Clinical and molecular characterization of IDH1/2 mutant cholangiocarcinoma

Florian Castet[1,2‡], Queralt Serra-Camprubí[2‡], Carles Fabregat-Franco[1,2], Helena Verdaguer[1,2], Gloria Castillo[1], Tian V.Tian[2], Teresa Macarulla[1,2*]

[1] Gastrointestinal Cancer Unit, Oncology Department, Vall d'Hebron University Hospital, 08035, Barcelona, Spain [2] Preclinical and Translational Research Program, Vall d'Hebron Institute of Oncology (VHIO), 08035 Barcelona, Spain. ‡ Joint first authors *Corresponding author; tmacarulla@vhio.net

BACKGROUND

- **Cholangiocarcinoma (CCA)** is the second most common liver cancer and a **leading cause of cancer-related death worldwide.**
- 15-20% of CCA tumours harbour **IDH1/2 mutations (IDH^{mt})** that can be targeted with IDH inhibitors, such as ivosidenib, which improve progression-free survival in second-line treatment.

GOAL: Provide a **clinical characterization of IDH^{mt} CCA** in routine clinical practice and **generate a collection of patient-derived xenografts (PDXs)** to perform drug efficacy evaluation.

DESIGN

PART 1: Clinical characterization of IDH^{mt} CCA

Key eligibility criteria
- Histologically confirmed advanced CCA
- Genomic profiling of primary or metastatic tumour.

→ IDH^{mt} CCA N=77
→ IDH^{wt} CCA N=254

Aims
1. Compare the clinical characteristics of IDH^{mt} vs IDH^{wt} CCA.
2. Evaluate the survival outcomes of IDH^{mt} patients treated with IDH inhibitors.

PART 2: Generation of a CCA PDX collection

Tumour pieces from **metastatic lesions** were implanted into **NOD.CB-17-Prkdc scid/Rj mice.** Upon growth of the engrafted tumours, a tumour piece was implanted into a new recipient mouse for the **model perpetuation.**

H&E staining, IHC of CCA markers (KRT19 and HepPar1), and NGS were used for **histological and genomic characterizations.**
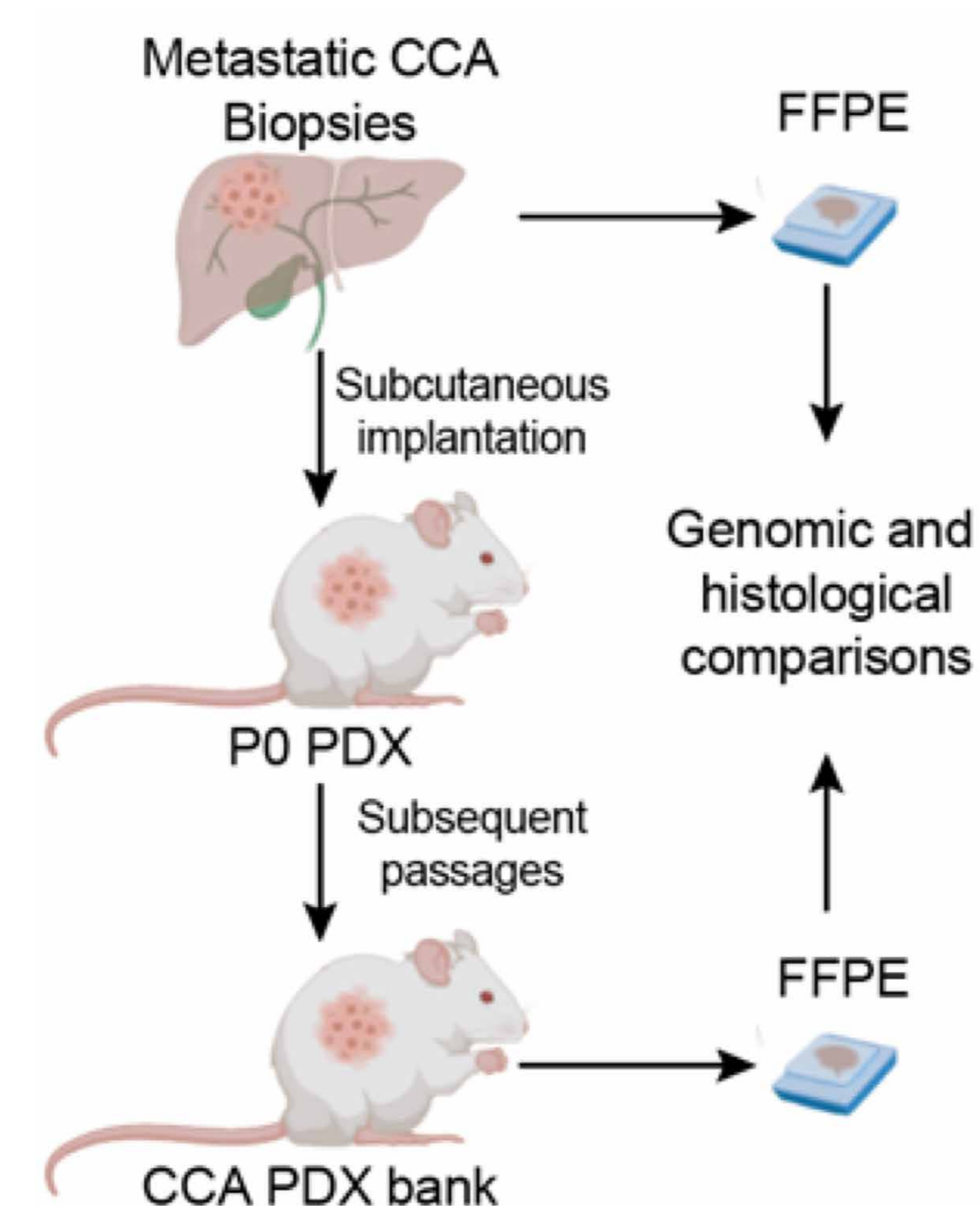
RESULTS

Table 1: Baseline characteristics comparing IDH^{mt} with IDH^{wt} patients.

	IDH^{mt} (N=77)	IDH^{wt} (N=254)	P-value
Age [Median (range)]	59 (35-84)	62 (27-92)	<0.01
Gender (Female, %)	50 (64.9%)	113 (44.4%)	<0.01
Stage IV at diagnosis (N, %)	55 (71.4%)	144 (54.6%)	0.02
Surgery (N, %)	17 (22%)	113 (44.4%)	<0.01
Adjuvant therapy (N, %)	6 (7.79%)	65 (25.5%)	<0.01
Metastasic location (N, %)			0.9
No visceral	10 (12.9%)	37 (14.5%)	
Visceral	62 (80.5%)	204 (80.3%)	
No metastasis	5 (6.4%)	13 (5.1%)	
First-line regimen (N, %)			0.7
Single agent	6 (7.7%)	26 (10.2%)	
Gem-based combination	60 (77.9%)	200 (78.7%)	
Other treatment	6 (7.7%)	12 (4.6%)	
Best supportive care	5 (6.4%)	16 (6.3%)	
MSI status (N, %)	1 (1.3%)	4 (1.5%)	1
OS [median (95% CI)]	19.5 (16.2-24.1)	15.1 (13.6-18.2)	0.3*

MSI: microsatellite instability, OS: overall survival. *Log-rank p-value

Figure 1: Overall and progression-free survival of IDH^{mt} patients who received 2L IDH inhibitors.

Median OS: 9.79mo (95% CI, 6.7-14.4mo)
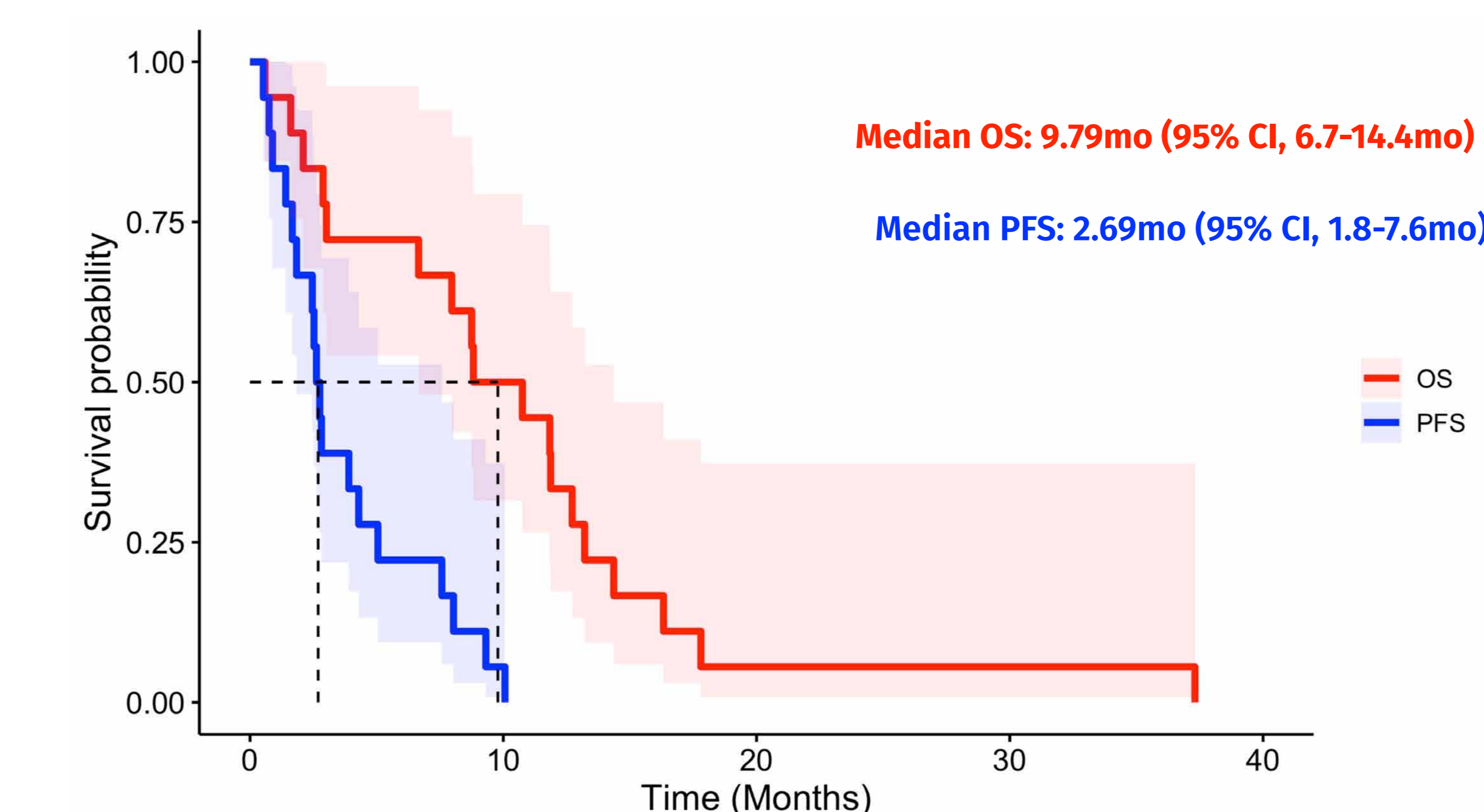
Median PFS: 2.69mo (95% CI, 1.8-7.6mo)

Figure 2: Histopathologic, immunohistochemistry (A) and mutational analysis confirmed that CCA_PDXs maintain the histologic and genomic features of the original biopsy specimens.
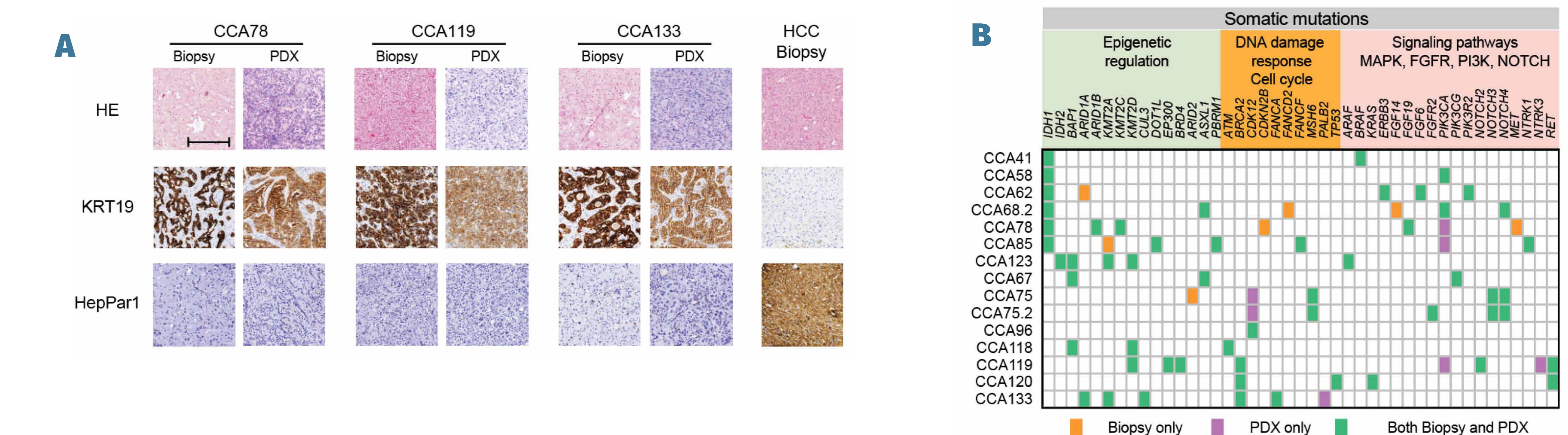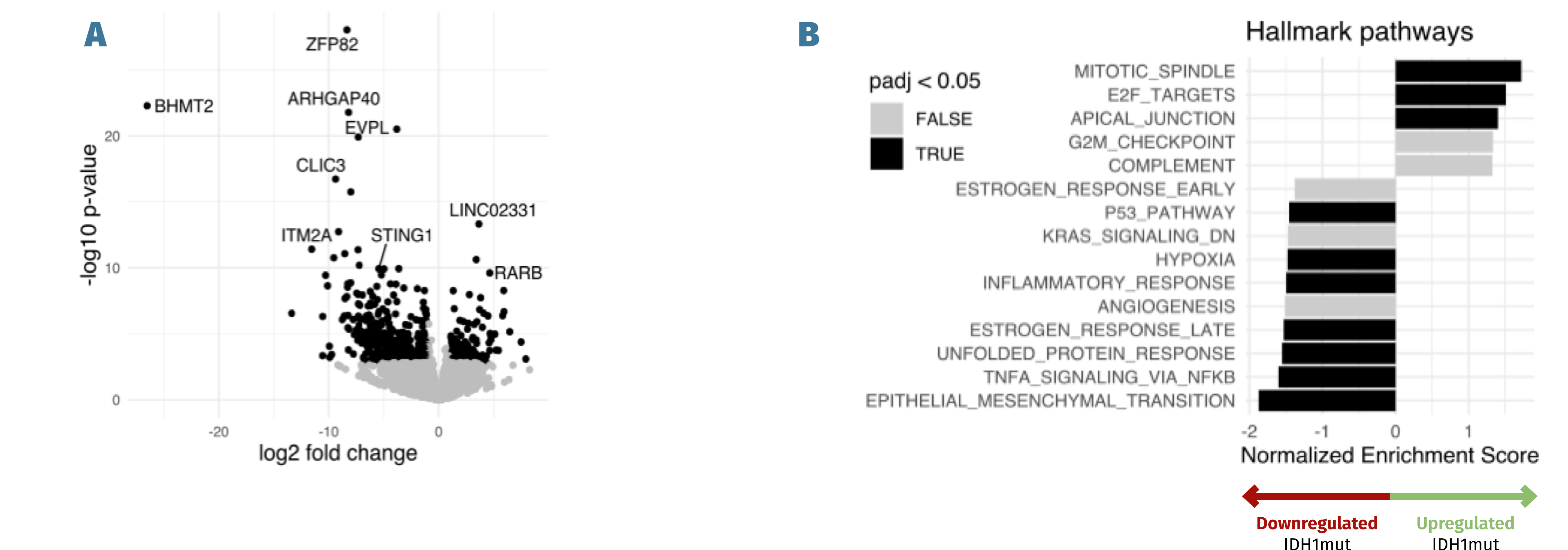

Figure 3: Differential gene expression analysis (A) and pathway enrichment (B) comparing IDH^{mt} with IDH^{wt} shows a downregulation of immune-related pathways in IDH^{mt} tumours.

CONCLUSIONS

- IDH^{mt} tumours are more frequent in young female patients, with more advanced disease at presentation. Patients treated with IDH inhibitors at our tertiary centre present **similar survival outcomes to those reported in the phase III ClarIDHy trial.**
- Genome-wide expression profiling of PDX derived from advanced CCA patients suggest the potential involvement of IDH1^{mt} in CCA tumour immune microenvironment alterations, suggesting a **potential synergistic effect of IDH inhibitors with immune modulating agents.**