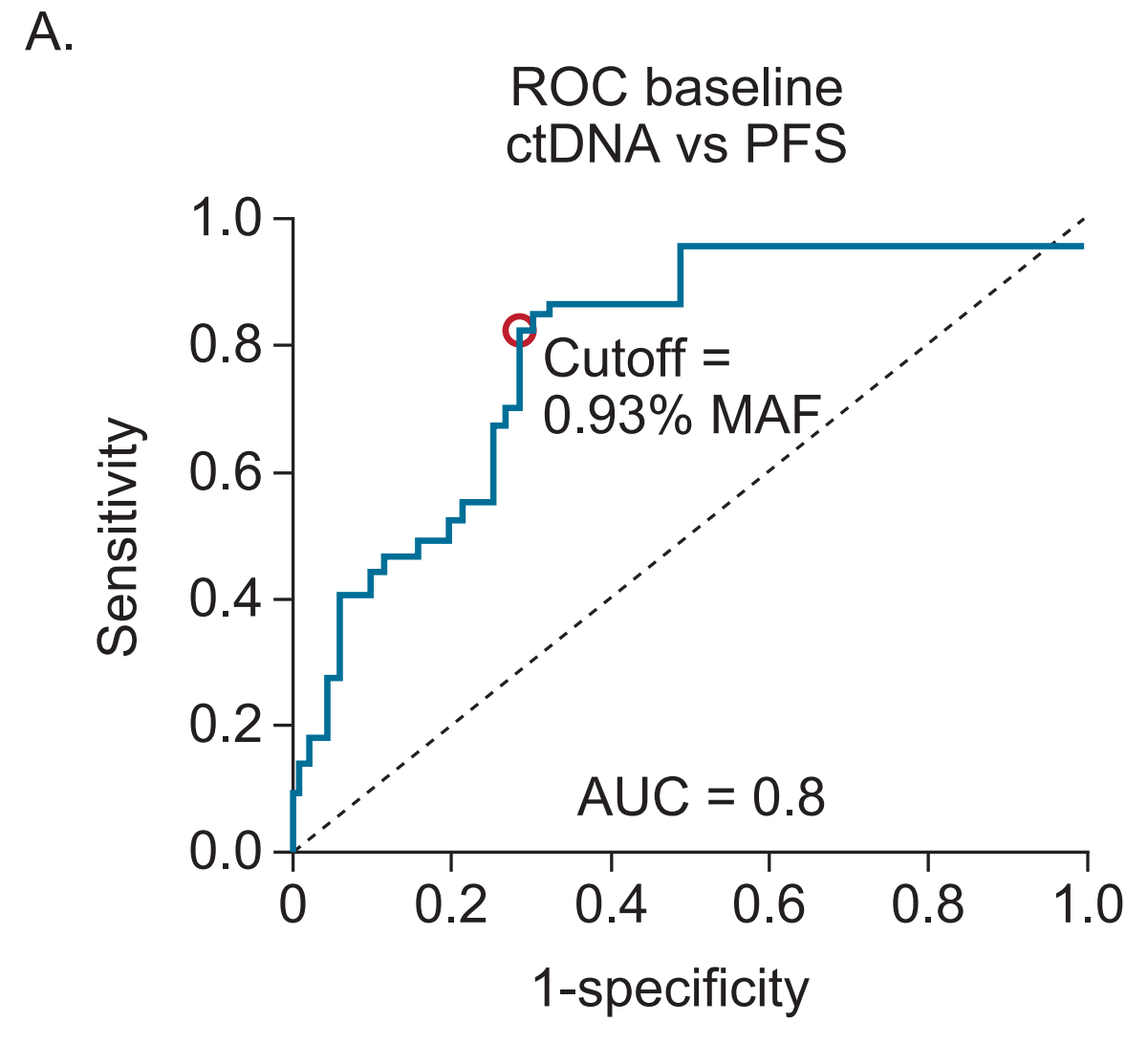
Multivariate output of baseline ctDNA: Cox proportional hazard ratio 1.71 (CI 1.07-2.75)
Wald chi-square test *P* = 0.258

tx, treatment; CI, confidence interval.

- As baseline ctDNA levels were the only significant variable that predicted PFS, a cutoff value was established through the use of a ROC analysis
- A cutoff level just below 1% mutant allele fraction (MAF; 0.93%) separated the population into groups with high and low predicted PFS, respectively
- Overall, all patients with PDGFRα D842V-mutant GIST treated with avapritinib experienced prolonged PFS regardless of baseline ctDNA levels (Figure 4)
  - In the group with low baseline ctDNA, only one patient had disease progression and the 12-month PFS rate was 95%
  - In the group with high baseline ctDNA, six patients had disease progression and the 12-month PFS rate was 65%

Figure 4. Association of low baseline ctDNA levels with superior PFS. (A) ROC for baseline ctDNA versus PFS; (B) PFS by ROC baseline ctDNA cutoff.

A.



B.

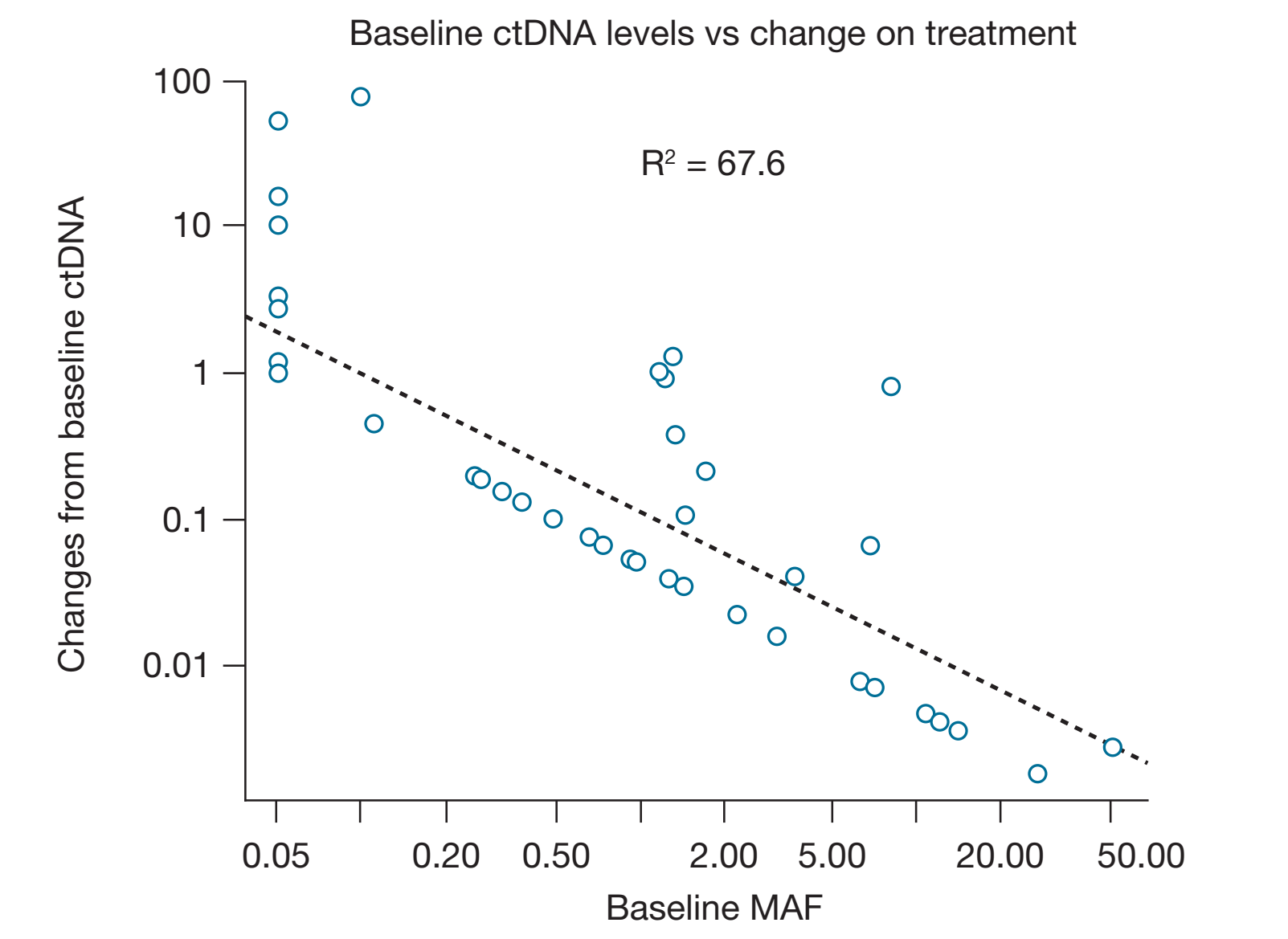
	12 month PFS rate
Avapritinib treated	
All patients (n = 53)	**85%**
Baseline ctDNA low (≤0.93% MAF; n = 32)	**95%**
Baseline ctDNA high (>0.93% MAF; n = 21)	**65%**
Standard of care (retrospective)	
All patients (n = 22)	**10%**

AUC, area under the curve.

Changes in ctDNA on treatment were strongly associated with baseline ctDNA

- In the majority of patients with PDGFRα D842V-mutant GIST treated with avapritinib, ctDNA levels fell below the limit of detection (0.05%) by two months on treatment
- The magnitude of ctDNA reduction by two months was limited by and strongly correlated to baseline ctDNA levels (Figure 5). Patients with low baseline ctDNA had a small dynamic range for reduction
- Large declines in on-treatment ctDNA levels were associated with high baseline ctDNA, an independent risk factor for progression
- All ctDNA increases by two months occurred in the low or undetectable baseline ctDNA cohort, which have a large dynamic range for increases and may be sensitive to assay variability. Only one patient with increasing ctDNA at two months progressed

Figure 5. Correlation of baseline and on-treatment ctDNA levels.



Conclusions

- Avapritinib demonstrated robust clinical activity in patients with PDGFRα D842V-mutant GIST, with a 12-month PFS rate of 85%
  - In the majority of patients, ctDNA levels fell below the limit of detection by two months
- In this genomically homogeneous population treated with avapritinib, analyses of ctDNA showed:
  - Lower baseline ctDNA levels were predictive of prolonged PFS
  - Large reductions in ctDNA on treatment were associated with high baseline ctDNA, but were not predictive of prolonged PFS
  - Compared to a retrospective study of patients treated with standard of care, patients with PDGFRα D842V-mutant GIST benefited from avapritinib treatment, regardless of baseline and change in on-treatment ctDNA levels
- Overall, these data indicate that baseline ctDNA levels may have utility as a predictive biomarker in patients with advanced GIST; however, changes in on-treatment ctDNA levels should be interpreted with caution and in the context of baseline ctDNA

References

1. Heinrich M, et al. Presented at: Connective Tissue Oncology Society Annual Meeting; November 8-11, 2017; Maui, HI, USA.
2. Bettegowda C, et al. *Sci Transl Med*. 2014;6(224):224ra224.
3. Calapre L, et al. *Cancer Lett*. 2017;404:62-69.

Acknowledgments

The authors acknowledge the patients participating in this study and their families, as well as the global network of investigators, research nurses, study coordinators, and operations staff. This study (ClinicalTrials.gov Identifier: NCT02508532) is sponsored by Blueprint Medicines Corporation. Editorial and medical writing support were provided by Christopher Jones, PhD, of Cello Health Communications, and were funded by Blueprint Medicines Corporation.

QR Code Disclaimer

Presenting author email: Suzanne_George@dfci.harvard.edu

Presented at the Annual Congress of the European Society for Medical Oncology (ESMO); October 19-23, 2018; Munich, Germany.