DDR1 expression is associated with a worse prognosis in intrahepatic cholangiocarcinoma

Amy Mueller[1], Laura A. Dillon[1], Xinwei Sher[1], Joseph P. Eder[1], Thomas Schürpf[1], Lawrence N. Kwong[2], G. Travis Clifton[1]

[1]Incendia Therapeutics, Boston, MA, USA; [2]MD Anderson Cancer Center, Houston, TX, USA

Background

- Discoidin Domain Receptor 1 (DDR1) is a receptor tyrosine kinase expressed on cancer cells that binds to collagen.
- DDR1 is associated with T-cell exclusion and poor outcomes in several cancer types and is the target of investigational drug therapy PRTH-101 [1,2].
- *DDR1* mRNA expression is known to be high in intrahepatic cholangiocarcinoma (iCCA).
- We evaluated the correlation of DDR1 protein expression with histologic and clinicopathologic factors and outcomes in iCCA.

Methods

- Surgical samples from 80 patients with iCCA who underwent resection at a single institution from 2004-2016 were evaluated by multiplexed immunofluorescence (mIF) and DDR1 immunohistochemistry (IHC) in a tissue microarray [3].
- IHC and mIF values across multiple samples from the same tumor were averaged for each of the patients.
- H score was determined from the DDR1 IHC. DDR1 was classified as high for an H score >150.
- Correlations between DDR1 H-score and clinicopathologic features and outcomes were compared using Spearman correlation (continuous variables), Wilcoxon Rank sum (binary features), or Kruskal-Wallis tests (categorical features).

References

1. Sun, X. et al. Tumour DDR1 promotes collagen fibre alignment to instigate immune exclusion. Nature. 2021 Nov;599(7886):673-678.
2. Liu, J. et al. A highly selective humanized DDR1 mAb reverses immune exclusion by disrupting collagen fiber alignment in breast cancer. J Immunother Cancer. 2023 Jun; 11(6): e006720.
3. Carapeto, F. et al. The immunogenomic landscape of resected intrahepatic cholangiocarcinoma. Hepatology. 2022 Feb;75(2):297-308.

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Results

- DDR1 expression was high in 87.7% (71/81) of iCCA There was IHC 3+ expression on 100% of tumor cells in 25% (20/80) of iCCA (H score = 300) (Figure 1).

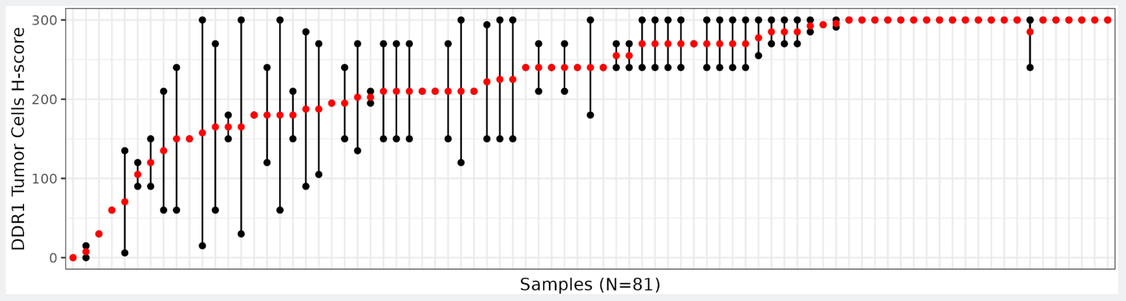

Figure 1. DDR1 IHC tumor cells H scores (range from 0 to 300) across samples. Black points represent measurements from individual cores taken from each tumor sample. Red points represent average measurements across 81 samples from 80 unique patients. Most samples have measurement from two cores.

- The DDR1 H score was positively correlated with the percentage of the tumor bed that was comprised of stroma (R=0.27, p=0.014) (Figure 2).
- Patients with perineural invasion (n=15) had higher DDR1 H scores (median 292.5, IQR 52.5) than patients without (n=65, median 240, IQR 105; p=0.011) (Figure 3).

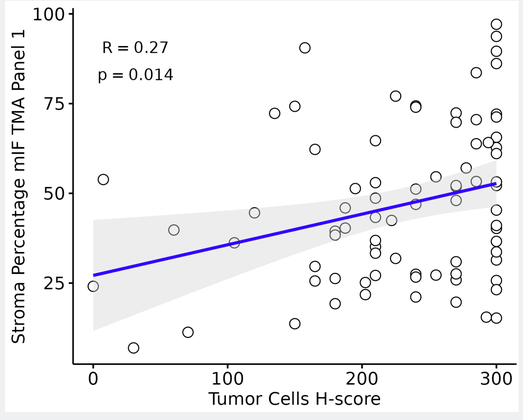

Figure 2. Scatterplot of DDR1 H score vs. percent of stroma in tumor bed calculated from MIF Panel 1 [Ref 3]. (R = 0.27, p = 0.014)

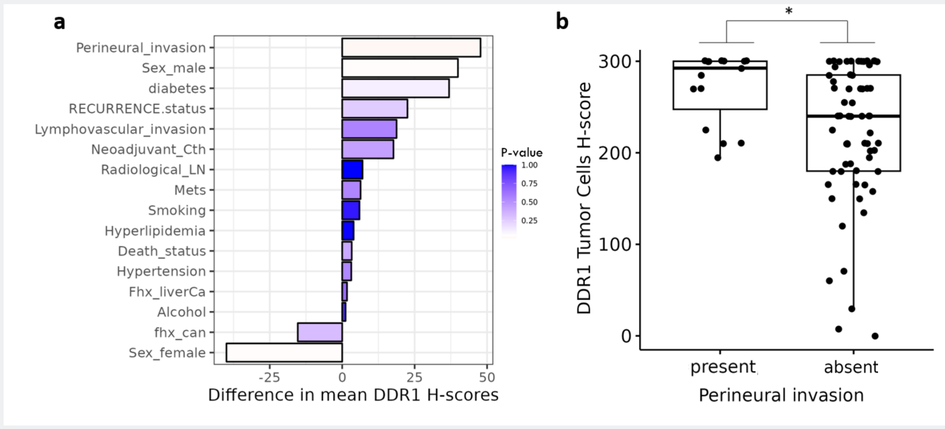

Figure 3. **a** Barplot of difference in average H scores in patients with vs. without each clinical feature, colored by Wilcoxon Rank Sum test p-values **b** Boxplot of DDR1 H scores grouped by perineural invasion status (Wilcoxon rank sum test p-value = 0.011)

- High DDR1 expression was associated with worse overall survival (p=0.048) and a trend towards worse disease-free survival (p=0.059), independent of stage (Figures 4, 5).

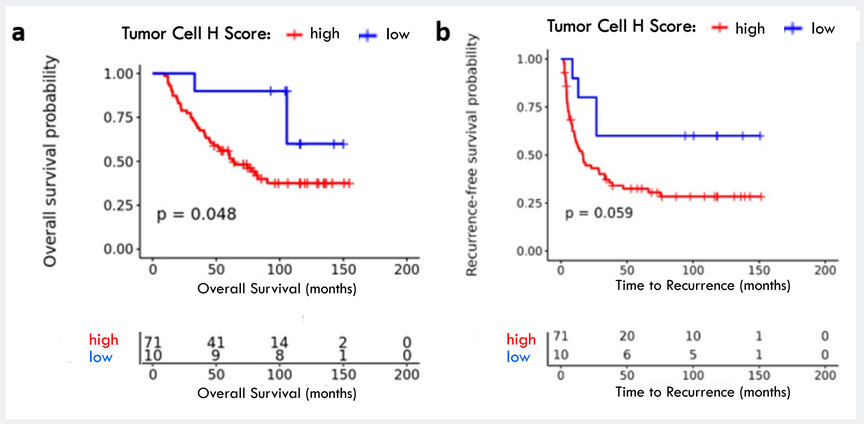

Figure 4. Kaplan Meier curves showing **a** overall survival **b** recurrence-free survival probability in DDR1 high (H score >150) vs. low (H score <= 150) group

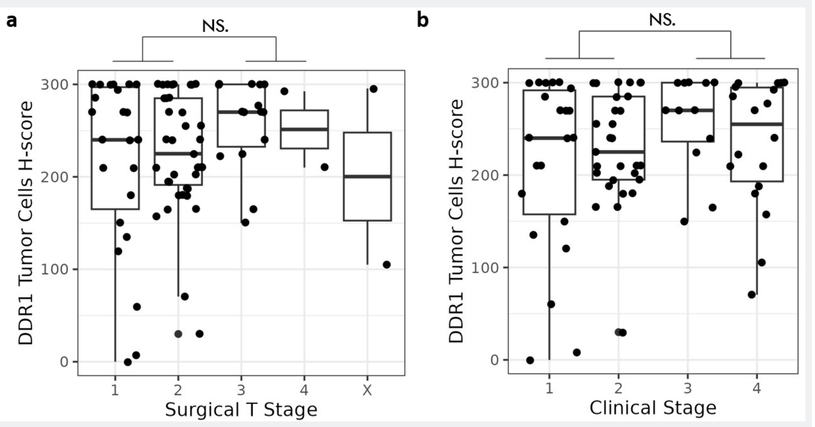

Figure 5. Boxplot of DDR1 H scores grouped by **a** Surgical T stage **b** Clinical stage; NS.: p-value > 0.05 Wilcoxon Rank Sum test

- No association between DDR1 H score and CD3+ or CD8+ density in central tumor (CT) or invasive margin (IM) (Figure 6).
- No association between DDR1 H score and tumor mutation status, including FGFR, IDH1 (Table1).

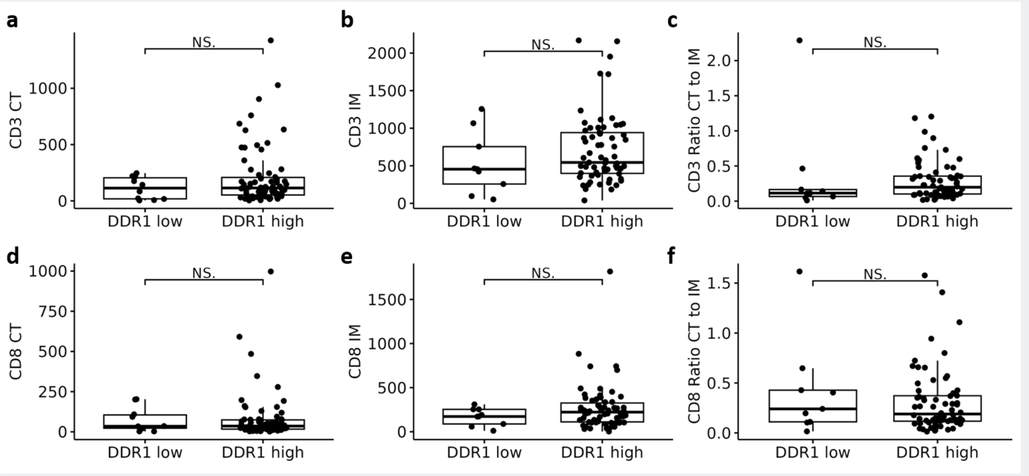

Figure 6. Boxplot grouped by DDR1 low (H score <=150) vs. high (H score > 150) for IHC measures **a** CD3 IHC in Central Tumor (CT) **b** CD3 IHC in Invasive Margin (IM) **c** CD3 ratio in CT to IM **d** CD8 IHC in CT **e** CD8 IHC in IM **f** CD8 ratio in CT to IM; NS.: p-value > 0.05 Wilcoxon Rank Sum test

Mutation	N (MUT)	Average DDR1 Hscore (MUT)	StDev DDR1 Hscore MUT)	Average DDR1 Hscore (WT)	StDev DDR1 Hscore WT)	P-value
IDH1	19	227.5	74.1	231	73.2	0.866
ARID1A	19	223.4	90.6	232.2	67.4	0.8439
BAP1	15	251.7	45.2	225.2	77.4	0.418
ATM	10	195.8	77.2	235	71.6	0.0636
BRCA2	9	261.7	33	226.2	75.7	0.3355
TP53	8	262.5	56.7	226.6	74	0.1395
PBRM1	7	208.3	95.2	232.2	71	0.6288
CDKN2A	6	272.5	27.5	226.8	74.5	0.1454
FGFR2	5	225.6	115.5	230.4	70.5	0.7289
IDH2	5	273	52.4	227.3	73.5	0.1044
KRAS	5	198.6	104.2	232.2	70.9	0.5657
NRAS	4	189.4	51	232.3	73.6	0.1263
BRAF	3	215	67.6	230.7	73.5	N/A
PIK3CA	1	300	N/A	229.3	73	N/A
PTEN	1	300	N/A	229.3	73	N/A
CCND1	0	N/A	N/A	230.1	73	N/A
EGFR	0	N/A	N/A	230.1	73	N/A
SMAD4	0	N/A	N/A	230.1	73	N/A

Table 1. Association of tumor mutations with DDR1 H score. P-values determined from the Wilcoxon Rank Sum test.

Conclusions

- DDR1 is highly expressed in the majority of iCCAs.
- DDR1 expression is associated with higher levels of stroma, which contains collagen, the ligand of DDR1.
- The prevalence of high DDR1 expression and associated poor survival outcomes make iCCA a relevant tumor type for evaluating novel DDR1-targeted therapies.