

Atebimetinib Reduces Tumor Volume and Preserves Body Mass: A Dual Mechanism for Extended Survival in Pancreatic Cancer

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Introduction

Median overall survival (mOS) of 17.3 months was recently reported in 55 first-line pancreatic cancer patients treated with atebimetinib + modified gemcitabine/nab-paclitaxel (mGnP), with 84% of evaluable patients having stable or increased weight at 3 months [1]. This is notable because pancreatic cancer patients typically lose weight due to cancer-associated wasting of muscle and other tissue (cachexia). Atebimetinib, a deep cyclic inhibitor of MEK, was designed for both anti-tumor activity and body mass preservation. Preclinically, atebimetinib counteracts gene expression changes associated with cachexia and sustains body weight, including at a dose producing no tumor growth inhibition [2]. Given the established contribution of cachexia to cancer mortality, we investigated the relationship between body mass preservation and OS in atebimetinib-treated patients.

Methods

Weight changes in atebimetinib-treated patients were compared with a benchmark study of patients treated with standard of care (SoC) [3]. As in [3], Bayesian logic was used to assign patients to one of four weight trajectory categories. Weight at diagnosis was extrapolated from the measured weight at the first day of treatment using a linear estimate derived from the rate of weight loss reported by [4]. Only weight measurements within the year prior to start of treatment and after 26 weeks were included to match the scope of data used in [3] and [4]. Patients with short weight trajectories given this time limitation were excluded from analysis.

OS in evaluable patients with stable or increased weight at 3 months was compared to OS in those with weight loss (April 24, 2026 data cutoff). Changes in patient reported outcomes on the FAACT-Anorexia Cachexia Subscale (ACS) and the role of tumor volume reduction were assessed.

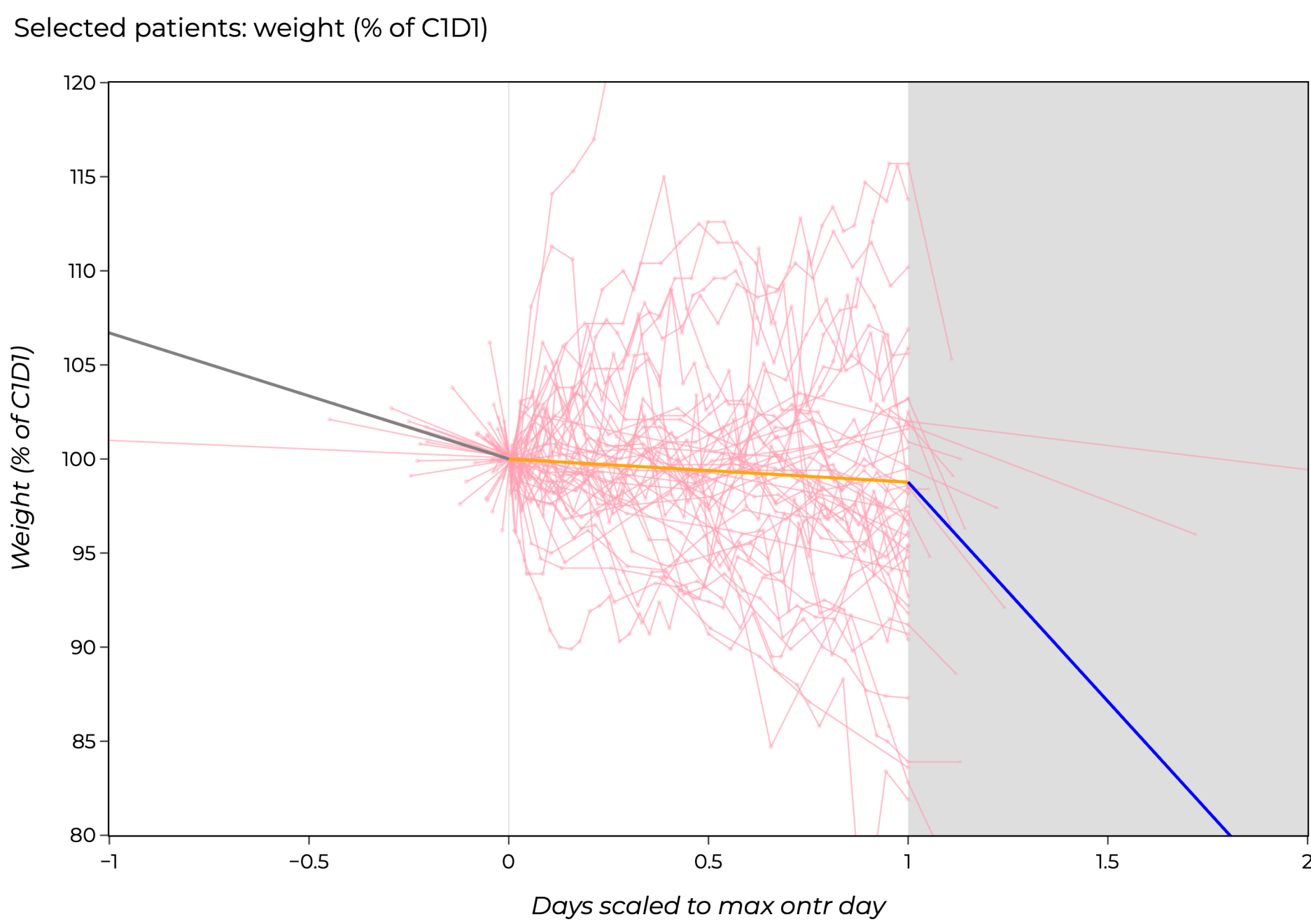
Weight stabilization during treatment

Disease	Phase	Atebimetinib Setting	Line	Evaluable Patients Weight Stable @ 3 months
PDAC (all comor)	2a	Atebi+mGnP	1L	84%
PDAC (all comor)	2a	Atebi+mFFX	1L	79%
PDAC (RAS mut)	2a	Atebimetinib	2L	83%
NSCLC (RAS mut)	2a	Atebimetinib	2L/3L	89%
MEL (RAS mut)	2a	Atebimetinib	2L/3L	92%

In each Phase 2a cohort, a majority of patients experienced weight stability or gain at 3mo on atebimetinib treatment.

N weight evaluable (C1D1 and 3mo): 37, 19, 12, 9, 12
Weight stability defined as within 5%.
Data cutoff Apr 24, 2026.

Scaled weight change (C1D1=0, EOT=1), atebi + mGnP:



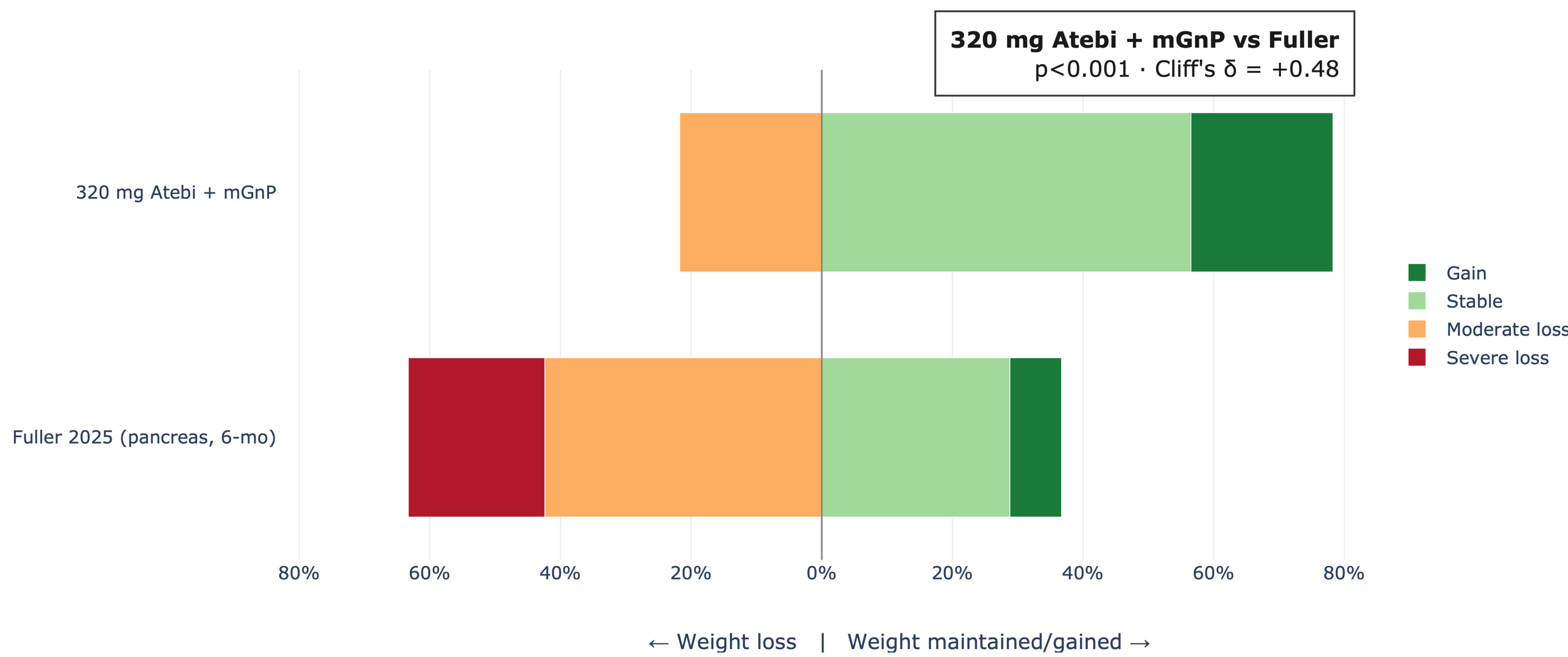
The median weight change was stabilized during treatment.

Pink: weight over time for individual patients
Black: median slope, screen to C1D1
Orange: median slope on treatment
Blue: median slope, EOT to SFU for available data

C1D1: Cycle 1 Day 1
EOT: End of Treatment
SFU: Safety Follow-Up

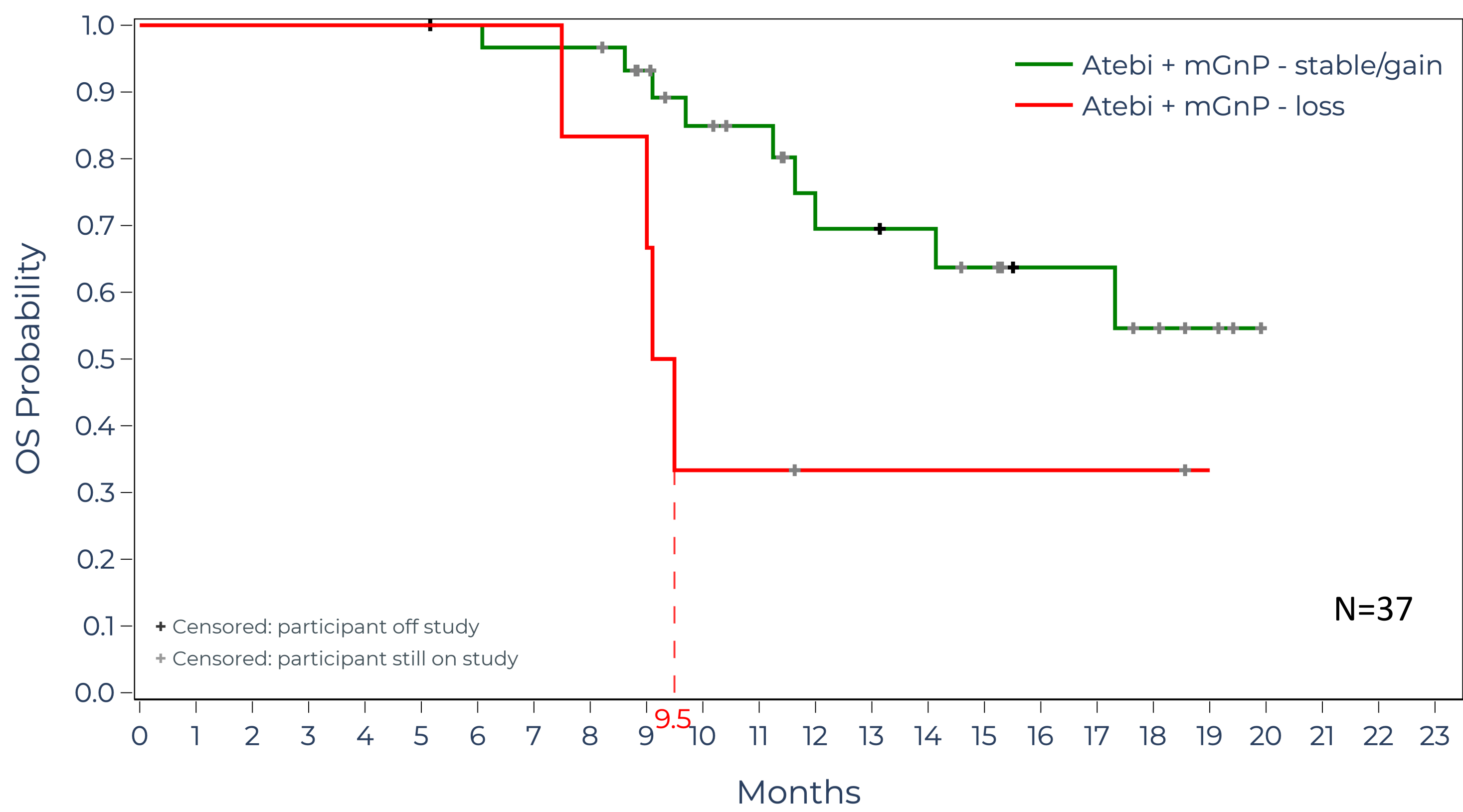
Weight trajectory distribution compared to reference population

The percentage of patients with stable or increasing weight was significantly higher for patients treated with atebimetinib + mGnP (n=23 evaluable for trajectory analysis) than for patients from the benchmark study [3] (Mann-Whitney U $p < 0.001$, Cliff's $\delta = +0.48$). The fraction of patients falling into the stable or gain categories was approximately two-fold higher in the atebimetinib + mGnP weight trajectory evaluable cohort (78%; 18/23) than in the reference dataset (37%; 824/2243).



Overall survival by weight stability

Longer OS in weight stable group



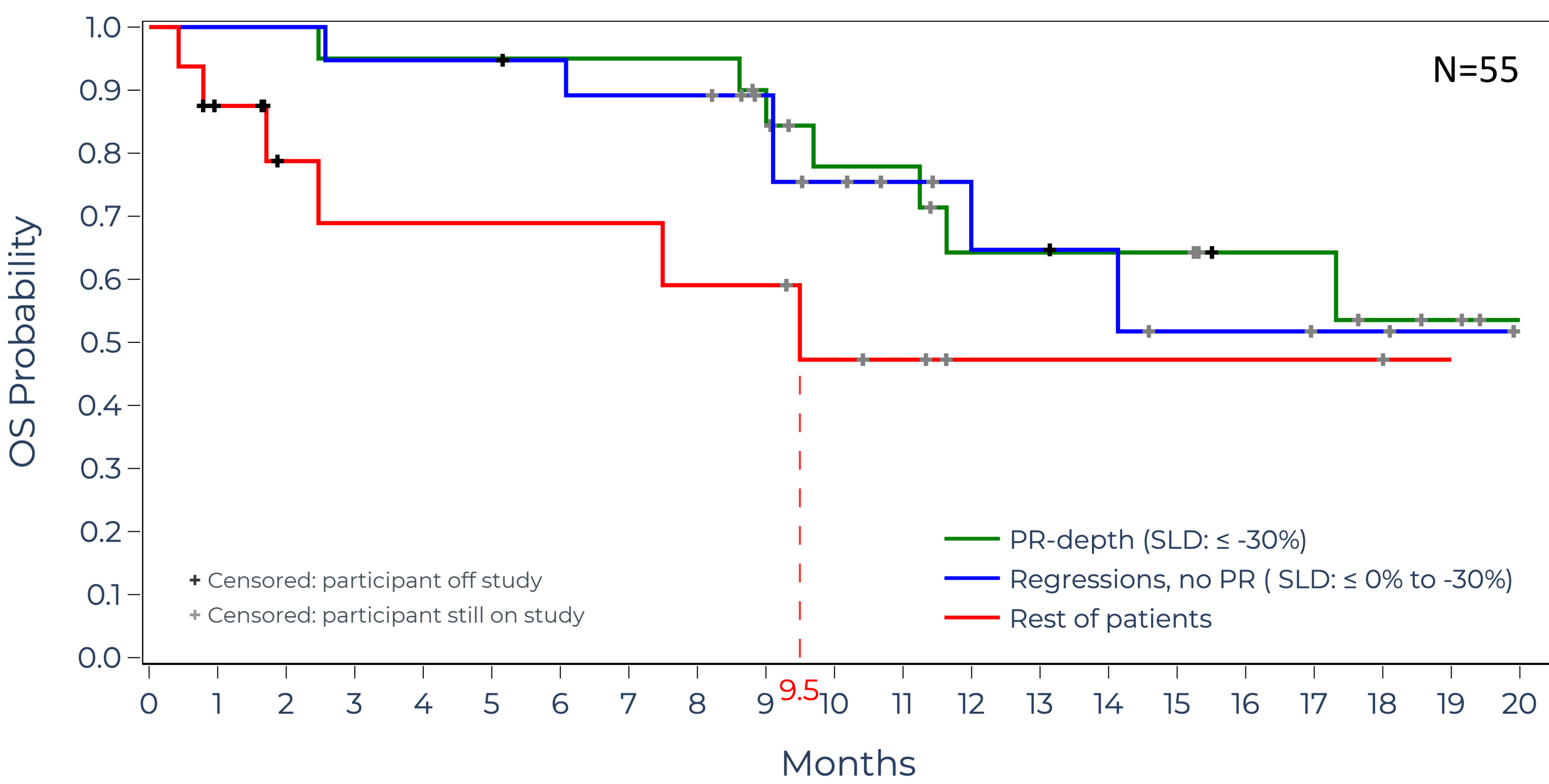
Atebi + mGnP - stable/gain
At risk 31 31 31 31 31 30 29 29 24 20 18 13 13 12 10 7 7 5 3 0 0 0 0

Atebi + mGnP - loss
At risk 6 6 6 6 6 6 6 6 5 5 2 2 1 1 1 1 1 1 1 0 0 0 0

As previously reported, 84% of patients having Cycle 1 Day 1 (C1D1) and 3 month weights showed weight stability (within 5%) or gain in the group treated with atebimetinib + mGnP; this is also consistent with observations on a smaller monotherapy dataset in the 2L pancreatic cancer setting. Examining the groups established by weight stable/gain versus weight loss at 3 months, in first-line pancreatic cancer patients treated with atebimetinib+mGnP, the 84% of evaluable patients with stable or increased weight at 3 months had significantly longer OS (mOS not reached; median follow up 15.2 mo) than those with weight loss (HR=3.13; log-rank $p = 0.049$).

Overall survival by tumor volume reduction

OS in patients with deeper tumor volume reductions (SLD $\leq$ -30%) was comparable to OS in patients with moderate tumor volume reductions (SLD 0% to -30%) and did not reach a median OS, while OS in patients without measured reduction in overall SLD did reach a median value. This suggests that the presence of tumor volume reductions was more important than their depth.



PR-depth (SLD: $\leq$ -30%)

At risk 20 20 20 19 19 19 19 19 19 16 12 12 9 9 9 9 6 6 4 2 0

Regressions, no PR (SLD: $\leq$ 0% to -30%)

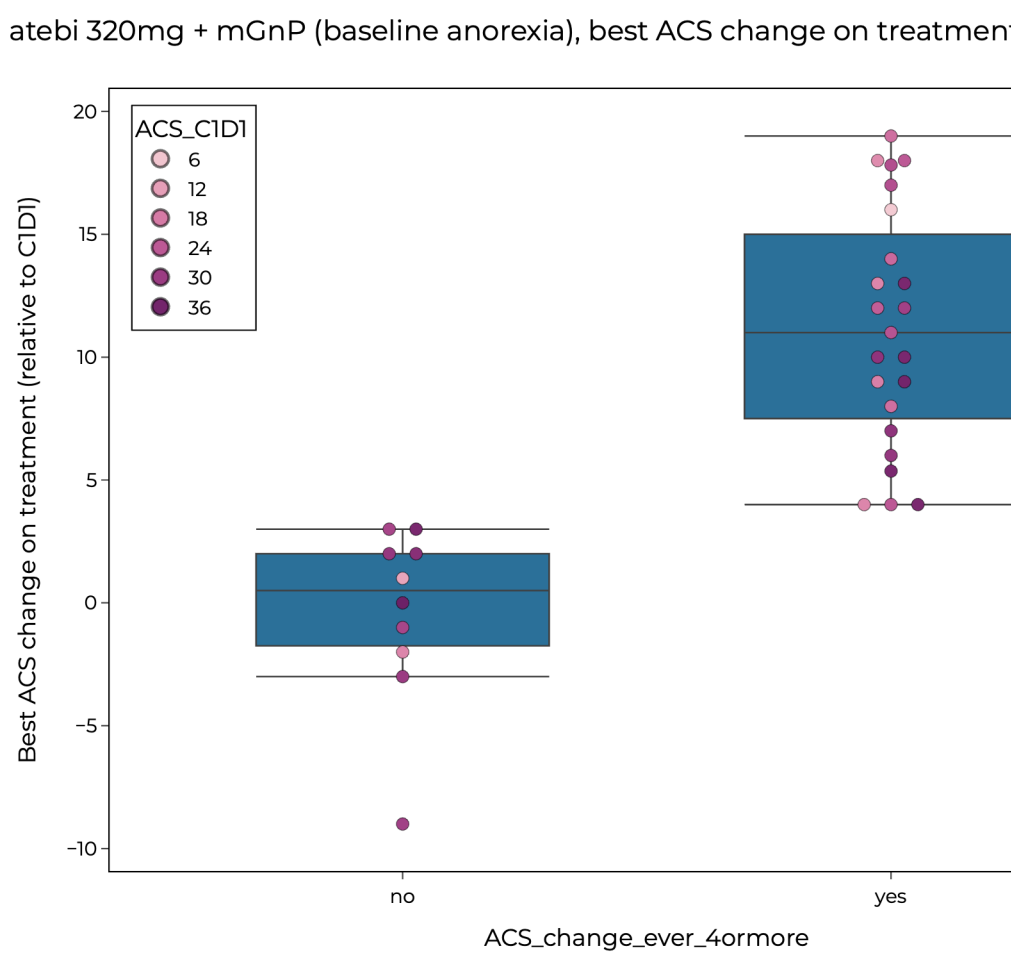
At risk 19 19 19 18 18 18 17 16 16 13 10 8 6 6 5 3 3 2 2 1 0

Rest of patients

At risk 16 12 8 7 7 7 7 7 6 6 4 3 1 1 1 1 1 1 1 0 0

Patient-reported outcome improvement in patients with baseline anorexia

Two-thirds (66%) of atebimetinib + mGnP-treated patients with low baseline A/CS scores (≤ 37) achieved at least a 4 point increase in A/CS score on treatment, across a range of RECIST responses (e.g., PR, SD, PD are all represented among patients receiving A/CS benefit).



ACS = Anorexia/ Cachexia Subscale of FAACT (Functional Assessment of Anorexia and Cachexia Therapy)

Conclusions

These findings support a dual mechanism by which atebimetinib may increase overall survival. Tumor volume reduction and preservation of body mass both predict longer OS in pancreatic cancer patients treated with atebimetinib+mGnP. Notably, longer OS was observed for patients experiencing any tumor volume reduction, not just reductions within the range of RECIST PR. Atebimetinib+mGnP is being evaluated in a Phase 3 study in first-line pancreatic cancer patients (NCT07562152).

References and Acknowledgements

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- King PJ, et al, Abstract 10-04, SCWD, 2024
- Fuller S, et al, JNCI, 117:8, 2025, 1729–1732
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