It is Time for Neoadjuvant Therapy in Pancreas Cancer

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Disclosures

- Advisory Boards here and there in last year
  - Genentech/Roche
  - Aduro
  - Corenerstone
  - Celgene
  - Taiho
  - Pharmacyclics
  - FivePrime
  - Pierre Fabre
  - Janssen
  - Boston Biomedical
  - Bayer
  - Arno
- Current Research Support
  - Amgen, Novartis (Array) , Abbvie, Immunomedics, Merrimack, Taiho, Genentech/Roche, Phoenix Biotech, Bayer, Incyte, Pharmacyclics, FIvePrime, Loxo, Vertex,
- DSMB
  - Momenta
  - Symphogen (not taking pay)
- There is more on sunshine act with some companies than I can explain

I apologize to anybody who thinks they gave me money and didn't get mentioned. You probably didn't give me enough to remember.

Surgery is our only Curative Therapy

- Surgery by itself is a poor option
  - 5 year survival rates for surgery alone are ~10%
    - This doubles with adjuvant chemotherapy
    - No prospective, randomized data that radiation changes this outcome
  - Practice matters
    - Retrospective data show that experienced surgeons and experienced hospitals have better outcomes
    - But top US institutions as recently as a decade ago still only had ~20% 5-year survivals
      - That is with adjuvant therapy

Cameron JL, et al Ann Surg 244:10-15, 2006

Adjuvant Chemotherapy Results

	Median OS	5-year survival	%R1
ESPAC-1 chemo	20.1 months	21%	19%
CONKO-001 gem	22.1 months	22.5%	19%
ESPAC-3 5FU	23.0 months	15.9%	35%
ESPAC-3 gemcitabine	23.6 months	17.5%	35%
ESPAC-4 cape-gem	28.0 months	29%	61%

.Neoptolemos, J, et al NEJM 35);1200-10 2004
Oettle H, et al JAMA 297:267-77, 2007
Neoptolemos, JP, et al JAMA2010;304:1073-81.(updated in ASCO 2016 presentation)
Neoptolemos J, et al ASCO 2016

Post-op Adjuvant Therapy

- Largely unsuccessful
  - Vast majority die
  - 5-year survival is just over 20%
    - Gem-cape data is still early but is 29%
  - 5 year survivors are not all disease free
- And these are the best patients who recover quickly post-op
- >20% of post-op patients do not recover for adjuvant therapy
- We don't have good current data on rate of R2 resection

Our Goal Should be R0 Resection

- ESPAC 4 used1 mm as definition of margins, 60% of patients had R1 resection
  - Note: there was no post-operative scan and some very high CA 19-9 levels so maybe there were some R2 resections
  - Therefore even in high quality institutions in Europe it is hard to get R0 resections
  - Outcomes on all trials, including ESPAC 4 are worse for R1 resected patients

Pancreas Cancer is Changing

- We have never really paid attention to AJCC staging as much as
  - Localized, resectable
  - Locally advanced, unresectable
  - Metastatic
- Now we have added borderline resectable
  - But we don't consistently define it
    - Guidelines from ESDO, ASCO, NCCN, AHPBA and Intergroup Task Force all differ slightly

ESDO Expert Opinion meeting Identified Key Weaknesses in the Guidelines

- AHPBA, NCCN and MD Anderson all use very similar definitions of borderline resectable, but
  - We are unclear if we have truly separated unresectable from borderline resectable
  - Terms about the radiographic findings including impingement, abutment, involvement and encasement while used commonly may not be as clearly defined as they could be
- I will add that we have not tested to see if there is consistency between radiologists in defining these findings

Differing Criteria for Borderline Resectable may Produce Different Results

- One study of FDR gemcitabine + capecitabine as neoadjuvant therapy (no XRT)
  - Local criteria used: 33 borderline resectable patients and 10 unresectable patients
  - NCCN criteria used: 18 borderline resectable, 25 unresectable
  - By local criteria, 15 BR went to surgery, 13 R0 resections and 1 of 2 UR who went to surgery had R0 resection
  - By NCCN criteria, 11 BR went to surgery, 9 R0 resections and 5 of 6 UR who went to surgery had R0 resection

Lee J-L, et al Surgery 2012, 152:851-62

Neoadjuvant Therapy

- Rationale
  - Closer to 100% of patients can be treated
  - Treating healthier patients
    - Not s/p surgery
  - May shrink tumors to
    - Improve surgical margins (R0)
    - Reduce operative difficulty/% of pancreas removed
- Added bonus
  - Abundant tissue for correlative studies
  - Better understanding of biology

3 Goals of Neoadjuvant Therapy

- Response
  - This may not be RECIST response
- Margin free resection
  - "Sterilize" the margins is the mantra
  - This largely requires creating a margin at the vessels
- Not interfering with ability to go to surgery
  - No increased operative mortality
  - Limited increase in operative morbidity
  - Limited risk for progressive disease

Combined Analysis of Published Neoadjuvant Data Shows Low Response Rates

These studies pre-date FOLFIRINOX and gemcitabine + nab-paclitaxel

	CR	PR	SD	PD
All patients (n = 330)	1.8%	18.8%	59.2%	18.9%
Resectable (n = 196)	0.8%	9.5%	73.9%	17%
Borderline/unresectable (n =134)	4%	31.8%	40.9%	21.8%

54.2% of all patients underwent resection
65.8% of resectable patients underwent resection
80.6% of these were R0
31.6% of borderline/unesectable patients underwent resection
62.2% of these were R0
All patients received chemo, 85% had chemoxrt
This preceded use of modern regimens of chemotherapy

Mura Assifi, et al Surgery 150:466-73, 2011

Combined Analysis Shows We Can Achieve R0 Resection

- Suggests that neoadjuvant therapy leads to high R0 resection rate
  - These studies had differing definitions of resectable, borderline and unresectable
  - Intriguingly, borderline and unresectable patients who had resection had the same survival (22.3months) as resectable patients (23 months)
    - Does this suggest our definitions of borderline resectable are just bad on these studies?
  - Did not differentiate chemo from chemoradiation

Mura Assifi, et al Surgery 150:466-73, 2011

More recent studies suggest sruvival differences for resectable and borderline resectable cancers.

- Japanese retrospective study
  - 377 patients with localized disease
    - 124 resectable (111 resected)
    - 83 borderline resectable with venous involvement (76 resected)
    - 170 borderline resectable with arterial involvement
      - 124 went straight to surgery (100 resected)
      - 46 had neoajuvant therapy (40 resected)

Hirono S, et al Pancreas epub ahead of print Apr 2016

Japanese retrospective study Resection and outcomes

377 patients with localized disease
- 124 resectable (111 resected)
- 83 borderline resectable with venous involvement (76 resected)
- 170 borderline resectable with arterial involvement
  - 124 went straight to surgery (100 resected)
  - 46 had neoadjuvant therapy (40 resected)

group	R0 resection (%)	Median PFS	Median OS (ITT)
resectable		21.1 months	20.9 months
Borederline resectable, venous			16.3 months
Borderline, rescectable, arterial	67% overall	14.4 months	13.7 months

Not randomized but R0 rate was 80% for neoadjuvant borderline resectable, arterial involvement patients and only 62% for those who did not get neaodjuvant therapy

Hirono S, et al Pancreas epub ahead of print Apr 2016

Response is an endpoint, but is RECIST the criteria?

- MDACC Retrospective Analysis
  - 122 of 129 patients with borderline resectable disease
  - RECIST 1.1 was used:
    - PR: 15 patients (12%): All resected
    - SD 84 patients (69%): 70 (84%) resected
    - PD: 23 patients (19%): 0 resected
    - Changed to resectable: 1 (0.8%) resected
  - 85 patients underwent resection
    - 95% had R0 resection
    - Median OS was 33 months (12 months for unresected)
    - RECIST response did not predict survival

Katz MHG, et al Cancer, 2012

We do not want to worsen surgical outcomes: Surgical AEs from Alliance Intergroup Trial

	Most common surgical AEs[1]		
AE, n (%)	**Total Grade 3+**	**Grade 3**	**Grade 4**
Anemia	5 (38%)	5 (38%)	0
Infection w/unkn ANC	4 (31%)	3 (23%)	1 (8%)
Infection w/normal or gr 1/2 ANC	2 (15%)	2 (15%)	0
Hemorrhage assoc w/surg, intra-op/post-op	2 (15%)	2 (15%)	0
Anorexia	2 (15%)	2 (15%)	0

*No grade 5 AEs,

[1]Regardless of attribution

1 death within 90 days of surgery

Neoadjuvant Therapy

- Thus far, we appear to be able to achieve R0 resections for both borderline resectable and resectable patients (and possibly locally advanced who get to resection)
- We get responses even before new regimens, though RECIST response may not be what is required
- Even the most toxic regimens still appear to have reasonable surgical outcomes

Criticism of Neoadjuvant Therapy Data

- Patients are selected as some patients never make it to surgery
  - It gives a bias for survival when comparing to post-op
- Argument against that criticism
  - If 90% of patients who get resected are not cured, this is a metastatic disease upon presentation
  - Therefore, eliminating patients with the most aggressive disease likely prevents unhelpful surgery
    - Admittedly we have not proven this theory

If Neoadjuvant Therapy, Many questions?

- Which treatment?
  - Chemotherapy
  - Chemoradiation
  - Chemotherapy followed by chemoradiation
- Which regimen?
  - FOLFIRINOX vs gemcitabine and nab-paclitaxel
- What duration?
  - Longer duration will allow more patients to progress and increase selection bias in results
- What are our endpoints?
  - OS, R0 resection rate, RECIST response, pathologic response

Does chemoradiation have a higher response rate than chemo alone?

- Very little evidence of this
- Primary pancreatic cancers
  - Appear less responsive than metastases (this is different from most other tumor types)
  - Are difficult to measure even with high quality scans

E4201: Locally Advanced pancreatic Cancer Trial Schema

Stratify:
- **PS (0 vs 1)**
- **Weight loss**

(>10% vs ≤10%)

R A N D O M I Z E

ARM A: INDUCTION
GEMCITABINE 1000mg/M2
Once weekly x 6 weeks

1 week rest

ARM A: CONSOLIDATION
GEMCITABINE 1000mg/M2
Once weekly x 3 weeks
Followed by 1 week rest x 5 cycles
1 cycle = 4 weeks

ARM B: INDUCTION
GEMCITABINE 600 mg/M2
Once weekly x 6 weeks
CONCURRENT RT 180 cGy/day
5 days week x 6 weeks
Total dose 50.40 Gy

4 weeks rest

ARM B: CONSOLIDATION
GEMCITABINE 1000mg/M2
Once weekly x 3 weeks
Followed by 1 week rest x 5 cycles
1 cycle = 4 weeks

E4201: Response is the Same for Chemo and ChemoXRT

	GEM alone N = 35	GEM plus XRT N = 34
Partial Resp.	5%	6%
Stable Disease	35%	68%
Progression	16%	6%
Inevaluable*	46%	21%

Can Chemotherapy Before ChemoXRT Provide Better Outcomes

- 70 patients with borderline (n = 24), or unresectable (n = 46) disease treated with chemoXRT
  - Two strategies
    - ChemoXRT with 50.4Gy (53% unresectable pre-treatment)
    - Chemo (gem based) followed by ChemoXRT if no PD after chemo (83% unresectable pre-treatment)
    - 20% in both strategies had resection
  - The patients who underwent chemo followed by chemoradiation had an improved OS (18.7 vs 12.4 months, p =0.02) compared to chemoXRT alone

Arvold ND, et al Cancer 2012;118:3026-35

Newer Chemo regimens

- FOLFIRINOX
  - 31% RR on phase III
  - All investigator assessment
- Gemcitabine + nab-paclitaxel
  - 23% RR on phase III by central review
  - 29% RR by investigator assessment

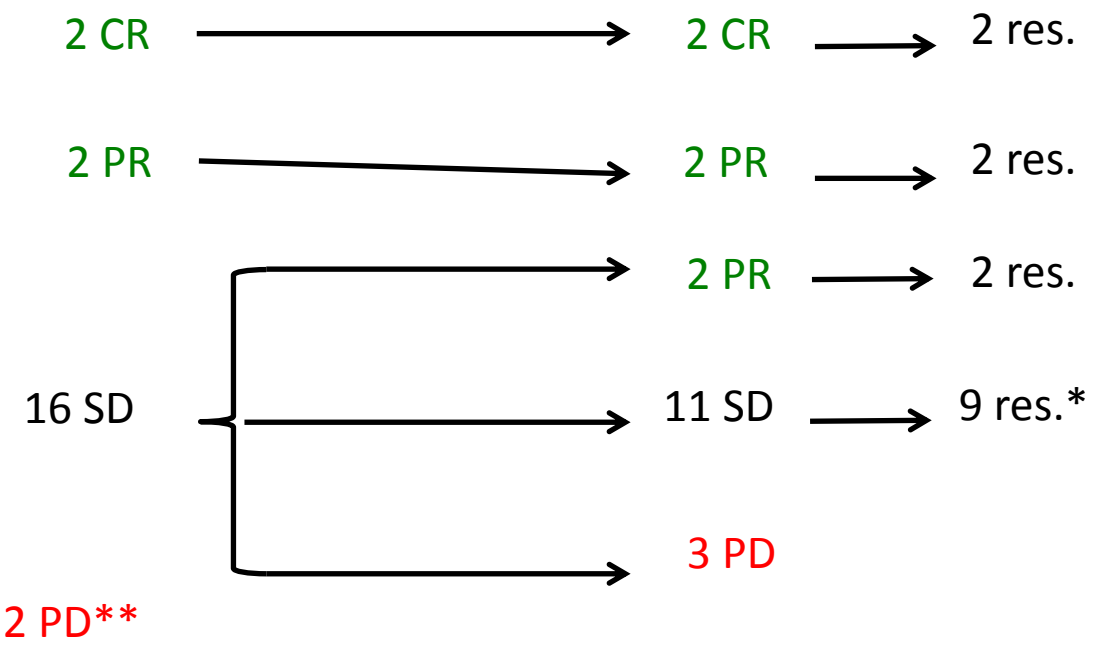
Preoperative mFOLFIRINOX followed by chemoradiation for borderline resectable PDAC

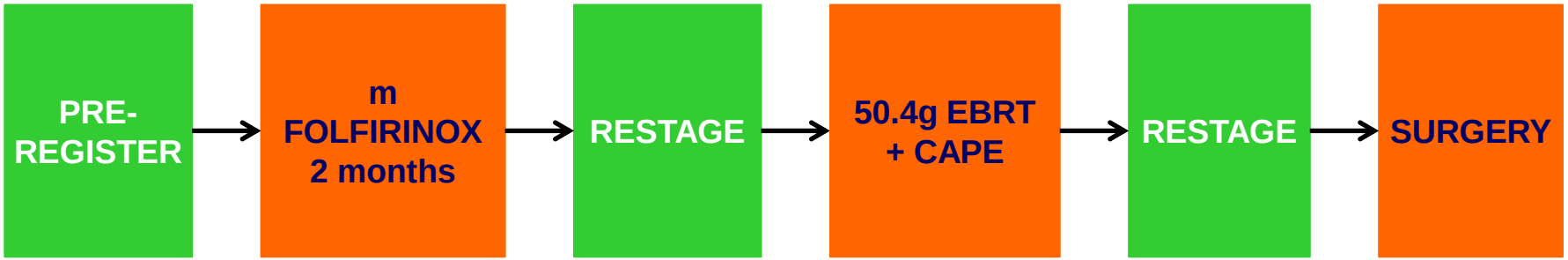
Initial results from Alliance Trial A021101

Matthew H.G. Katz, Qian Shi, Syed Ahmad, Joe Herman, Robert Marsh, Eric Collisson, Lawrence Schwartz, Robert Martin, William Conway, Mark Truty, Hedy Kindler, Andrew M. Lowy, Tanios Bekaii-Saab, Philip Philip, Dana Cardin, Noelle LoConte, Alan Venook

RECIST Response

Best Response:
CR: 2 (9%)
PR: 4 (18%)
SD: 14 (64%)
PD: 2 (9%)





1 mets identified at surgery, 1 refused surgery
** 1 local progression kept on protocol, 1 metastatic

Surgery and pathology

Pancreatectomy (N=15)	N	%*
Portal V resection	12	80
Hepatic A resection	4	27

* Among 15 patients who underwent pancreatectomy

Pathologic variable	N	%*	%**
R0	14	64	93
N0	10	46	67
< 5% residual cells	7	32	47
pCR	2	9.1	13

* Among patients who initiated mFOLFIRINOX (n = 22)
** Among patients who underwent pancreatectomy (n = 15)

Gemcitabine and nab-paclitaxel as Neoadjuvant Therapy

- Alvarez-Gallego, et al ASCO 2016
  - 58 patients with Resectable (15), borderline (16) or locally advanced (27) enrolled
  - Cycle numbers varied and 24 also received chemo-xrt
    - 17 had PD, 6 unresectable
    - 35 resected
      - 12 resectable, 8 borderline, 15 LA
      - BY Ryan Grade Pathological Response, 18 were poor responders, 17 good responders
      - Good responders had 30.6 month OS, poor had 16.5 months

Peri-operative Experiences

- Marsh, et al ASCO 2016
  - 21 “resectable” patients treated with mFOLFIRINOX x 8 cycles (4 pre and 4 post)
    - 17 were resected with 94% R0 rate
    - OS 33.4 months
- Barbour, et al ASCO 2016
  - 42 “resectable” patients treated with 4 cycles of gem-nab-paclitaxel (2 pre and 2 post)
    - Only 60% got post-op treatment
    - 30 were resected, 50% R0
      - Truth is that per NCCN, 7 were borderline and 3 locally advanced

Conclusions

- Post-operative adjuvant therapy is limited
  - Most still die
  - Not all patients recover post-op in time to receive it
- Pre-operative therapy may
  - Reduce unnecessary surgeries in patients with aggressive disease
  - Reduce R1 resection rate
  - Has hope for improving long-term outcomes
  - May add to our understanding of disease biology
  - **Needs prospective studies and consistent definitions**

Slides Provided By

- Matt Katz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