Recent Advances and Trends in the Management of Locally Advanced Pancreatic Cancer
Incremental Progress

Jill Lacy, MD
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Disclosures

Celgene
AstraZeneca
Navigant
Keyquest

Jill Lacy, MD
Teaching points

• Definitions and “staging” evaluation
• Management
  • improving outcomes
  • consensus guidelines
  • unresolved issues
• Response assessment in patient selection for surgery
• Challenges and future directions
Locally Advanced Pancreatic Cancer (LAPC)

• 30-40% of patients with newly diagnosed pancreatic cancer present with non-metastatic locally advanced unresectable disease (LAPC)
• Historically, survival marginally better than metastatic PC, <12 mo
• Historically, negligible % of patients were able to undergo surgery, <5%
• Patients suffer significant morbidity referable to local tumor burden
• Patterns of failure and biology not well understood*
  • <30% non-metastatic (5/18)
  • >70% metastatic (13/18)

*J Clin Oncol 2009 Apr 10;27(11):1806-13
LAPC: Definition

• Non-metastatic PC comprised of continuum from resectable to unresectable based on involvement of adjacent vascular structures
• Consensus organizations have defined anatomic criteria which delineate three categories of non-metastatic PC:
  – resectable
  – borderline resectable
  – locally advanced unresectable
• Definitions provide guidance for management and needed for clinical trials
• BUT are not uniform and subject to inter-observer variability
Locally Advanced Unresectable Pancreatic Cancer: We know it when we see it

Encasement of SMA or celiac axis*

OR

Extensive involvement of SMV and/or PV that precludes resection and/or reconstruction

AND

No evidence of metastatic disease including metastatic non-regional LNs

*Encasement: >180° contact
Definition of LAPC
NCCN Version 3.2017

• No distant metastases

• Head/uncinate process
  – Solid tumor contact with SMA or CA >180° (encasement)
  – Solid tumor contact with first jejunal branch of SMA
  – Unreconstructable SMV/PV due to tumor involvement or occlusion (tumor or bland thrombus)
  – Contact with most proximal draining jejunal branch into SMV

• Body/tail
  – Solid tumor contact with SMA or CA >180° (encasement)
  – Unreconstructable SMV/PV due to tumor involvement or occlusion (tumor or bland thrombus)
  – Contact with CA and aortic involvement
Borderline Resectable Pancreatic Cancer
on the continuum of vascular involvement

More limited vascular involvement than LAPC and technically may be resectable

BUT:

• High risk for a positive margin of resection (R1 resection)
• Requires more complex operation w/ vascular resection and reconstruction, with higher morbidity
• Multiple anatomic definitions have been proposed and used
• Definitions are often institution and/or operator dependent.
Borderline Resectable: Lack of Uniform Criteria

Criteria differ:
- Extent to which tumor involvement of SMV-PV discriminates borderline resectable from resectable
- Extent to which involvement of celiac trunk discriminates borderline resectable from LAPC
What is Borderline Resectable Pancreatic Cancer?

ASCO Guidelines Panel Approach: “punt”

• Categorizes initial diagnoses as those for whom upfront surgery is recommended versus those for whom preoperative therapy is recommended before resection.

• This categorization captures the oncology provider’s intent in reducing the rate of incomplete resection

• Has chosen not to use the terms “resectable” and “borderline resectable.”

• Continues to support the use of these terms in the context of clinical trials, where clear definitions of eligibility are necessary.

AJCC Staging vs Practical Clinical Staging

• AJCC staging system does not address resectability

• NCCN: For clinical staging purposes, use a four-tier clinical classification system based imaging studies:
  (1) Resectable
  (2) Borderline resectable
  (3) Locally advanced unresectable
  (4) Disseminated
Diagnosis and Evaluation:
Imaging is key

• CT scan chest/abd/pelvis
  – Provides staging in terms of metastatic vs non-metastatic

• If no mets: repeat CT with biphasic “pancreatic protocol CT” to assess vascular involvement/resectability
  – Findings on pancreatic protocol may change management in >50% of pts

• EUS
  – Complements CT in assessing vascular involvement, esp portal vein
  – Biopsy (required)

• Diagnostic laparoscopy with peritoneal washings in selected patients
  – Consider in patients with high CA19-9 in whom surgery may be considered
Diagnosis and Evaluation:
Multidisciplinary Discussion is Key

NCCN Guidelines: Black Box Warning!

Decisions about diagnostic management and resectability should involve multidisciplinary consultation at a high-volume center with use of appropriate imaging studies.
Management of Locally Advanced Pancreatic Cancer
LAPC Management: Current State of Affairs

- Optimal management is controversial
- No internationally-embraced standard approach.
- Initial chemotherapy with a combination regimen in fit patients is the current recommendation of NCCN and ASCO*
- But no clear evidence to support one regimen over another
- Limited prospective data with “modern” chemotherapy

*J Clin Oncol 2016 Aug 1;34(22):2654-68
LAPC Management: Many Unresolved Questions

• What is optimum initial chemotherapy regimen?
  – FOLFIRINOX vs Gem/Abraxane vs other dilemma?

• What is optimum duration of chemotherapy?
  – Role of maintenance chemotherapy?

• What is role of post-chemotherapy radiation?
  – Does it confer a survival benefit?
  – Does it confer a PFS or QOL benefit?
  – Which RT technique and dose is best?
LAPC Management: Many Unresolved Questions

• What is the role of surgery?
  – Who should undergo surgical exploration (local-only biology)?
  – Can we predict resectable disease after “neoadjuvant” therapy?
  – Does surgery confer a survival, PFS, or QOL benefit?
  – Does surgery cure anyone?
LAPC Management: Meaningful Progress

• Prior to 2010, survival <11 months with gemcitabine-based chemo
• FOLFIRINOX* has had meaningful impact on outcomes of LAPC
• Multiple retrospective series, one prospective trial\textsuperscript{2} and one meta-analysis\textsuperscript{3} have demonstrated median survival >24 months with upfront FOLFIRINOX
• 25 to >40% able to undergo resection after FOLFIRINOX
• Emerging experience with gemcitabine/nab-paclitaxel encouraging

\textsuperscript{*}Folinic acid, 5-Flourouracil, Irinotecan, Oxaliplatin.
\textsuperscript{1}Stein et al. Br J Cancer. 2016 Mar 29;114(7):737-43
\textsuperscript{2}Suker et al. Lancet Oncol. 2016 Jun;17(6):801-10
\textsuperscript{3}FOLFIRINOX v Gem for metastatic PC. NEJM. 2011;364:1817-25
FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis

• 13 studies w/ 315 pts with LAPC who received FOLFIRINOX
• 63% also received radiotherapy
• 26% underwent surgery (74% R0 resections)
• Median overall survival 24.2 mo
• Survival substantially better than historical controls with LAPC
• Survival compares favorably with survival of resected patients
Keywords: metastatic pancreatic cancer; locally advanced pancreatic cancer; FOLFIRINOX

Final analysis of a phase II study of modified FOLFIRINOX in locally advanced and metastatic pancreatic cancer

Stacey M Stein1,7, Edward S James1,7, Yanhong Deng2, Xiangyu Cong2, Jeremy S Kortmansky1, Jia Li1,3, Carol Staugaard1, Doddamane Indukala4, Ann Marie Boustani4, Vatsal Patel4, Charles H Cha5, Ronald R Salem5, Bryan Chang6, Howard S Hochster1 and Jill Lacy*.1

1Department of Medicine, Section of Medical Oncology, Yale School of Medicine, 333 Cedar Street, New Haven, CT 06510, USA; 2Yale School of Public Health, 300 George Street, New Haven, CT 06510, USA; 3VA Connecticut Healthcare System, 950 Campbell Avenue, West Haven, CT 06516, USA; 4Department of Diagnostic Radiology, Yale School of Medicine, 333 Cedar Street, New Haven, CT 06510, USA; 5Department of Surgery, Yale School of Medicine, 333 Cedar Street, New Haven, CT 06510, USA and 6Department of Therapeutic Radiology, Yale School of Medicine, 333 Cedar Street, New Haven, CT 06510, USA
FOLFIRINOX in LAPC: Yale Trial Design
Stein. Br J Cancer 2016

Locally Advanced and Borderline PC (NCCN criteria)

mFOLFIRINOX x 8 cycles
CT scan after cycle 4 and 8*

If stable or responding after 8 cycles, additional treatment per investigator’s discretion

Continue FOLFIRINOX*
Radiation with concurrent chemotherapy*
Surgical Resection

Primary endpoint: PFS
Secondary endpoints:
- RR
- OS
- Resection rate

*Surgery allowed if deemed resectable before completion of induction FOLFIRINOX or after additional therapy
FOLFIRINOX in LAPC: Yale Results
Stein. Br J Cancer 2016

Patient Disposition During FOLFIRINOX Induction

Reasons for FOLFIRINOX discontinuation:
- Withdrew, 2 patients
- Opted for chemoRT (stable disease), 4 pts
- Treatment delays, 5 pts
  - Unresolved infection, 2 pts
  - Adverse events, 3 pts

20 pts* 65%
11 pts 35%

*Includes 4 pts deemed resectable prior to 8 cycles
FOLFIRINOX in LAPC: Yale Results

• 31 patients in locally advanced cohort

• Response to induction FOLFIRINOX (RECIST):
  – 17.2% partial response; 82.7% stable disease
  – No patients progressed

• Surgery: 41.9% (13) underwent surgery (all R0 resections)
  – 6 of 13 had chemoRT prior to surgery
  – 9 had node-negative disease (stage 0, I, IIA in 1, 2, and 6 pts)

• Median progression free survival 17.8 mo

• Median survival 26.6 mo
Phase 2 LAPACT Trial of nab®-Paclitaxel Plus Gemcitabine for Patients With Locally Advanced Pancreatic Cancer

Pascal Hammel, 1 Jill Lacy, 2 Fabienne Portales, 3 Albert Sobrero, 4 Roberto Pazo-Cid, 5 Jose L. Manzano Mozo, 6 Eric Terrebonne, 7 Scot Dowden, 8 Jack Shiansong Li, 9 Teng Jin Ong, 9 Thomas Nydam, 9 Philip A. Philip 10

1 Hôpital Beaujon, Clichy, France; 2 Yale Cancer Center, New Haven, CT; 3 Institut régional du Cancer de Montpellier (ICM), Montpellier, France; 4 Azienda Ospedaliera Universitaria San Martino, Genova, Italy; 5 Hospital Miguel Servet, Zaragoza, Spain; 6 Hospital Universitari Germans Trias i Pujol, Barcelona, Spain; 7 Hospital Haut Leveque, Giround, France; 8 Tom Baker Cancer Center, Calgary, Canada; 9 Celgene Corporation, Summit, NJ; 10 Karmanos Cancer Institute, Detroit, MI

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LAPCT Study design: multicenter, single arm, phase 2 trial

**Objective:** To assess the safety and efficacy of 6 cycles of induction therapy with nab-paclitaxel + gemcitabine followed by Investigator’s Choice (IC) of treatment in patients with newly diagnosed LAPC.

- **Primary Endpoint:** TTF\(^e\)
- **Secondary Endpoints:** DCR,\(^f\) ORR, PFS, OS, safety, and QOL\(^g\)
- **Posthoc Evaluation:** Analysis of investigator’s choice of treatment, including resection rate and quality (R0 vs R1)
- **Key Exclusion Criteria:** Endocrine/mixed-origin pancreatic tumors, borderline resectable disease
- **Sample Size:** An estimated 100 patients (assumes 10% dropout rate) in the ITT population provides 80% power to detect a 30% increase in the median TTF from 5.1 (median TTF from the MPACT trial\(^1\)) to 6.6 months

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\(^a\) Eligibility determined on the basis of vascular (SMV, PV, SMA, and CA) involvement or unresectable lymph nodes. \(^b\) Surgical intervention was allowed prior to completion of 6 cycles of nab-paclitaxel + gemcitabine if disease was deemed operable by the treating medical team. \(^c\) For patients without PD or unacceptable toxicity after induction. \(^d\) Concurrent capecitabine or gemcitabine + radiation according to institutional practice. \(^e\) Time from first dose of study therapy to treatment failure, defined as discontinuation of study therapy due to PD, death by any cause, or the start of a non-protocol-defined anticancer therapy. \(^f\) After 6 cycles of therapy; CR, PR, and SD (for ≥ 16 weeks). \(^g\) QOL outcomes were assessed using the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life questionnaires (QLQ), EORTC QLQ-C30 and QLQ-PAN26.

LAPACT: Patient disposition During Nab/Gem Induction

Percentages are based on the 107 enrolled patients; 1 patient enrolled but discontinued prior to the induction phase.

Patients designated for surgery prior to completing 6 cycles of induction were considered to have completed the induction phase.

**Reasons for Discontinuation of Induction**
- Adverse event (n = 20; 18.7%)
- Progressive disease (n = 8; 7.5%)
- Physician decision (n = 6; 5.6%)
- Withdrawal by patient (n = 3; 2.8%)
- Protocol violation (n = 4; 3.7%)
- Nonadherence to study drug (n = 1; 0.9%)
- Death (n = 2; 1.9%)
- Other (n = 1; 0.9%)
## LAPACT: Efficacy during induction

### Best Response During the Induction Phase (*nab*-Paclitaxel + Gemcitabine treatment Only)

<table>
<thead>
<tr>
<th>Best Response by RECIST v1.1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ITT Population (N = 107)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response, n (%)</td>
<td>0</td>
</tr>
<tr>
<td>Partial response, n (%)</td>
<td>35 (32.7)</td>
</tr>
<tr>
<td>All stable disease, n (%)</td>
<td></td>
</tr>
<tr>
<td>Stable disease ≥ 16 weeks</td>
<td>48 (44.9)</td>
</tr>
<tr>
<td>Stable disease ≥ 24 weeks</td>
<td>35 (32.7)</td>
</tr>
<tr>
<td>Disease control rate (complete response + partial response + stable disease), n (%)</td>
<td></td>
</tr>
<tr>
<td>Disease control rate based on stable disease ≥ 16 weeks</td>
<td>83 (77.6)</td>
</tr>
<tr>
<td>Disease control rate based on stable disease ≥ 24 weeks</td>
<td>70 (65.4)</td>
</tr>
<tr>
<td>Progressive disease, n (%)</td>
<td>5 (4.7)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Excluding tumor assessments after non-protocol-defined anticancer therapy or surgery.  
<sup>b</sup> 1 patient (0.9%) was not evaluable and 4 patients (3.7%) did not have a postbaseline assessment.

*ITT*, intent to treat; *RECIST*, Response Evaluation Criteria In Solid Tumors.
• Median best percentage change from baseline in sum of longest diameter of target lesions was 18.5%
• 39 of 102 patients (38.2%) had a > 30% reduction in sum of longest diameter of target lesions

a Investigator assessed.
SLD, sum of longest diameters.
Progression-free survival\textsuperscript{a}

\textbf{ABSTRACT 204: nab-Paclitaxel plus Gemcitabine—Pascal Hammel, MD}

\textsuperscript{a} As of month 12, 27 patients have not progressed or died.

\begin{table}[h]
\centering
\begin{tabular}{llllllll}
\hline
\textbf{Months} & \textbf{0} & \textbf{3} & \textbf{6} & \textbf{9} & \textbf{12} & \textbf{15} & \textbf{18} & \textbf{21} & \textbf{24} \\
\hline
\textbf{No. at Risk} & \textbf{107} & \textbf{97} & \textbf{85} & \textbf{68} & \textbf{40} & \textbf{23} & \textbf{14} & \textbf{7} & \textbf{0} \\
\hline
\end{tabular}
\end{table}

\textbf{Events/N} \textit{All patients} 80/107

\textbf{Median, mo (90\% CI)} 10.8 (9.26 – 11.63)
Overall survival$^a$

Events/N:
- Estimated 12-month OS: 72% (90% CI, 64.5% – 78.9%)

As of month 12, 49 patients were still alive.

$^a$ As of month 12, 49 patients were still alive.
EORTC QLQ-C30 Measurements

The QLQ-C30 QoL was completed by patient: screening, on day 1 of each A+G cycle, and at the 28-day follow-up visit during the induction phase.
Quality of life during induction

- Patients’ overall global health status and overall QOL was maintained through day 1 of cycle 6

* Patients were asked to rate their overall health and quality of life during the past week.
Gem + Nab-paclitaxel in LAPC: LAPACT Summary

- First prospective study to evaluate Nab/Gem in LAPC
- No new safety signals
- Response to induction Nab/Gem encouraging
  - 32.7% partial response; 57.9% stable disease
  - 4.7% progression
- R0 or R1 resection rate 15%
- Quality of life maintained in most patients
- Median progression free survival 10.8 mo (TTF 8.8 mo)
- Median survival unavailable (72% alive at one year)
## Cross Trial Comparisons of Induction Chemotherapy in LAPC

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Induction Regimen</th>
<th>Completed induction</th>
<th>DCR during induction</th>
<th>RR during induction</th>
<th>PFS (mo)</th>
<th>OS (mo)</th>
<th>12 mo survival</th>
<th>Resection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCALOP</td>
<td>Gem/Cape&lt;sup&gt;1&lt;/sup&gt; 3 mo</td>
<td>64.9%</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>12.7</td>
<td>53%</td>
<td>?</td>
</tr>
<tr>
<td>N 114</td>
<td>Gem+/Erlotinib&lt;sup&gt;2&lt;/sup&gt; 4 mo</td>
<td>60.9%</td>
<td>?</td>
<td>?</td>
<td>7.5</td>
<td>12.8</td>
<td>54%</td>
<td>4%</td>
</tr>
<tr>
<td>LAP07</td>
<td>Modified FOLFIRINOX&lt;sup&gt;3&lt;/sup&gt; 4 mo</td>
<td>65%</td>
<td>100%</td>
<td>17.2%</td>
<td>17.8</td>
<td>26.6</td>
<td>86%</td>
<td>42%</td>
</tr>
<tr>
<td>N 442</td>
<td>Gem/nab-paclitaxel&lt;sup&gt;4&lt;/sup&gt; 6 mo</td>
<td>57%</td>
<td>77.6% (at 4 mo)</td>
<td>32.7%</td>
<td>10.8</td>
<td>72%</td>
<td>15%</td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup> Post-induction: randomized to RT wth Cape or Gem (Lancet Oncol 2013 Apr;14(4):317-26)

<sup>2</sup> Post-induction: randomized to RT or continued chemo (JAMA 2016 May 3;315(17):1844-53)

<sup>3</sup> Post-induction: investigators choice chemo, RT, or surgery (Br J Cancer 2016 Mar 29;114(7):737-43)

<sup>4</sup> Post-induction: investigators choice chemo, RT, or surgery (Abs 204 ASCO GI Symposium 2018)
LAPC Management:

- What to do after induction chemotherapy in non-progressors?
  - Continue chemotherapy
  - Radiation and if so what technique
    - LAP07 trial showed no survival benefit for RT after gemcitabine +/- erlotinib induction in non-progressor\(^1\)
    - Advances in chemo and RT limit application of LAP07 to current practice
  - Surgery (? preceded by RT)
  - Irreversible electroporation (?)

\(^1\)Hammel et al. *JAMA* 2016;315(17):1844-53
LAPC Management:

• What to do after induction chemotherapy in non-progressors?
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¹Hammel et al. JAMA 2016;315(17):1844-53
LAPC: Who should undergo surgical exploration?

Limitations of CT Imaging After Induction Therapy

- May show persistent significant vascular involvement in pts who achieve R0 resection
- Of limited value in differentiating residual tumor from fibroinflammatory tissue after pre-op treatment.
- Usual size criteria for response (RECIST) are insufficient to evaluate “biologic” response of LAPC
CT evaluation after neoadjuvant FOLFIRINOX for borderline and locally advanced pancreatic adenocarcinoma: French Experience

- 36 pts with BR/LAPC (NCCN) resected after FFX (+ RT, 12): 31 R0, 5 R1
- Criteria for exploration: improving PS, decreasing CA19-9, no progression
- Significant response to FFX by RECIST on CT: PR in 17/36 (47%)
- Stable disease vs response by RECIST unable to predict R0 resection
- Decreased arterial/venous involvement unable to predict R0 resection
- NCCN classification post-induction FFX unable to predict R0 resection: R0 resection possible in pts with post-treatment LAPC by NCCN

Resection Status According to NCCN Classification

MGH Experience

- 40 pts with BR/LAPC (AHPBA guidelines) who underwent surgery received pre-op FOLFIRINOX
- 19 pts still classified as LA and 9 as BR after FOLFIRINOX
- 92% had R0 resections after FOLFIRINOX
- FOLFIRINOX assoc w/ low lymph node positivity (35%)

Conclusions:
- After pre-op FOLFIRINOX, imaging no longer predicts unresectability
- After pre-op FOLFIRINOX, pathologic predictors of survival are improved

MGH Experience

- 141 pts (BR/LA) surgically explored after FFX(10%) or FFX f/b RT (90%)*
- 110 pts (78%) resected (R0 80.6%, R1 19.4%)
- No pre-op factors accurately predictive of resectability were identified
- Predictors of short survival in resected pts
  - high pre-op CA19-9
  - tumor size > 3 cm
- Median OS of all FOLFIRINOX-treated pts 34.2 and 37.7 mo for resected pts (vs 25.1 mo for upfront resected pts)

*Excluded pts who progressed or died on FOLFIRINOX
Selection of Pts for Surgery: Authors’ Recommendations

- “Surgery should be considered after neoadjuvant CRT in pts who have shown a partial regression of tumor-to-vessel contact, irrespective of the degree of decrease in tumor size or the degree of residual vascular involvement” ¹

- “Patients should be chosen for surgery on the basis of lack of disease progression, good functional status, and decrease in cancer antigen 19-9” ²

- “Inability of imaging to predict resectability after neoadjuvant therapy may lead to operating systematically on all pts without obvious progression after neoadj therapy” ⁴

- “On the basis of the absence of reliable imaging and/or clinical markers of resectability, we advocate for surgery of all borderline resectable and LAPC patients after neoadjuvant FOLFIRINOX in absence of metastatic disease” ³,⁵

Limitations

• Retrospective studies of only those FFX-treated pts who went on to surgical exploration
• Strong selection bias
• Mix of LAPC and BR and lack of uniform definitions
• Role of RT impossible to tease out
• Long-term disease-free survival rate unknown
• Studies needed to
  – better define criteria that predict R0 v R1 resection v unresectable disease
  – to identify predictors of long-term disease-free survival after surgery
Standard of Care for Locally Advanced and Borderline Pancreatic Cancer: Convergence

FOLFIRINOX 4-12 cycles or to maximum response*

Distant mets: alternate chemotherapy, trial
Local progression: RT vs alternate chemotherapy

Continue FOLFIRINOX+

Radiation +

Surgical Exploration

*Gemcitabine and nab-paclitaxel esp in older, less fit pts; CT scan every 6-8 weeks
+Followed by surgical exploration in appropriate candidates
Standard of Care for Locally Advanced and Borderline Pancreatic Cancer: Convergence

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Standard of Care for BR and LAPC: Unanswered questions

- Which chemo? FOLFIRINOX vs Gem plus nab-paclitaxel
- Role of RT (or other local ablative therapies)?
- Optimum RT modality?
- Response assessment after chemotherapy and chemoRT?
- Selection of patients for resection?
  - Predictors of R0 resection AND long-term disease-survival??
LAPC: Challenges

– Need for reliable biomarkers to sort local-only biology from metastatic biology (? SMAD4)
– Need for well designed RCTs to optimize current standard of care
– Strong beliefs on value of components of treatment has hampered trial design to answer key questions
– Need for clinical trials with novel agents focused on LAPC
Clinical Trials in LAPC
Phase III RCTs

- FOLFIRINOX vs FOLFIRINOX followed by SBRT (US)
- Chemotherapy (FOLFIRINOX or Gem monotherapy) vs Chemotherapy followed by chemoradiation (German CONKO-007)
- Irreversible Electroporation vs SBRT after FOLFIRINOX (CROSSFIRE Trial) (Netherlands)
- FOLFIRINOX vs Gemcitabine (NEOPAN)
- Gem/Cap vs Gem/Cap + GV1001 vaccine (LAPC and metastatic)
- Gemcitabine vs Gemcitabine + micellar cisplatin NC-6004 (LAPC and metastatic)
Clinical Trials in LAPC
Phase I and II

- SBRT: 12 studies
  - Dose escalation
  - With immune checkpoint inhibitors
  - With vaccine
  - With concurrent chemotherapy

- Irreversible electroporation: 4 studies

- Standard radiation with alternative concurrent chemotherapy (Abraxane, nelfinivir, S-1)

- Approved chemotherapy drugs (with or without RT)
Clinical Trials in LAPC
Phase I and II

➢ Novel agents with or without RT or chemotherapy
  • Theragene (Replication-competent Adenovirus-mediated Double Suicide Gene Therapy)
  • Oregovomab (anti-CA125)
  • Intra-tumoral gene delivery of CYL-02 (plasmid DNA encoding mouse somatostatin receptor and fusion protein of human deoxycytidine kinase and uridine monophosphate kinase)
  • CG200745 PPA (hypomethylating agent)
  • ATRA (stromal ablation strategy)
  • Intra-tumoral NanoPac (Nanoparticulate Paclitaxel)
  • Ceritinib
  • Tocilizumab (targets IL6 receptor)
  • Nelfinavir (radiosensitizer)
LAPC: Summary

- Distinctions/definitions of borderline resectable and LAPC are somewhat arbitrary and difficult to implement accurately and consistently
- Therapeutic approach for pts with vascular involvement has converged -> upfront combination chemotherapy followed by physician’s discretion
- Response assessment/patient selection for surgery after chemotherapy +/- RT remains a challenge
- Survival and resection rates are increasing with “modern” chemotherapy
- Are we curing more pts with ”modern” neoadjuvant approaches??
- Need for biological predictors of disseminated disease
- Need for high quality RCTs and evaluation of novel agents
Thank You