Characterizing genomic, transcriptomic and clinical landscape in CCNE/CCND amplified biliary tract cancer

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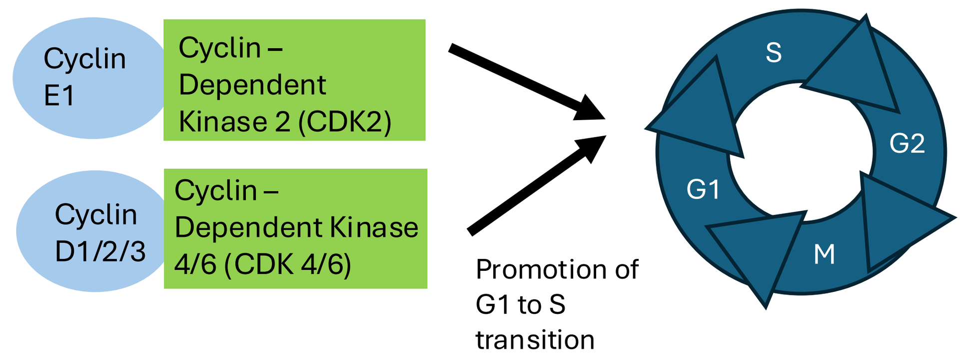
Background

The impact of cell cycle regulator amplifications on clinical outcomes and tumor microenvironment in biliary tract cancer (BTC) remains undefined in the chemo-immunotherapy era. The CCNE/CCND family of cyclin-encoding genes have been identified as oncogenes associated with poor prognosis and immune evasion in other solid tumor malignancies. However, a paucity of data exists in the biliary tract cancer population.



This study characterizes clinical outcomes alongside genomic and transcriptomic profiles in CCNE1 or CCND1/2/3 cyclin amplified BTC.

Methods

- 263 BTC patients were included in survival analysis
- Cohorts were stratified into cyclin amplified (N=71,CCNE1 or CCND1/2/3 Copy Number ≥6) and non-amplified control (N=192)
- Comparison of first-line therapy median progression-free survival (PFS) and median overall survival (OS) was performed [Kaplan-Meier/Log-Rank]
- Genomic analysis of co-mutations (N=63) and co-amplifications (N=62) was performed on an amplified subgroup
- Transcriptomic profiling in amplified (N=19) and control subgroups (N=179) was performed utilizing 29 established gene signatures (Bagaev et al, Cancer Cell 2021) quantifying immune cell infiltration and stromal features
- Differential gene expression was assessed in markers of chemotherapy resistance

Clinical Outcomes

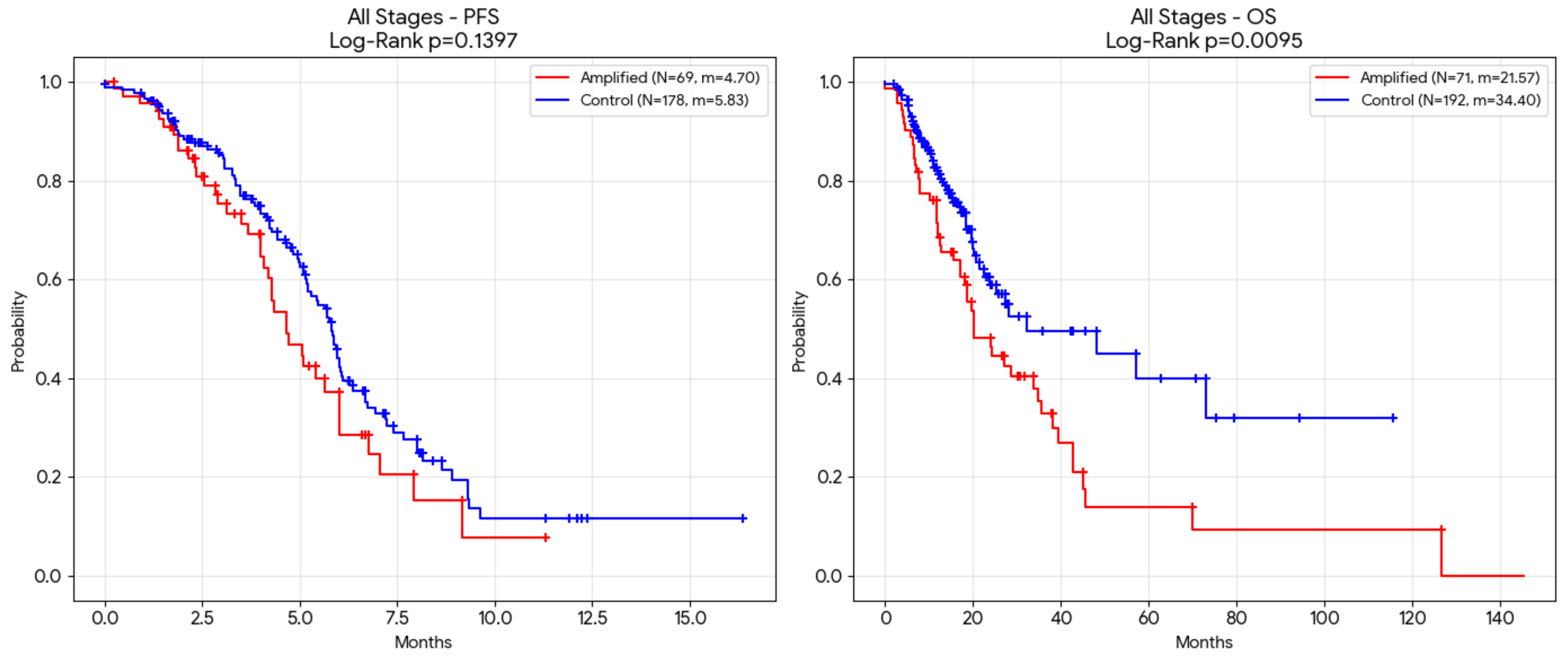


Fig 1A The amplified cohort (copy number ≥ 6 of CCNE1 or CCND1/2/3) had significantly inferior median overall survival compared to control

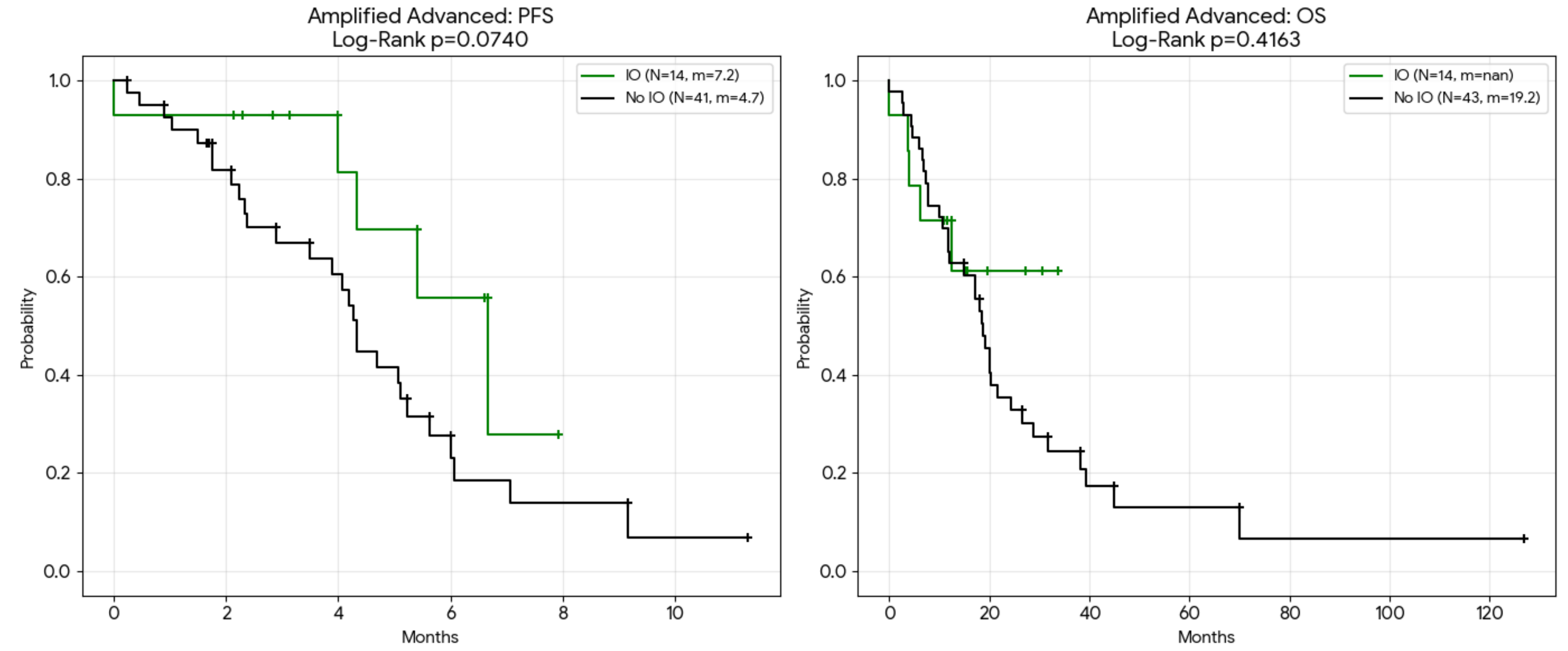


Fig 1B In the advanced stage (stage 3-4) amplified cohort, the addition of immunotherapy to chemotherapy did not significantly improve median overall survival or first-line therapy median progression free survival, although a trend towards improved improved first-line therapy median progression free survival was noted

Genomic Analysis

- Within the amplified cohort, frequent co-amplified genes included FGF19/4 (36%), MYC (23%), **HER2/ERBB2 (19%), EGFR (16%)**, and **MET (16%)**
- Within the amplified cohort, a dominant co-mutations was **TP53 (66.7%)**, associated with P53 loss

Gene Co-Amplification	Adjusted Frequency
FGF19	35.5%
FGF4	33.9%
MYC	22.6%
MDM2	19.4%
ERBB2	19.4%
FGF3	17.7%
EGFR	16.1%
KRAS	16.1%
MET	16.1%

Transcriptomic Analysis

Comparison of RNA expression within selected gene signatures

Gene Signature	P-Value	Direction in Amplified Cohort	Interpretation
B cells	< 0.001	DOWN	Severe lack of humoral immunity.
NK cells	0.002	DOWN	Reduced innate cytotoxicity.
Endothelium	0.003	DOWN	Less vascularized.
Th2 signature	0.004	DOWN	Reduced helper T-cell activity.
T cells	0.008	DOWN	General T-cell exclusion.
Cancer-Associated Fibroblasts	0.009	DOWN	Lower stromal fibroblast content.
Tumor Proliferation	0.053	UP (Trend)	High cell division rates.

Comparison of RNA expression of selected chemotherapy resistance genes

Gene	Function	Amplified Mean	Control Mean	P-Value	Interpretation
RRM1	Gemcitabine Target	56.6	45.8	0.040	Upregulation (Resistance)
ABCC2	Platinum Efflux Pump	56.3	26.4	0.044	Upregulation (Resistance)
TYMS	5-FU Target	68.7	42.5	0.062	Trend toward High (Resistance)
RRM2	DNA Repair / Gem Res	71.6	34.0	0.110	Trend toward High
GSTP1	Platinum Detox	325.5	213.6	0.130	Trend toward High

Conclusions

- CCNE1 or CCND1/2/3 amplified BTC patients exhibited inferior median OS
- The addition of immunotherapy to chemotherapy failed to improve median OS in the amplified cohort, in contrast to the control cohort
- Genomic analysis of the amplified cohort revealed a background of genomic instability with a dominant TP53 mutation
- Transcriptomic analysis revealed an immune-depleted microenvironment and the upregulation of genes associated with chemotherapy resistance

Summary:

CCNE/CCND gene amplification identifies a biologically distinct, aggressive biliary tract cancer subtype characterized by poor prognosis & intrinsic resistance mechanisms to standard chemo-immunotherapy.

- Biliary tract cancer patients with CCNE1 or CCND1/2/3 amplification exhibited inferior median overall survival compared to the non-amplified control cohort
- The amplified cohort was characterized by an “immune desert” phenotype associated with immunotherapy resistance and upregulated expression of chemotherapy resistance genes
- The CCNE/CCND family of genes represent potential prognostic and therapeutic targets in biliary tract cancer patients

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