MEETING SUMMARY
ASCO GI 2019, San Francisco, USA

Asst. Prof. Efrat Dotan
Fox Chase Cancer Center,
Philadelphia, USA

CANCERS OF THE LIVER, LOWER INTESTINE
AND PANCREAS TRACT
DISCLAIMER

Please note: The views expressed within this presentation are the personal opinions of the author. They do not necessarily represent the views of the author’s academic institution or the rest of the GI CONNECT group.

This content is supported by an Independent Educational Grant from Bayer.
EFFICACY AND SAFETY OF DABRAFENIB AND TRAMETINIB IN PATIENTS WITH *BRAF* V600E–MUTATED BILIARY TRACT CANCER (BTC): A COHORT OF THE ROAR BASKET TRIAL

Wainberg ZA, *et al.* ASCO GI 2019, Abst #187
This study was part of the basket study for rare tumors with \textit{BRAF} V600E mutation. This abstract reported the data on the biliary tract cancers in this study (N=33 patients).

Retrospective studies report incidence of about 5% of \textit{BRAF} mutations in patients with biliary cancers, predominantly in intrahepatic tumors.

The combination of dabrafenib (\textit{BRAF} inhibitor) and trametinib (MEK inhibitor) has demonstrated efficacy in \textit{BRAF} V600E mutated cancers including melanoma, NSCLC.

The \textbf{ROAR study} evaluated 9 different rare tumors with \textit{BRAF} V600E mutations, including biliary tract cancer.

This analysis focussed on the \textit{biliary tract cancer cohort}.

\textit{Wainberg ZA, et al. ASCO GI 2019, Abst #187}

\textit{BRAF}, B-Raf proto-oncogene, serine/threonine kinase; MEK, Mitogen-Activated Protein Kinase Kinase; N, number of patients; NSCLC, non-small-cell lung carcinoma
ROAR STUDY DESIGN

Phase II, open label, single-arm study (BTC cohort)

Patients eligibility:
- BTC
- \textit{BRAF} V600E mutation
- Advanced or metastatic cancer
- Treated with $\geq 1$ prior systemic therapy

Treatment:
dabrafenib 150mg BID + trametinib 2mg QD until disease progression or unacceptable toxicity

Primary endpoint:
Investigator assessed ORR

Secondary endpoints:
PFS, DOR, OS and safety

---

Wainberg ZA, \textit{et al.} ASCO GI 2019, Abst #187
BID, twice daily; \textit{BRAF}, B-Raf proto-oncogene, serine/threonine kinase; BTC, biliary tract cancer; DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QD, once daily
ROAR STUDY
PATIENT ENROLMENT AND CHARACTERISTICS

BTC cohort

557 patients screened

49 patients BRAF V600E mutation

35 patients were enrolled; 32 with centrally confirmed mutation

Patient characteristics:
- Median age 57
- 43% male
- ECOG 0-1 (1 patient was ECOG 2)
- Most patients with adenocarcinoma
- Most with stage IV
- 80% receiving 2 prior lines of therapy

Wainberg ZA, et al. ASCO GI 2019, Abst #187
BRAF, B-Raf proto-oncogene, serine/threonine kinase; BTC, biliary tract cancer; ECOG, Eastern Cooperative Oncology Group; Perf, performance
ROAR STUDY
RESULTS: EFFICACY

• Median duration of treatment was 6 months (range, 2-32 months)
• At the data cut off 67% of patients discontinued treatment mostly due to progression (60%)
• **ORR 42% (95% CI, 25.5-60.8) by investigator review**, 36% (95% CI, 20.4-54.9) by independent review
• Duration of response at 6 months was 66% (95% CI, 32-86%)
• 15 patients (45%) had durable stable disease
• Median PFS 9.2 (95% CI, 5.4-10.1) months
• Median OS 11.7 (95% CI, 7.5-17.7) months

Wainberg ZA, *et al.* ASCO GI 2019, Abst #187
ORR, overall response rate; OS, overall survival; PFS, progression-free survival
• Adverse events were as expected with the combination, mostly (n=35):
  – Pyrexia (40%)
  – Rash (29%)
  – Nausea (23%)
  – Diarrhoea (23%)
  – Fatigue (23%)
  – Chills (20%)
• **BRAF V600E** mutation occur in about 5% of patients with biliary cancers

• This is the first prospective study analysing the benefit of dabrafenib and trametinib in biliary cancer

• Efficacy was comparable to first line chemotherapy in this disease

• ORR of 42% and median PFS of 9.2 months and median OS of 11.7 months

• This is one of several actionable mutations in this disease and should be evaluated for all patients with biliary cancers

• **Based on these results, tumors harbouring this mutation should receive treatment with dabrafenib and trametinib**

---

Wainberg ZA, *et al.* ASCO GI 2019, Abst #187

*BRAF*, B-Raf proto-oncogene, serine/threonine kinase; ORR, overall response rate; OS, overall survival; PFS, progression free survival
RANDOMIZED, OPEN LABEL, PERIOPERATIVE PHASE II STUDY EVALUATING NIVOLUMAB ALONE VERSUS NIVOLUMAB PLUS IPILIMUMAB IN PATIENTS WITH RESECTABLE HCC

Kaseb AO, et al. ASCO GI 2019, Abst #185
PERIOPERATIVE IMMUNOTHERAPY FOR RESECTABLE HCC: INTRODUCTION

- No data are available for neoadjuvant or adjuvant therapy in HCC
- HCC is a very immunogenic tumor, with activity of PD-1 inhibitors which are currently approved for treatment of metastatic disease
- This is the first perioperative study in this patient population

Kaseb AO, et al. ASCO GI 2019, Abst #185
HCC, hepatocellular carcinoma; PD-1, programmed cell death protein 1
PERIOPERATIVE IMMUNOTHERAPY FOR RESECTABLE HCC: DESIGN

Phase II, randomised study

Patients: with HCC eligible for surgical resection
Total N=30

Arm A: Nivolumab
- Nivolumab 240mg Q2wk X3 doses
- Followed by surgery at week 6 and adjuvant nivolumab 240mg Q2wk for up to 2 years

Arm B: Nivolumab + Ipilimumab
- Nivolumab 240mg Q2wk X3 doses + ipilimumab 1mg/kg on day 1
- Followed by surgery at week 6 and adjuvant nivolumab 240mg Q2wk + ipilimumab 1mg/kg Q6wk X4 doses for up to 2 years

Neoadjuvant immunotherapy, surgical resection, followed by adjuvant immunotherapy

Primary endpoint: Safety
Secondary endpoint: ORR; CRR; Time to progression

Kaseb AO, et al. ASCO GI 2019, Abst #185
CRR, complete response rate; HCC, hepatocellular carcinoma; ORR, overall response rate; Q, every; wk, week

13
PERIOPERATIVE IMMUNOTHERAPY FOR RESECTABLE HCC: RESULTS (1)

• Report of the first interim analysis of 8 evaluable patients

• 3/8 patients showed pathologic CR following surgery

<table>
<thead>
<tr>
<th>Results</th>
<th>Arm A: Nivolumab (N=5)</th>
<th>Arm B: Nivolumab + Ipilimumab (N=3)</th>
<th>Arms: A and B (N=8, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety: Grade 3</td>
<td>1*</td>
<td>2*</td>
<td>3 (37.5%)</td>
</tr>
<tr>
<td>Adverse event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy: pCR</td>
<td>2</td>
<td>1</td>
<td>3 (37.5%)</td>
</tr>
</tbody>
</table>

* Did not affect resectability of tumour

• Results show overall good tolerance to the regimen without any affect on the surgical complications

• Further evaluation of their tissue showed significant increase in lymphocyte infiltration and immune reaction

Kaseb AO, et al. ASCO GI 2019, Abst #185
CR, complete response; HCC, hepatocellular carcinoma; N, number of patients
PERIOPERATIVE IMMUNOTHERAPY FOR RESECTABLE HCC:
CONCLUSIONS

- This is the first study evaluating peri-operative approach in resectable HCC showing encouraging results with about a third of the patients with pathologic CR.

- The study is ongoing, and if this rate of response continues may result in a shift in the way we approach resectable HCC.

Kaseb AO, et al. ASCO GI 2019, Abst #185
CR, complete response; HCC, hepatocellular carcinoma; N, number of patients
RANDOMIZED PHASE II/III TRIAL OF NEOADJUVANT CHEMOTHERAPY WITH GEMCITABINE AND S1 VERSUS UPFRONT SURGERY FOR RESECTABLE PANCREATIC CANCER (PREP-02/JSAP05)

Unno M, et al. ASCO GI 2019, Abst #189
NEOADJ CHEMOTHERAPY IN PANCREATIC CANCER:

INTRODUCTION

- This trial was based on a phase II single arm study completed in Japan using neoadjuvant gemcitabine and S1 which showed a 2 year overall survival of 55.9%\(^1\)

- This data led to the current study\(^2\)


Neoadj, neoadjuvant; S1, Tegafur/gimeracil/oteracil
NEOADJ CHEMOTHERAPY IN PANCREATIC CANCER: DESIGN

Phase II/III, multicentre, randomised study

Patients: Histological confirmed resectable PDAC
Target sample size N=163 in each arm

Randomisation 1:1

Arm A: Upfront surgery with adjuvant S1 for 6 months

Arm B: Neoadj gemcitabine and S1
Gemcitabine 1000 mg/m² day 1+8 + Oral S1 40 mg/m² twice daily days 1–14 for 2 cycles → surgery → Adjuvant S1 for 6 months

Primary endpoint:
Phase II resection rate;
Phase III OS

Secondary endpoint:
adverse events;
resection rate;
recurrence-free survival; RTS;
NM; TMK

Unno M, et al. ASCO GI 2019, Abst #189
N, number of patients; NM, nodal metastases; Neoadj, neoadjuvant; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; RTS, residual tumor status; S1, Tegafur/gimeracil/oteracil; TMK, tumor marker kinetics
NEOADJ CHEMOTHERAPY IN PANCREATIC CANCER: PATIENT ENROLMENT

• 182 patients were enrolled on the neoadjuvant therapy arm of which 140 underwent resection

• 180 patients were enrolled on the upfront surgery arm of which 129 underwent resection

• Patient’s characteristics were well-balanced between the two arms
NEOADJ CHEMOTHERAPY IN PANCREATIC CANCER:
RESULTS – EFFICACY (1)

<table>
<thead>
<tr>
<th>Results</th>
<th>Arm A: Upfront surgery</th>
<th>Arm B: Neoadj gemcitabine + S1</th>
<th>Statistical analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase II:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resection rate</td>
<td>82%</td>
<td>93%</td>
<td></td>
</tr>
<tr>
<td>Phase III:</td>
<td></td>
<td></td>
<td>HR, 95% CI; 0.72 (0.55-0.94, P=0.015)</td>
</tr>
<tr>
<td>Median OS</td>
<td>26.6 months</td>
<td>36.7 months</td>
<td></td>
</tr>
<tr>
<td>2-year OS rate</td>
<td>52.5%</td>
<td>63.7%</td>
<td></td>
</tr>
</tbody>
</table>

Unno M, et al. ASCO GI 2019, Abst #189
CI, confidence interval; HR, hazard ratio; Neoadj, neoadjuvant; OS, overall survival; P, probability; S1, Tegafur/gimeracil/oteracil
NEOADJ CHEMOTHERAPY IN PANCREATIC CANCER: RESULTS – EFFICACY (2)

The phase III study portion:

• Subgroup analysis showed improved survival in most subgroups

• Pathologic evaluation showed higher lymph node positivity in the upfront surgery arm versus the neoadjuvant arm

• Recurrence patterns showed higher liver recurrence in the upfront surgery arm versus the neoadjuvant arm
NEOADJ CHEMOTHERAPY IN PANCREATIC CANCER: RESULTS, ADVERSE EVENTS

- Adverse events of neoadjuvant therapy showed expected rate of haematological toxicities
- There was no effect on ability to perform surgery or surgical complications

Unno M, et al. ASCO GI 2019, Abst #189
Neoadj, neoadjuvant
NEOADJ CHEMOTHERAPY IN PANCREATIC CANCER: CONCLUSIONS

• This is the first prospective study to prove the feasibility and benefit of neoadjuvant therapy in resectable PDAC tumors

• Results of multiple ongoing studies in this area, using agents that are available in US and Europe, are eagerly awaited

• This is likely to become the recommended approach for the management of resectable PDAC tumors

Unno M, et al. ASCO GI 2019, Abst #189
Neoadj, neoadjuvant; PDAC, pancreatic ductal adenocarcinoma
REACH GI CONNECT VIA TWITTER, LINKEDIN, VIMEO AND EMAIL OR VISIT THE GROUP’S WEBSITE

http://www.giconnect.info

Follow us on Twitter @giconnectinfo
Join the GI CONNECT group on LinkedIn
Watch us on the Vimeo Channel GI CONNECT
Email antoine.lacombe@cor2ed.com
Dr. Antoine Lacombe
Pharm D, MBA
Phone: +41 79 529 42 79
antoine.lacombe@cor2ed.com

Dr. Froukje Sosef
MD
Phone: +31 6 2324 3636
froukje.sosef@cor2ed.com