

Early on-treatment prediction of long-term PFS using a joint AI-imaging and ctDNA model in the CROWN study

Conclusions

- This exploratory analysis using 7-year cutoff data from the phase 3 CROWN study (NCT03052608) showed that early circulating tumor DNA (ctDNA) and artificial intelligence (AI)-based imaging tumor burden measures were significantly associated with 7-year progression-free survival (PFS) in patients with advanced ALK-positive non-small cell lung cancer (NSCLC)
- In this exploratory CROWN analysis, integrating early ctDNA dynamics and AI-based imaging measures into a joint model provided better prediction of long-term PFS than individual univariate models, including standard radiological assessments
- Future work will evaluate whether incorporating other ctDNA analysis methods and additional computed tomography (CT)-based radiomic features can further improve the predictive performance of the joint model for long-term PFS



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Background

- In the phase 3 CROWN study, after 7 years of follow-up, median PFS (mPFS) was still not reached (NR) with lorlatinib in patients with advanced ALK-positive NSCLC¹
 - However, early predictors of long-term treatment outcomes remain incompletely defined
- ctDNA has been used for monitoring response to treatment in patients with ALK-positive NSCLC^{2,3}
- A prior analysis from CROWN showed that genomic variant-based ctDNA reduction at cycle 2 day 1 (C2D1) was associated with better outcomes vs no ctDNA reduction in patients treated with lorlatinib but not in those treated with crizotinib. However, ctDNA change was not quantifiable in many patients due to low shedding⁴
- In this ad hoc exploratory analysis using CROWN data from the 7-year cutoff, we evaluated whether early ctDNA, Response Evaluation Criteria in Solid Tumors (RECIST) assessments, and AI-based imaging measures of tumor burden, individually and jointly, were associated with 7-year PFS

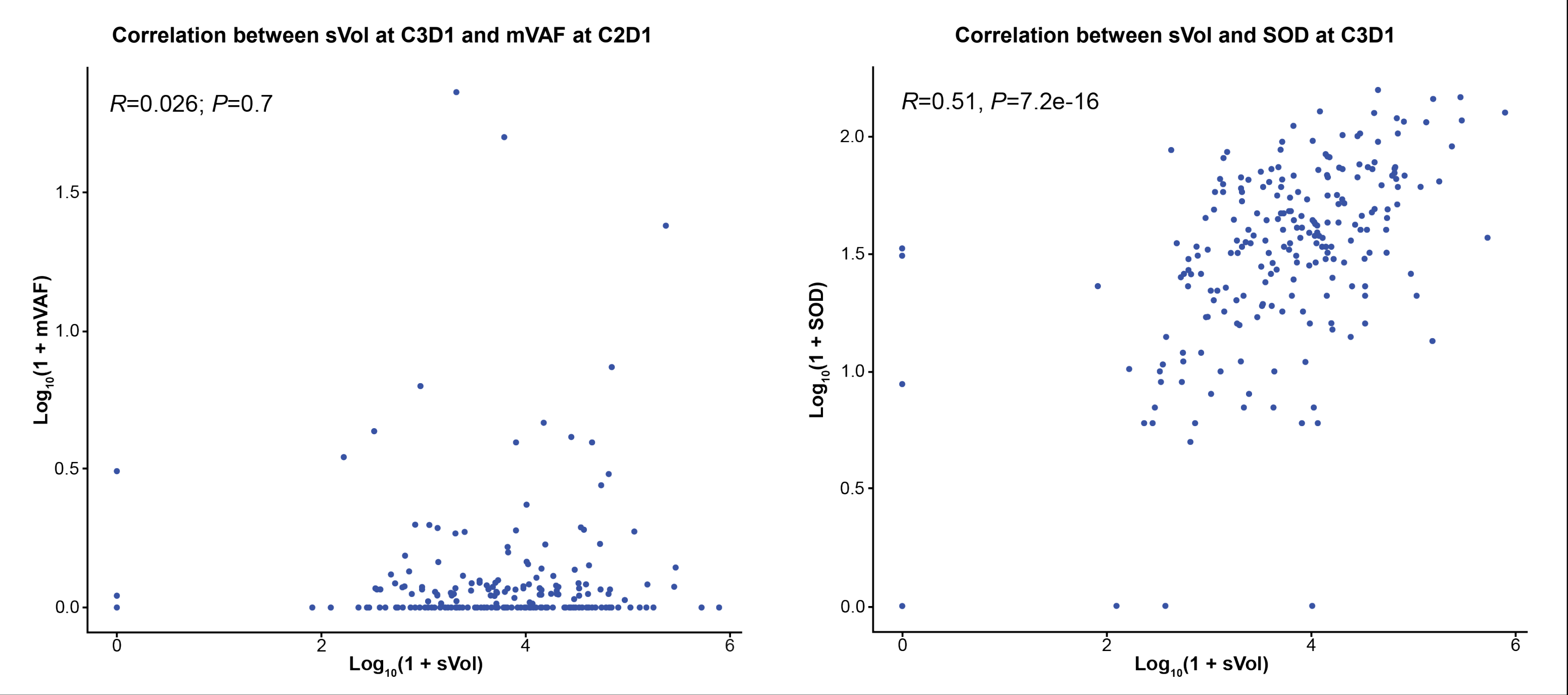
Methods

- CROWN is an ongoing, international, open-label, randomized, phase 3 trial comparing lorlatinib vs crizotinib in patients with previously untreated advanced ALK-positive NSCLC⁵
- 296 patients were randomized 1:1 to receive lorlatinib 100 mg once daily (n=149) or crizotinib 250 mg twice daily (n=147); treatment course was measured in 28-day cycles⁵
- Patients with evaluable baseline and early ctDNA (C2D1) plus baseline and first on-treatment imaging (RECIST and AI-derived sum of lesion volumes [sVol]) were included in the evaluable subset for this analysis (**Figure 1**)
 - ctDNA was assessed from blood samples using maximum variant allele frequency (mVAF) at baseline and C2D1
 - Tumor burden was assessed at baseline and cycle 3 day 1 (C3D1) using:
 - Investigator-assessed RECIST version 1.1 objective response (OR) and sum of diameters (SOD) from CT and/or magnetic resonance imaging scans (≤2 target lesions per organ; ≤5 total)
 - A deep learning-based platform,⁶⁻⁸ which was used to track and measure brain metastases ≥2 mm and lung tumors ≥10 mm in diameter. The sVol was calculated
- Associations with 7-year PFS were evaluated using univariate models and a joint model integrating mVAF and sVol, adjusted for treatment arm
- The joint risk score was developed by integrating sVol and mVAF. To account for highly skewed distributions and differing measurement scales, both metrics were standardized using a rank-based inverse normal transformation (INT), which mapped patient percentiles onto a standard normal distribution
 - This allows the metrics to be directly compared and summed into a single, equally weighted joint risk score: INT(sVol) + INT(mVAF), where $INT(x) = \Phi^{-1}(-1) \left[\frac{rank(x)}{n+1} \right]$
 - Consequently, an elevated joint risk score indicates that a patient ranks highly in either or both of these risk factors

Results

- This evaluable subset included 221 patients (74.7%) from CROWN
- Relationships between sVol and mVAF or SOD were assessed using Pearson correlation analyses (**Figure 2**)
 - No association was observed between sVol and mVAF
 - This suggests that sVol and mVAF are independent measures of tumor burden and provide complementary prognostic information, supporting their evaluation in a joint model
 - A positive correlation was observed between radiographic measurements sVol and SOD

Figure 2. Correlation of C3D1 sVol with C2D1 mVAF and C3D1 SOD



- Across both treatment arms, patients classified as low risk consistently had longer mPFS than those classified as high risk across all models (**Figures 3, 4, and 5**)
- The AI-based imaging + ctDNA joint model showed the strongest separation between low- and high-risk patients, indicating better early on-treatment prognostic discrimination than any individual measure
 - Joint model vs sVol:** hazard ratio (HR) 0.41 vs 0.72 (lorlatinib); 0.44 vs 0.49 (crizotinib)
 - Joint model vs mVAF:** HR 0.41 vs 0.49 (lorlatinib); 0.44 vs 0.70 (crizotinib)
 - Joint model vs RECIST SOD:** HR 0.41 vs 0.64 (lorlatinib); 0.44 vs 0.67 (crizotinib)

Figure 3. 7-year PFS by joint model risk score and sVol

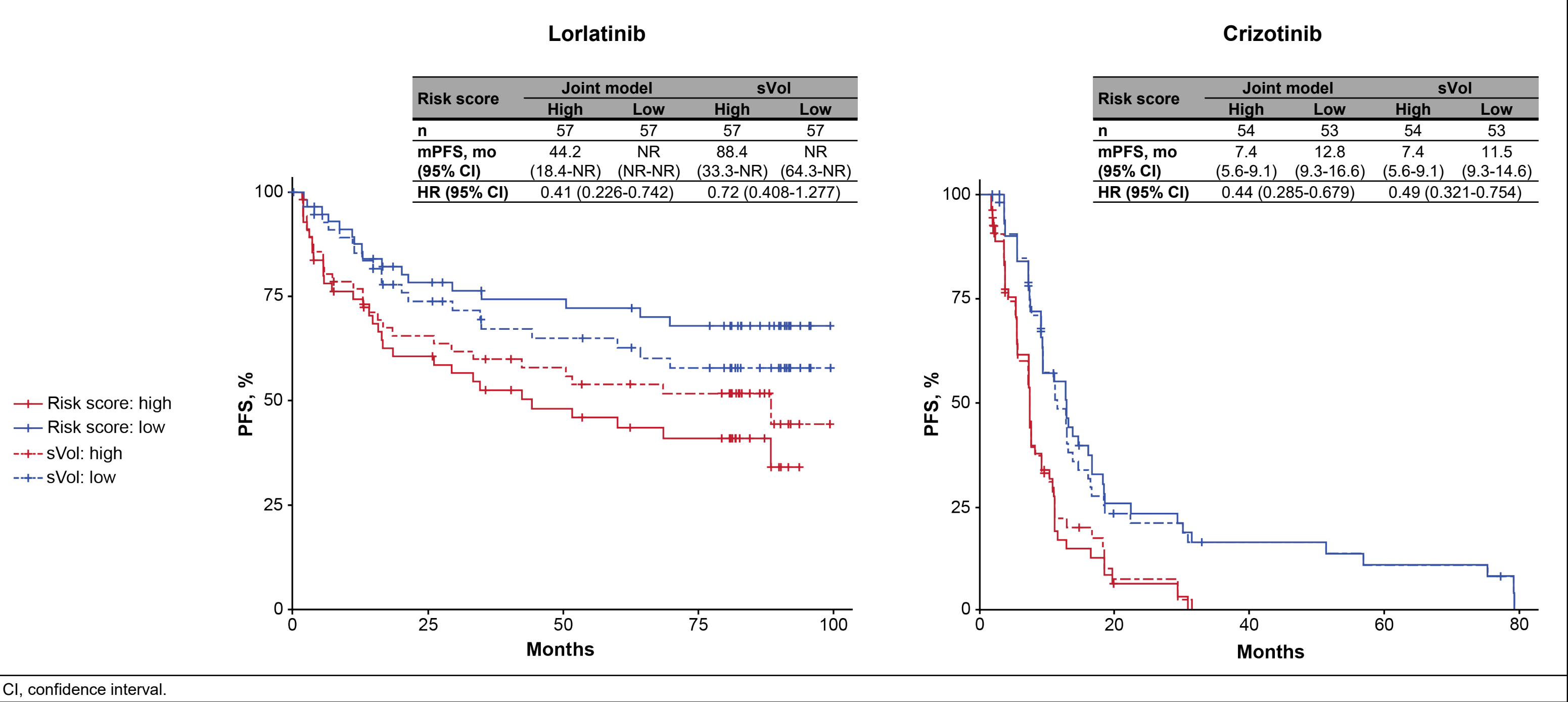


Figure 1. Ad hoc exploratory analysis population and early on-treatment assessments

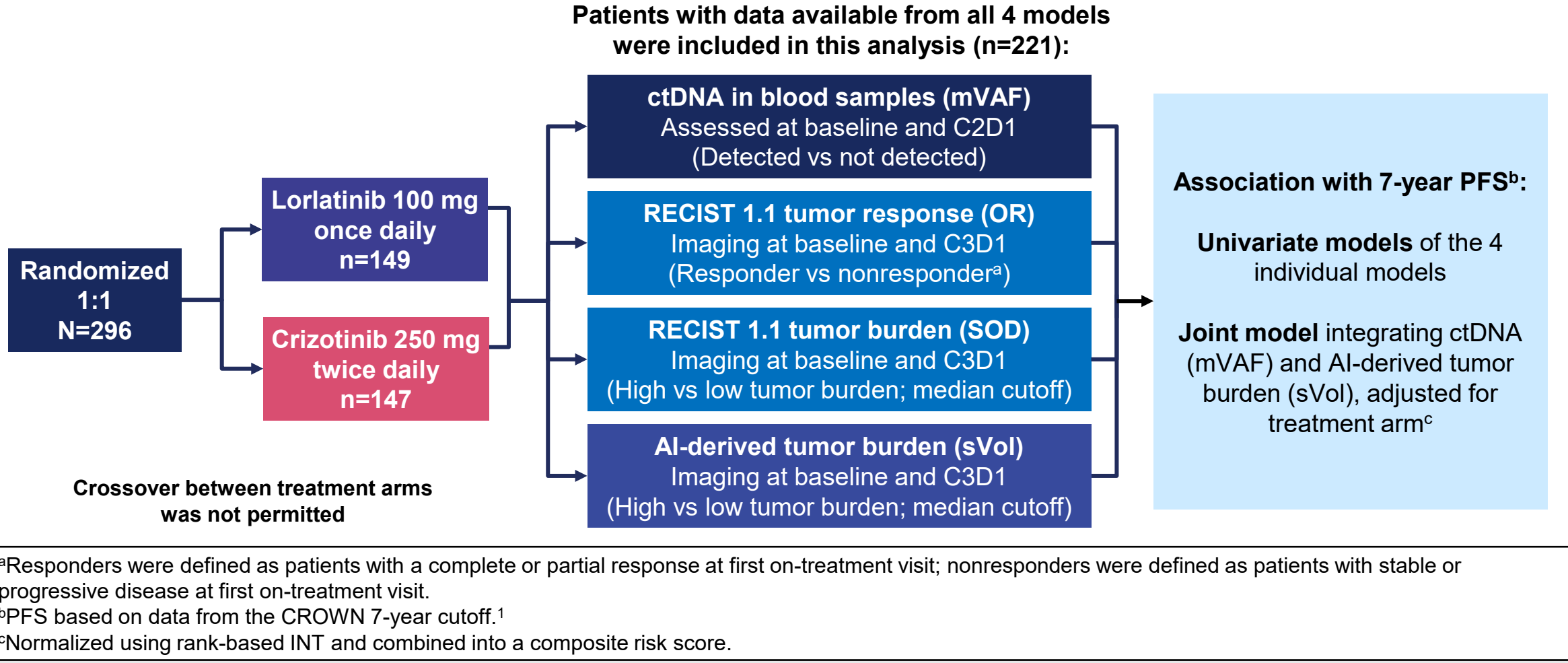


Figure 4. 7-year PFS by joint model risk score and mVAF

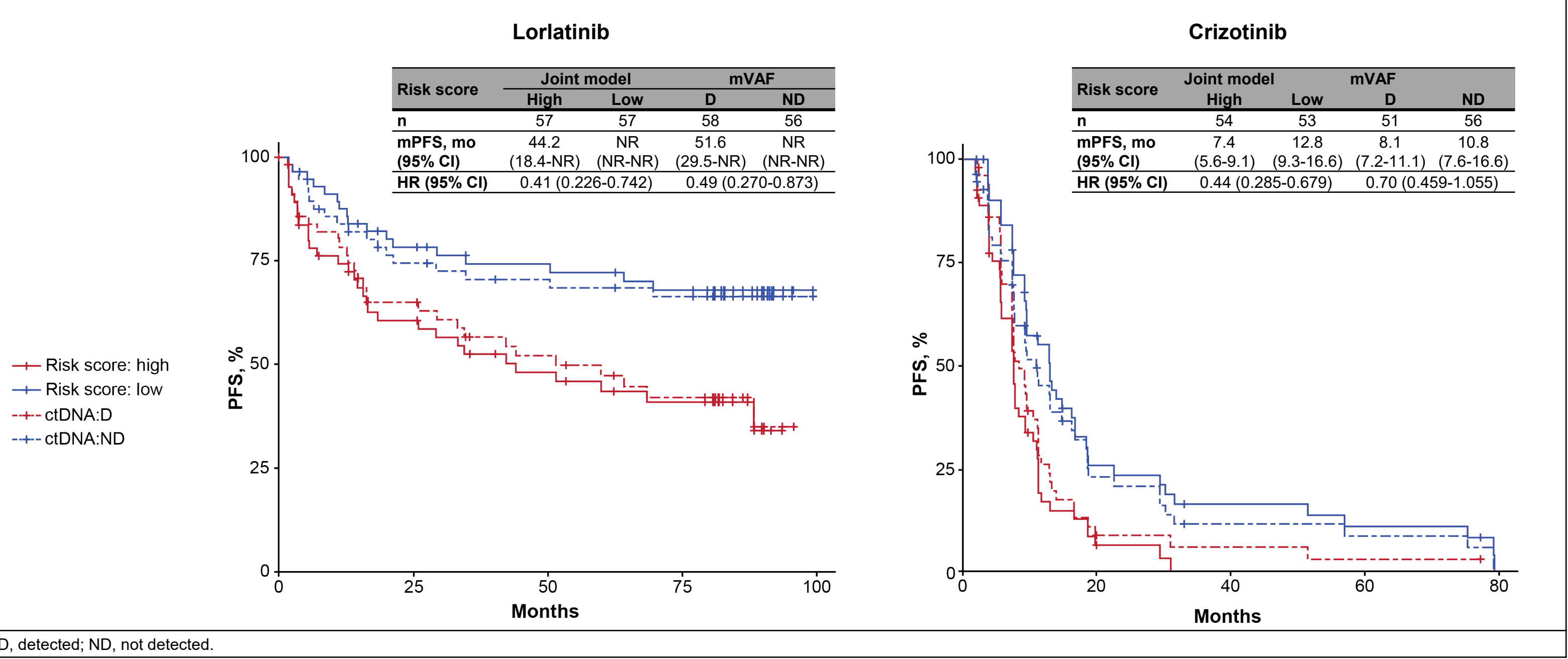
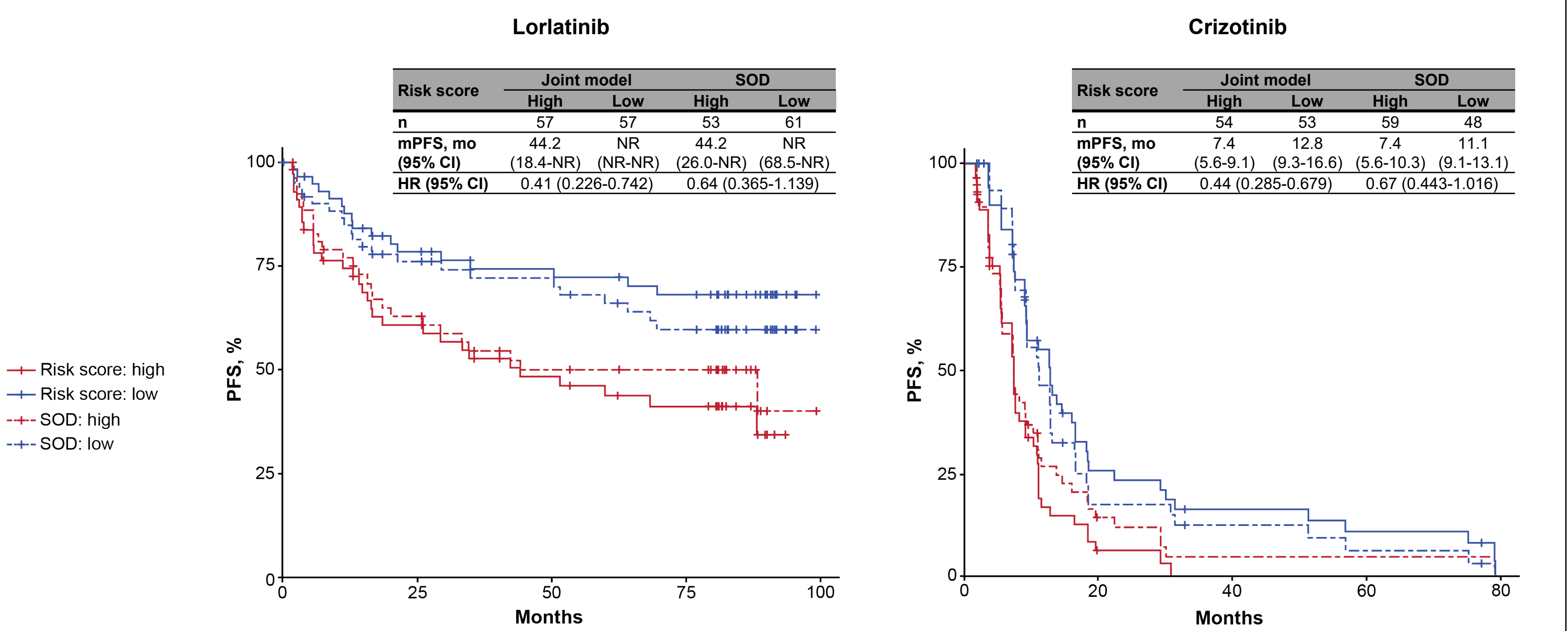


Figure 5. 7-year PFS by joint model risk score and RECIST SOD



- Three univariate models (ctDNA mVAF, RECIST SOD, and AI-based imaging sVol) were significantly associated with 7-year PFS (**Table 1**)
- Association of the univariate model considering only RECIST objective responses (responder vs nonresponder) with 7-year PFS was not statistically significant
- The joint model integrating sVol and mVAF showed the greatest prognostic separation between low-risk vs high-risk patients (HR, 0.45; 95% CI, 0.321-0.637; P=5.4×10⁻⁶)

Table 1. Association of early ctDNA and AI-based imaging assessments with 7-year PFS* (n=221)

Variable (binary)	Univariate model ^b				AI-based imaging + ctDNA joint model ^b
	ctDNA (mVAF) C2D1	RECIST (OR) C3D1	RECIST (SOD) C3D1	AI-based imaging (sVol) C3D1	Risk score (INT sVol + INT mVAF)
n	112 vs 109 (ND vs D)	164 vs 57 (R vs NR)	109 vs 112 (low vs high ^c)	110 vs 111 (low vs high ^c)	110 vs 111 (low vs high ^c)
HR (95% CI)	0.64 (0.456-0.891)	0.92 (0.636-1.337)	0.66 (0.470-0.915)	0.59 (0.424-0.833)	0.45 (0.321-0.637)
P value	0.008	0.668	0.013	0.002	5.4×10 ⁻⁶

NR, nonresponder (stable disease + progressive disease); R, responder (complete response + partial response).
*Clinical and previously reported ctDNA data are based on the CROWN 7-year PFS publication.
^bAll models use treatment arm as a covariate.
^cFor RECIST SOD and AI-based sVol models, patients were stratified into low and high tumor burden groups at C3D1 using the median as cutoff: SOD, 36 mm; sVol, 6705.88 mm³; joint model risk score, -0.0493.