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Multimodal Integrative Genomics and Pathology Analyses in Neoadjuvant Nivolumab Treatment for Borderline Resectable HCC

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Background

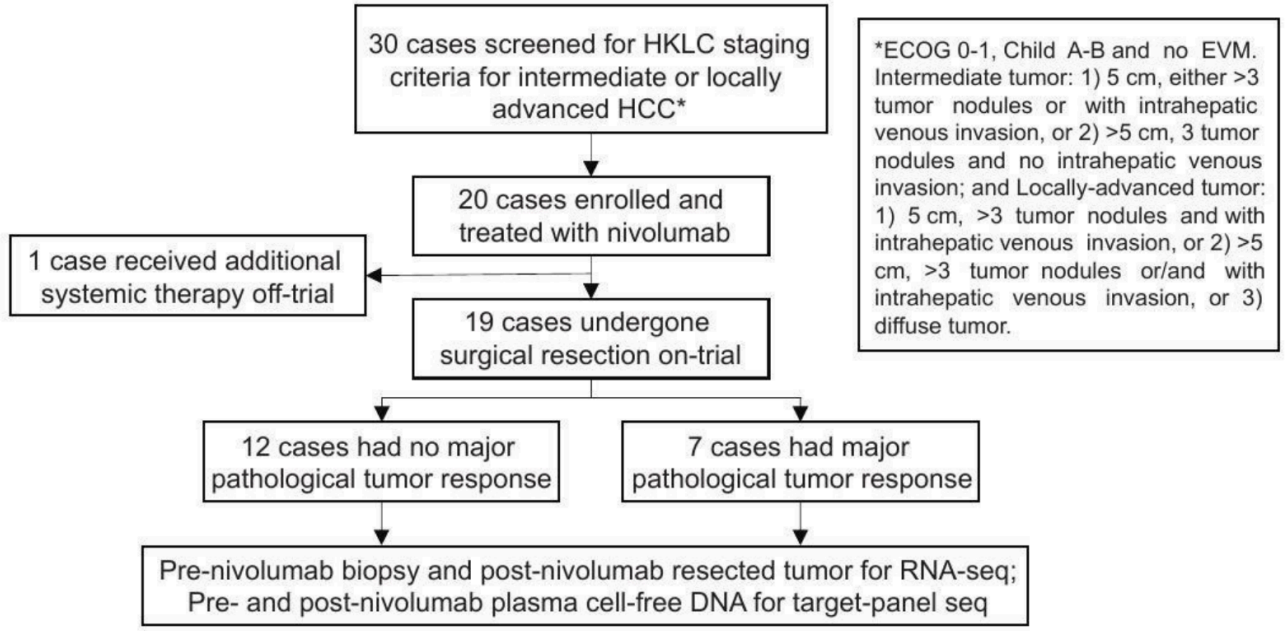
- Immunotherapy has resulted in pathologic responses in hepatocellular carcinoma (HCC) but the benefits and molecular mechanisms of neoadjuvant immune checkpoint blockade are largely unknown.

Aim

- In this study, we evaluated the efficacy and safety of pre-operative nivolumab (anti-PD1) in patients with intermediate and locally-advanced HCC and determined the molecular markers for predicting treatment response.

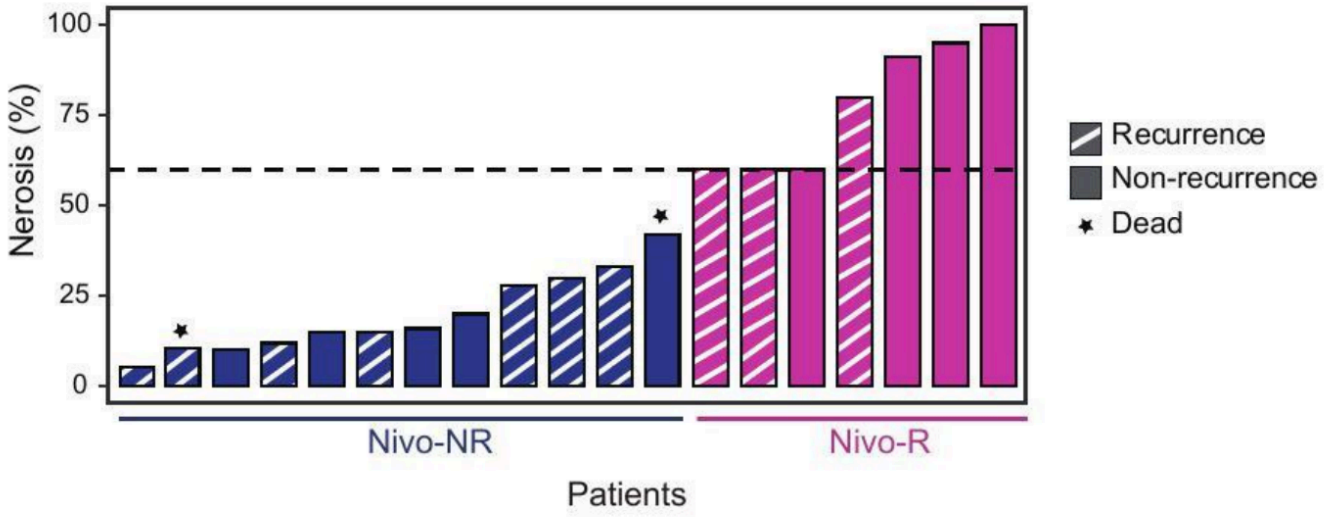
Methods - Workflow

- Between July 2020 and November 2021, 20 treatment-naïve HCC patients with intermediate and locally advanced tumors received preoperative nivolumab at 3 mg/kg for 3 cycles prior to surgical resection. Nineteen patients underwent surgical resection on-trial.



Results - Patients' treatment response

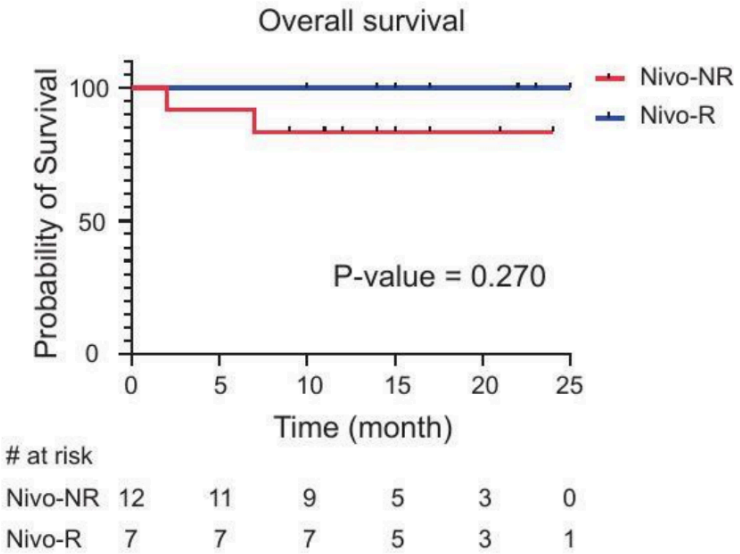
- Seven (36.8%) of the 19 patients had major pathologic tumor necrosis (≥60%) in the post-nivolumab resection specimens, with 3 having almost complete (>90%) tumor necrosis. The tumor necrosis was hemorrhagic and often accompanied with increased or dense immune cell infiltrate at the border of the tumors.



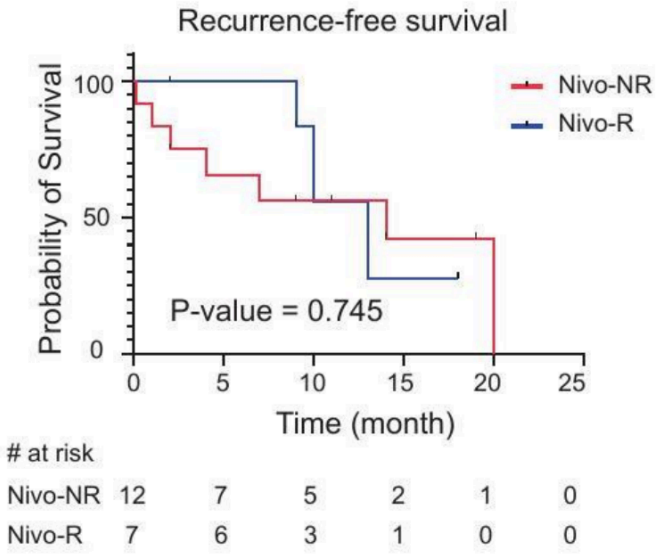
The percentages of pathological tumor necrosis in the resected hepatectomy specimens and follow-up of patients regarding disease recurrence.

Results - Patients' treatment response (cont'd)

Patients'outcome



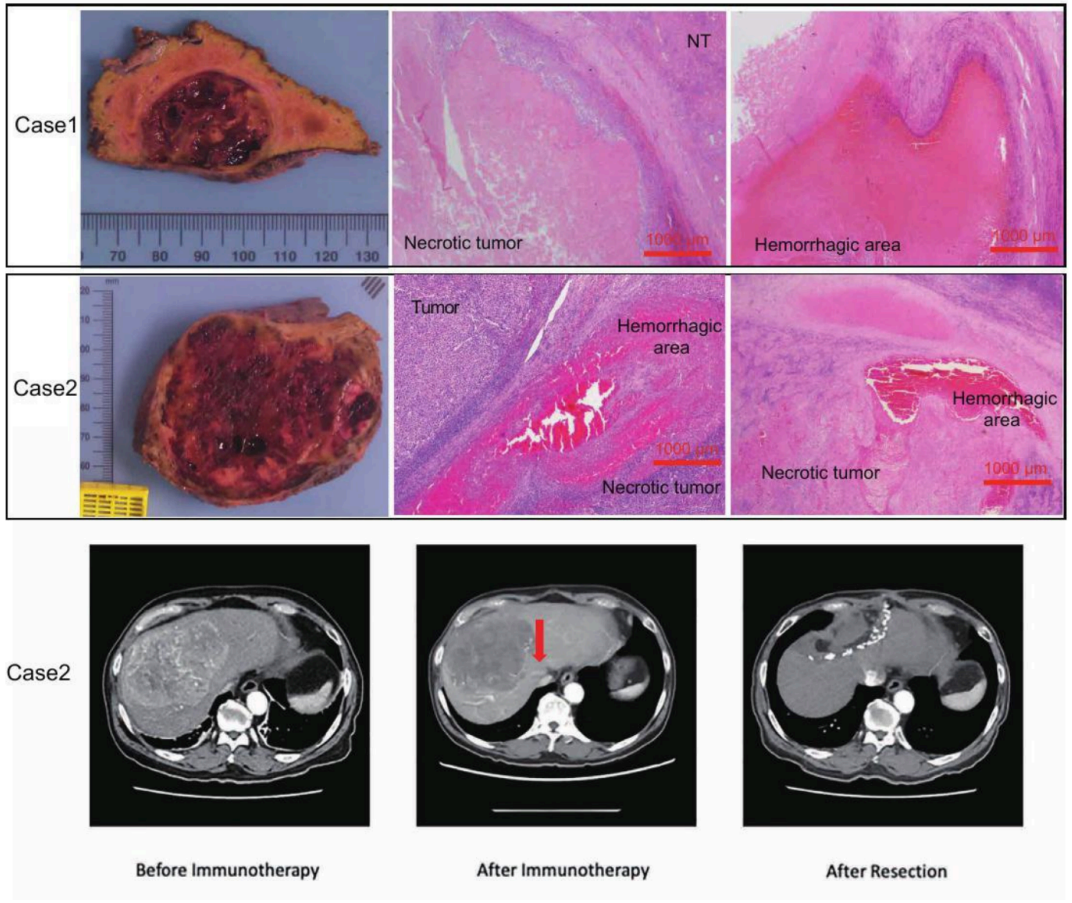
1-year overall survival	
Nivo-R	100%
Nivo-NR	83.3%



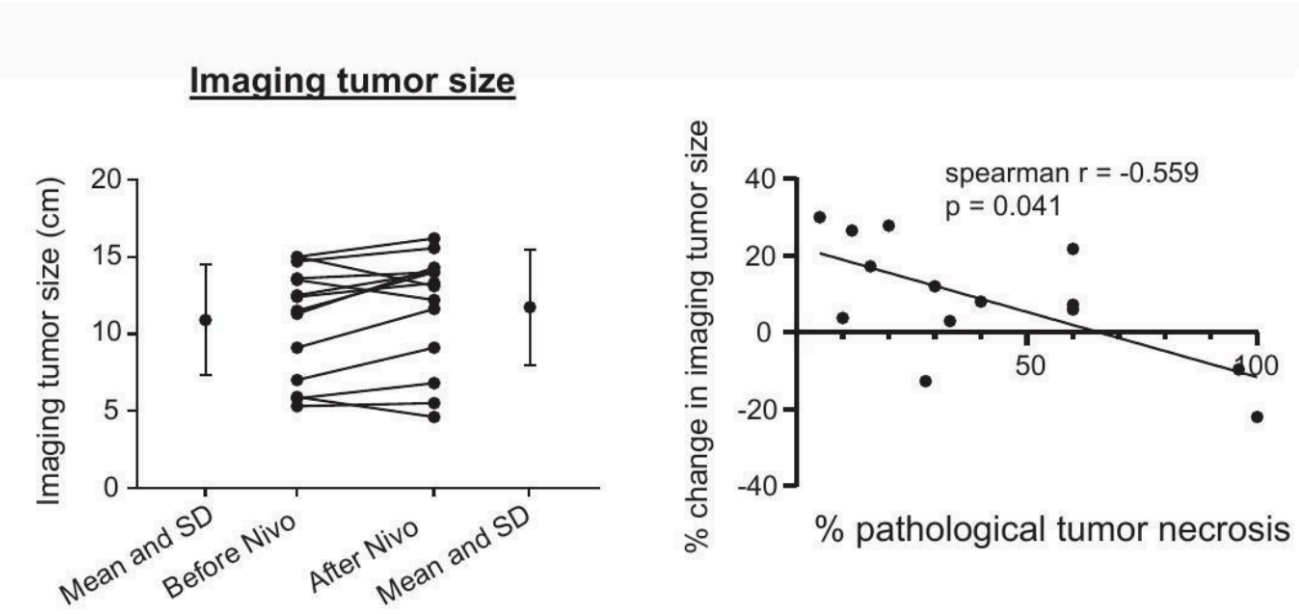
1-year recurrence rate	
Nivo-R	28.6%
Nivo-NR	41.7%

Overall and recurrence-free survival of the patients. The 1-year overall survival rate was higher and the 1-year tumor recurrence rate, respectively, was lower in the nivo-R group than the nivo-NR group.

Results

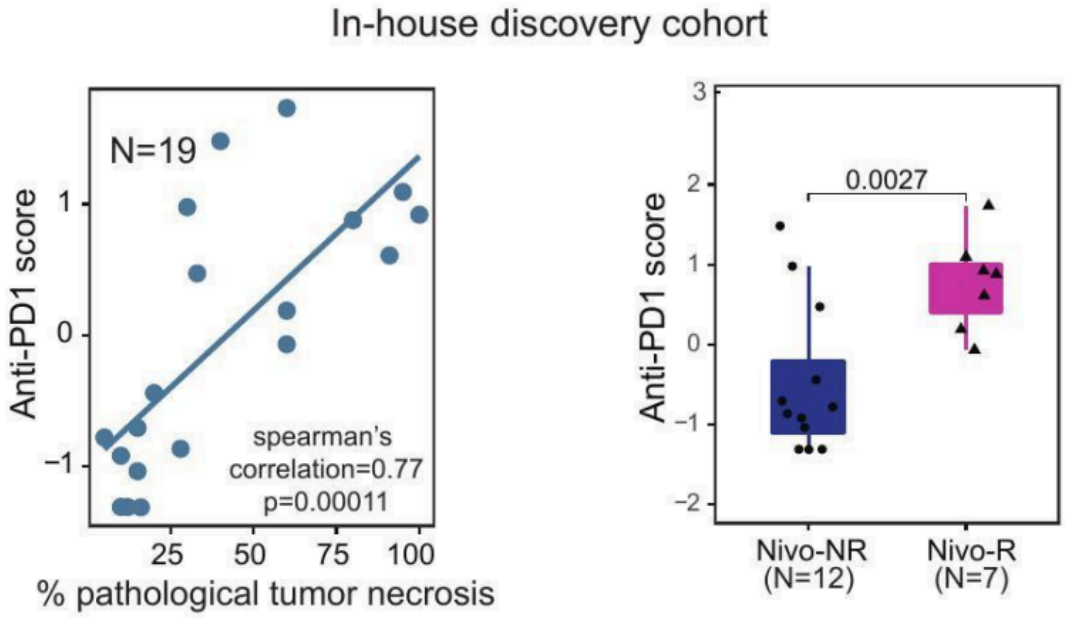


Representative cases showing gross pathology and histology of the resected specimens after preoperative nivolumab treatment. Serial CT scan of the tumor change of a patient after neoadjuvant anti-PD1 treatment (case 2).

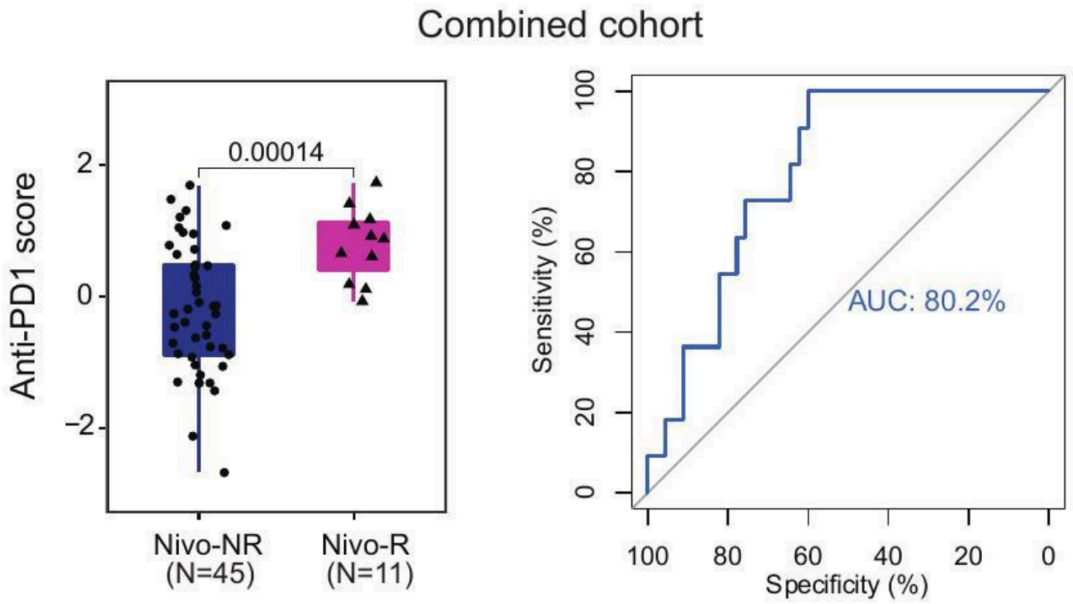


CT imaging tumor size of the 19 patients (left panel) and correlation between % change of CT imaging tumor size and % of pathologic tumor necrosis in the resected liver specimens (right panel).

CNV-based anti-PD1 score predicted patients' response towards anti-PD1 blockade



Anti-PD1 score associated with tumor necrosis outcome in nivolumab treated patients (left panel). Nivolumab responsive and nonresponsive patients differed in terms of anti-PD1 score using in-house sample cohort (2-sided t-test, right panel).



ROC analysis of using anti-PD1 score as biomarker to predict treatment outcome using combined sample cohort (in-house cohort and Korean cohort by Hong et al.)

Hong, J.Y., et al., Hepatocellular carcinoma patients with high circulating cytotoxic T cells and intra-tumoral immune signature benefit from pembrolizumab: results from a single-arm phase 2 trial. Genome Med, 2022. 14(1): p.1.

Results

- The tumor necrosis was hemorrhagic and often accompanied with increased or dense immune cell infiltrate at the border of the tumors.
- None of the patients developed major adverse reactions contradicting hepatectomy.
- RNA-sequencing analysis on both pre-nivolumab tumor biopsies and post-nivolumab resected specimens showed, in cases with major pathologic necrosis, the proportion of CD8 T cells in the HCC tissues predominantly increased after treatment.

Conclusion

- This paper was demonstrated that use of nivolumab is safe and effective in the neoadjuvant setting for intermediate and locally-advanced HCCs.
- Significant immune cell-related tumor necrosis observed in the postnivolumab hepatectomy specimens signifies that successful restoration of cytotoxic immunity is the key determinant for immune checkpoint blockade (ICB) response.
- A short course of neoadjuvant therapy may deliver durable therapeutic outcome in a small subset of patients. In addition, non-invasive cfDNA biomarker could potentially predict anti-PD1 ICB response.