WCGC3

EC5 Report
Montreal, October 2013
10th Anniversary

J. Maroun MD

Conflict of Interest

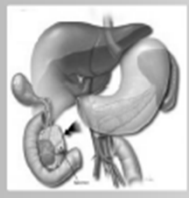
Research Funding and Invited Speaker:

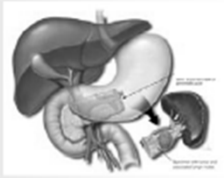
- **Sanofi**
- **Roche**
- **Amgen**

Main Topics

1. **Pancreatic Cancer**
2. **Rectal Cancer**
3. **Metastatic Colorectal cancer**

Surgical Aspects of Pancreas Cancer





Sulaiman Nanji MD, PhD, FRCS, CIP
Assistant Professor of Surgery, Queen's University
EC5 Conference, Montreal
October 18, 2013

Pancreatectomy has evolved

- HPB sub-specialization
- Advanced and safer surgical techniques
- Regionalization to high volume centres
- Better peri-operative care
- Better management of complications
- Multi-disciplinary team approach

Ontario Volume/Outcome Study of Pancreatic Cancer Resection 1988-1994

	Hospital Volumes		
Characteristics	Low (<22)	Mod (22-42)	High (>42)
No. of Hospitals	56	10	2
Total Cases	354	282	206
% Teaching Hosp.	39	65	100
Post-op Mortality (%)	14.4	12.8	3.4

Simunovic M, *CMAJ* 1999; 160: 643-8

What is the appropriate imaging modality for the regional staging of pancreatic cancer prior to determining resectability?

- **Triphasic CT is the preferred pre-operative imaging.**
- **If resectability questionable endoscopic ultrasound (EUS) or MRI can be complementary.**
- **Selective use of laparoscopy and PET scans can be considered to rule out metastatic disease.**

- **The ideal upfront resectable patient has the following characteristics:**
  - **Lack of metastatic disease**
  - **Lack of distant lymph node involvement**
  - **Lack of SMV or Portal vein involvement and normal tissue planes around SMA + Celiac axis**

- **Patients with potentially resectable pancreatic cancer should be assessed by a multidisciplinary team including a surgeon with pancreatic expertise in a high volume centre with access to medical and radiation oncology, interventional radiology, gastroenterology, anesthesia, intensive care support, and nutrition.**

What are the advantages to neoadjuvant treatment in pancreatic cancer?

- **Sparing of surgical morbidity and mortality in patients who have rapidly progressive non-curative disease**
  - **Early treatment of micro metastases**
  - **Increased rates of R0 resection**

What are the disadvantages of neoadjuvant treatment in pancreatic cancer?

- Requirement for pre-operative biopsy with risk of tumor seeding
- Potential chemotherapy and radiation toxicity delaying surgical resection
- Potential for post-operative complications

- Possibility of patients progressing with this approach, leaving patients non-surgical, although the curability of individuals with rapidly progressive disease is debatable.

Is there such a thing as downsizing borderline resectable pancreatic adenocarcinoma?

- Randomized controlled trials data assessing neoadjuvant treatment in downsizing borderline resectable pancreatic cancer is lacking.
- Given the lack of high level evidence, upfront surgery versus neoadjuvant treatment in borderline resectable pancreatic cancer is debatable.
- Due to the limited evidence, we cannot endorse one approach over the other. These cases should be discussed in a multidisciplinary setting.
- We encourage enrolling borderline resectable pancreatic cancer patients on clinical trial.
- We recommend clinical investigation with newer chemotherapy regimens, such as FOLFIRINOX or Nab-Paclitaxel plus Gemcitabine, to assess their role in downstaging borderline pancreatic cancers.

RECTAL CANCER

- **Discussion in multidisciplinary cancer conferences prior to the initiation of primary treatment is recommended.**
- **The report of the synoptic pelvic MRI should be available at the time of the presentation**

Who benefits from neoadjuvant rectal radiotherapy ?

- **Based on NCCN guidelines, the standard of care is to administer neoadjuvant RT to patients with cT3/T4,N0 or any T and lymph node positive (N+) disease.**
- **New emerging data will help stratify patients according to risk of recurrence and describe who may be spared neoadjuvant or adjuvant treatment.**

What duration of neoadjuvant RT should be used in rectal cancer?

- For resectable stage 2 or 3 disease, there is no difference on OS or DFS when short vs long course RT is used (Level 1)
- Both options are validated.
- Short course RT has less acute toxicity and may be preferable for elderly or if there are concerns that patients may not be able to complete long course treatment.

What is the role for brachytherapy in the upfront treatment of rectal cancer?

- Brachytherapy is emerging as an option in the neoadjuvant treatment of rectal cancer.
- Sparing of a greater volume of normal tissue.
- Early data shows promising results
- High-Dose Brachytherapy is to be tested in RCT against External Beam Radiotherapy prior to making further recommendations regarding its use in rectal cancer.

What is the significance of a Pathologic Complete Response?

- **pCR is defined as a specimen where you do not see any cancer cells (Tumour regression grading =1).**
- **An individual meta-analysis has shown that pCR is prognostic (Maas, 2010)**

Is there a role for oxaliplatin-containing chemotherpay in long course neoadjuvant ChemoRadiation for rectal cancer?

- **Trimodality therapy with neoadjuvant chemotherapy (either infusion 5FU or capecitabine) and radiation followed by surgery is considered an acceptable standard of care for T3/T4 or LN positive disease.**
- **We do not endorse the use of oxaliplatin in neoadjuvant chemoradiotherapy for rectal cancer, given the lack of evidence for superiority over fluorpyrimidines alone, and the greater toxicity associated with combination chemotherapy. (level 1)**

Can surgical resection be avoided in patients with clinical complete response after neoadjuvant CRT?

- **Systematic reviews show decreased local recurrence and distant failure and improved overall survival among rectal cancer patients with cCR after neoadjuvant CRT compared to patients without cCR.**
- **No RCT to date has randomized patients with cCR to observation versus surgery.**
- **We still endorse surgical resection following neoadjuvant CRT, even in those patients with cCR.**
- **Future prospectives trials are needed**

Following resection of rectal cancer, what adjuvant chemotherapy should be considered?

- **Due to downstaging effects, we still recommend making chemotherapy decisions based on clinical stage estimate prior to concurrent CRT.**
- **Acceptable adjuvant chemotherapies based on extrapolation from colon cancer data include: FOLFOX/CAPOX/XELOX, 5FU/LV, Xeloda for 4 to 6 months.**

Should we intensify neoadjuvant treatment of rectal cancer with biologics to ensure obtaining a pCR?

The addition of biologics (i.e.: cetuximab, bevacizumab) to neoadjuvant rectal cancer treatment has not been shown to improve the rate of pCR.

Systemic Therapies for "Refractory" Metastatic Colorectal Cancer

Scott Berry MD, MHSc, FRCPC
Sunnybrook Odette Cancer Centre
Toronto, Canada

Sunnybrook
HEALTH SCIENCES CENTRE

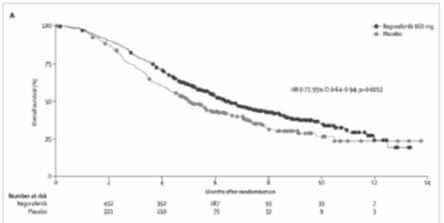
The Toronto Ritual Dance !!!

The Pot and Kettle!!!!

OVERVIEW

- CORRECT:Regorafenib vs Placebo(Pos.)
- Co. 20:Cetuximav +/- Brivanib (neg.)
- X-Pect: Capecitabine +/- Perifosine (neg.)
- TAS- 102

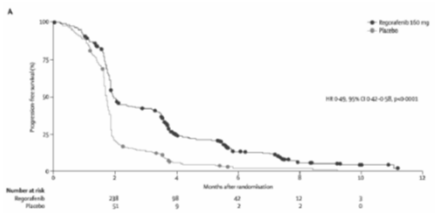
Regorafenib - Overall Survival



Grothey Lancet 2013; 381: 303–12

Issues with Toxicity and QOL

Regorafenib - PFS



Grothey Lancet 2013; 381: 303–12

Randomized Phase II

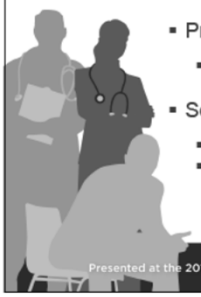
- Patients with 2nd or 3rd line mCRC
- No prior Rx with CAP in metastatic setting
- Prior Rx with 5-FU or 5-FU based regimen

R

Perifosine 50 mg PO QD
Capecitabine 825 mg/m² BID d 1 – 14
N = 20

Cycle = 21 Days

Placebo PO QD
Capecitabine 825 mg/m² BID d 1 – 14
N = 18



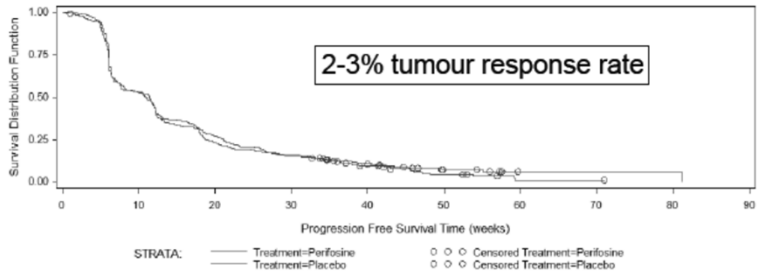
- Primary Objective:
  - To compare time to progression (TTP) of P-CAP vs. CAP as 2nd or 3rd line Rx
- Secondary Objective:
  - To compare overall response rate (CR + PR) and overall survival (OS)
  - To evaluate the safety of P-CAP vs. CAP

Bendell JCO 2011

Presented at the 2012 ASCO Annual Meeting. Presented data is the property of the author. ASCO Annual '12 Meeting

Progression Free Survival – All Patients

K343 - Kaplan-Meier Plot of Progression Free Survival Time in Weeks
ITT Population



2-3% tumour response rate

Duration of PFS (weeks) = (date of progression or death due to any case – randomization date + 1)/7.

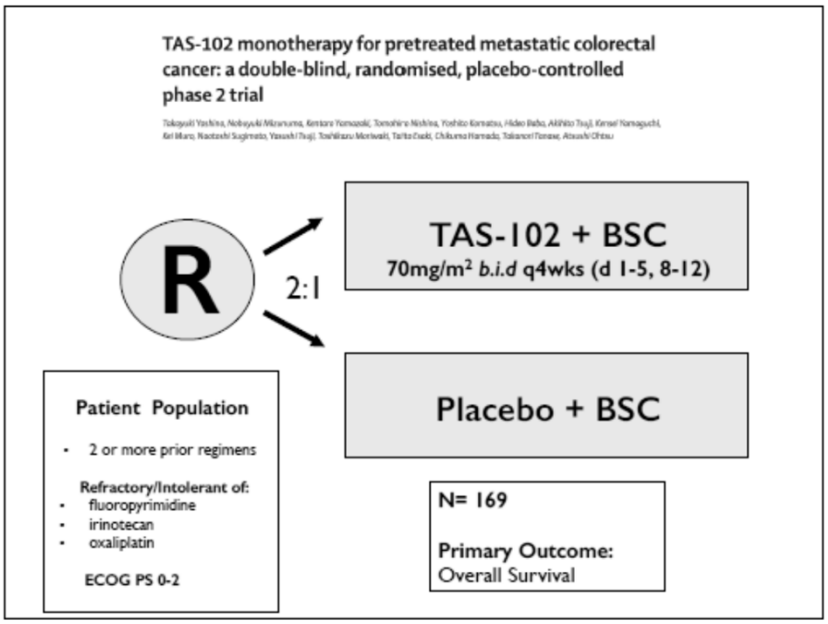
PRESENTED AT: ASCO Annual '12 Meeting

TAS102

- **TAS-102** is a new oral anticancer agent that combines trifluorothymidine and thymidine phosphorylase inhibitor at a molar ratio of 1:0.5
  - trifluorothymidine inhibits thymidylate synthase and DNA synthesis
  - thymidine phosphorylase inhibitor prevents the degradation of trifluorothymidine

TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomised, placebo-controlled phase 2 trial

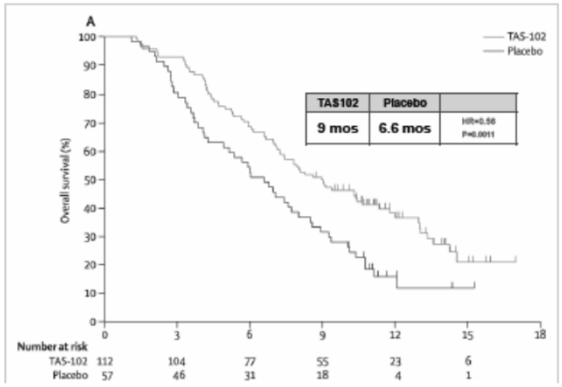
Takayuki Yoshino, Nobuyuki Mizunuma, Kentaro Yamazaki, Tomohiro Nishina, Yoshito Komatsu, Hideo Baba, Akihito Tsuji, Kensei Yamaguchi, Kei Muro, Naotoshi Sugimoto, Yasushi Tsuji, Toshiharu Moriwaki, Taito Esaki, Chikuma Hamada, Takanori Tanase, Atsushi Ohtsu



TAS102 - Results

	TAS102	Placebo	HR p-value
Response Rate (%)	1%	0%	
Disease Control Rate (%)	43.8%	10.5%	P<0.0001
PFS (median, mos)	2 mos	1 mos	HR=0.41 P<0.0001
OS (median, mos)	9 mos	6.6 mos	HR=0.56 P=0.0011

TAS102 - Overall Survival



Yoshino *Lancet Oncol* 2012; 13: 993-1001

TAS102 - Adverse Events (Grade 3/4)

	TAS-102 (N=112)	*Placebo (N = 57)*
	Grade 3/4 %	*Grade 3/4 %*
Hematological		
Neutropenia	50.4	0.0
Leukopenia	28.3	0.0
Anemia	16.8	5.3
Lymphopenia	9.7	3.5
Thrombocytopenia	4.4	0.0
Non-Hematological		
Fatigue	6.2	3.5
Diarrhea	6.2	0.0
Nausea	4.4	0.0
Anorexia	4.4	3.5
Febrile neutropenia	4.4	0.0
Vomiting	3.5	0.0

TAS102 - KRAS

- Interesting subset analysis based on the KRAS status of the patients' tumours:
  - KRAS WT OS HR = 0.70
  - KRAS MUT OS HR = 0.44
  - However:
    - ? Biologic rationale
    - Needs to be validated in future trials

Question: What is the role of regorafenib in third or fourth line treatment of metastatic CRC treatment?

- **Regorafenib should be considered in patients with refractory metastatic CRC who have been treated with standard treatment including [illegible] cetuxima**
- **This treatment is applicable to patients that are both Kras wild type and Kras mutant with good performance status Regorafenib's modest survival benefits need to be considered in relation to its toxicities and lack of impact on QOL.**
- **Patients should be enrolled in a clinical trial when possible.**

What about TAS102 ???

THANK YOU