Systemic treatment of metastatic pancreatic cancer: 1st line

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Disclosure

Participation to advisory boards:
- ROCHE
- MERCK SERONO
- AMGEN
- NOVARTIS
- SANOFI
- BAYER
- SIRTEX
- LILLY
- SERVIER

Speaker in symposiums:
- ROCHE
- MERCK SERONO
- NOVARTIS
- SANOFI
- LILLY
- TERUMO

Research funding:
- ROCHE
- MERCK SERONO
- PFIZER

My wife is the Head of The Oncology Business Unit in Sandoz Company
More and more patients
Gemcitabine era 1997

Burris, 1997

• Gemcitabine improve benefit responses

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Clinical Survival</th>
<th>% patients surviving</th>
<th>Median survival (months)</th>
<th>5FU n=63, 4.8% censored</th>
<th>Gem n=63, 12.7% censored</th>
</tr>
</thead>
<tbody>
<tr>
<td>5FU</td>
<td>6 months</td>
<td>46%</td>
<td>5.55</td>
<td>4.41</td>
<td></td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>6 months</td>
<td>24%</td>
<td>6 months</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 months</td>
<td>18%</td>
<td>9 months</td>
<td>2%</td>
<td></td>
</tr>
</tbody>
</table>

Log-Rank Test p = 0.0025
Metastatic disease “old” Conclusion

• Treatment of pancreatic neoplasms remains a challenge
• We have seen some recent improvements
  – Gem + erlotinib, new standard
  – Gem + capecitabine ?
  – To a less extent : Gem + cisplatin
  – Other combination CT ?
• But we urgently need
  – Translational research to find new targets
  – A better definition of strategy
First step: Folfirinox single arm

- 47 patients
- 76% metastatic disease
- No toxic death
- ORR: 26%
- Improvement of all functional scales QoL

Folfirinox phase III: a new standard of care for fit patients

- Folfirinox trial
FOLFIRINOX Delays QoL Deterioration Despite Less Favorable Toxicity Profile

Time until definitive deterioration >20 points in EORTC Core Quality of Life questionnaire global health status

→ nab®-Paclitaxel is the First Tumor-Targeted Nanomedicine to Leverage the Natural Transport Properties of Albumin

130 nm in size\(^1,2\)

- A single molecule of albumin can bind up to 6 or 7 molecules of paclitaxel\(^5\)

nab-Paclitaxel + Gemcitabine in Patients With Metastatic Pancreatic Cancer: Phase I/II

Study design MPACT

Planned N = 842
- Stage IV
- No prior treatment for metastatic disease
- KPS ≥70
- Measurable disease
- Total bilirubin ≤ULN

nab-Paclitaxel: 125 mg/m² IV qw 3/4 weeks
+ Gemcitabine: 1000 mg/m² IV qw 3/4 weeks

1:1, stratified by KPS, region, liver metastasis

- Primary Endpoint:
  - OS
- Secondary Endpoints:
  - PFS and ORR by Independent Review (RECIST)
- Safety and Tolerability
  - by NCI CTCAE v3.0

- With 608 events, 90% power to detect OS HR = 0.769 (2–sided α = 0.049)
- 1 interim analysis for futility
- Treat until progression
- CT scans every 8 weeks

Overall survival

FOLFIRINOX and nab-P + GEM as first-line therapy: 2 standards…

**Overall Survival**\(^{[a]}\)

<table>
<thead>
<tr>
<th></th>
<th>Median (mo)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine</td>
<td>6.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FOLFIRINOX</td>
<td>11.1</td>
<td></td>
</tr>
</tbody>
</table>

HR (95% CI) = 0.57 (0.45–0.73)

**Updated Overall Survival**\(^{[b,c]}\)

<table>
<thead>
<tr>
<th></th>
<th>Median, mo (95% CI)</th>
<th>Events/n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gem + nab-paclitaxel</td>
<td>8.7 (7.89–9.69)</td>
<td>380/431</td>
</tr>
<tr>
<td>Gem</td>
<td>6.6 (6.01–7.20)</td>
<td>394/430</td>
</tr>
</tbody>
</table>

HR (95% CI) = 0.72 (0.62–0.83)

P <0.001

**Number at risk**

<table>
<thead>
<tr>
<th></th>
<th>Gemcitabine</th>
<th>FOLFIRINOX</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>171 134 89 48 28 14 7 6 3 2 2 2 2 1</td>
<td>171 146 116 81 62 34 20 13 9 5 3 2 2 2 2</td>
</tr>
</tbody>
</table>

**Patients at risk**

<table>
<thead>
<tr>
<th></th>
<th>Gem</th>
<th>Gem + nab-p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>431 357 284 208 144 84 48 34 25 16 10 6 5 2 1 0</td>
<td>430 340 231 149 90 47 27 19 14 8 4 2 0 0 0 0</td>
</tr>
</tbody>
</table>

### 1st-line Nab-P+GEM vs FOLFIRINOX: Cross-trial comparisons….

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Nab-P+Gem (n = 431)</th>
<th>FOLFIRINOX (n = 171)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>29%</td>
<td>32%</td>
</tr>
<tr>
<td>PFS, months</td>
<td>5.5</td>
<td>6.4</td>
</tr>
<tr>
<td>OS, months</td>
<td>8.5</td>
<td>11.1</td>
</tr>
<tr>
<td>1 year, %</td>
<td>35</td>
<td>48</td>
</tr>
<tr>
<td><strong>Safety, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>3</td>
<td>5.4</td>
</tr>
<tr>
<td>Growth factors</td>
<td>26</td>
<td>43</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17</td>
<td>23</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>17</td>
<td>9</td>
</tr>
</tbody>
</table>

MPACT trial population (nab-p + GEM) included patients with poorer PS and had no age limit.

Meta-analysis of retrospective or cohort study comparing nab-P+GEM and FOLFIRINOX

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peixoto 2015</td>
<td>0.1133</td>
<td>0.2114</td>
<td>7.6%</td>
<td>1.12 [0.74, 1.69]</td>
<td>2015</td>
</tr>
<tr>
<td>Wang 2017</td>
<td>-0.1863</td>
<td>0.0797</td>
<td>13.4%</td>
<td>0.83 [0.71, 0.97]</td>
<td>2017</td>
</tr>
<tr>
<td>Muranaka 2017</td>
<td>0.0677</td>
<td>0.409</td>
<td>3.2%</td>
<td>1.07 [0.48, 2.39]</td>
<td>2017</td>
</tr>
<tr>
<td>Kang 2018</td>
<td>-0.4155</td>
<td>0.0786</td>
<td>13.5%</td>
<td>0.66 [0.57, 0.77]</td>
<td>2018</td>
</tr>
<tr>
<td>Tahara 2018</td>
<td>-0.7381</td>
<td>0.4445</td>
<td>2.8%</td>
<td>0.48 [0.20, 1.14]</td>
<td>2018</td>
</tr>
<tr>
<td>Cartwright 2018</td>
<td>0.0583</td>
<td>0.0892</td>
<td>13.0%</td>
<td>1.06 [0.89, 1.26]</td>
<td>2018</td>
</tr>
<tr>
<td>Kim 2018</td>
<td>0.1484</td>
<td>0.0966</td>
<td>12.7%</td>
<td>1.16 [0.96, 1.40]</td>
<td>2018</td>
</tr>
<tr>
<td>Hegewisch-Becker 2018</td>
<td>0.0953</td>
<td>0.057</td>
<td>14.3%</td>
<td>1.10 [0.98, 1.23]</td>
<td>2018</td>
</tr>
<tr>
<td>Dhir 2018</td>
<td>0.2852</td>
<td>0.2345</td>
<td>6.8%</td>
<td>1.33 [0.84, 2.11]</td>
<td>2018</td>
</tr>
<tr>
<td>Terashima 2018</td>
<td>0.1655</td>
<td>0.0948</td>
<td>12.7%</td>
<td>1.18 [0.98, 1.42]</td>
<td>2018</td>
</tr>
</tbody>
</table>

Total (95% CI) 100.0% 0.99 [0.84, 1.16]

Heterogeneity: $\tau^2 = 0.04, \chi^2 = 46.15, df = 9 (P < 0.00001)$; $I^2 = 80$

Test for overall effect: $Z = 0.12 (P = 0.90)$

Favours GEM + NAB-P
Favours FOLFIRINOX

PRODIGE 35 Panoptimox (phase II)

Main endpoint: 6-month PFS rate

(H₀: 30%, H₁: 45%, α=5%, 1-β=90%)

M+ pancreatic K
No previous CT or RT
ECOG WHO 0-1
n= 276 pts

FOLFIRINOX
12 cycles then stop

FOLFIRINOX 8 cycles
then LV5FU2 (rechallenge of FOLFIRINOX if PD)

FOLFIRI.3 (2 months) / gemcitabine (2 months)
Until PD

Oxaliplatine 85 mg/m², Irinotecan 180 mg/m², LV 200 mg/m², 5FU bolus 400 mg/m², 5FU infusion 2400 mg/m² 46h; cycles de 14 jours
LV 200 mg/m², 5FU bolus 400 mg/m², 5FU infusion 2400 mg/m² 46h; cycles de 14 jours
Irinotecan 90 mg/m² à J₁, LV 200 mg/m², 5FU bolus 400 mg/m², 5FU infusion 2400 mg/m² 46h, Irinotecan 90 mg/m² à J₃; cycles de 14 jours
Gemcitabine 1000 mg/m² à J₁, J₈, J₁₅; cycles de 28 jours

L. Dahan, et al., ASCO® 2018, Abs #4000
PRODIGE 35 Panoptimox (phase II) : main endpoint

<table>
<thead>
<tr>
<th></th>
<th>FOLFIRINOX 6 months (n = 87)</th>
<th>FOLFIRINOX / LV5FU2 (n = 91)</th>
<th>FIRGEM (n = 88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-month PFS rate n (%) [IC 95%]</td>
<td>41 (47%) [35.1 – 53.1]</td>
<td>40 (44%) [35.1 – 53.1]</td>
<td>30 (34%) [25.7 – 43.3]</td>
</tr>
</tbody>
</table>

- FOLFIRINOX 6 months : similar results when compared to PRODIGE 11
- FOLFIRINOX / LV5FU2 : No major difference
- FIRGEM : less active

L. Dahan, et al., ASCO® 2018, Abs #4000
mFOLFIRINOX??

- Different FOLFIRINOX
  - PRODIGE 11
  - PRODIGE 24
- With or without bolus
- Irinotecan 180 or 150 mg/m²
- 50 consecutive patients
  - 18 first classical doses
  - 32 followings reduction of 20% 5FU and irinotecan…

Cavanna L et al. Oncotargets Ther 2019;12:3077-85
➔ All drugs together??

98 patients enrolled
ORR: 37% vs 10%

Pancreas M+:
FIRGEMAX – PRODIGE 37 (phase II)

• Sequentila combined treatment seemed promising...

Main endpoint: 6-month PFS rate (H0=40%, H1 :60%).

Phase IIIR
– Stage IV
– Pancreatic cancer
– ECOG WHO 0 or 1

Sequential (alternating regimen every 2 months) Gem-NabPacli / FOLFIRI.3

1:1

N=127 pts

Gem-NabPacli
FIRGEMAX – PRODIGE 37 (phase II) : PFS

Negative study, but clear improvement...

6-month PFS rate (%)

<table>
<thead>
<tr>
<th></th>
<th>Gem-NabPacl n=60</th>
<th>Sequential n=62</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-month PFS rate (%)</td>
<td>14 (23.3%)</td>
<td>28 (45.2%)</td>
</tr>
</tbody>
</table>

ITT Population

HR=0.71
95%CI : 0.49 – 1.04

Per protocol Population

HR=0.57
IC 95% : 0.36 – 0.90

Taïeb J, et al., ASCO® 2018, Abs #4107
CA 19-9: Response to Palliative Chemotherapy

Group A, decline in CA 19-9 level > 89%; Group B, decline in CA 19-9 level between 50% and 9%; Group C, decline in CA 19-9 level < 50%

Rationale of PARPi against metastatic pancreatic cancer

- 4-7% of metastatic pancreatic cancer patients harbor a germline BRCA1 and/or BRCA2 mutations (gBRCAm)\(^{[a,b]}\)

- Olaparib, a PARP inhibitor, has demonstrated clinical benefits in gBRCAm ovarian and breast cancers\(^{[c,d]}\)

- In subset of phase II olaparib trial, olaparib showed promising efficacy outcome with median PFS of 4.6 months and ORR of 21.7% in patients who previously received gemcitabine (1-8 prior lines of therapy).

POLO: A Phase 3 International PARPi Maintenance Study in Patients Who are gBRCA Mutated

- mPCA
- Prior platinum therapy (no progression on first-line platinum-based chemotherapy ≥ 16 weeks)
- Germline BRCA mutated
- ECOG 0-1

N = 154

Primary endpoint = PFS by independence review
Secondary endpoints: PFS2 (second progression), ORR, OS, safety, HRQoL

Olaparib 300 mg PO daily
Placebo 300 mg PO daily

POLO phase 3 trial: Survival outcomes

Progression-free survival

Overall survival

NCCN Now Recommends Germline Testing in Newly Diagnosed Pancreatic Cancer Irrespective of Family History

  - Germline testing should be considered is recommended for any patient with confirmed pancreatic cancer using comprehensive gene panels for hereditary cancer syndromes. Genetic counseling is recommended for patients who test positive for pathogenic mutation or for patients with a positive family history of cancer
  - Tumor/somatic gene profiling is recommended for patients with locally advanced/metastatic disease who are candidates for anticancer therapy, to identify uncommon but actionable mutations
  - Genetic risk evaluation recommended for any individual diagnosed with pancreatic cancer

PARP Targeting Potency: High to Low

Talazoparib
Niraparib
Rucaparib, Olaparib
Veliparib

MMR Deficiency Predicts Response of Solid Tumors to PD-1 Blockade


## PDAC and MSI-h/dMMR

<table>
<thead>
<tr>
<th>Author (Year) Country</th>
<th>Cases (n)</th>
<th>Number of MSI/dMMR (%)</th>
<th>IHC</th>
<th>PCR</th>
<th>NGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connor AA, et al. 2016&lt;sup&gt;a&lt;/sup&gt; Canada</td>
<td>255</td>
<td>4 (1.6%)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Humphris JL, et al. 2017&lt;sup&gt;b&lt;/sup&gt; Australia</td>
<td>385</td>
<td>4 (1%)</td>
<td>Yes</td>
<td>---</td>
<td>Yes</td>
</tr>
<tr>
<td>Lupinacci RM, et al. 2018&lt;sup&gt;c&lt;/sup&gt; France</td>
<td>445</td>
<td>8 (1.6%)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hu ZI, et al. 2018&lt;sup&gt;d&lt;/sup&gt; United States</td>
<td>833</td>
<td>7 (0.8%)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

### Features<sup>e</sup>

<table>
<thead>
<tr>
<th>Feature</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medullary; acinar cell Lynch Syndrome associated</td>
<td>KRAS wild-type</td>
</tr>
<tr>
<td>IPMN associated</td>
<td>Good prognosis</td>
</tr>
</tbody>
</table>

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MSI and pancreatic cancer

- MSI pancreatic cancer respond to immunotherapy...
- 0.8% of the pancreatic cancer.....
Milestone trials in pancreatic cancer

1997

1L Gemcitabine[a]
Better than 5-FU
median OS 5.65 mo

2007

1L Erlotinib + GEM[b]
NCIC trial
better than GEM
median OS 6.24 mo

2011

1L Nab-P + GEM[d]
MPACT trial
Better than GEM, median OS 8.5 mo

2013

1L FOLFIRINOX[c]
PRODIGE trial
better than GEM, median OS 11.1 mo

2016

nal-IRI + 5-FU/LV[e]
NAPOLI trial
Better than 5-FU/LV
Median OS 6.1 mo

2019

Olaparib[f]
POLO trial
Better than placebo
gBRCAm & platinum sensitive

Conclusion

- FOLFIRINOX and gemcitabine plus nab-paclitaxel are standard first-line chemotherapy in mPAC patients
- Gemcitabine alone remains the standard of care for a lot of patients
- Best supportive care remains very important in the management of these patients
- Olaparib is the first targeted agent which has proven the improvements in response rates and progression-free survival in gBRCA-mutant mPAC patients with platinum-sensitivity
Major changes ???

Maintenance olaparib BRCA1 gmt
FUTURE HOPES
Randomized Phase II HALO-109-202 Trial: Gemcitabine + nab-paclitaxel ± PEGPH20

- Phase III randomized HALO-301 trial of nab-paclitaxel/gem ± PEGPH20 in metastatic PDA with high HA ongoing; primary endpoint PFS and OS. Results ASCO 2020
- Phase Ib/II FOLFIRINOX ± PEGPH20: Negative results

PANC-003 randomised phase III trial

Metastatic pancreatic cancer
- 18-75 Age Range
- First line treatment

CPI-613:

CPI-613®, mFolfirinox (5-fluoruracil, leucovorin, irinotecan, oxaliplatin)

Folfirinox (5-fluoruracil, leucovorin, irinotecan, oxaliplatin)

100 patients already included
New immunotherapy?? IMM-101
Bispecific Antibodies

Bispecific antibody Cibisatamab

Bispecific Antibody: anti-CEA and anti-CD3

Intra-tumor T cell staining
Control | CEA CD3 TCB

CD8

CD4
Integrated Genomic Analysis Revealed Potential Novel Targets

N = 456 PDAC tissues
32 recurrently mutated genes
10 pathways & processes
Defects of DNA Damage Response Mechanisms

- DNA repair system
  - 9% to 10% of patients with PDAC have germline or somatic BRCA mutations
  - In total, 24% have defects in DDR (mutations in BRCA1/2, PALB2, ATM, CHK1/2...) and/or show a genomic unstable phenotype with DDR insufficiency
- Accumulation of genetic alterations
- Promotion of genomic instability
- Enhance therapeutic resistance

Eryaspase + Gemcitabine...
PARP Inhibitors and Platinum in Patients Who Are BRCAm


The Pilot Study

Gemcitabine and Cisplatin + Veliparib

Stage III-IV gBRCA-positive ECOG PS 0-1

R

Gemcitabine Cisplatin Veliparib

Gemcitabine Cisplatin

Veliparib

The current RP2 study
N = 107, primary endpoint = RR