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MARIPOSA

IPRO-α response rate as a potential early endpoint correlating with overall survival in MARIPOSA, a phase 3 trial in *EGFR*-mutated NSCLC

Benjamin Ackerman[1], Daniel Backenroth[1], Ariel Bourla[1], John Xie[1], Tao Sun[1], Sujay Shah[2], Kiran Patel[3], Brooke Donohue[4], Angela Dauti[5,*], Levon Demirdjian[6], Omar F Khan[7], Natasha B Leighl[8], Felipe S Torres[9], Srinivas Raman[10], Melissa D Curtis[11], Felix Baldauf-Lenschen[11], Alison L Mitro[11], Thomas J Hennessy[11], Joel Greshock[3]

[1]Johnson & Johnson, Raritan, NJ, USA; [2]Johnson & Johnson, Spring House, PA, USA; [3]Johnson & Johnson, Wayne, PA, USA; [4]Johnson & Johnson, Los Angeles, CA, USA; [5]Johnson & Johnson, New Brunswick, NJ, USA; [6]Johnson & Johnson, San Diego, CA, USA; [7]Institute of Biomedical Engineering, University of Toronto, Toronto, ON, Canada; [8]Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada; [9]University Medical Imaging Toronto, University of Toronto, Toronto, ON, Canada; [10]BC Cancer, Vancouver, BC, Canada; [11]Altis Labs, Toronto, ON, Canada.

*Presenting author: adauti@ITS.JNJ.com

Key Takeaway

AI-based early endpoints, such as IPRO-α response rate, may identify treatment benefit in clinical trials that is not captured by traditional outcome measures, and future work will assess the performance of IPRO-α in additional clinical trials

Conclusions

IPRO-α response rate was notably higher for the amivantamab + lazertinib arm starting at 16 weeks, which reflects the true clinical benefit demonstrated in the MARIPOSA trial

Evidence generated by additional studies in randomized trials may suggest that IPRO-α response rate is a promising surrogate endpoint, thereby supporting clinical development

Timely and accurate prognostication is also critical to inform treatment decisions and stratify patients in clinical trials, adding to the value of this algorithm's outputs, which can be generated during an ongoing trial to supplement early efficacy data availability

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Disclosure

AD is an employee of and may hold stock in Johnson & Johnson.

Background

- Response Evaluation Criteria in Solid Tumors (RECIST) v1.1[1] assessments from computed tomography (CT) imaging have been used to measure early endpoints, such as objective response rate (ORR) and progression-free survival (PFS), to enable accelerated approvals in oncology trials
- Despite their utility, these traditional measures are subject to inter-rater variability[2,3] and do not always reflect the magnitude of long-term clinical benefit, highlighting the need for optimized early endpoints that may more reliably anticipate overall survival (OS)[4,5]
  - Rich imaging data are collected routinely in clinical trials at unprecedented scale, and radiomics and machine learning can help unlock additional insights from these available images
  - In future clinical trials, radiomics data and other data modalities can be used to provide more objective disease assessments, potentially improve trial efficiency, and bring novel medications to patients faster
- We investigated a new outcome measure using imaging-based prognostication (IPRO)-α (**Figure 1**), an AI-derived score trained on real-world data that measures patient-level changes in prognosis between baseline and on-treatment imaging assessments
- In this retrospective analysis, we assessed whether IPRO-α response rates could serve as an early endpoint that aligns with the demonstrated OS benefit of amivantamab + lazertinib versus osimertinib in the MARIPOSA trial[6]

Methods

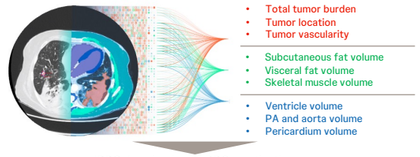
- A fully automated AI pipeline extracted over 5,000 interpretable features from each scan to generate IPRO-α scores for the approximately 10,000 baseline and on-treatment CT scans from the MARIPOSA trial (ClinicalTrials.gov identifier: NCT04487080; n=858 participants), starting from the baseline period until Week 48
  - The IPRO-α algorithm was trained on a real-world dataset of patients with advanced non-small cell lung cancer (NSCLC), including imaging, clinical, and outcomes data from Canadian health systems, to provide a comprehensive evaluation of radiographic change
- IPRO-α response was defined as a ≥50% improvement in IPRO-α score relative to baseline
  - The treatment effect was estimated using a rate ratio for amivantamab + lazertinib versus osimertinib IPRO-α response at various assessment time points throughout the study duration (every 8 weeks)
  - Changes in IPRO-α scores from baseline to on-treatment time points were analyzed to understand the association between this measurement and traditional clinical trial endpoints
- IPRO-α was used to analyze CT scans in this study

Results

Overview of the algorithm and data outputs

- IPRO-α is an AI model that estimates survival outcomes directly from routine medical imaging (eg, thoracic CT scans; **Figure 2**)
  - It quantifies imaging biomarkers including volumetric tumor burden, body composition (eg, skeletal muscle, fat), and cardiovascular features that all may contribute to survival outcomes
  - Higher scores indicate a better prognosis, while lower scores indicate a poorer prognosis
- 774 of 858 participants (90%) had evaluable baseline and on-treatment IPRO-α scores generated; 380 in the amivantamab + lazertinib arm, 394 in the osimertinib arm
  - Response was confirmed (per RECIST v1.1) in 336 (amivantamab + lazertinib) and 314 participants (osimertinib) in MARIPOSA[7]

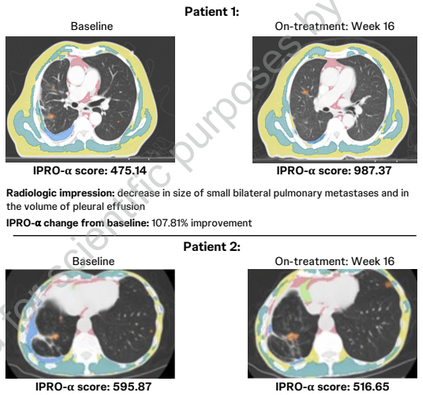
Figure 1: Derivation of IPRO-α scores from CT imaging



IPRO: **I**maging-based **PRO**gnostication

CT, computed tomography; IPRO, imaging-based prognostication; PA, pulmonary artery.

Figure 2: Case examples that illustrate imaging features on two sets of scans with different IPRO-α scores



Radiologic impression: decrease in size of small bilateral pulmonary metastases and in the volume of pleural effusion

IPRO-α change from baseline: 107.81% improvement

Radiologic impression: stable right lung primary tumor. Mixed response of left lung metastases, with decreased size of some small metastases and increased size of another. Unchanged small right pleural effusion and moderate pericardial effusion. Stable severe depletion of skeletal muscle, subcutaneous fat, and visceral fat, consistent with cachexia

IPRO-α change from baseline: 13.29% worsening

IPRO, imaging-based prognostication.

Relationship with ORR

- Starting at Week 16 through Week 48, the confidence intervals (CIs) for IPRO-α response ratio excluded the null value and demonstrated a favorable treatment effect for amivantamab + lazertinib versus osimertinib (**Table 1**)

Table 1: Cumulative amivantamab + lazertinib versus osimertinib IPRO-α response ratios at each landmark using imaging assessment response rate ratios by landmark imaging assessment

Assessment week	IPRO-α response rate ratio (95% CI)	IPRO-α response odds ratio (95% CI)
8	1.02 (0.74–1.42)	1.03 (0.98–1.55)
16	1.33 (1.03–1.71)	1.45 (1.02–2.05)
24	1.25 (1.00–1.48)	1.37 (1.00–1.90)
32	1.23 (1.01–1.50)	1.37 (1.00–1.87)
40	1.22 (1.02–1.47)	1.37 (1.01–1.86)
48	1.22 (1.02–1.45)	1.38 (1.03–1.87)

CI, confidence interval; IPRO, imaging-based prognostication.

- While ORR measurements did not detect the treatment effect of amivantamab + lazertinib, IPRO-α response rate identified the true clinical benefit starting at Week 16 (**Table 1**) through Week 48 (end of study; **Table 2**) using rate and odds ratios

Table 2: Longitudinal ORR and IPRO-α–based response estimates

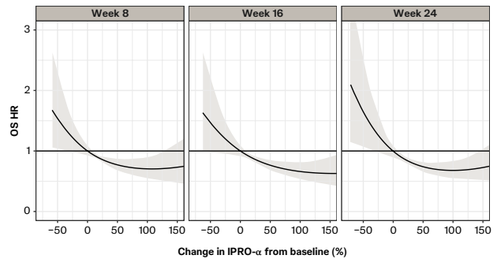
Endpoint	Treatment effect in amivantamab + lazertinib arm	Treatment effect in osimertinib arm	Treatment effect odds ratio (95% CI)
MARIPOSA ORR (RECIST-based) measurements[7] (median follow-up, 22 mo)	86%	85%	1.15 (0.78–1.70)
IPRO-α–based response measurements (cumulative at Week 48)	43%	36%	1.38 (1.03–1.87)

CI, confidence interval; IPRO, imaging-based prognostication; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors.

Relationship with OS

- When comparing OS estimates with IPRO-α change over time, decreases in IPRO-α were consistently associated with OS detriment, while increases in IPRO-α were associated with OS benefit (**Figure 3**)
  - OS hazard ratio (HR) >1 indicates a higher hazard of death, which is associated with a negative change in IPRO-α from baseline
  - Conversely, OS HR <1 is associated with a positive change in IPRO-α from baseline, which indicates an improved prognosis at Week 16

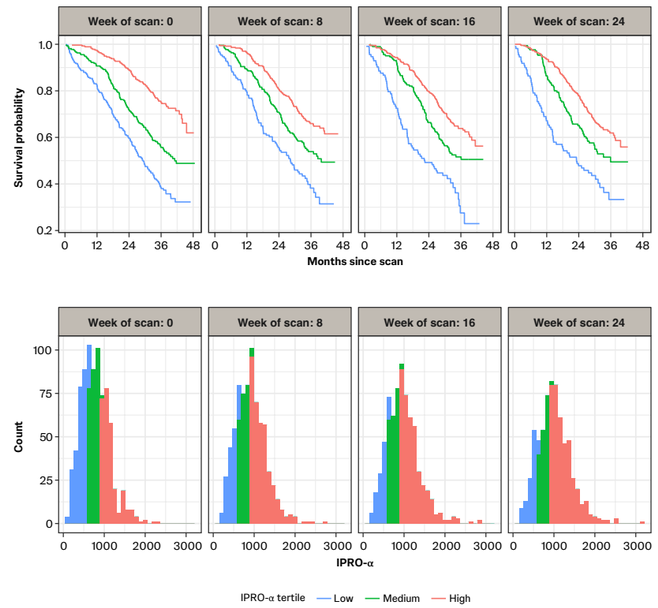
Figure 3: Association between IPRO-α change from baseline and OS: a pooled landmark analysis across study arms



HR, hazard ratio; IPRO, imaging-based prognostication; OS, overall survival.

- When patients were grouped into tertiles (low, middle, high) by their IPRO-α score at each assessment, their survival outcomes were consistently stratified (**Figure 4**)
  - Higher scores were associated with longer survival
  - This was observed in both treatment groups, showing that IPRO-α on its own is a meaningful prognostic factor in this retrospective analysis

Figure 4: OS estimates by IPRO-α tertile at given assessment time points across study arms



IPRO, imaging-based prognostication; OS, overall survival.

Notable and differentiated insights compared with traditional imaging endpoints in oncology clinical trials

- These results demonstrate that AI algorithms that quantify radiographic change can generate informative early endpoints for clinical trials
  - Such AI-based endpoints may complement traditional measures, and they warrant prospective inclusion as secondary or exploratory endpoints and further validation in future studies (**Figures 3** and **4**)
- The largest IPRO-α–based treatment effect was observed at Week 16, with IPRO-α response rates following a similar pattern at later time points (**Table 1**; 1.33 [95% CI, 1.03–1. 71])
  - This temporal pattern suggests that AI-processed imaging can deliver early, measurable efficacy signals that are detectable well before some conventional endpoints mature
- Based on this post-hoc analysis, the CIs for IPRO-α response rate ratios excluded the null value for the amivantamab + lazertinib arm starting at 16 weeks, mirroring the true clinical benefit demonstrated in the MARIPOSA trial (**Table 2**)
  - IPRO-α response rate identified treatment effects that were not captured by traditional RECIST-based ORR trial response measurement

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