Molecular Profiling (MP)-Selected Therapy for the Treatment of Patients with Advanced Pancreaticobiliary Cancer (PBC)

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ABSTRACT

Background:
For patients (pts) with advanced PBC who are able to pursue additional therapy, treatment selection is often empiric and clinical benefits are usually modest. Our goal was to study clinical outcomes of MP-guided treatment in advanced PBC.

Methods:
This retrospective analysis included pts with advanced PBC whose tissue samples underwent MP (immunohistochemistry [IHC], microarray [MA], and sequencing analyses) using Target Now® (Caris Life Sciences, Irving, TX). These pts received ≥1 lines of therapy for advanced PBC before their treatment was guided by MP. The MP-guided therapy was considered to have clinical benefit if the TTP ratio between the longest TTP on MP-guided therapy and the TTP on the last therapy pre-MP was ≥1.3.

Results:
Out of 20 pts included in the analysis, 16 had advanced cancer of the pancreas. Median age was 59 yrs (range: 30-81), 85% were male, and 60% had PS of 1. Pts had 1-4 treatment regimens (median: 1) prior to MP. MP identified 1-7 (median: 4) actionable targets per pt. The most commonly identified targets by IHC were: negative or low TS (80%), high TOPO1 (70%), negative or low ERCC1 (52%), and high SPARC (40%). In all 14 pts that had MA results, multiple actionable targets were identified. Of 14 pts with KRAS sequencing analysis, 10 pts (71%) had mutations. Post-MP, pts had 1-4 (median: 1) treatment regimens, most commonly FOLFIRI/XELIRI, FOLFOX/XELOX, capecitabine, and nab-paclitaxel. The total number of regimens post-MP was 33, of which 29 were evaluable for decision impact analysis. In 24 (83%) of cases, treatment decision was modified due to the MP results. Out of the 20 pts, 4 received ≤1 cycle of MP-guided therapy during rapidly progressing disease and were excluded from the clinical outcome analysis. Of the 16 evaluable pts, 6 (37.5%) had a TTP ratio of ≥1.3 (one-sided exact binomial test vs a null hypothesis of ≤15% with TTP ratio ≥1.3, P=0.0056; therefore the null hypothesis is rejected).

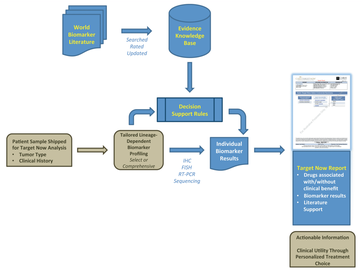
Conclusions:
In our retrospective analysis of a small, yet well-defined, cohort of pts with advanced PBC, MP often influenced treatment decisions and over a third of pts experienced a longer TTP (compared to the last regimen pre-MP), highlighting the promise in MP for treatment selection.

BACKGROUND

- Results from the CONKO-003 trial have indicated that patients with advanced pancreaticobiliary cancer (PBC) can derive meaningful benefit from treatment in 2nd line and beyond.[1]
- A retrospective study by Zhang et al demonstrated that 2nd line chemotherapy had an independent positive correlation to overall survival benefit, contributing approximately half of the median overall survival (3.3 of 7 months).[2]
- Von Hoff et al reported that molecular profiling revealed that pancreatic cancer was rich in actionable targets.[3]
- Treatment choice is challenging in this group of patients who can still benefit from treatment because there are
  - many potential drugs
  - many potential combinations
  - NO standard of care
  - Problems in obtaining access to drugs via medical insurance

An approach based on biological selection of appropriate treatments for sub-groups of patients makes sense in this difficult-to-treat population.

CARIS TARGET NOW™



TARGET NOW™ EXPERIENCE IN ISRAEL

- Provided by Oncotest-Teva (distributers of Caris Life Sciences in Israel) beginning in 2008.
- 584 tests performed to date
  - Colon 139 cases, Breast 110 cases, Pancreas 59 cases, Bile duct 20 cases, Gastric 39 cases, Esophageal 12 cases, Ovarian 36 cases, NSCLC 33 cases, Others 136 cases

STUDY DESIGN

- The aim of the current investigation was to retrospectively study the data from locally advanced and metastatic pancreatic cancer patients who have had their tumor profiled using the Target Now® commercial assay.
- All patients had received at least one treatment line for advanced pancreatic cancer prior to TN-directed therapy.
- The analysis of the clinical outcome data, including response rates and PFS, was done to determine if molecularly-selected therapy, as a result of Target Now® analysis, offers any measurable benefit to patients over physician-selected treatment.

Primary Study Objective

Compare progression free survival (PFS) for therapy selected by molecular profiling with PFS for the last line of therapy on which the patient progressed.

If PFS_B/PFS_A ratio was ≥1.3, MP-selected therapy was defined as having benefit for patient.

PFS: length of time during and after treatment in which a patient is living with a disease that does not get worse.

Temple, R. *Clinical Measurement in Drug Evaluation*. Ningano W. Thicker GT, eds. John Wiley and Sons Ltd: 1995; Von Hoff, D.D. c 1999; Dhani et al. Clinical Cancer Research 2009; 15: 118-123

PARTICIPANTS

- The study was conducted in 3 major medical centers in Israel, where tumors were sent for TN analysis between December 2008 and August 2012
  - Rambam Health Care Campus in Haifa (Dr Epelbaum)
  - Tel Aviv Sourasky medical Centre in Tel Aviv (Dr Shacham-Shmueli, Dr Geva)
  - Hadassah Medical Hebrew University Hospital in Jerusalem (Dr Hubert)

49 patients received actionable reports — **29 patients were not considered for evaluation** = **20 patients evaluable for MP guided treatment**

- 11 did not receive any further treatment
- 10 were lost to FU or had incomplete data
- 3 had immature data
- 3 had no prior treatment for advanced disease
- 2 had insufficient tissue

- 4 patients were excluded from PFS hypothesis study since they had ≤1 cycle of treatment
- 16 patients received > 1 cycle of treatment and were considered evaluable for PFS/OS follow-up

DEMOGRAPHICS

Patient Demographics and Disposition (n=20 patients)

Age	Median 59 y (range 30-81)
Gender	85% Male
Performance Status	60% PS1
Last Line of Therapy Received Prior to Study Entry	
Received up to 1st Line Line Metastatic Treatment	13 (4 adjuvant)
Received up to 2nd Line Line Metastatic Treatment	5
Received up to 3rd Line Metastatic Treatment	1
Received up to 4th Line Metastatic Treatment	1

Molecular Profiling Guided Treatment Choices (n=20 patients)

1st Line Advanced
- 7x Gemcitabine, platinum
- 6x Gemcitabine alone
- 5x gemcitabine, erlotinib
- 1x cisplatin, fluorouracil, calcium folinate
- 1x capecitabine, oxaliplatin, fluorouracil, folinic acid

2nd Line Advanced
- 2x Capecitabine, irinotecan
- 1x capecitabine
- 1x PARP inhibitor
- 1x gemcitabine, everolimus
- 1x Fluorouracil, cisplatin
- 1x fluorouracil, leuovorin

3rd Line Advanced
- 1x erlotinib
- 1x epirubicin, cisplatin, fluorouracil

RESULTS

Molecular Profiling Identifies Actionable Targets (n=20 patients)

(n=20)	Median	Range
Actionable Targets per Patient	4	1–7

Druggable targets reported included

Biomarker	Result	Percentage
TS	Negative or low in 16/20	80%
TOPO1	High in 15/20	75%
ERCC1	Low in 10/19 cases	52%
RRM1	Negative or low in 2/18 (intermediate in 13 cases)	11%
KRAS	Mutated in 10/14 cases	71%
SPARC	Positive in 8/20 cases	40%
PDGFR	High in 4/14	29%
MRP1	Negative in 2/16	13%
TOPO2	High in 2/19	11%
MGMT	Negative in 2/19	11%

Molecular Profiling Influenced or Confirmed Therapeutic Decision in all Patients

Concordance between Treatment of Physician's Choice (recorded prior to receipt of TN report) and Actual Therapy administered (n=20)

Treatment of Physician's choice was captured prior to receipt of report in 19 of 20 patients.

32 lines of treatment were administered post MP, of which 29 were evaluable

In 24 lines (83%), the treatment decision was revised based on the molecular profiling results.

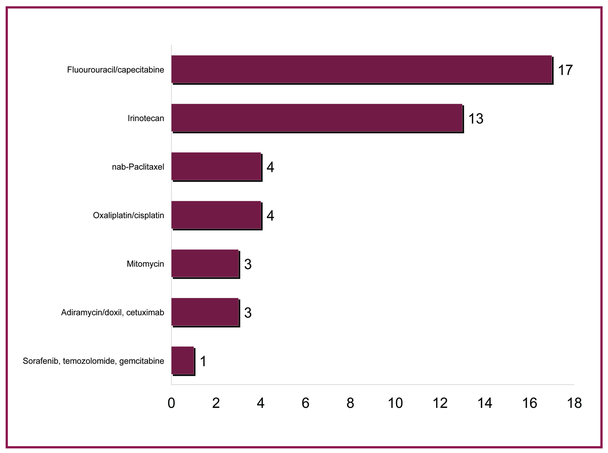
First line of TN-Guided Treatments

5 of 19 patients (26%) had their treatment decision confirmed.
14 of 19 patients (74%) had their treatment decision revised.

Subsequent Lines of TN-Guided Treatments

10 of 10 treatments (100%) administered after completion of 1st TN-Guided Therapy were revised from the original planned therapy choice

Molecular Profiling Guided Treatment Choices (n=20 patients)



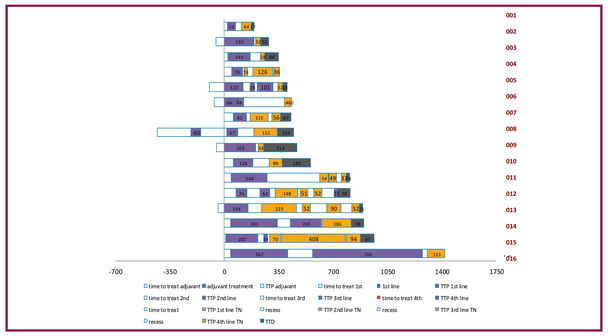
The graph above shows the drugs recommended by the Target Now report which were used alone or in combination in all lines (32) administered following receipt of the molecular profiling information (1–4 lines per pt, median:1)

Comparison of TTP and Response in Prior versus TN-guided Therapy (per patient)

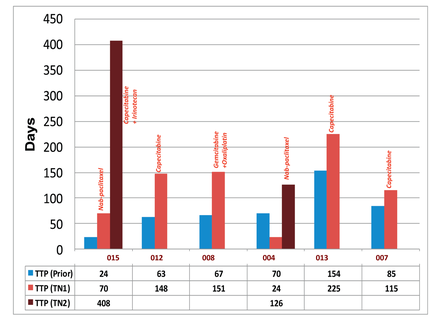
	Median TTP Prior (n=16)	Median PFS TN-Guided (n=16)
TTP/PFS	3.8 m	2.2 m

	Response Rate (All Lines Administered Prior to TN)	%	Response Rate (TN Guided – All Lines Administered)	%
Disease Control Rate (SD+MR+PR)	11/16	69	8/16	50
PD as Best Response	5/16	31	8/16	50

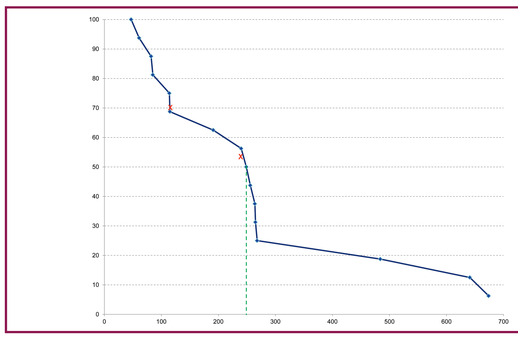
Time to Progression across Multiple Lines (n=16 evaluable patients)



Time to Progression for Patients with PFS Ratio ≥1.3



Overall Survival from 1st Administration of TN-Guided Therapy



CONCLUSIONS

- 6 of 16 evaluable patients (37.5%) had a PFS ratio of ≥ 1.3
  - Similar to the results reported in the Bisgrove Study
  - Sample size was not large enough for statistical significance to be calculated
- TN identified a high number of actionable targets associated with treatment benefit per patient
- The TN report contributed to treatment choice in all cases, leading to treatment revisions in 83% of post-report decisions.
- Outcomes (RR, PFS and OS) were better than reported previously in the patient population

REFERENCES

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2. Zhang et al. (2011) Overall Survival of Patients with Advanced Pancreatic Cancer Improved with an Increase in Second-Line Chemotherapy after Gemcitabine-Based Therapy J Pancreas (Online) 2011 12(2):131–137
3. Von Hoff et al. (2011) Actionable targets in pancreatic cancer detected by immunohistochemistry (IHC), microarray (MA) fluorescent in situ hybridization (FISH), and mutational analysis. J Clin Oncol 29: 4548–4554