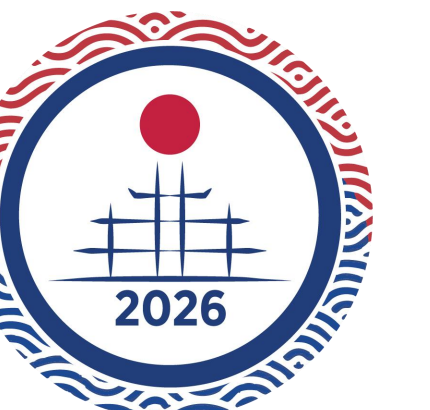




C-MET overexpression as an efficacy predictive biomarker in MET amplification-driven NSCLC: explore analyses of KUNPENG study



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INTRODUCTION

MET amplification is an actionable driver alteration in non-small-cell lung cancer (NSCLC), notably associated with poor prognosis¹⁻³. Prior studies showed median PFS of 2.5-4.9 months with standard chemo /immunotherapy in MET-amplified NSCLC patients⁴⁻⁵.

KUNPENG study with vebreltinib, a highly selective MET inhibitor, brought promising benefit in NSCLC with MET amplification, with a mPFS of 7.2 months⁶. Here, we presented exploratory analyses of KUNPENG to see if c-MET IHC overexpression may help to further enrich more beneficial patients.

METHODS

Design:

FISH positivity is defined by the GCN ≥ 6 cutoff from the KUNPENG study. c-MET protein expression was stained by IHC in 136 patients from KUNPENG with sufficient tissue sections.

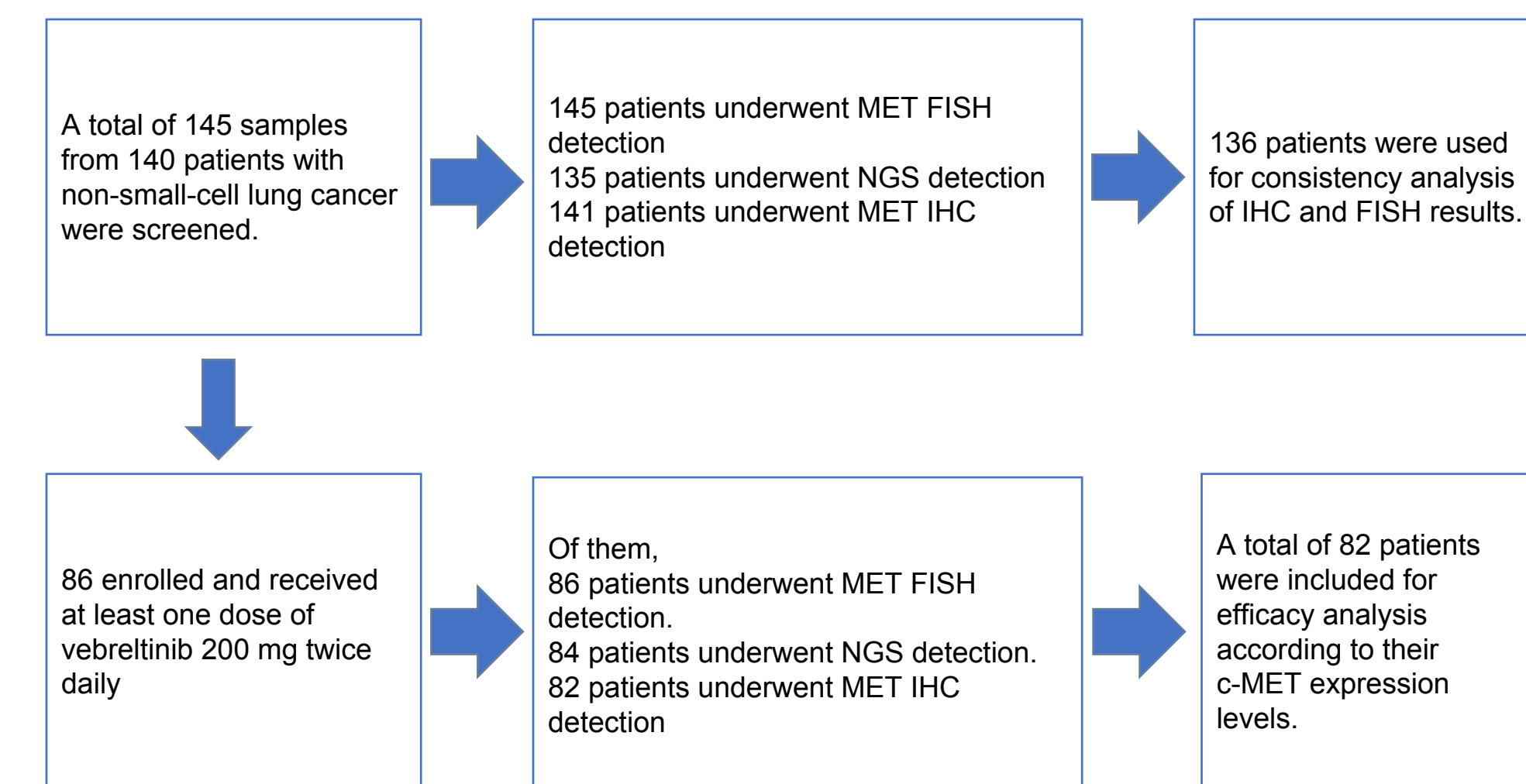


Figure 1: Flow diagram of patient selection and enrollment with MET biomarker results from FISH (GCN ≥ 6), c-MET IHC, and NGS.

Among them, 82 patients were treated with vebreltinib. Staining intensity (1+, 2+ and 3+) and H-score were evaluated by pathologists. Furthermore, the drug efficacy were independently assessed in patients in the different subtype.

RESULTS

Here, we present exploratory analyses of the KUNPENG study. We found that 78.3% of MET-amplification-positive patients exhibited c-MET IHC 3+/2+ expression, as compared with 36.0% MET-amplification-negative patients. Among the 27 patients with IHC 3+ staining, 26 patients were MET-amplification-positive. A similar trend was observed in patients with an IHC H-score ≥ 240 .

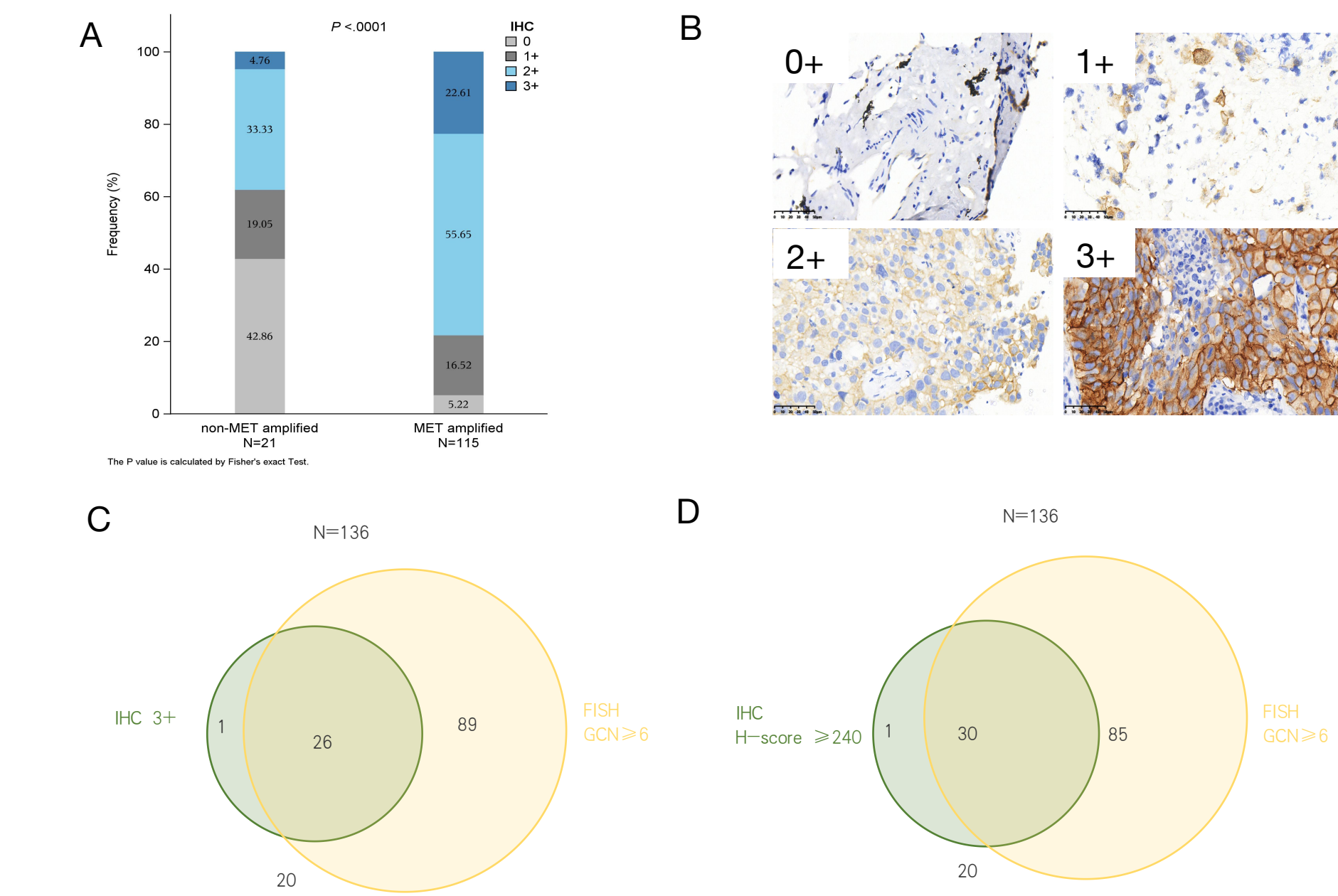


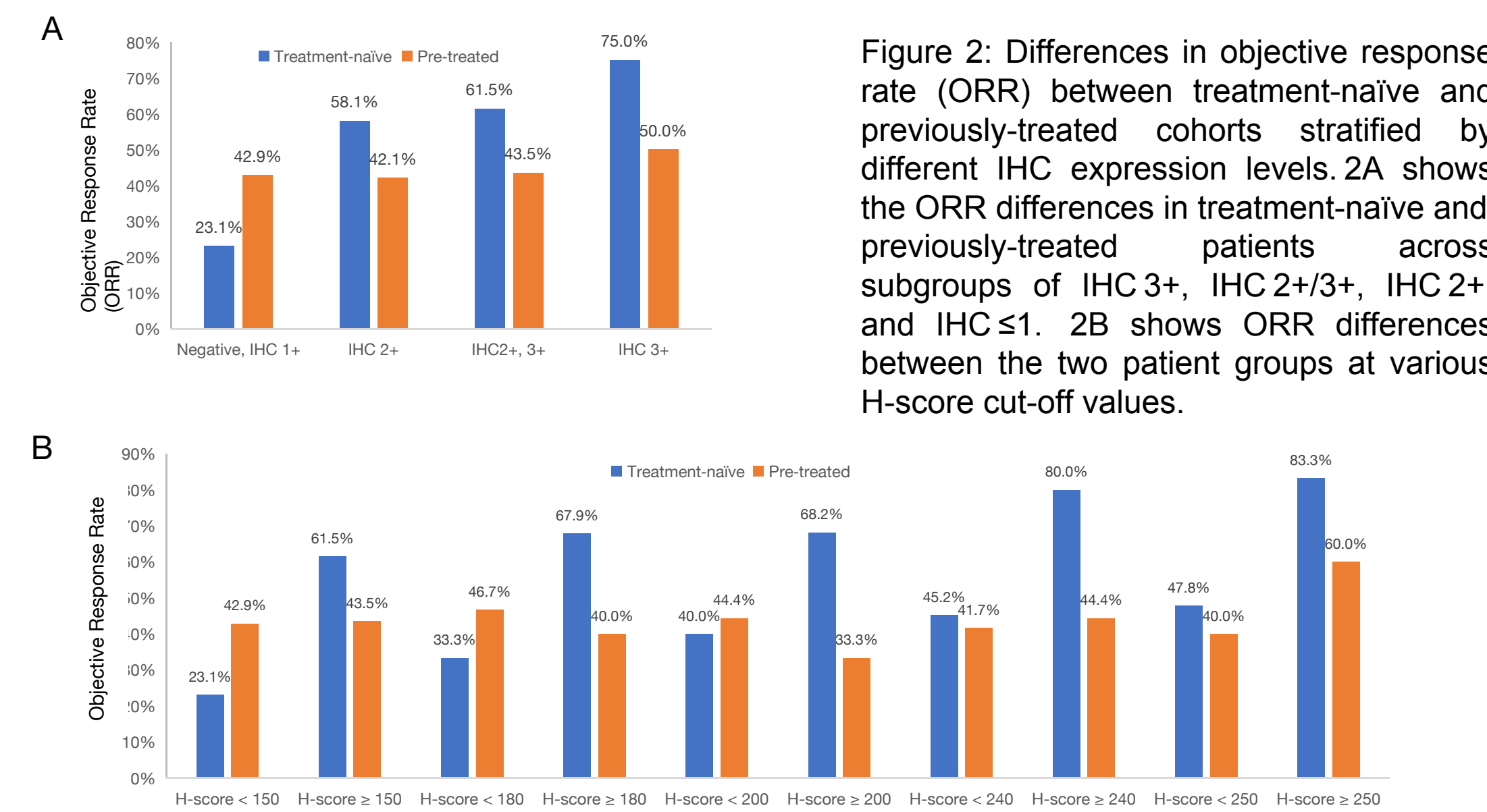
Figure 1: Agreement analysis between immunohistochemistry (IHC) and fluorescence in-situ hybridization (FISH) results in 136 patients. 1A shows the proportions of patients with different c-MET expression levels (3+, 2+, $\leq 1+$) stratified by FISH status (GCN ≥ 6 and GCN < 6). 1B displays representative immunohistochemical staining images for c-MET IHC scores of 3+, 2+, 1+, and 0. 1C presents a Venn diagram illustrating the overlap between c-MET IHC 3+ and MET FISH GCN ≥ 6 . 1D shows a Venn diagram of the overlap between c-MET IHC H-score ≥ 240 and MET FISH GCN ≥ 6 .

	IHC $\leq 1+$ (N=20)	IHC 2+ (N=50)	IHC 3+ (N=12)	H-score <240 (N=67)	H-score ≥ 240 (N=15)	FISH MET polysomy (N=10)
ORR, n (%)	6 (30.0)	26 (52.0)	8 (66.7)	29(43.3)	11(73.3)	6 (60.0)
95% CI	(9.9, 50.1)	(38.2, 65.8)	(40.0, 93.3)	(31.4,55.1)	(51.0,95.7)	(29.6, 90.4)
DCR, n (%)	13 (65.0)	39 (78.0)	12 (100)	49(73.1)	15 (100)	9 (90.0)
95% CI	(44.1, 85.9)	(66.5, 89.5)	(100.0, 100.0)	(62.5,83.7)	(100.0,100.0)	(71.4,100.0)
Median DoR, months	NE	11.1	12.6	11.1	11.0	6.5
95% CI	(3.7, NE)	(3.8,14.5)	(3.7, NE)	(3.8,16.8)	(3.7, NE)	(3.7, NE)
Median PFS, months	9.2	6.2	13.6	7.4	12.0	9.2
95% CI	(2.6, NE)	(4.5,12.0)	(3.7, NE)	(4.6,12.9)	(4.6, NE)	(4.7, NE)
Median OS, months	14.5	12.9	13.9	11.7	17.1	18.0
95% CI	(4.4, NE)	(8.9,16.0)	(5.9,34.8)	(8.4,16.0)	(11.0, NE)	(4.0, NE)

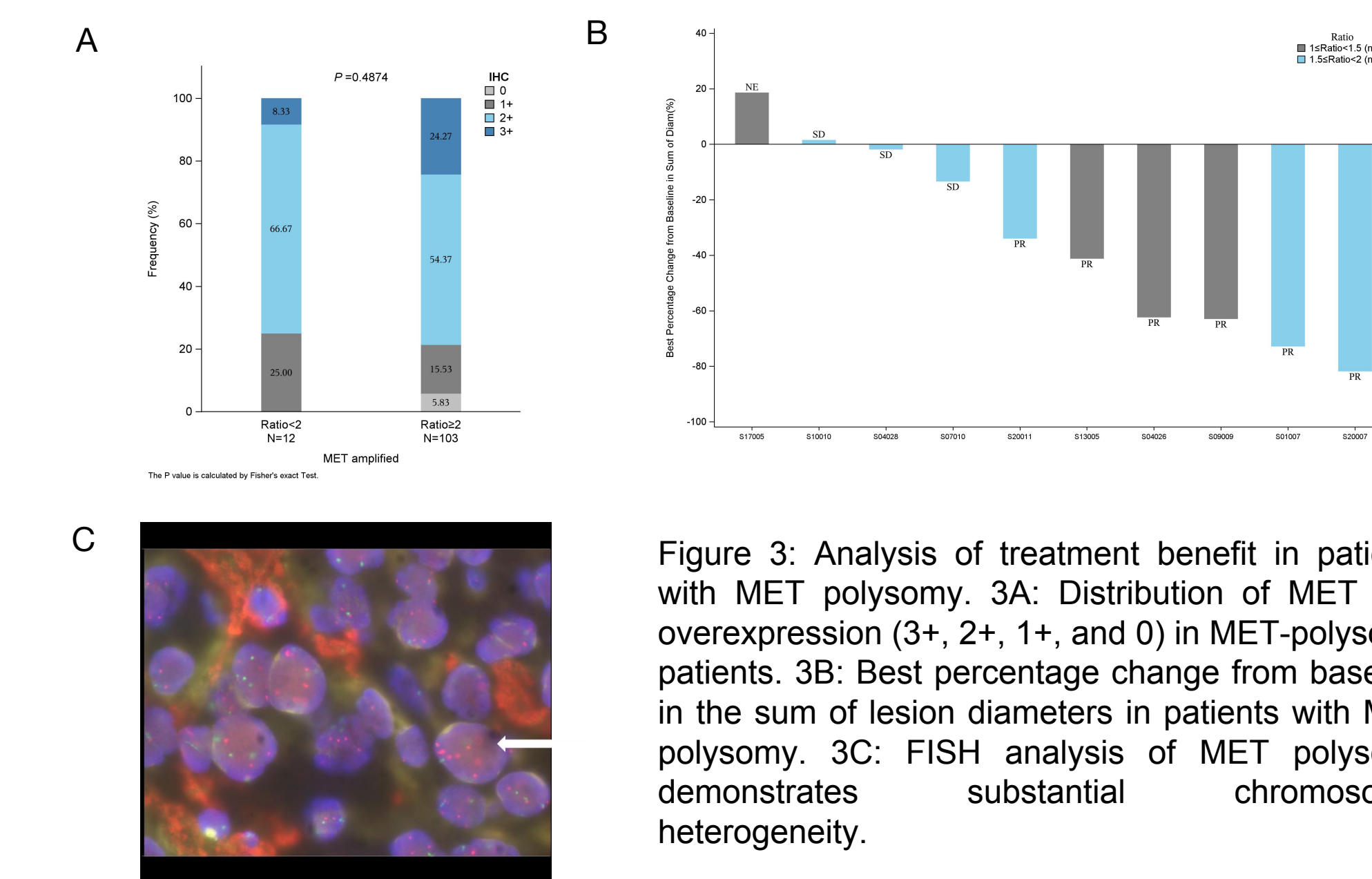
Table 1: The vebreltinib efficacy analysis of the MET IHC ($\leq 1+$, 2+, 3+, H-score < 240 and ≥ 240) and MET polysomy.

Treatment benefit showed an upward trend as c-MET protein expression levels increased. A total of 12 (14.0%) patients was identified as having high c-MET overexpression (IHC 3+), and these patients achieved an objective response rate (ORR) of 66.7%, a mPFS of 13.6 months, and a median overall survival (mOS) of 13.9 months. Two patients of this subgroup lost follow-up at very early time.

For patients with c-MET overexpression defined by an H-score ≥ 240 (n=15; 18.3%), the ORR was 73.3%, with an mPFS of 12.0 months and an mOS of 17.1 months.



In treatment-naïve patients, therapeutic benefit gradually increased with elevated c-MET protein expression, with objective response rates (ORRs) of 75.5%, 61.5%, 58.1%, and 23.1% for IHC 3+, IHC 2+/3+, IHC 2+, and IHC ≤ 1 subgroups, respectively. However, this upward trend was not obvious in previously-treated patients. Analysis based on H-score demonstrated a consistent trend between treatment-naïve and previously-treated patients across different H-score levels.



The patients with MET FISH polysomy can also benefit from vebreltinib. Chromosome 7 polysomy was identified in 10 (11.6%) patients, with an ORR of 60.0%, mPFS of 9.2 months, and mOS of 18.0 months. Marked heterogeneity in treatment benefit was noted across these patients, possibly resulting from polysomy heterogeneity.

DISCUSSION AND CONCLUSION

Actionable Take Away Message

- Using the maximally-selected rank test to screen cutoff values ranging from 140 to 250 in increments of 10, we identified that patients with a c-MET cutoff of H-score ≥ 240 derived better clinical benefit.
 - C-MET overexpression defined by IHC 3+ or an H-score ≥ 240 can serve as a predictive biomarker for the therapeutic efficacy of vebreltinib, especially in treatment-naïve patients.
 - Patients with MET polysomy with GCN ≥ 6 and MET/CEP7 < 2 can also obtain therapeutic benefits from vebreltinib treatment.
- ### Future Direction for Research
- Prospective cohort studies are further required to validate the c-MET IHC overexpression predictive value.
 - C-MET IHC overexpression (3+ or H-score ≥ 240) can be included as a stratification factor alongside MET amplification for MET-TKI clinical trials.

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