THE CROSSROADS: Drug Development, Biomarkers, and Colorectal Cancer

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DEPT. OF ONCOLOGY
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Objectives:

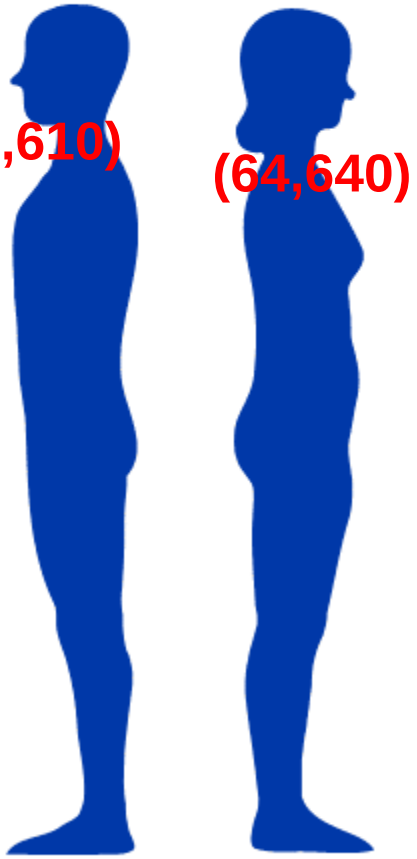
After attending this activity, participants will be able to:

- **Appreciate the role that genetics plays in the therapy and pathogenesis of colorectal cancer including the latest therapy option**
- **Understand the concept of drug development in oncology, with a special emphasis on colorectal cancer**
- **Develop a basic understanding on screening, diagnosis, and management of colorectal cancer**
-

Estimated New Cancer Cases* in the US in 2018

140,250

	Males 856,370	Females 878,980	
Prostate	19%		
Lung & bronchus	14%		13% Lung & bronchus
Colon & rectum	9%		7% Colon & rectum
Urinary bladder	7%		7% Uterine corpus
Melanoma of skin	6%		5% Thyroid
Kidney & renal pelvis	5%		4% Melanoma of skin
Non-Hodgkin lymphoma	5%		4% Non-Hodgkin lymphoma
Oral cavity & pharynx	4%		3% Pancreas
Leukemia	4%		3% Leukemia
Liver & intrahepatic bile duct	4%		3% Kidney & renal pelvis
All other sites	22%		21% All other sites
	(75,610)	(64,640)	30% Breast

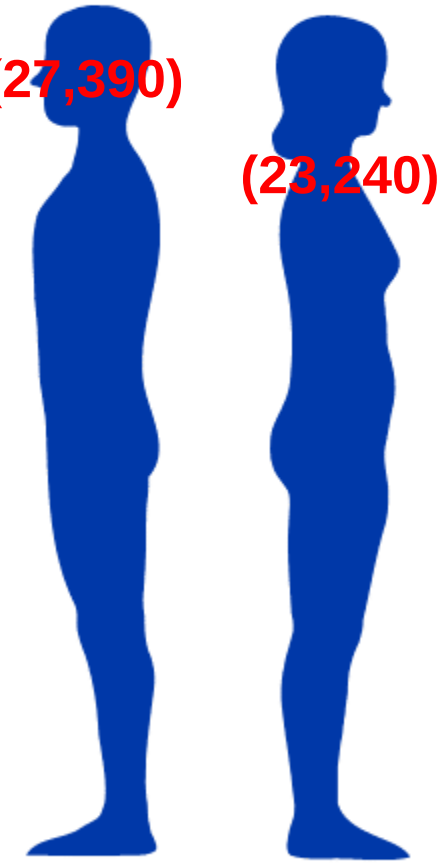


*Excludes basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

Estimated Cancer Deaths in the US in 2018

Males 323,630		Females 286,010	
Lung & bronchus	26%	25%	Lung & bronchus
Prostate	9%	14%	Breast
Colon & rectum	8%	8%	Colon & rectum
Pancreas	7%	7%	Pancreas
Liver & intrahepatic bile duct	6%	5%	Ovary
Leukemia	4%	4%	Uterine corpus
Esophagus	4%	4%	Leukemia
Urinary bladder	4%	3%	Liver & intrahepatic bile duct
Non-Hodgkin lymphoma	4%	3%	Non-Hodgkin lymphoma
Kidney & renal pelvis	3%	3%	Brain & other nervous system
All other sites	24%	24%	All other sites

(27,390)



(23,240)

50,630

Trends in Five-year Relative Survival Rates (%), 1975-2013

Site	1975-1977	1987-1989	2007-2013
All sites	49	55	69
Breast (female)	75	84	91
Colorectum	50	60	66
Leukemia	34	43	64
Lung & bronchus	12	13	20
Melanoma of the skin	82	88	94
Non-Hodgkin lymphoma	47	51	73
Ovary	36	38	47
Pancreas	3	4	9
Prostate	68	83	99
Urinary bladder	72	79	78

5-year relative survival rates based on patients diagnosed in the 9 oldest SEER registries from 1975-1977, 1987-1989, and 2007-2013, all followed through 2014.
Source: Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute, 2017.

Risk Factors for Colorectal Cancer

- Aging
- Personal history of CRC or adenomas
- High-fat, low-fiber diet
- Inflammatory bowel disease
- Family history of CRC
- Hereditary colon cancer syndromes

ARTICLE

doi:10.1038/nature11252

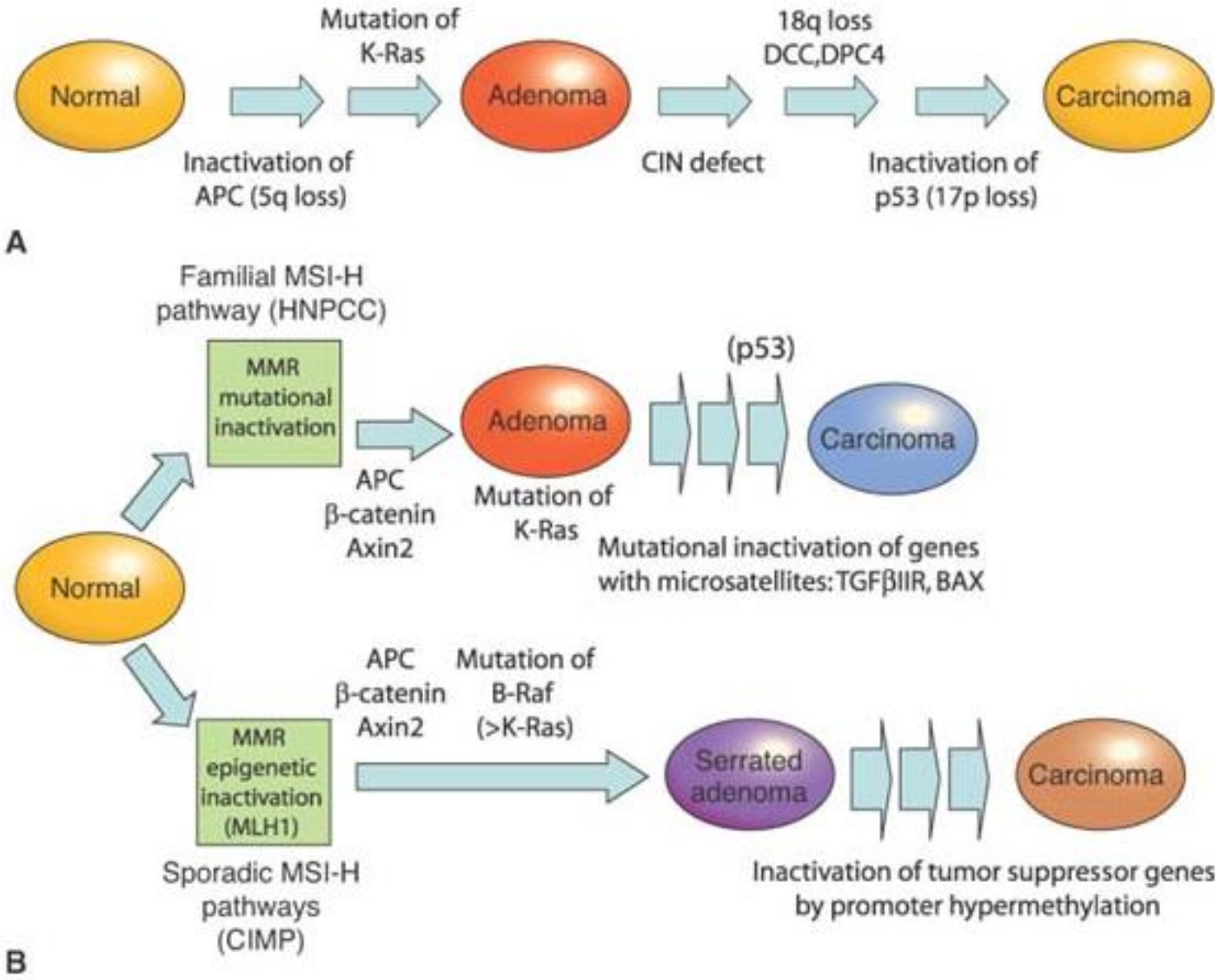
Comprehensive molecular characterization of human colon and rectal cancer

The Cancer Genome Atlas Network*

To characterize somatic alterations in colorectal carcinoma, we conducted a genome-scale analysis of 276 samples, analysing exome sequence, DNA copy number, promoter methylation and messenger RNA and microRNA expression. A subset of these samples (97) underwent low-depth-of-coverage whole-genome sequencing. In total, 16% of colorectal carcinomas were found to be hypermutated: three-quarters of these had the expected high microsatellite instability, usually with hypermethylation and *MLH1* silencing, and one-quarter had somatic mismatch-repair gene and polymerase ε (*POLE*) mutations. Excluding the hypermutated cancers, colon and rectum cancers were found to have considerably similar patterns of genomic alteration. Twenty-four genes were significantly mutated, and in addition to the expected *APC*, *TP53*, *SMAD4*, *PIK3CA* and *KRAS* mutations, we found frequent mutations in *ARID1A*, *SOX9* and *FAM123B*. Recurrent copy-number alterations include potentially drug-targetable amplifications of *ERBB2* and newly discovered amplification of *IGF2*. Recurrent chromosomal translocations include the fusion of *NAV2* and WNT pathway member *TCF7L1*. Integrative analyses suggest new markers for aggressive colorectal carcinoma and an important role for *MYC*-directed transcriptional activation and repression.

TCGA Network. Nature 487, 330-337 (2012)

Three Genetic pathways to colorectal carcinoma.



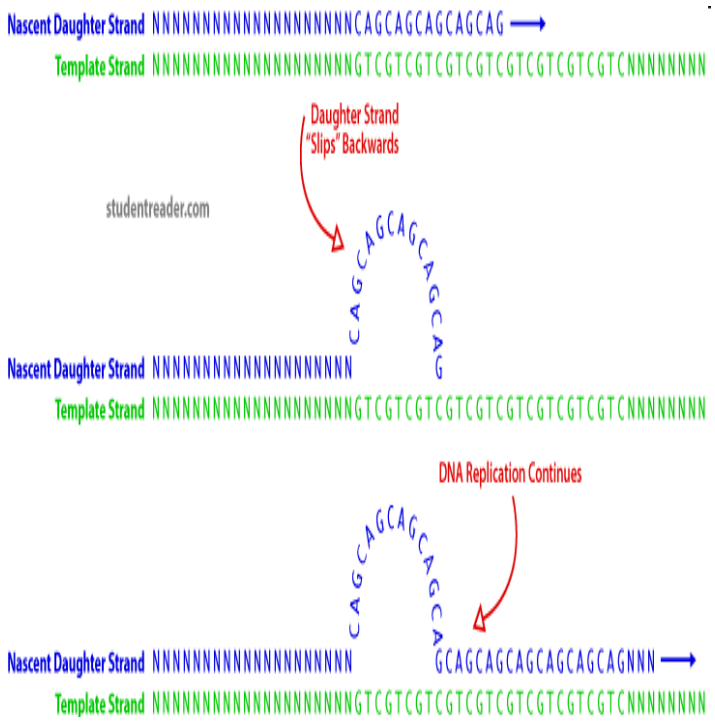
65-80% CIN

10-15% MSI

~10% Serrated polyp

De Vita. Cancer principles & Practice of Oncology, 9th ed.

Mismatch Repair (MMR) deficiency and Microsatellite Instability (MSI)



- MMR deficiency leads to MSI and high concordance rate noted
- Microsatellites are mono or dinucleotide repeats
- Single base pair insertion/deletion leads to instability : >1 (high), 1 (low)
- Right sided, poorly differentiated, lymphocyte infiltration, mucinous
- Better prognosis, lower rate of metastases

- **Screening**
- **Familial CRC**
- **Diagnosis and Staging**
- **Treatment**

  Early stage - surgery

  Intermediate stage - adjuvant chemotherapy

  Advanced stage
- **Use of biomarkers in CRC: towards personalized medicine**
- **Drug Development at Montefiore Einstein**

Figure. Screening for Colorectal Cancer: Clinical Summary

Population	Adults aged 50 to 75 y	Adults aged 76 to 85 y
Recommendation	Screen for colorectal cancer starting at age 50 y. Grade: A	The decision to screen for colorectal cancer is an individual one. Grade: C

Risk Assessment	For the vast majority of adults, the most important risk factor for colorectal cancer is older age. Other associated risk factors include family history of colorectal cancer, male sex, and black race.	
Screening Tests	There are numerous screening tests to detect early-stage colorectal cancer, including stool-based tests (gFOBT, FIT, and FIT-DNA), direct visualization tests (flexible sigmoidoscopy, alone or combined with FIT; colonoscopy; and CT colonography), and serology tests (*SEPT9* DNA test). The USPSTF found no head-to-head studies demonstrating that any of these screening strategies are more effective than others, although they have varying levels of evidence supporting their effectiveness, as well as different strengths and limitations.	
Starting and Stopping Ages	The USPSTF concluded that the evidence best supports a starting age of 50 y for the general population. The age at which the balance of benefits and harms of colorectal cancer screening becomes less favorable varies based on a patient's life expectancy, health status, comorbid conditions, and prior screening status. The USPSTF does not recommend routine screening for colorectal cancer in adults 86 y and older.	
Treatment and Interventions	Treatment of early-stage colorectal cancer generally consists of local excision or simple polypectomy for tumors limited to the colonic mucosa or surgical resection (via laparoscopy or open approach) with anastomosis for larger, localized lesions.	
Balance of Benefits and Harms	The USPSTF concludes with high certainty that the net benefit of screening for colorectal cancer is substantial.	The USPSTF concludes with moderate certainty that the net benefit of screening for colorectal cancer in adults aged 76 to 85 y who have been previously screened is small. Adults who have never been screened are more likely to benefit. Screening is most appropriate for those healthy enough to undergo treatment and those without comorbid conditions that significantly limit their life expectancy.
Other Relevant USPSTF Recommendations	The USPSTF has made a recommendation on aspirin use for the primary prevention of cardiovascular disease and colorectal cancer in average-risk adults. This recommendation is available on the USPSTF website (www.uspreventiveservicestaskforce.org).	

USPSTF website

Summary of Screening Options

Test	Type	Involves	Interval	Sensitivity	Specificity
Stool	gFOBT	Kit for blood	1 yr	30-50%	80%
	FIT	Kit for blood	1 yr	65-70%	85%
	FIT DNA	Kit for DNA	1-3 yr	More	Less
Direct Visualization	Colonoscopy	Scope	10 yr	95-98%	90%
	Flex sig	Scope	5 yr	Lower	??
	CT colonography	CT imaging	5 yr	84%	90%
Combination	Flex sig, FIT		10/1 yr	< c-scope	??

***Guaiac fecal occult blood test**

***Fecal immunochemical test**

USPSTF, JAMA 315: 2564, 2016

JNCCN 14:1033, 2016

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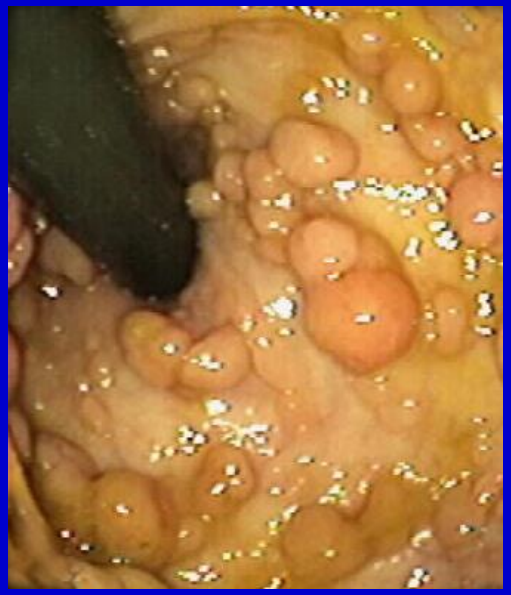
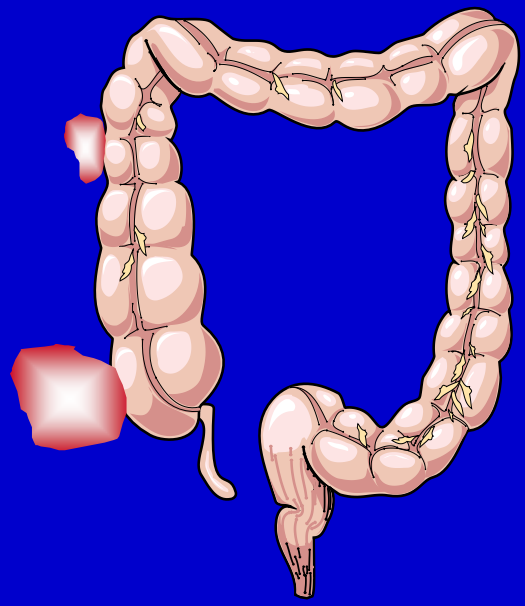
FAP



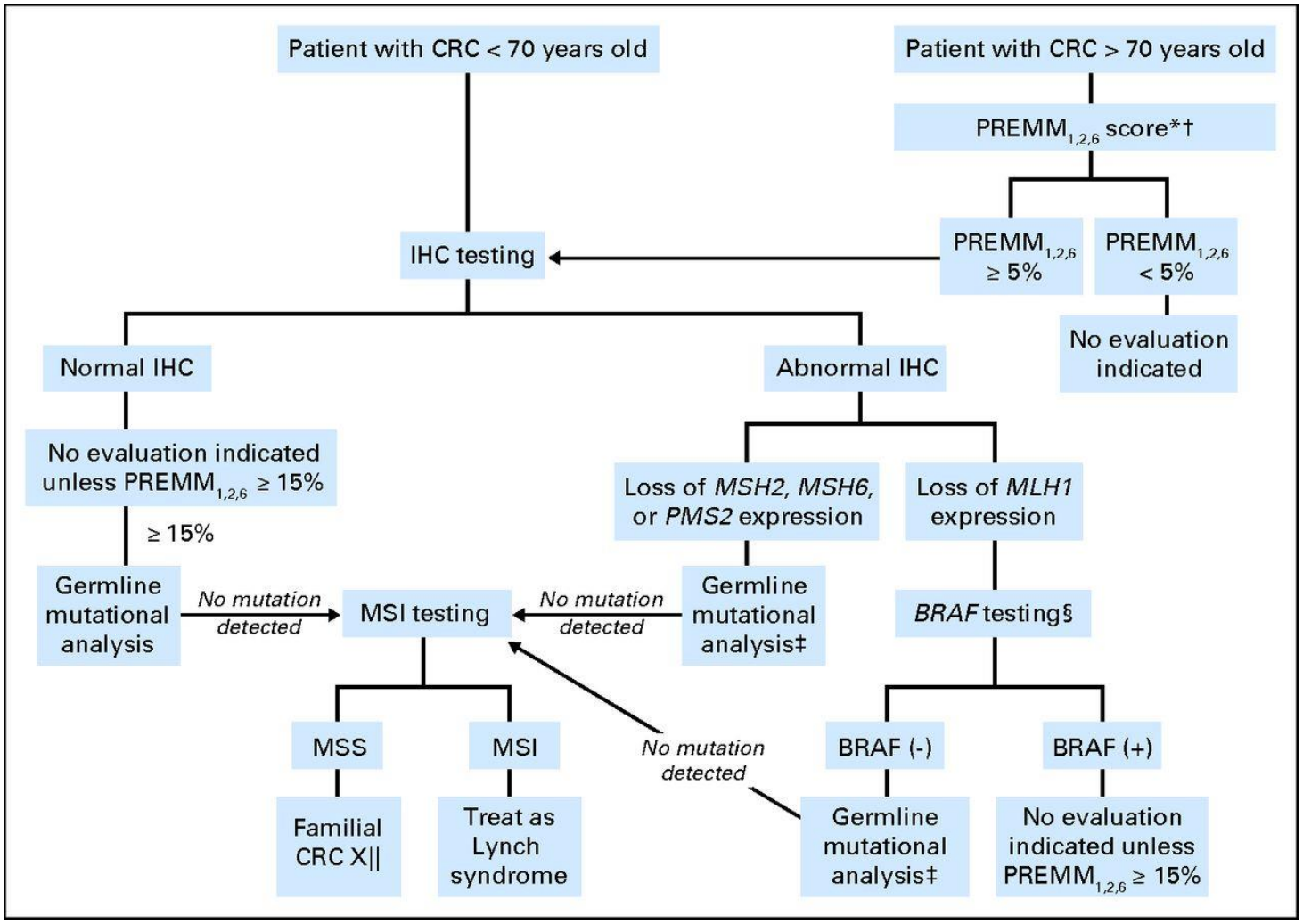
Germline APC mutation
Autosomal Dominant
Penetrance 100%
> 100 adenomas
Rectosigmoid dominant
Risk of extracolonic tumors
(upper GI, desmoid, osteoma, thyroid, brain, other)
Screen at age 10-12

HNPCC



Germline MMR mutation
Autosomal Dominant
Penetrance 60-80%
Impressive Family history
Proximal colon dominant
Extracolonic cancers:
(endometrium, ovary, stomach, urinary tract, small bowel, bile ducts, sebaceous skin tumors)
Screen at age 20-25

Proposed algorithm for systematic evaluation for Lynch syndrome in patients with colorectal cancer



Fay Kastrinos, and Sapna Syngal JCO 2012;30:1024-1027

Cancer Screening for Lynch affected patients

Table 10. Guidelines for screening at-risk or affected persons with Lynch syndrome

Intervention	Recommendation	Strength of recommendation
Colonoscopy	Every 1–2 y beginning at age 20–25 y or 2–5 y younger than youngest age at diagnosis of CRC in family if diagnosis before age 25 y Considerations: Start at age 30 y in MSH6 and 35 in PMS2 families Annual colonoscopy in MMR mutation carriers	Strong recommendation: Level of evidence (III): well-designed and conducted cohort or case-controlled studies from more than 1 group with cancer GRADE rating: moderate
Pelvic examination with endometrial sampling	Annually beginning at age 30–35 y	Offer to patient: Level of evidence (V): expert consensus GRADE rating: low
Transvaginal ultrasound	Annually beginning at age 30–35 y	Offer to patient: Level of evidence (V): expert consensus GRADE rating: low
EGD with biopsy of the gastric antrum	Beginning at age 30–35 y and subsequent surveillance every 2–3 y can be considered based on patient risk factors	Offer to patient: Level of evidence (V): expert consensus GRADE rating: low
Urinalysis	Annually beginning at age 30–35 y	Consideration: Level of evidence (V): expert consensus GRADE rating: low

EGD, esophagogastroduodenoscopy; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation.

Task Force. Am J Gastro 109:1159, 2014

Management of Lynch affected patients

Table 12. Guidelines for management of affected persons with Lynch syndrome

Intervention	Recommendation	Strength of recommendation
Colectomy with ileorectal anastomosis	Patients with colon cancer or colorectal neoplasia not removable by endoscopy Consideration for less extensive surgery in patients older than age 60–65 y	Strong recommendation: Level of evidence (III): well-designed and conducted cohort or case-controlled studies from more than 1 group with cancer GRADE rating: moderate
Hysterectomy and bilateral salpingo-oophorectomy	After childbearing or age 40 y	Recommendation: Level of evidence (IV): observation study GRADE rating: moderate
Daily aspirin	Treatment of an individual patient with aspirin is a consideration after discussion of patient-specific risks, benefits, and uncertainties of treatment is conducted	Consideration: Level of evidence (I): randomized controlled study GRADE rating: moderate

Task Force. Am J Gastro 109:1159, 2014

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- **Diagnosis and Staging**
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Diagnosis of CRC

"Tissue is the issue"

"No meat, no treat"

Core biopsy on endoscopy or metastatic site – lung or liver or LN

FNA from metastatic site

Staging

T - The extent of invasion of the intestinal wall

T0 - no evidence of tumor

Tis- cancer in situ (intraepithelial or lamina propria)

T1 - invades submucosa

T2 - invades muscularis propria

T3 - invades through the muscularis propria into pericolorectal tissues

T4 - invasion completely through the wall of the colon

T4a – penetrates visceral peritoneum

T4b - invades or adherent to surrounding organs

N - the extent of lymphatic node involvement

N0 – no lymph nodes involved

N1 – 1-3 lymph nodes involved (N1a – 1 LN, N1b – 2-3 LN, N1c – mesentric tumor deposits)

N2 - $\geq$ 4 lymph nodes involved (N2a – 4-6 LN, N2b – $\geq$ 7 LN)

M - the extent of metastases

M0 - no metastasis

M1 – metastases present (M1a: single organ,;M1b: $\geq$2 organs; T1c: peritoneal surface

Staging and Survival (AJCC v 7)

Stage	TNM		5 year survival
I	T1,2	N0 M0	97%
IIa	T3	N0 M0	88%
IIb	T4a	N0 M0	80%
IIc	T4b	N0 M0	58%
IIIa	T1-2	N1 M0	85%
IIIb	T3	N2 M0	65%
IIIc	T4 or T4b	N2 M0 N1-2	30%
IV	T1- 4	N0-2M1	8%

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TREATMENT DEPENDS ON STAGE

- STAGE I COLON AND RECTUM – SURGERY ONLY

- STAGE II COLON– SURGERY WITH/WITHOUT CHEMOTHERAPY
- STAGE II RECTAL– SURGERY, RADIATION AND CHEMOTHERAPY

- STAGE III COLON– SURGERY WITH CHEMOTHERAPY
- STAGE III RECTAL– SURGERY, RADIATION AND CHEMOTHERAPY

- STAGE IV COLON AND RECTUM – CHEMOTHERAPY ONLY

Principles of Surgery

- Minimally invasive procedure is an option (laparoscopic colectomy)
- All involved lymph nodes to be removed
- Sample at least 12 nodes for complete staging (if < 12, consider therapy as stage III)
- For metastesectomy, of liver or lung, intent should be complete removal, debulking is of no benefit (including removal of primary tumor)

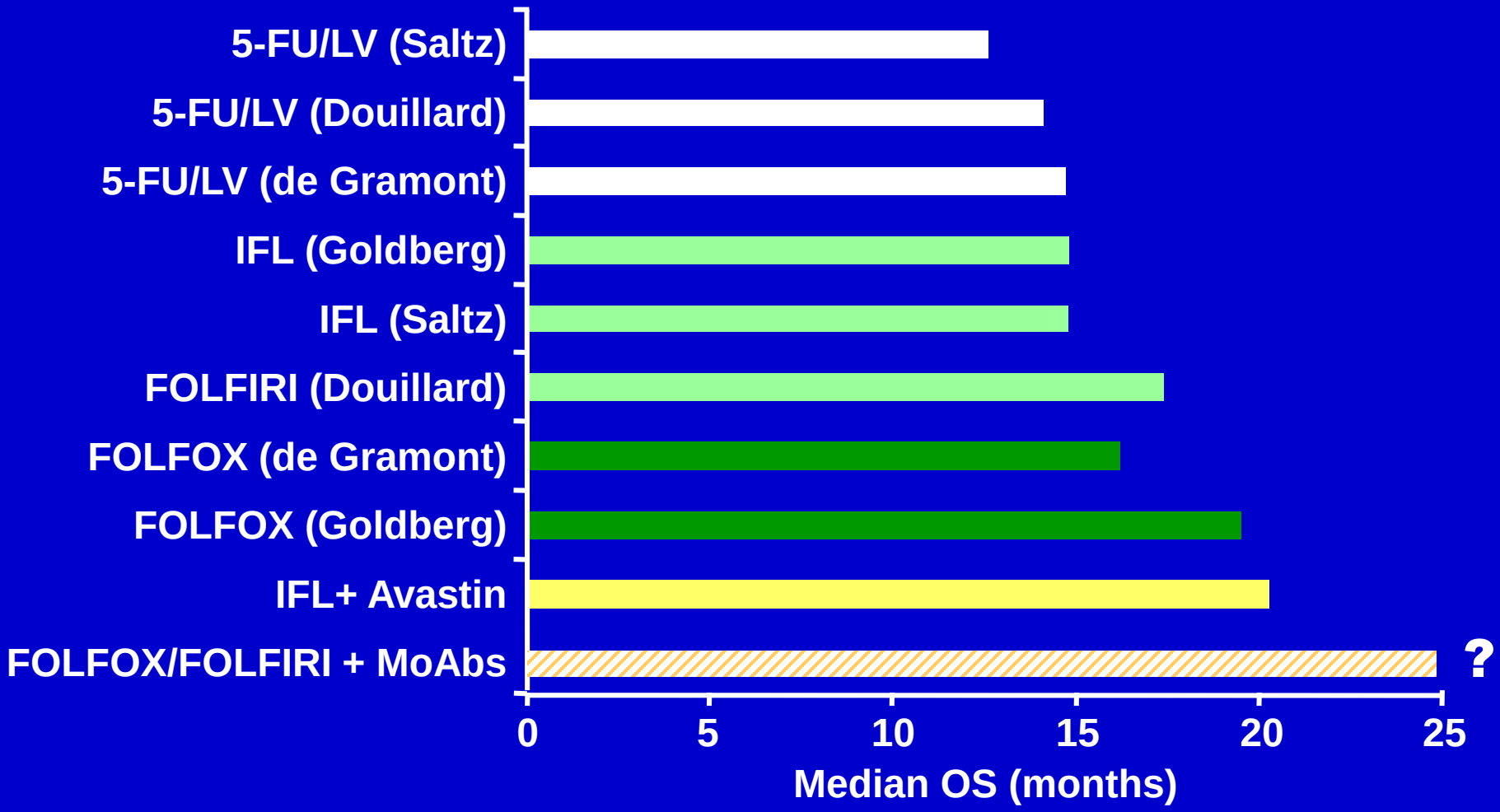
Principles of Adjuvant Therapy

- Goal of adjuvant therapy is cure (delaying relapse is less important)
- Stage II colon cancer – prefer single agent therapy with 5-FU or capecitabine
- Stage III colon cancer – add oxaliplatin
- Stage II and III rectal cancer – add radiation

Chemotherapy/Drug Names (US FDA approved)

- 5-FU (5-Fluorouracil) – cytotoxic, stage II-IV CRC
- Oxaliplatin (Eloxatin) – cytotoxic, stage III-IV CRC
- Irinotecan (Camptosar) – cytotoxic, stage IV CRC
- Capecitabine (Xeloda) – 5-FU pro drug, cytotoxic, stage II-IV CRC
- Bevacizumab (Avastin) – mAb – VEGF, stage IV CRC
- Cetuximab (Erbitux) – mAb – EGFR, stage IV Ras WT CRC
- Panitumumab (Vectibix) – mAb – EGFR, stage IV Ras WT CRC
- Aflibercept (Zaltrap) – fusion protein – VEGF, stage IV CRC
- Ramucirumab (Cyramza) – mAb – VEGF, stage IV CRC
- Regorafenib (Stivarga) – TKI – VEGF, stage IV CRC
- Trifluridine and tipiracil (Lonsurf) – cytotoxic, stage IV CRC
- Pembrolizumab (Keytruda) – anti PD-1, MSI high tumors/ stage IV CRC
- Nivolumab (Opdivo) – anti PD-1, MSI high stage IV CRC

Overall Survival for First-line Combination Regimens



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Why personalized medicine?

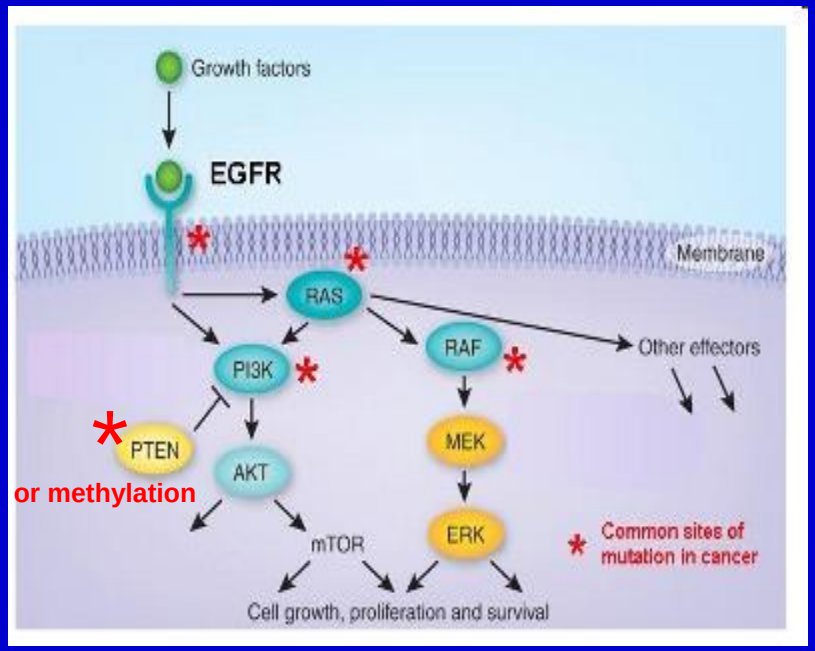
- Because everyone is talking about it!? and it is the “in” thing??

Why personalized medicine?

- Because everyone is talking about it!? and it is the “in” thing?? – ABSOLUTELY NOT!
- “First do no harm”
- It is the right approach to patients
- Limit toxicity from intervention
- Reduce health care costs

  (a staggering $ 3.4 trillion in 2016)

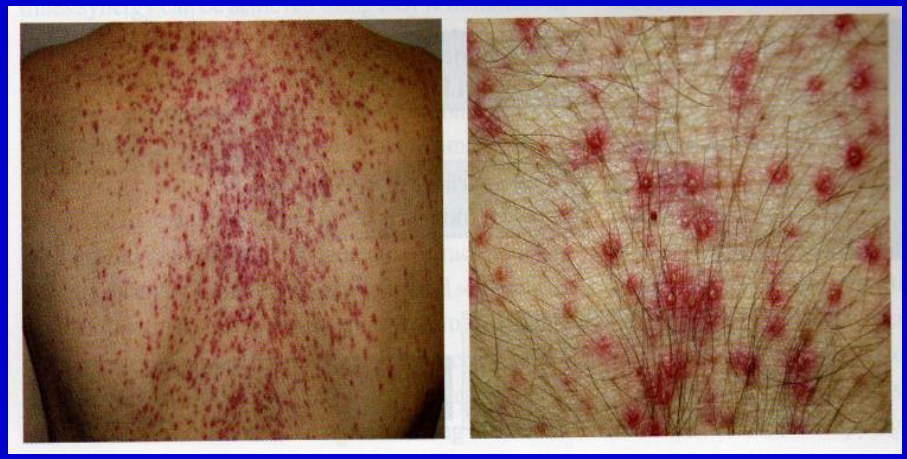
The EGF-MAPK-PI3K Pathway and anti EGFR agents



Cetuximab is IgG1, chimeric
Panitumumab is IgG3, human

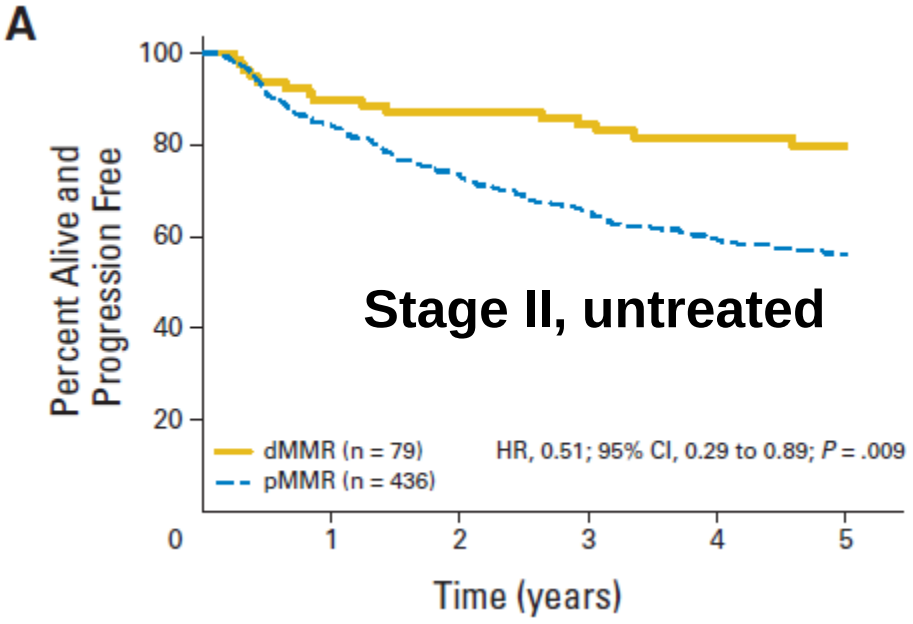
Tumors with Kras and Nras mutations do not respond to these drugs

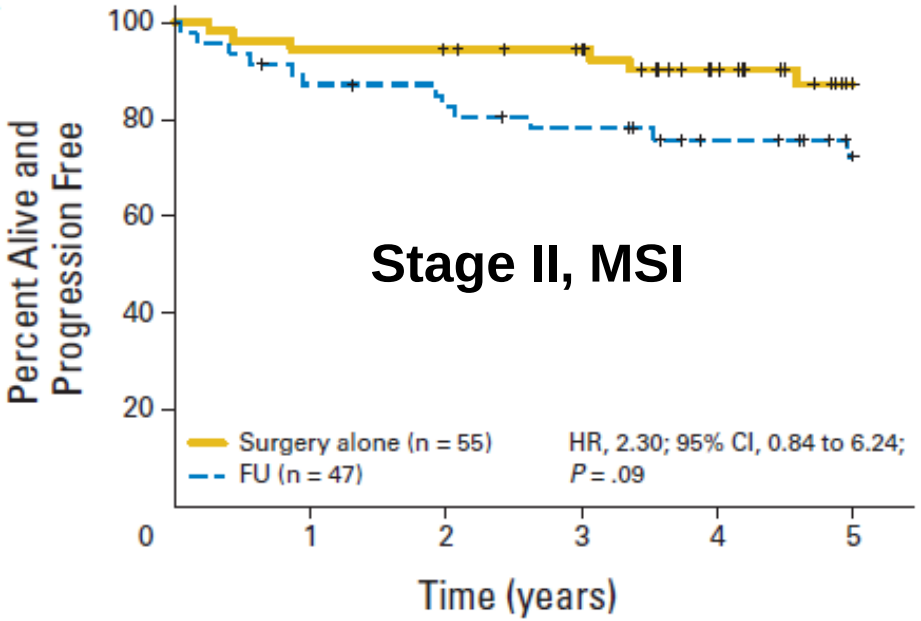
- **Exclusivity for EGFR**
- **Prevent binding of EGF or TGF to EGFR and prevents tyrosine kinase activation**



Typical anti EGFR induced skin rash

MSI as prognostic/predictive marker



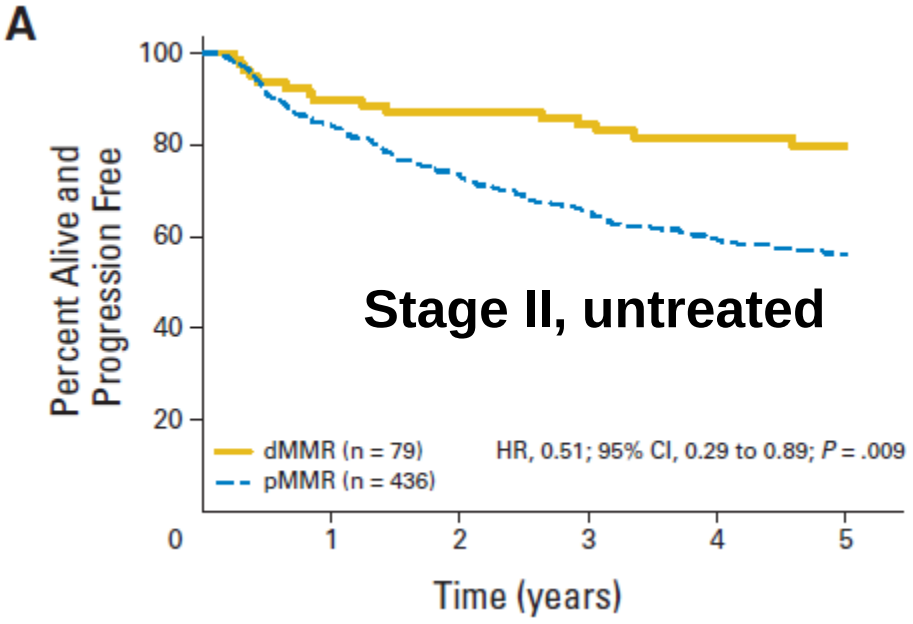


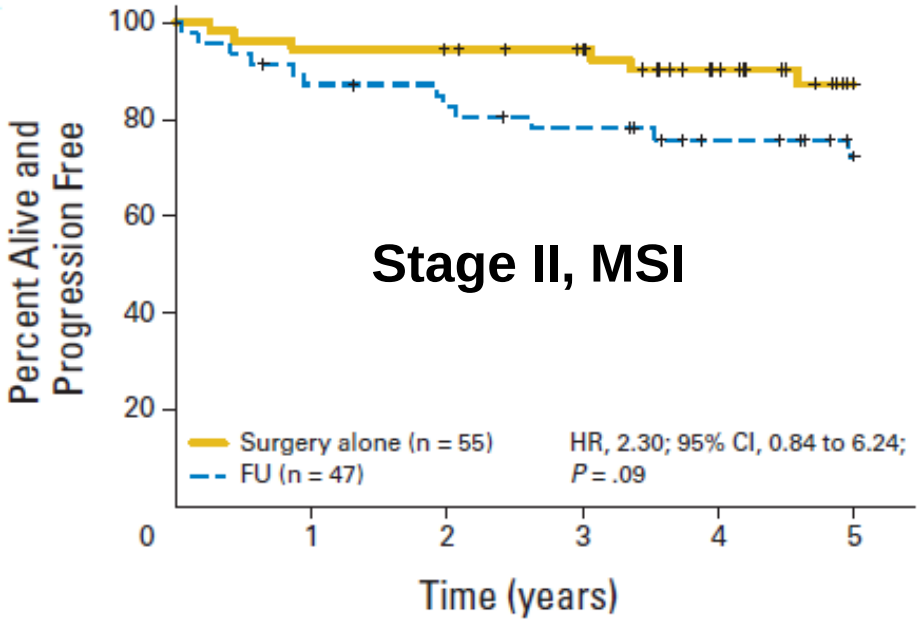
Untreated patients
MSI better outcome

Treated patients
5-FU - worse outcome

Sargent DJ, J Clin Oncol 28:3219-26, 2010

MSI as prognostic/predictive marker





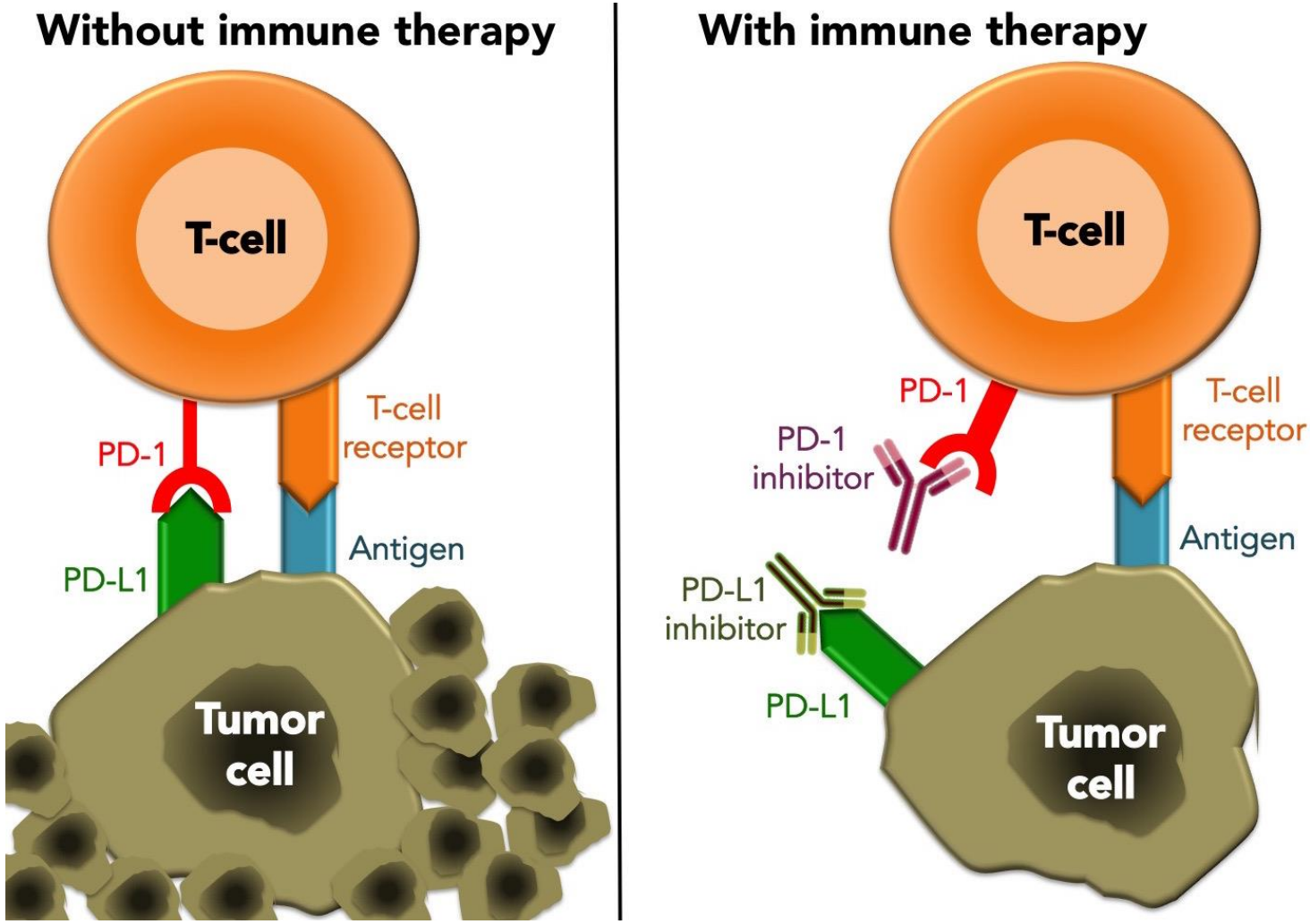
Untreated patients
MSI better outcome

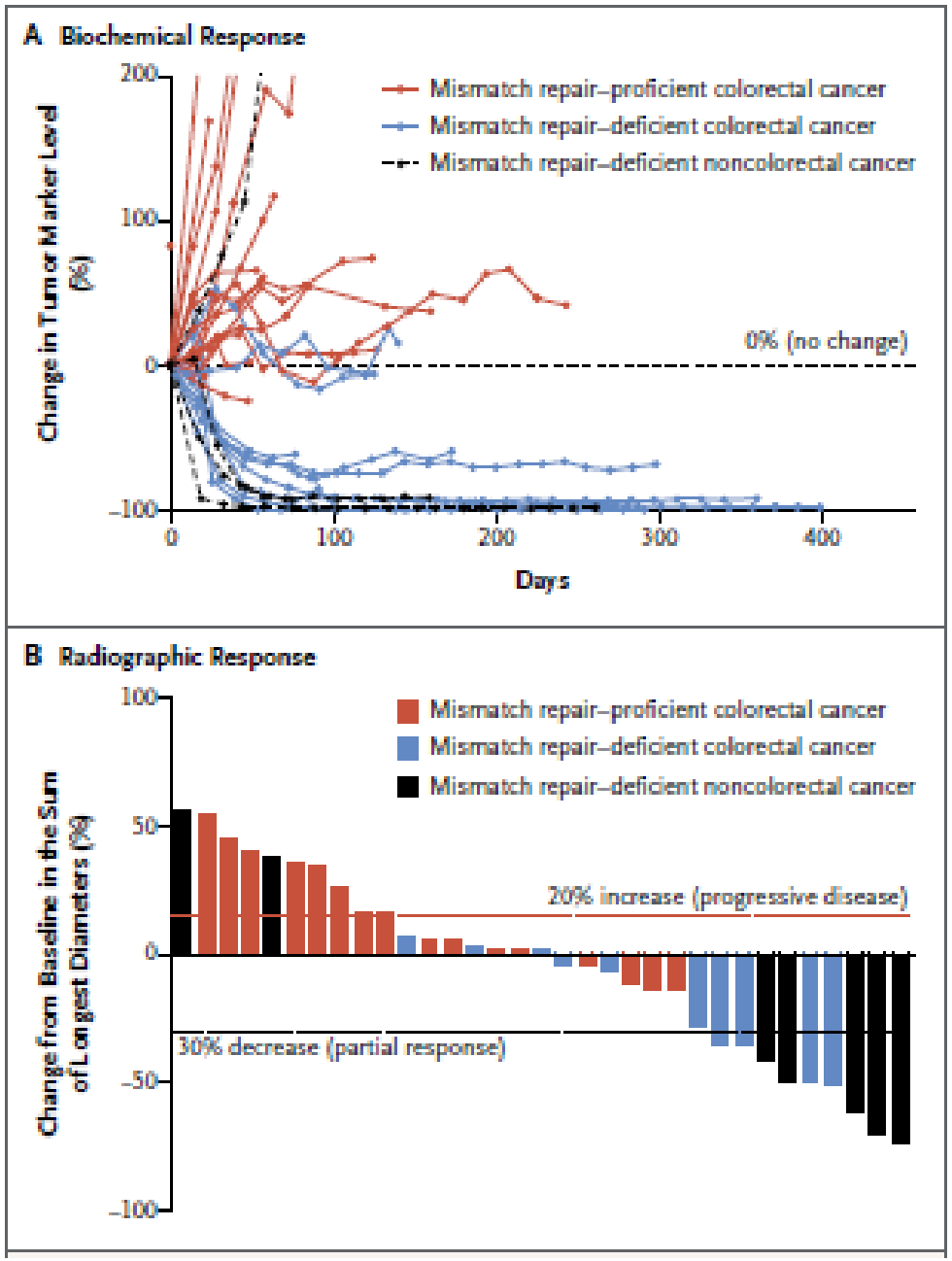
Treated patients
5-FU - worse outcome

Remember the Hippocratic oath:
First do no harm !!

Sargent DJ, J Clin Oncol 28:3219-26, 2010

The dawn of immunotherapy:
Programmed Death Pathway



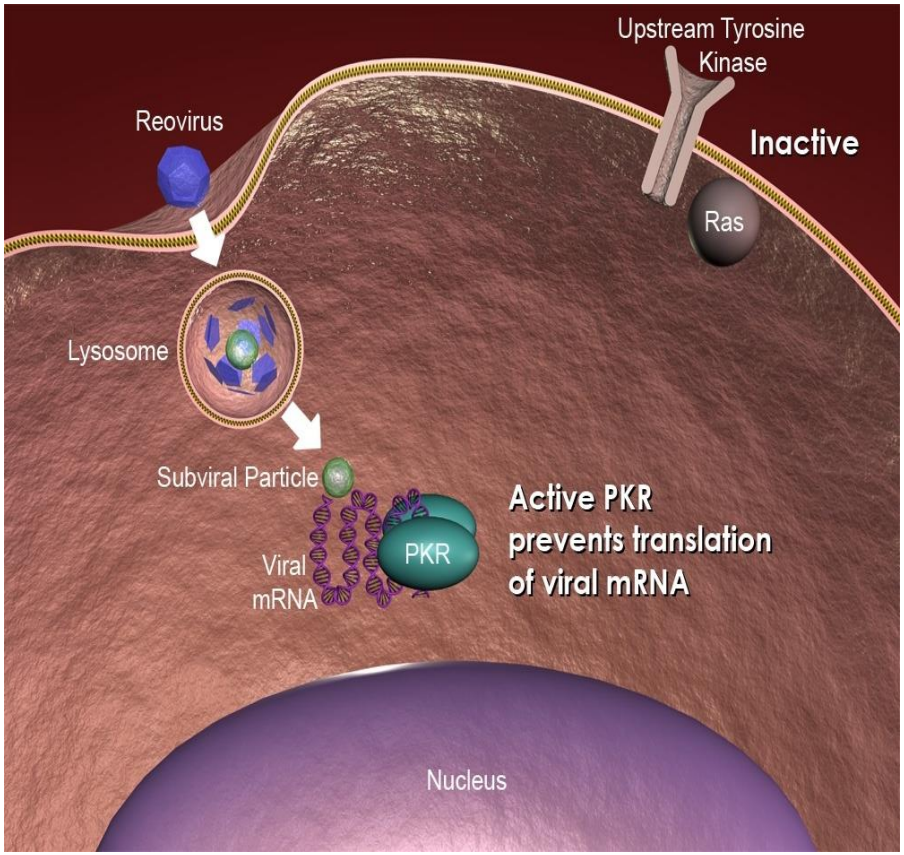


Immunotherapy in CRC

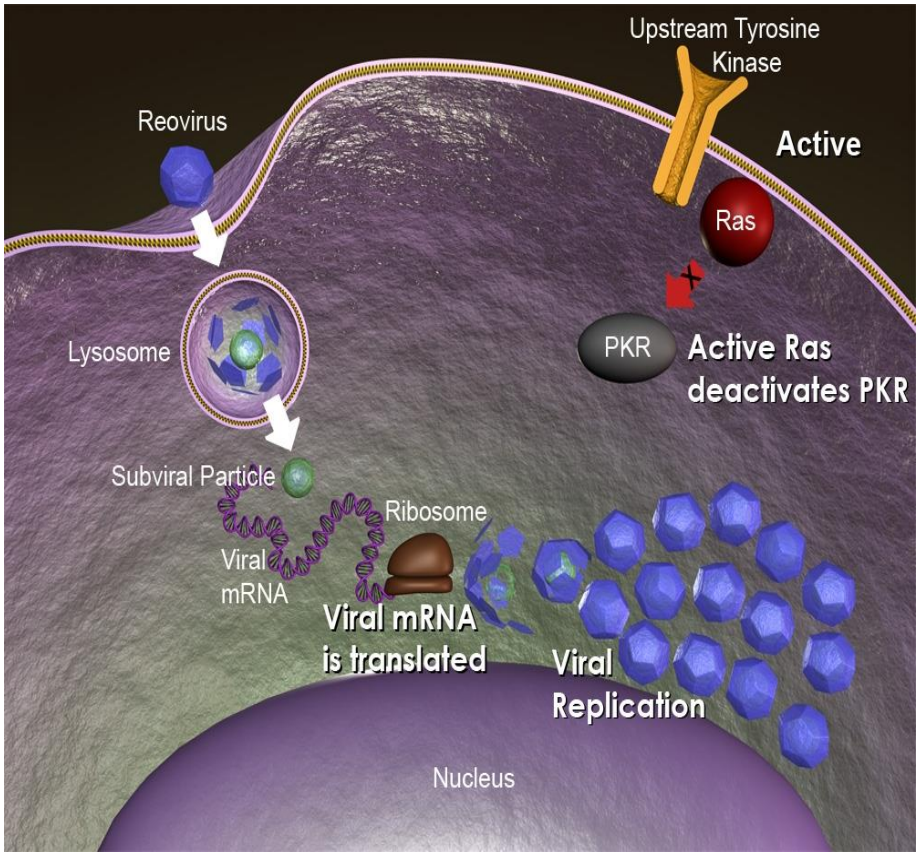
Pembrolizumab is an anti PD1 mAb

Le NEJM 372:2509, 2015

Reovirus growth in a Ras activated cell



K-ras WT cell



K-ras mutant cell

Courtesy: Oncolytics

Invest New Drugs
DOI 10.1007/s10637-009-9279-8

PHASE I STUDIES

Intravenous administration of Reolysin®, a live replication competent RNA virus is safe in patients with advanced solid tumors

Radharani Gollamudi · Mohammad H. Ghalib · Kavita K. Desai · Imran Chaudhary · Benny Wong · Mark Einstein · Matthew Coffey · George M. Gill · Karl Mettinger · John M. Mariadason · Sridhar Mani · Sanjay Goel

Received: 4 May 2009 / Accepted: 8 June 2009

Summary *Background* Reolysin® is reovirus serotype 3-Dearing strain, a double-stranded replication-competent RNA non-enveloped icosahedral virus. It induces cytopathic and anti-cancer effects in cells with an activated ras pathway due to inhibition of the dsRNA-activated protein kinase. *Methods* This was a single center dose escalation trial of Reolysin administered intravenously every 4 weeks in doses ranging from 1×10^{8} to 3×10^{10} tissue culture infective dose $(TCID)_{50}$. Serum for neutralizing antibody, and serum, stool, saliva, and urine for viral shedding were collected. Tumor samples were analyzed for activating mutations in the ras and braf oncogenes. *Results* Eighteen patients received 27 doses of Reolysin in 6 dose cohorts accomplishing a 300 fold dose escalation without a protocol-defined dose limiting toxicity. Drug related grade 2 toxicities included fatigue and fever (1 patient each). All patients developed neutralizing antibody during the course of the study. Viral shedding was observed in 6 patients. One patient with anthracycline and taxane refractory breast cancer experienced a partial response (PR) and her tumor had a ras G12A mutation. Biopsy from her chest wall mass showed evidence of necrosis and viral replication by electron microscopy. Overall clinical benefit (1 PR + 7 stable disease) rate was 45%, and appeared higher in patients with viral shedding (67%) than those without (33%). *Conclusion*

Presented in part at the 36th Annual Meeting of the American Society of Clinical Oncology, Chicago, 2007.

Radharani Gollamudi and Mohammad H. Ghalib contributed equally to the paper.

Gollamudi, Invest New Drugs 28:641-9, 2010

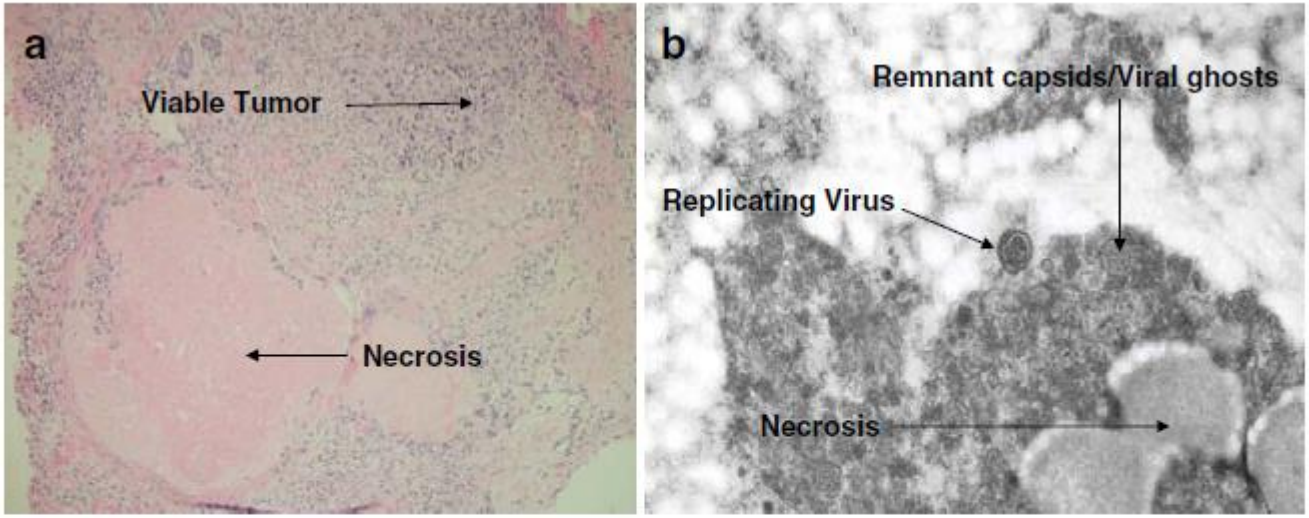
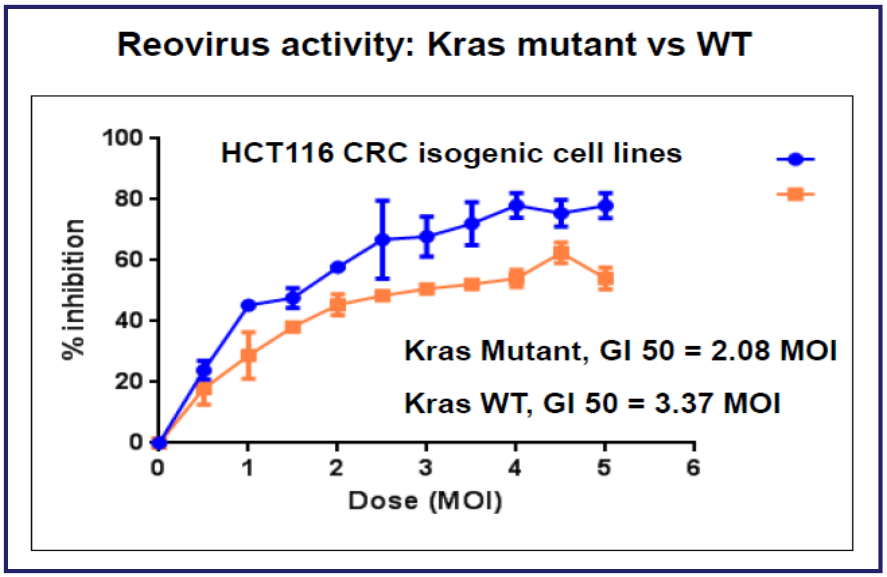


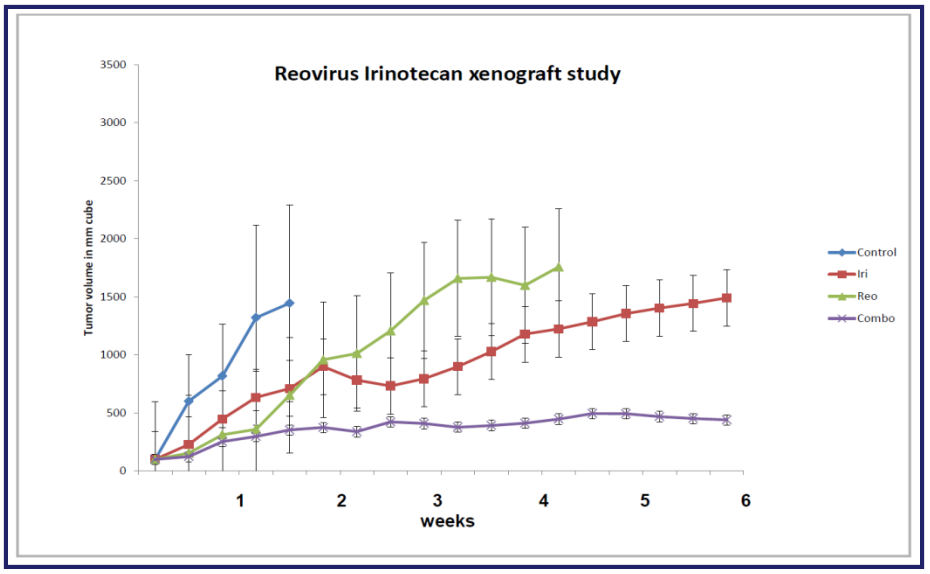
Fig. 2 Biopsy taken from a chest wall mass of a 60 year old woman with anthracycline and taxane pre treated breast cancer. The biopsy was taken 93 days after the first dose of Reolysin, (48 h after the third dose). Panel 2a: Pharmacodynamic Effect: Hematoxylin and Eosin stain of the biopsy showing extensive necrosis (also seen in 2b) of the tumor suggestive of anti-tumor activity. Panel 2b: Virokinetics: Electron Microscopy of the same biopsy specimen showing viral replication and remnant capsids/ghosts, typical of findings after prolonged interval between viral exposure and tissue collection, and with evidence of tissue necrosis

Gollamudi, Invest New Drugs 28:641-9, 2010

Oncolytic reovirus preferentially induces apoptosis in KRAS mutant colorectal cancer cells, and synergizes with irinotecan

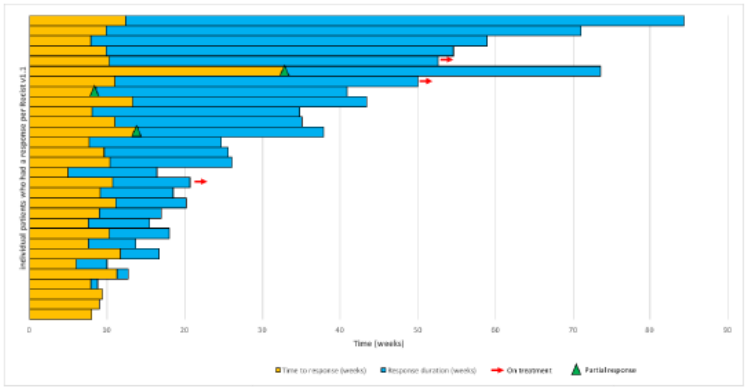
Radhashree Maitra[1], Raviraja Seetharam[1], Lydia Tesfa[2], Titto A.Augustine[2], Lidija Klampfer[1,2,5], Matthew C. Coffey[3], John M. Mariadason[4], and Sanjay Goel[1,2]



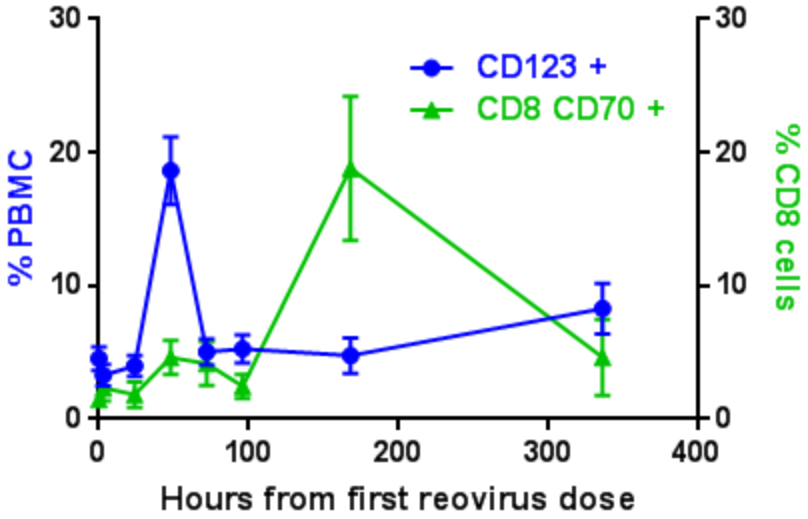


Maitra et al, Oncotarget, 2014

Time to and duration of response as assessed per RECIST v1.1



Time to response = time to BEST overall response
Duration of response = time from BEST overall response till PD or last tumor measurement (withdrawal of consent, off study)



Dose Cohorts

Dose Level	Reovirus	Irinotecan	# patients	Prior FOLFIRI	Bevacizumab	DLT
1	1 X 10^{10} $TCID_{50}$	150 mg/m2	3	Yes	No	0
2	3 X 10^{10} $TCID_{50}$	150 mg/m2	12	Yes	No	0
3	3 X 10^{10} $TCID_{50}$	180 mg/m2	6	Yes	No	2**
2 (new)	3 X 10^{10} $TCID_{50}$	150 mg/m2	7	No	Yes	0
3 (new)	3 X 10^{10} $TCID_{50}$	180 mg/m2	8	No	Yes	0

DLT=dose limited toxicity
** = DLT was grade 4 thrombocytopenia in a heavily pretreated patient (incl FOLFIRI)
**= DLT was urosepsis in a patient with prior FOLFIRI treatment

Goel et al. ESMO 2017

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$$$ - the real stuff!!

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Patients who made this possible