Selection of Optimal Treatment Strategies in Metastatic Colorectal Cancer

Alan P. Venook, MD

UCSF Helen Diller Family Comprehensive Cancer Center

National Comprehensive Cancer Network®

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ADVANCED COLORECTAL CANCER META-ANALYSIS PROJECT

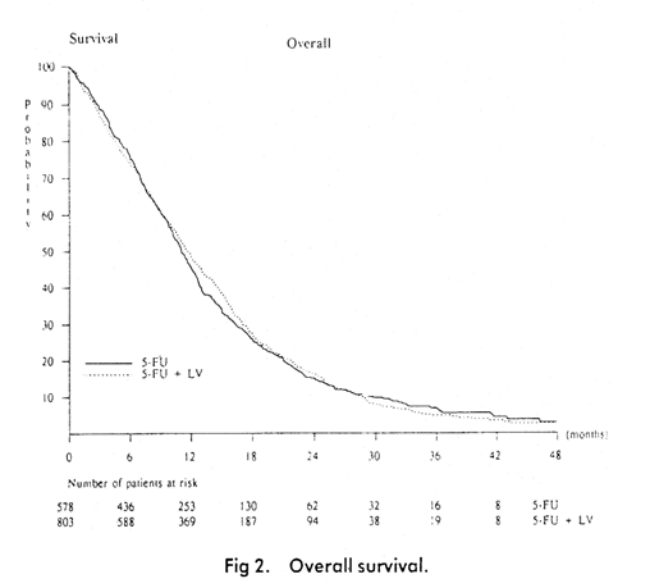


Fig 2. Overall survival.

J Clin Oncol, 1992

How to Improve Survival in CRC: 1990

MORE EFFECTIVE TREATMENT

- Get beyond 5FU / Develop new therapies
- Ablative / surgical techniques
- Multidisciplinary care / Lifestyle adjustments

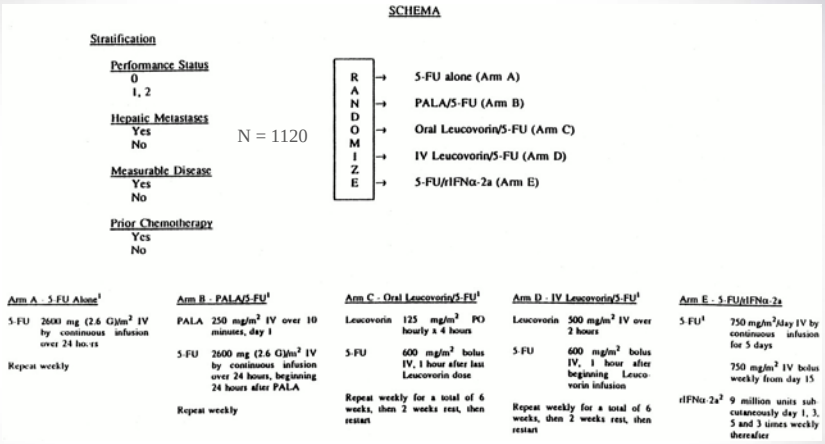
IMPROVE STAGING

- Find metastatic disease and treat earlier
- Incorporate tumor biology

CURE MORE PATIENTS

- Identify and cure “curable” patients
- Move new treatments into earlier setting

ECOG 2290 / CALGB 9092



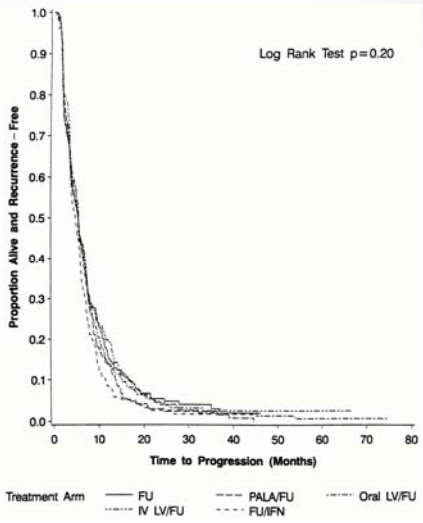
Based on SWOG 7-arm trial
--5FU push inferior

Peter J. O’Dwyer et al. JCO 2001;19:2413-2421

C. Leichman, JCO, 1995

JOURNAL OF CLINICAL ONCOLOGY ASCO

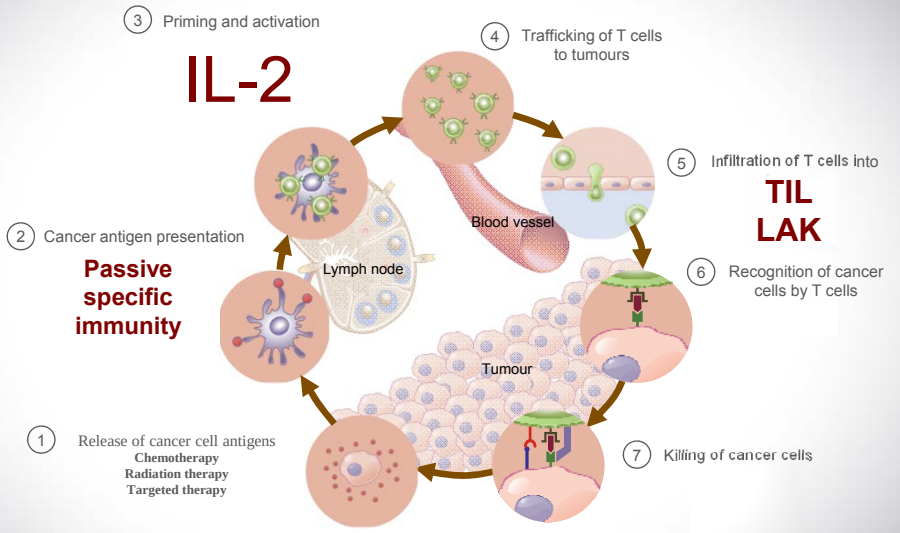
Fig 2.



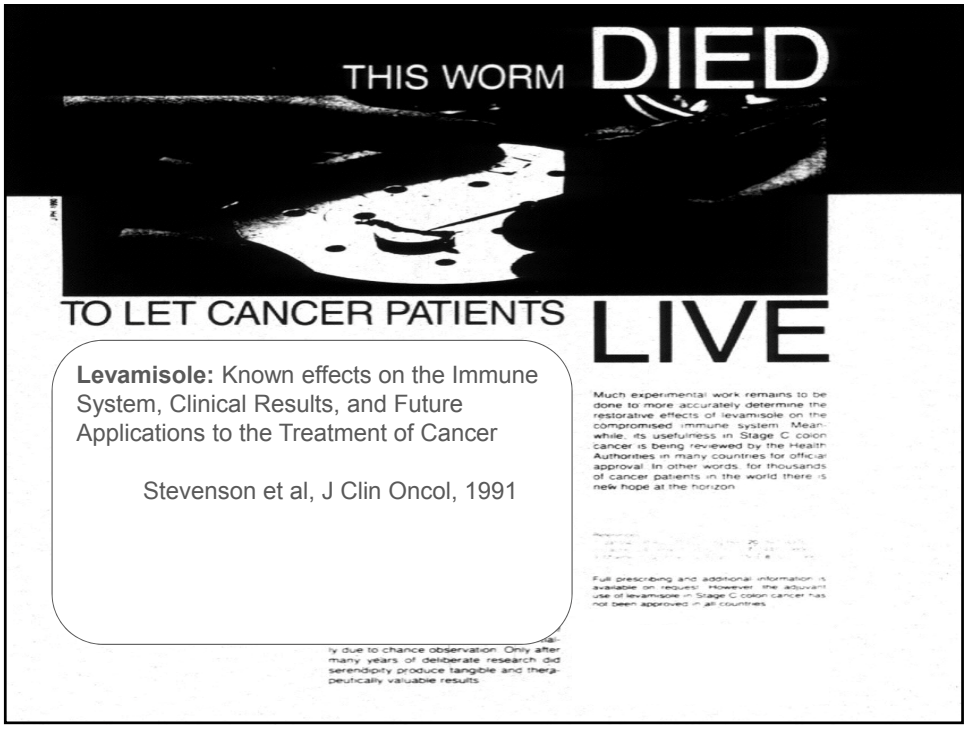
Peter J. O'Dwyer et al. JCO 2001;19:2413-2421

JOURNAL OF CLINICAL ONCOLOGY ASCO

Therapies that might affect the cancer-immunity cycle circa 1990



Chen & Mellman. Immunity 2013



Levamisole: Known effects on the Immune System, Clinical Results, and Future Applications to the Treatment of Cancer

Stevenson et al, J Clin Oncol, 1991

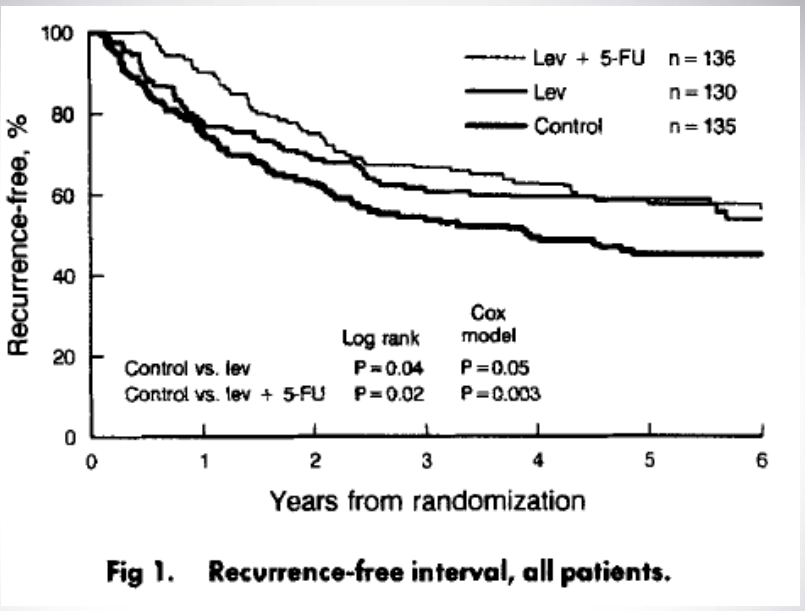


Fig 1. Recurrence-free interval, all patients.

Laurie et al, J Clin Oncol, 1989

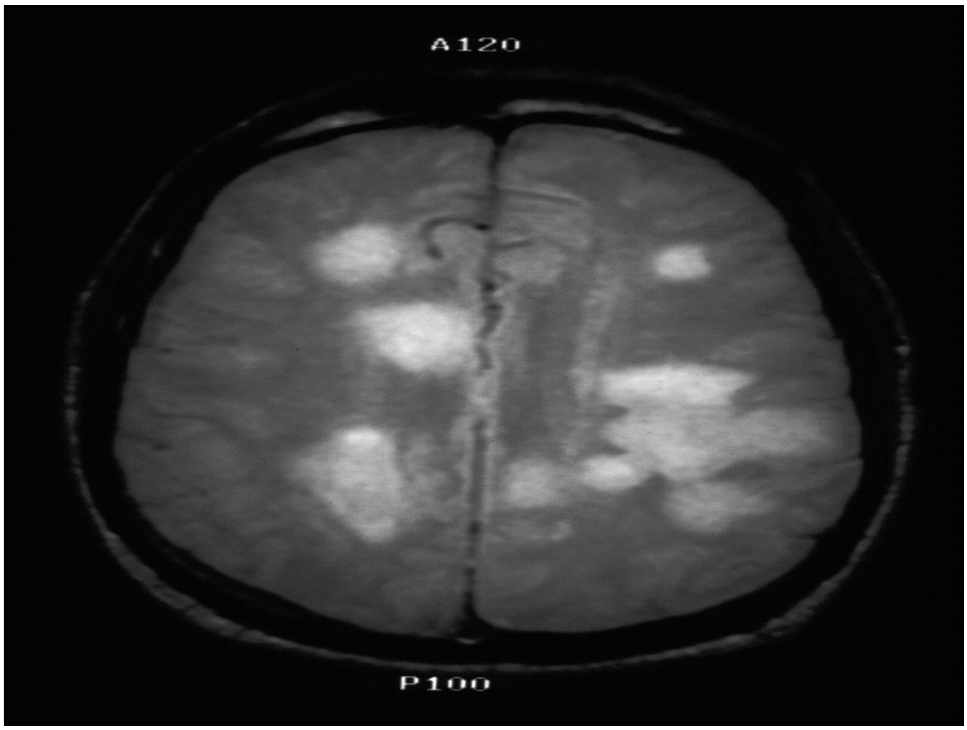
The Efficacy and the Group C Status of Levamisole And 5-Fluorouracil for Patients with Dukes' C Colon Cancer

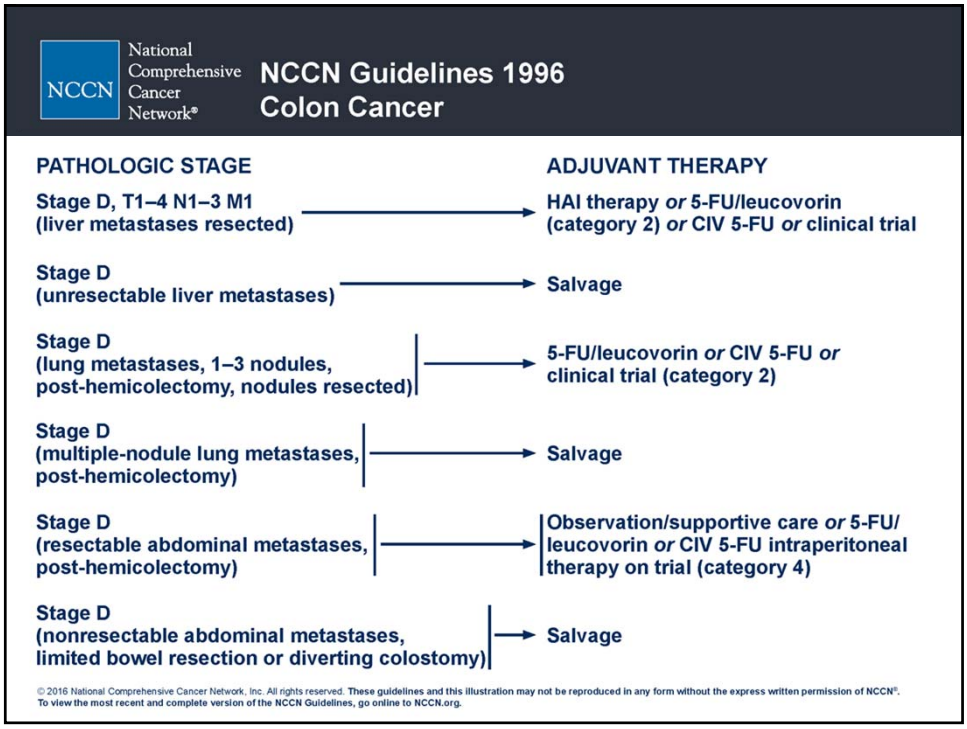
NCI Advisory, 10/89

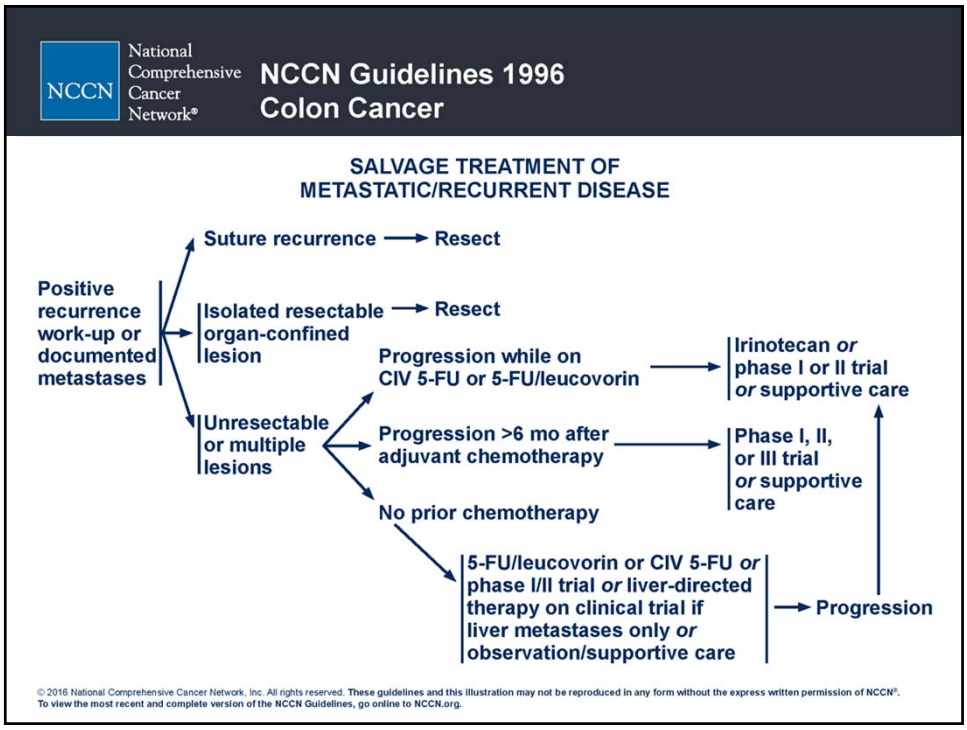
Summary

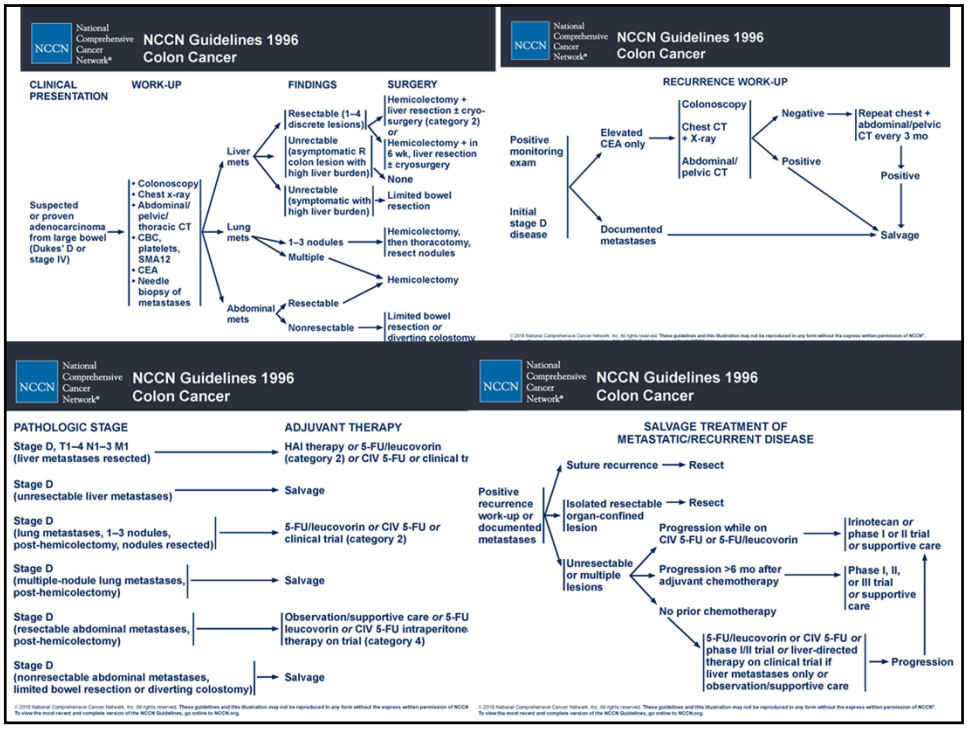
This announcement describes the efficacy and the availability of adjuvant levamisole and 5-fluorouracil (5-FU) through a Group C Protocol, for patients with completely resected Dukes' C colon cancer. This treatment substantially reduces the risk of dying of recurrent colon cancer.

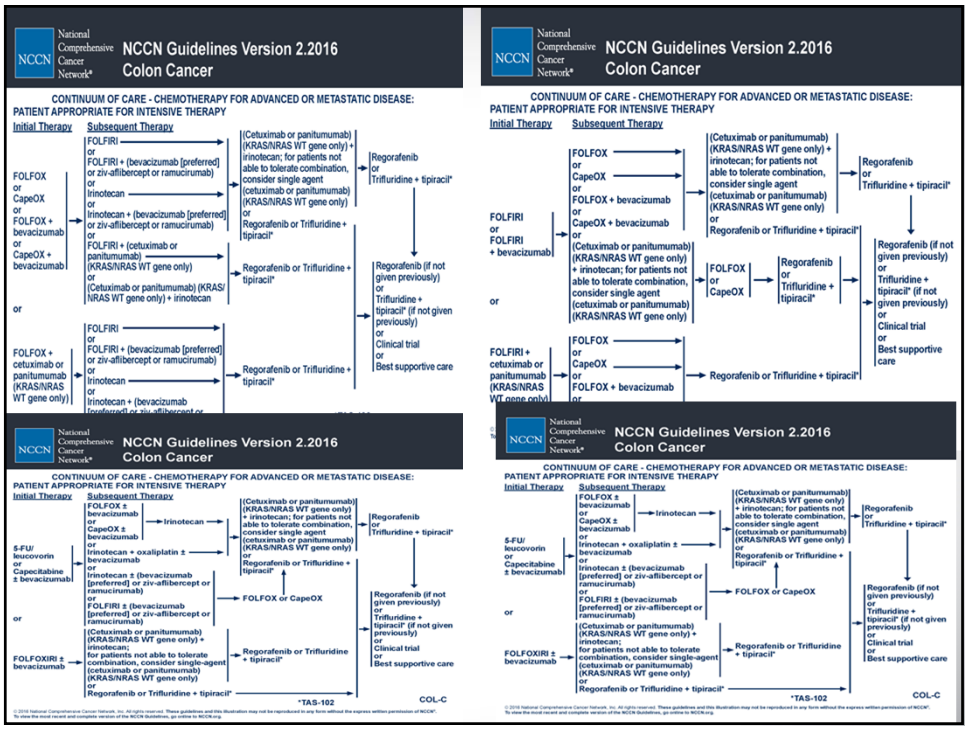
Post-Surgical Treatment	Percent Overall 5-Year Survival	Percent 5-Year Survival for Dukes' C
None	55%	37%
Levamisole + 5FU	62%	49%











NCCN Guidelines Version 3.2013
結腸癌

ガイドライン索引
結腸癌　目次
考察

治療

切除不能[g]な同時性の肝のみおよび/または肺のみの転移

- **全身療法**（FOLFIRI または FOLFOX または CapeOX[bb]±ベバシズマブ[cc] または FOLFIRI または FOLFOX±パニツムマブまたは FOLFIRI±セツキシマブ［KRAS 野生型遺伝子のみ］[e, dd] または FOLFOXIRI［カテゴリー2B］）
- **閉塞または著しい出血の切迫したリスクがある場合にのみ 結腸切除 [g] を考慮**

→ **切除可能への変更が目的として妥当であれば、2 ヵ月毎に切除可能 [g] への変更を 再評価する**

→ **切除可能に変更** → **結腸癌および 転移巣の同時または二期的切除[g]**

切除不能のまま → [切除不能進行・転移癌に対する化学療法（COL-C）を参照]

→ **切除不能癌に対する有効な化学療法レジメン**（[COL-Cを参照]）[aa]（カテゴリー2B）**または 術前補助療法を 受けた 患者には、経過観察ま たは短期の化学療法を 考慮**

補助療法[y]（6ヵ月間の周術期治療が望ましい）

→ **サーベイランス**

Stage IVで無再発の場合

- **現病歴と診察を3～6ヵ月毎に2年間、その後は6ヵ月毎に計5年間**
- **CEAを3～6ヵ月毎×2年間、その後6ヵ月毎×3～5年間**
- **胸部/腹部/骨盤CT[h]を3～6ヵ月毎×2年間、その後6～12ヵ月毎に最長で計5年間**
- **大腸内視鏡検査[b]を1年経過時に、ただし閉塞病変により術前に検査が実施されていない場合は3～6ヵ月経過時**
  - **➢進行性腺腫があれば、1年後に繰り返す**
  - **➢進行性腺腫[u]がなければ、3年後に再検、その後は5年毎に繰り返す[v]**

[b] すべての結腸癌患者は家族歴のカウンセリングを受けるとともに、リスク評価について検討すべきである。遺伝性非ポリポーシス大腸癌（HNPCC）、家族性大腸腺腫症（FAP）、およびattenuated FAPが疑われる患者は、NCCN大腸癌スクリーニングガイドラインを参照。

[e] 病理学的レビューの原則（COL-A 4 of 5） - KRASおよびBRAF遺伝子変異検査を参照。

[g] 手術の原則（COL-B 2 of 3）を参照。

[h] CTでは静注または経口の造影剤を使用するべきであり、腹部および骨盤CTでは不十分な場合や静注造影剤を用いたCTが禁忌である場合には、造影腹部/骨盤MRIと非造影胸部CTを検討すること。

[u] 絨毛状ポリープ、1 cm超のポリープ、または高異型度。

[v] Rex DK, Kahi CJ, Levin B, et al. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and the US Multi- Society Task Force on Colorectal Cancer. Gastroenterology 2006;130(6):1865-71.

[y] 50歳未満の患者には、全例に対してミスマッチ修復（MMR）蛋白の検査を考慮すべきである。

[aa] 肝動注療法±5-FU/ロイコボリンの全身投与（カテゴリー2B）も、この手技に関する腫瘍外科および腫瘍内科の両分野に経験を有する施設では、選択肢の1つである。

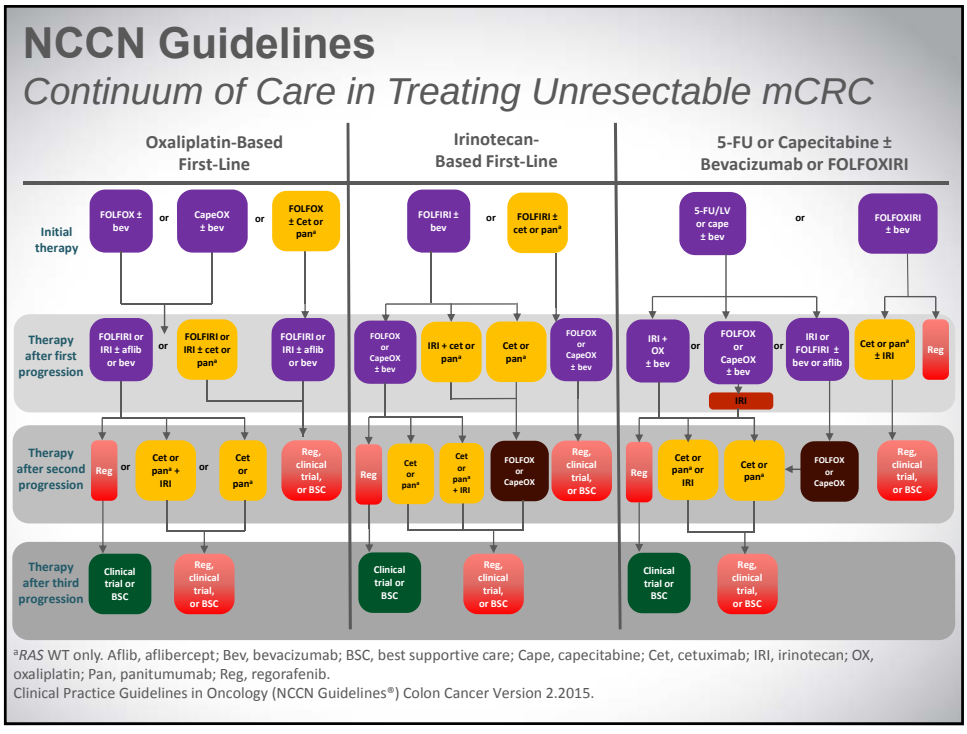
[bb] このレジメンに対する安全性および有効性のデータの大部分は、カペシタビンを開始用量1,000 mg/m^2 1日2回14日間の用量で投与し、21日毎に繰り返す療法が標準であるヨーロッパで展開されたものである。北米の患者はヨーロッパの患者よりもカペシタビン（他のフルオロピリミジンも同様）による強い毒性を経験する可能性があり、カペシタビンをより低用量とする必要があることをエビデンスが示唆している。より低い開始用量のカペシタビンでのCapeOxの相対的効果は、大規模ランダム化試験で確認されていない。

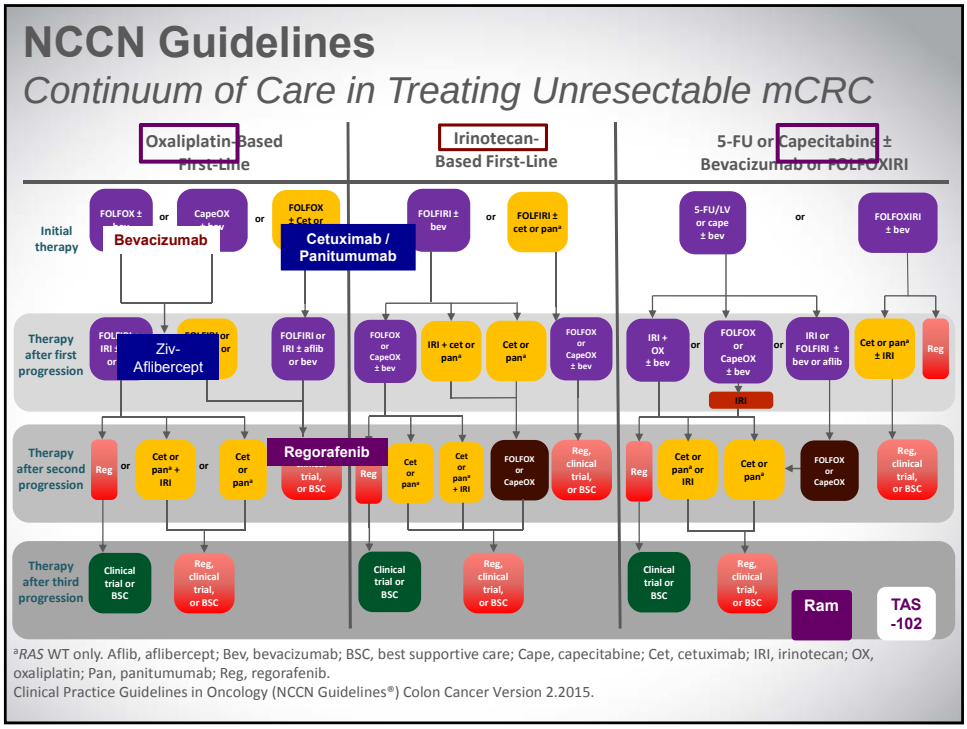
[cc] 5-FUベースのレジメンとの併用において、術前または術後のベバシズマブ投与の安全性は十分には評価されていない。ベバシズマブの最終投与と待機的手術との間隔は少なくとも6週間は空け、術後少なくとも6～8週間経過してからベバシズマブを再開すべきである。特に65歳以上では、脳卒中をはじめとする動脈イベントのリスクが高い。ベバシズマブの使用は創傷治癒を妨げる可能性がある。

[dd] 有効な化学療法と併用した一次治療での抗EGFR療法の是非を BRAF V600E変異の状態に基づいて判断するにはデータが不十分である。

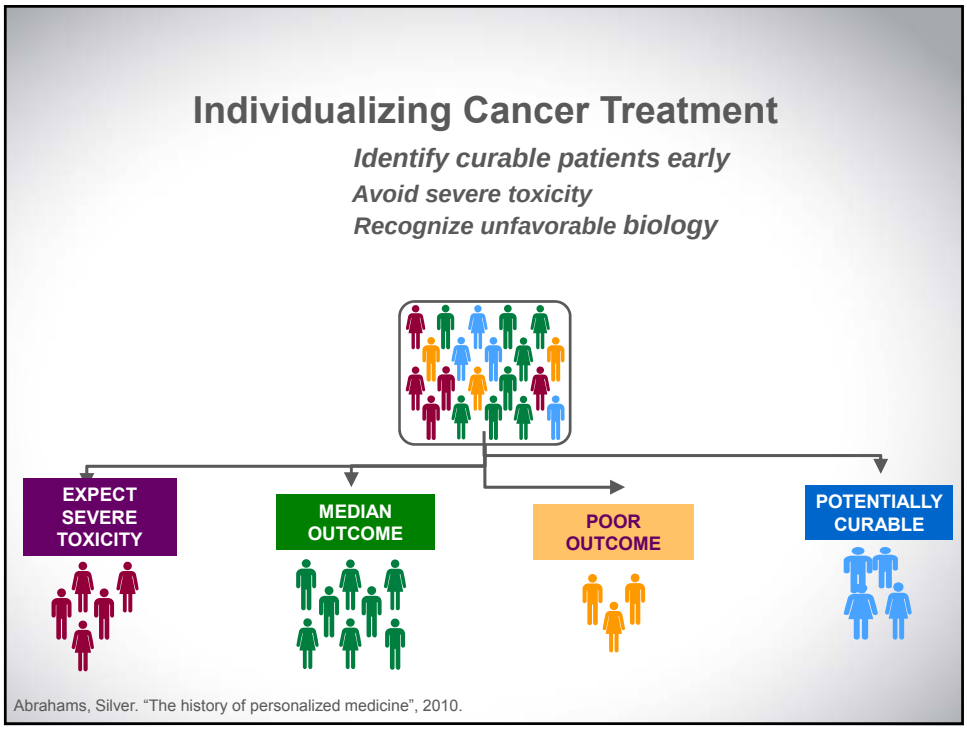
注意：特に指定のない限り、すべての推奨はカテゴリー2Aである。臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

[再発（COL-9 を参照）]





[a]*RAS* WT only. Aflib, aflibercept; Bev, bevacizumab; BSC, best supportive care; Cape, capecitabine; Cet, cetuximab; IRI, irinotecan; OX, oxaliplatin; Pan, panitumumab; Reg, regorafenib.
Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Colon Cancer Version 2.2015.



Abrahams, Silver. "The history of personalized medicine", 2010.

BIOMARKERS

- "Predictive, personalized, preemptive, and participatory"

www.nih.gov/strategicvision.htm

GOALS

- Identify patients most likely / unlikely to benefit
- Spare patients toxicity and harm
- Avoid opportunity cost and expense of futile therapy
- Overview of prognosis

Candidate Biomarkers for CRC: Tumor or blood

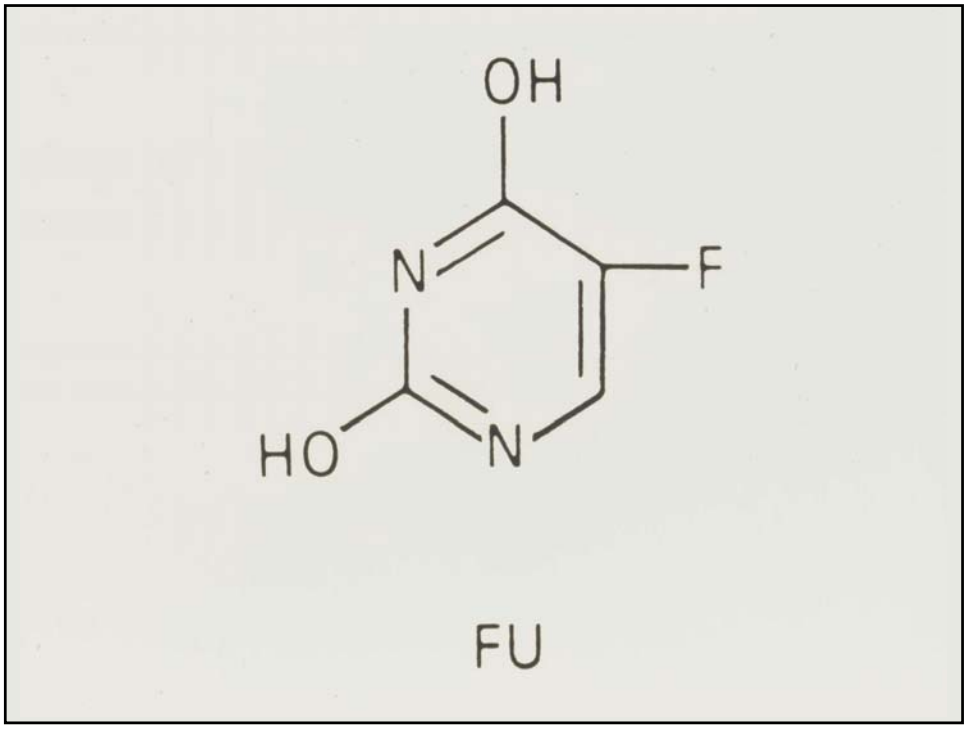
DRUG	MARKER
Fluoropyrimidines	TS, DPD, TP, MSI, MTHFR expression/polymorphisms
Irinotecan	UGT polymorphisms, MSI, transporter polymorphisms
Oxaliplatin	ERCC1, GST P1, XPD expression, transporter

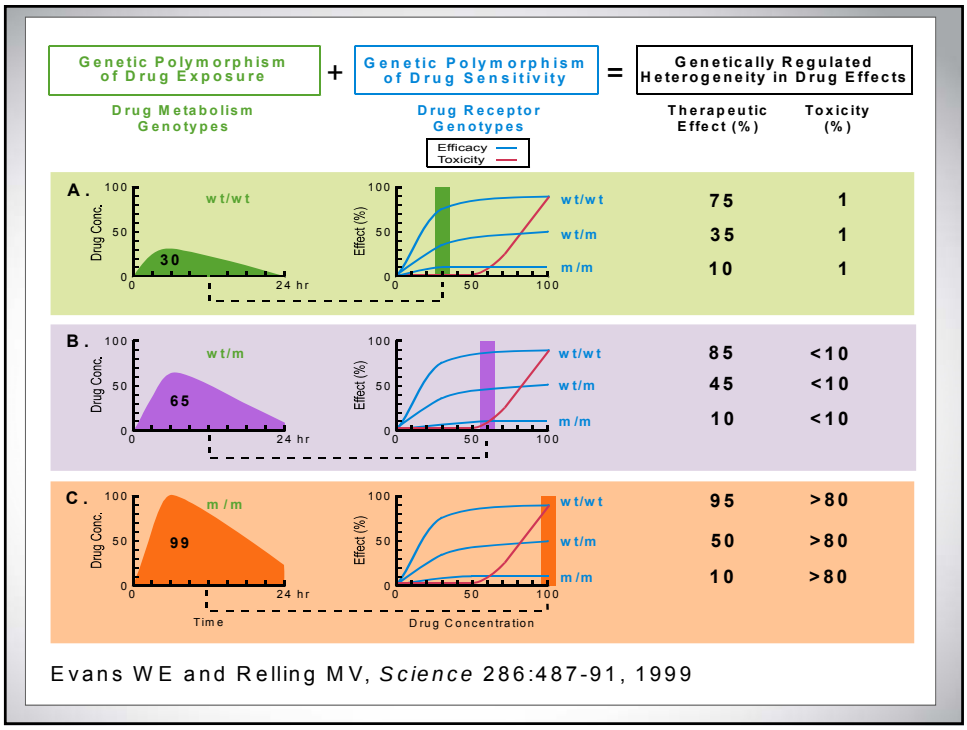
DPD -- Rare deficiency, extreme toxicity
Can be used to optimize AUC

TP-- Possible correlation with capecitabine

UGT 1A1 – increased tox 10% patients, related to schedule

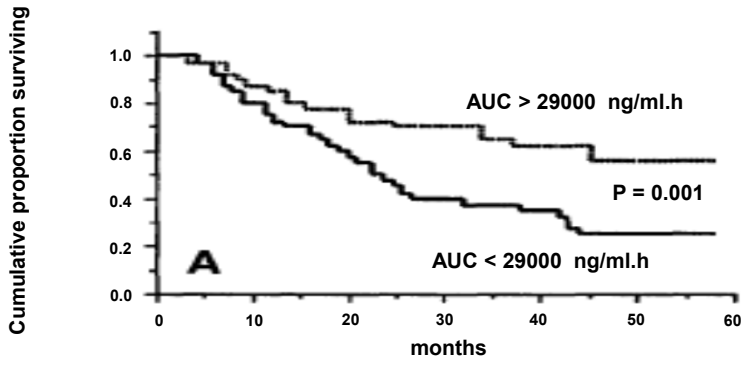
ERCC-1 – Possible efficacy





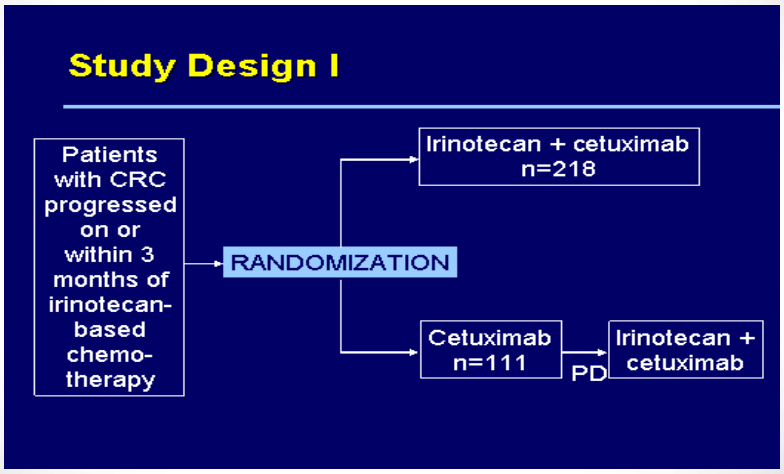
Evans WE and Relling MV, *Science* 286:487-91, 1999

Relationship between Systemic Exposure and Survival



Milano et al., J Clinical Oncology 1994; 12: 1291

Cetuximab Therapy: IMC-007



Cunningham et al, N Engl J Med, 2004

‘BOND’ – Correlation of Response Rate and EGFR Expression

	Combination (%)	Monotherapy (%)
% EGFR-expressing		
≤ 10 %	22.9	7.1
> 10 - ≤ 20 %	20.0	31.3
> 20 - ≤ 35 %	22.2	0.0
> 35 %	24.2	9.4
faint	20.8	4.8
weak/moderate	24.7	12.7
strong	22.7	11.8

‘BOND’ – Correlation of Response Rate and EGFR Expression

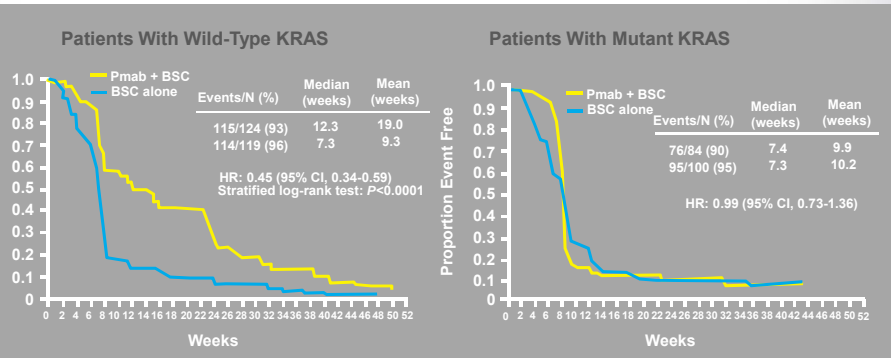
FDA approves cetuximab to treat patients with advanced CRC that has spread….accelerated approval program…

For patients whose tumors express EGFR… Approve test kit…that detects a protein in the body (HER-1)… presence of this protein indicates patient is eligible for colon cancer treatment…

February 12, 2004

KRAS As a Biomarker for Panitumumab Response in Refractory Metastatic CRC

- PFS log HR significantly different depending on KRAS status (*P*<0.0001)
- Percentage decrease in target lesion greater in patients with wild-type *KRAS* receiving panitumumab



Amado RG et al. *J Clin Oncol.* 2008;26:1626-1634.

Mutant RAS and Outcome with EGFR Inhibitors

		PRIME[1,2]			OPUS[3,4]			CRYSTAL[3,5]	
	Treatment	PFS	OS	Treatment	PFS	OS	Treatment	PFS	OS
KRAS Ex2 WT	Panitumumab + FOLFOX4 (n = 325)	10.0	23.9	Cetuximab + FOLFOX4 (n = 82)	8.3	22.8	Cetuximab + FOLFIRI (n = 316)	9.9	23.5
	FOLFOX4 (n = 331)	8.6	19.7	FOLFOX4 (n = 97)	7.2	18.5	FOLFIRI (n = 350)	8.4	20.0
		HR 0.80*	HR 0.88		HR 0.57*	HR 0.86*		HR 0.70*	HR 0.80*
KRAS Ex2 MT	Panitumumab + FOLFOX4 (n = 221)	7.4	15.5	Cetuximab + FOLFOX4 (n = 77)	5.5	13.4	Cetuximab + FOLFIRI (n = 214)	7.4	16.2
	FOLFOX4 (n = 219)	9.2	19.2	FOLFOX4 (n = 59)	8.6	17.5	FOLFIRI (n = 183)	7.7	16.7
		HR 1.27*	HR 1.17		HR 1.72*	HR 1.29		HR 1.17	HR 1.04
No *RAS* MT	Panitumumab + FOLFOX4 (n = 259)	10.1	25.8	Cetuximab + FOLFOX4 (n = 36)	12.0	20.7	Cetuximab + FOLFIRI (n = 178)	11.4	28.4
	FOLFOX4 (n = 253)	7.9	20.2	FOLFOX4 (n = 46)	5.8	17.8	FOLFIRI (n = 189)	8.4	20.2
		HR 0.72*	HR 0.77*		HR 0.43*	HR 0.83*		HR 0.56*	HR 0.69*
Any *RAS* MT	Panitumumab + FOLFOX4 (n = 272)	7.3	15.5	Cetuximab + FOLFOX4 (n = 94)	5.6	13.4	Cetuximab + FOLFIRI (n = 246)	7.4	16.4
	FOLFOX4 (n = 276)	8.7	18.7	FOLFOX4 (n = 78)	7.8	17.8	FOLFIRI (n = 214)	7.5	17.7
		HR 1.31*	HR 1.21*		HR 1.59*	HR 1.35		HR 1.10	HR 1.05

*Statistically significant.
HR, hazard ratio; PFS, progression-free survival.

1. EU SmPC panitumumab 2. Douillard. 2013; 3. EU SmPC cetuximab; 4. Tejpar. 2014; 5. Ciardiello. 2014.

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		HR 0.80*	HR 0.88		HR 0.57*	HR 0.86*		HR 0.70*	HR 0.80*
	Panitumumab			Cetuximab +			Cetuximab +		
No *RAS* MT	+ FOLFOX4 (n = 259)	10.1	25.8	FOLFOX4 (n = 36)	12.0	20.7	FOLFIRI (n = 178)	11.4	28.4
	FOLFOX4 (n = 253)	7.9	20.2	FOLFOX4 (n = 46)	5.8	17.8	FOLFIRI (n = 189)	8.4	20.2
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		HR 1.31*	HR 1.21*		HR 1.59*	HR 1.35		HR 1.10	HR 1.05

***RAS* mutations: negative predictor of outcomes may preclude anti-EGFR activity**

*Statistically significant.
HR, hazard ratio; PFS, progression-free survival.

1. EU SmPC panitumumab 2. Douillard. 2013; 3. EU SmPC cetuximab; 4. Tejpar. 2014; 5. Ciardiello. 2014.

Expanded *RAS*: Refining Patient Population

Current actionable mutations:
KRAS codons *12, 13, 61, 117, 146;*
NRAS codons 12, 13, 61, 117, 146;
BRAF codon 600

- Use tumor tissue (FFPE) if available. Primary tumor ok.
- If tumor tissue not available, consider cfDNA (circulating free); wait 3 weeks after chemo or radiation to draw blood sample to avoid tumor necrosis/apoptosis effects [less evidence]

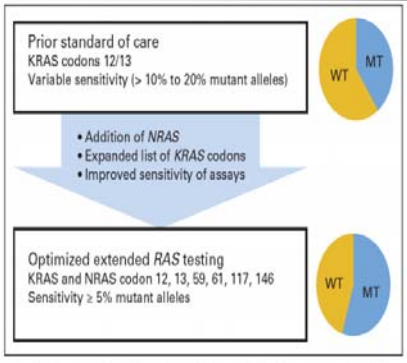
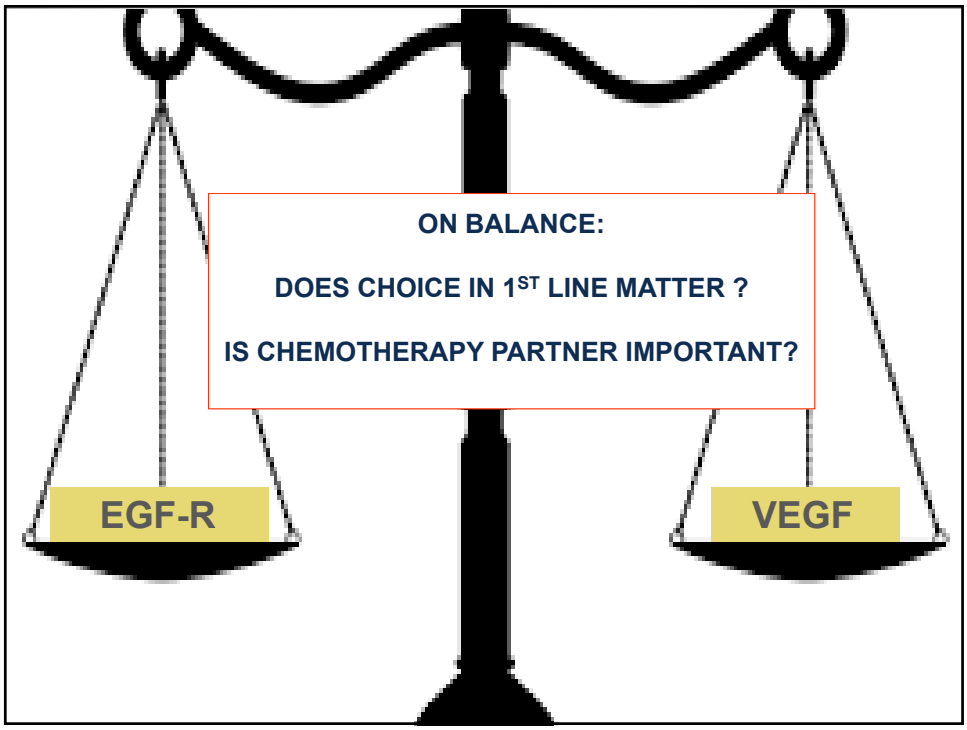


Fig 1. Advances in *RAS* testing. Optimal clinical implementation of *RAS* testing involves expansion of number of tested codons to include less common mutations and use of assays with sufficient sensitivity for *RAS*-mutant alleles. To date, preponderance of clinical data reported on expanded *RAS* mutations has used 5% threshold for detection of mutated (MT)/wild-type (WT) alleles; therefore, this represents a reasonable threshold while additional analyses are conducted.

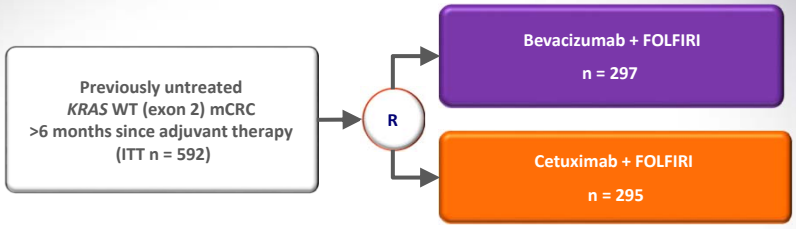
Atreya, Corcoran & Kopetz: Comments and Controversies. J Clin Oncol, March 2015

Comprehensive bevacizumab biomarker program across multiple indications

Study	Plasma	Blood mRNA	Blood DNA	Tumor IHC	Tumor mRNA	Tumor DNA	Other
	Multi-analyte IMPACT platform for angiogenesis-relevant proteins (eg VEGF-A)	VEGF-A splice forms, VEGF-C, -D, VEGFR-1, -2, and -3, PlGF, and NRP 1	SNPs of 30+ angiogenesis-relevant genes	VEGF-A, VEGFR2, NRP1, CD31	Angiogenesis-relevant genes, anti-angio-signature, tumor BM (eg ERCC-1)	eg KRAS, BRAF	eg VEGF-A, serum proteomics
ML18147	X	X	X	X	X	X	
AVANT BO17920	X	X	X	X	X	X	
AVAGAST AVF4200	X	X	X	X	X	X	
NO16966				X	X		
MAVERICC ML25710	X	X	X	X	X	X	x (urine)
CALBG 80405	Collaboration		Collaboration	Collaboration	Collaboration	Collaboration	Collaboration (serum)
NASBP C-08	Collaboration		Collaboration	Collaboration			
AVITA BO17706	X		X				
CALBG 80303	Collaboration		Collaboration				Collaboration (serum)
AVOREN BO17705	X		X				
BEVLIN MO21609	X			X	X	X	
E4599	X		X				
AVAIL BO17704	X		X				
ABIGAIL BO2105	X	X	X	X	X	X	
BEYOND YO25404 (China Lung)	X		X	X	X	X	
AVAall MO22097	X	X	X	X	X	X	
AVAglio BO21990	X	X	X	X	X	X	
BEATRICE	X	X	X	X			
BETH	X	X	X	X			
AVEREL	X	X	X			X	
MERIDIAN	X	X	X	X			
TANIA	X	X	X				
GOG0218	Collaboration	Collaboration	Collaboration	Collaboration			
ICON7	Collaboration	Collaboration	Collaboration	Collaboration			
ROSIA	X	X	X	X			
BERNIE BO20924	X	X	X	X	X	X	
HERBY BO25041	X	X	X	X	X	X	



FIRE-3 Design



- **Primary endpoint**: ORR (in *KRAS* WT [exon 2])
- **Secondary endpoints**: OS, PFS, R0 resection rate, safety
- **Exploratory analyses**
  - Extended *RAS* WT (*KRAS/NRAS* WT exon 2, 3, and 4) subpopulation
  - Second-line treatments following progression
  - Tumour location and gender

Results in ITT *KRAS* WT population
- No difference in ORR *(primary endpoint not met)*
- No difference in PFS or R0 resection rate
- OS statistically longer with cetuximab

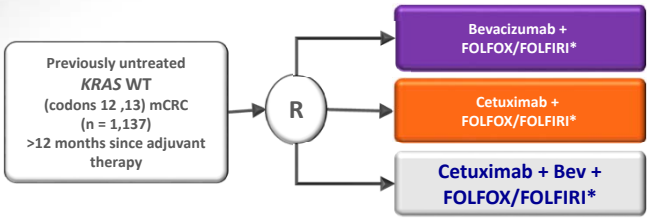
Heinemann, et al, Lancet Oncology, 2014

FIRE-3 Secondary Endpoint OS: Cetuximab vs Bevacizumab in *RAS* WT*

OS	Cetuximab + FOLFIRI		Bevacizumab + FOLFIRI		HR (95% CI)	*p* value
	Median, months	95% CI	Median, months	95% CI		
KRAS exon 2 WT (ITT population) (n = 592)[1]	28.7	24.0–36.6	25.0	22.7–27.6	0.77 (0.62–0.96)	0.017
RAS* WT **(n = 400)[2]**	**33.1**	**24.5–39.4**	**25.0**	**23.0–28.1**	**0.697 (0.54–0.90)**	**0.0059**
Other *RAS* MT (n = 65)[1,3]	16.4	15.9–27.6	20.6	17.0–28.4	1.20 (0.64–2.28)	0.57
All *RAS* MT[2] (n = 188)[2**]	20.2	16.4–23.4	20.6	17.1–26.3	1.05 (0.77–1.44)	0.75

**KRAS/NRAS* exon 2, 3, and 4 WT.
***All *RAS* MT population consists of non-ITT *KRAS* exon 2 MT and ITT other *RAS* MT. Heinemann, 2014

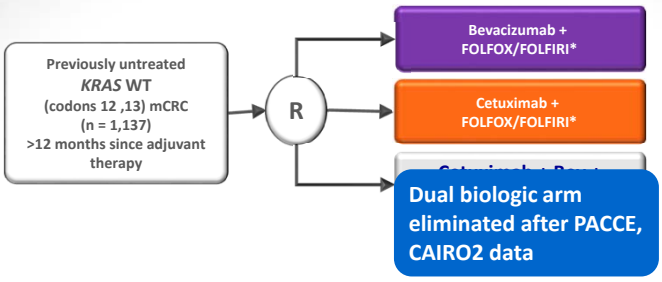
CALGB/SWOG 80405 Design



- **Primary endpoint**: **OS** (in *KRAS* WT [exon 2])
- **Secondary endpoints**: ORR, PFS, TTF, DOR, safety, and QOL

*Use of FOLFOX or FOLFIRI was at the physician's discretion
TTF, treatment to failure; DOR, duration of response.
Venook. 2014.

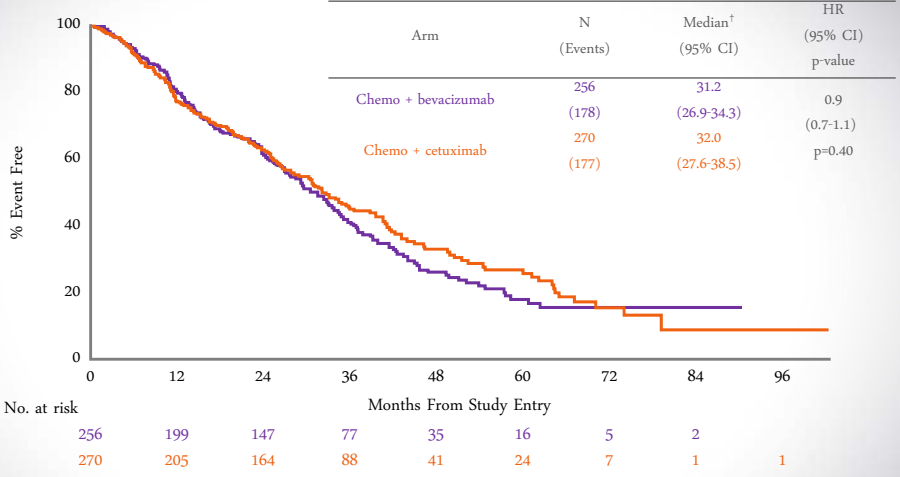
CALGB/SWOG 80405 Design



- **Primary endpoint**: **OS** (in *KRAS* WT [exon 2])
- **Secondary endpoints**: ORR, PFS, TTF, DOR, safety, and QOL

*Use of FOLFOX or FOLFIRI was at the physician's discretion
TTF, treatment to failure; DOR, duration of response.
Venook. 2014.

CALGB 80405: overall survival by arm
(All RAS wild type patients)



Arm	N (Events)	RAS WT Median† (95% CI)	HR (95% CI) p-value
Chemo + bevacizumab	256 (178)	31.2 (26.9-34.3)	0.9 (0.7-1.1) p=0.40
Chemo + cetuximab	270 (177)	32.0 (27.6-38.5)	

No. at risk								
256	199	147	77	35	16	5	2	
270	205	164	88	41	24	7	1	1

*These findings may not apply to KRAS mutation codons 12 and 13

†Median, months

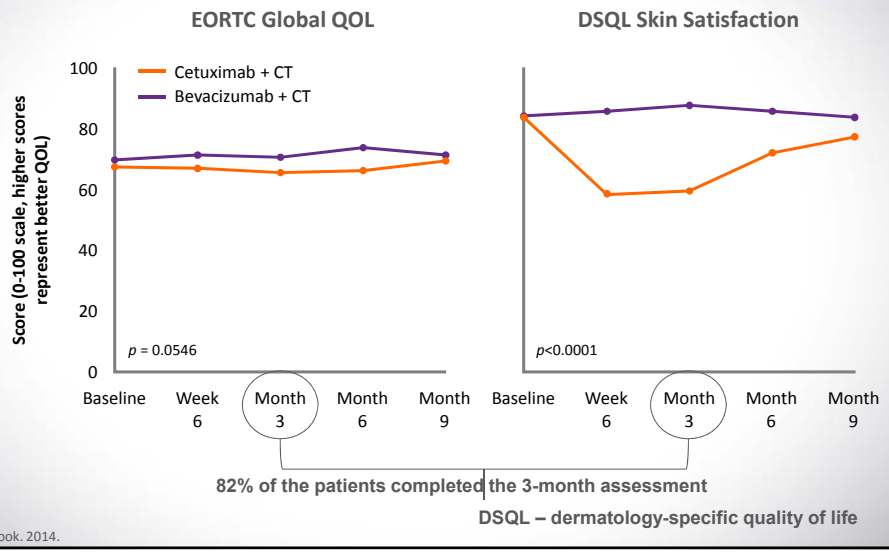
Lenz, et al. ESMO 2014. Abstract 501O

FIRE-3 v CALGB/SWOG 80405
RAS status / FOLFIRI comparison

FOLFIRI backbone / RAS status	FIRE 3 BEV v CETUX	CALGB/SWOG 80405 BEV v CETUX
KRAS WT codons 12, 13		
PFS	10.3 v 10.0 mos	11.6 v 10.3 mos
OS	25.0 v 28.7 mos HR: 0.77 (p=0.017)	33.4 v 28.9 mos HR: 0.92 (p=0.34)
ALL RAS WT		
PFS	10.2 v 10.4 mos	11.9 v 12.7 mos
OS	25.0 v 33.1 mos	35.2 v 32.0 mos

No difference in R0 resection rate / long term NED

CALGB 80405: DSQL During First 3 Months



Venook. 2014.

How to Improve Survival in CRC: 1990

MORE EFFECTIVE TREATMENT

- Get beyond 5FU / Develop new therapies
- Ablative / surgical techniques
- Multidisciplinary care / Lifestyle adjustments

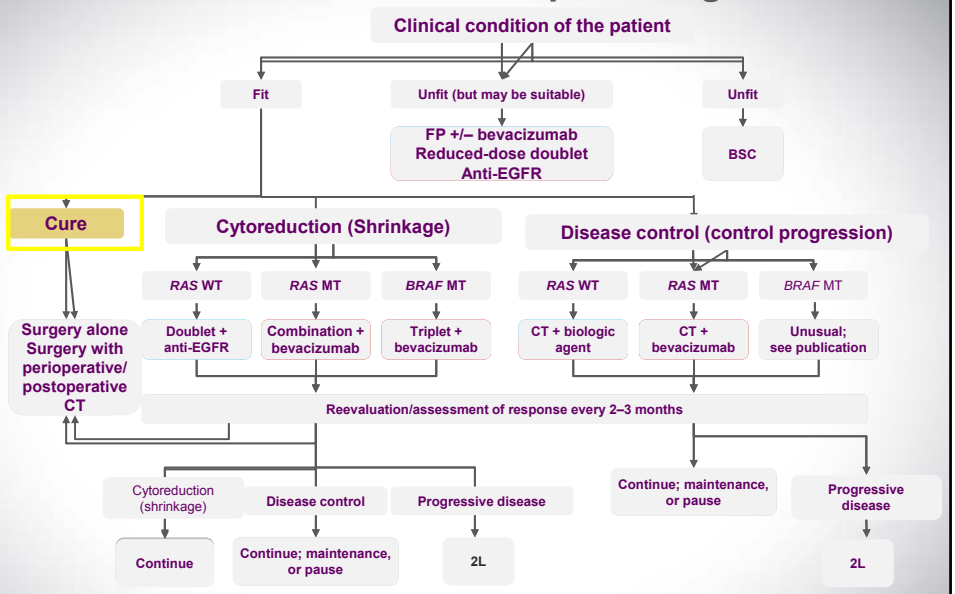
IMPROVE STAGING

- Find metastatic disease and treat earlier
- Incorporate tumor biology

CURE MORE PATIENTS

- Identify and cure “curable” patients
- Move new treatments into earlier setting

Treatment of mCRC: Proposed algorithm



BSC, best supportive care; CT, chemotherapy; EGFR, epidermal growth factor receptor; FP, fluoropyrimidine; MT, mutant; WT, wild-type 2L, second-line
van Cutsem E, Arnold D, Cervantes A. WCGC 2015. Session XIX: Metastatic Colorectal Cancer.; 41

Continuum of Care in metastatic CRC: Decisions, Decisions, Decisions

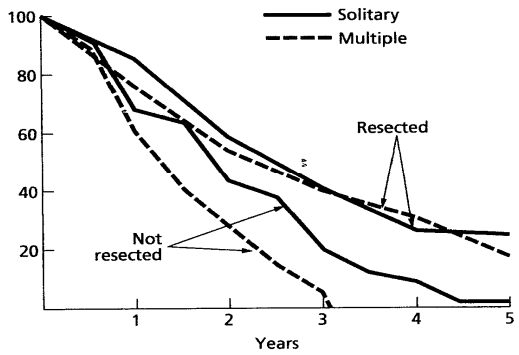
1st Line

- Goals of therapy
- Chemo intensity
- Biologic –
  - yes/no
  - Which
- Number of cycles

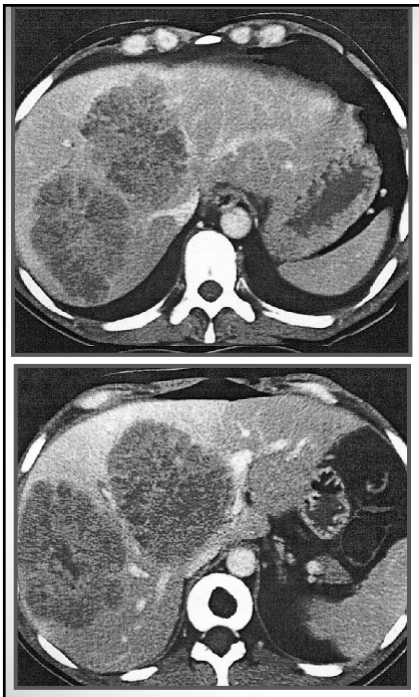
Importance of initial treatment

- Usually longest duration of therapy
- Major toxicity / complication could impact subsequent options
- Cannot miss window of opportunity
- Treat to achieve extreme outcomes

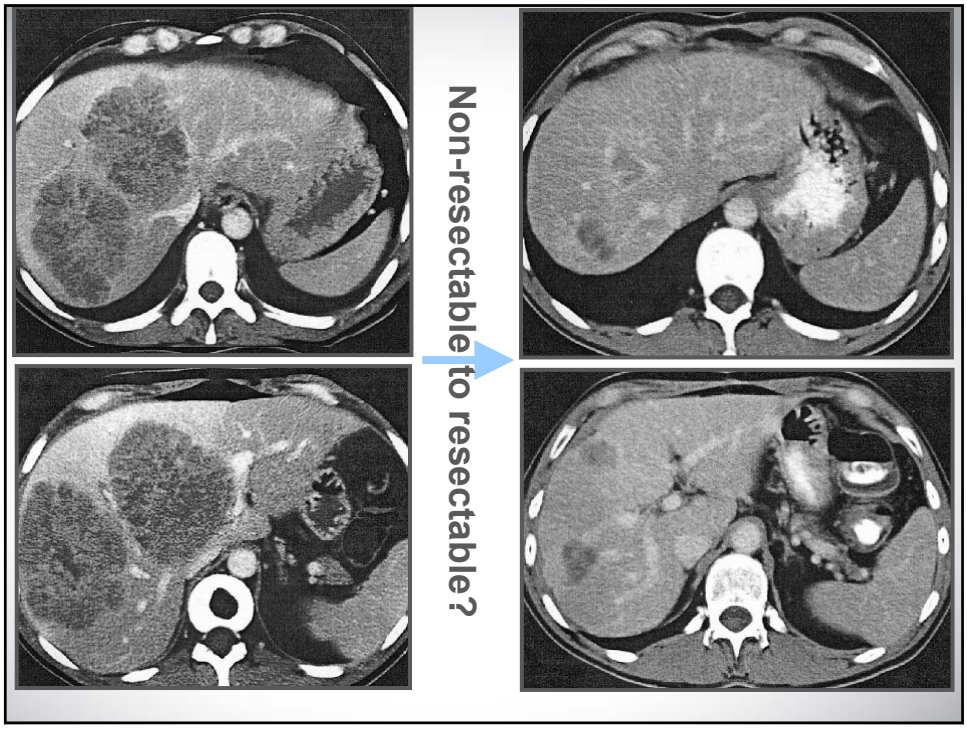
Metastectomy: survival at 5 years in metastatic CRC



Adson, World J Surg 1987, 11, 511-520



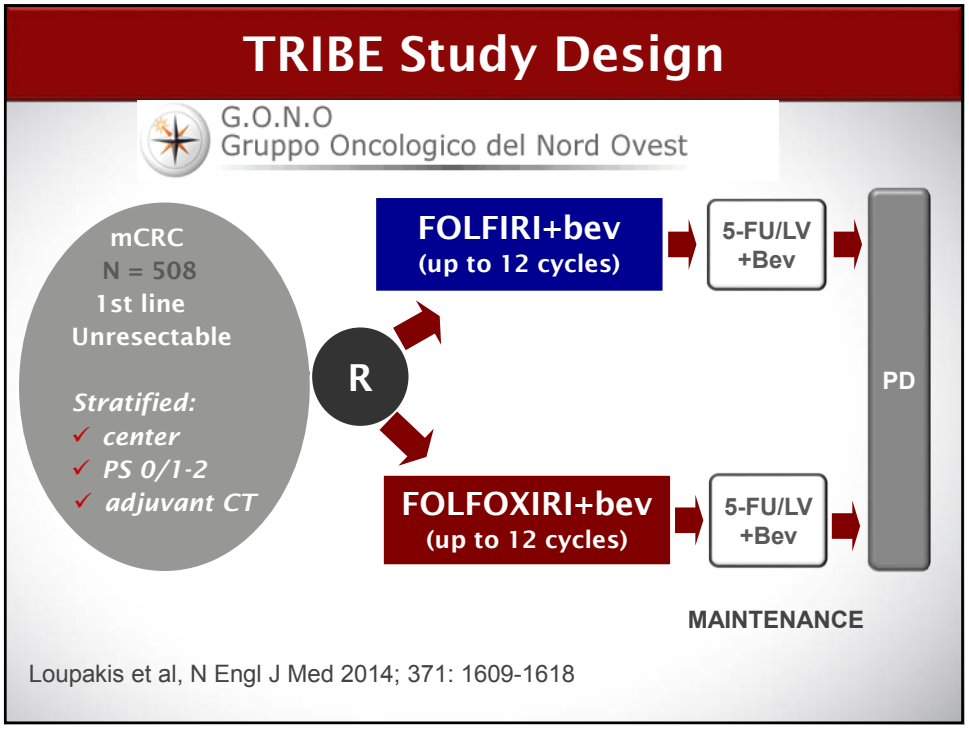
UNRESECTABLE METASTATIC DISEASE

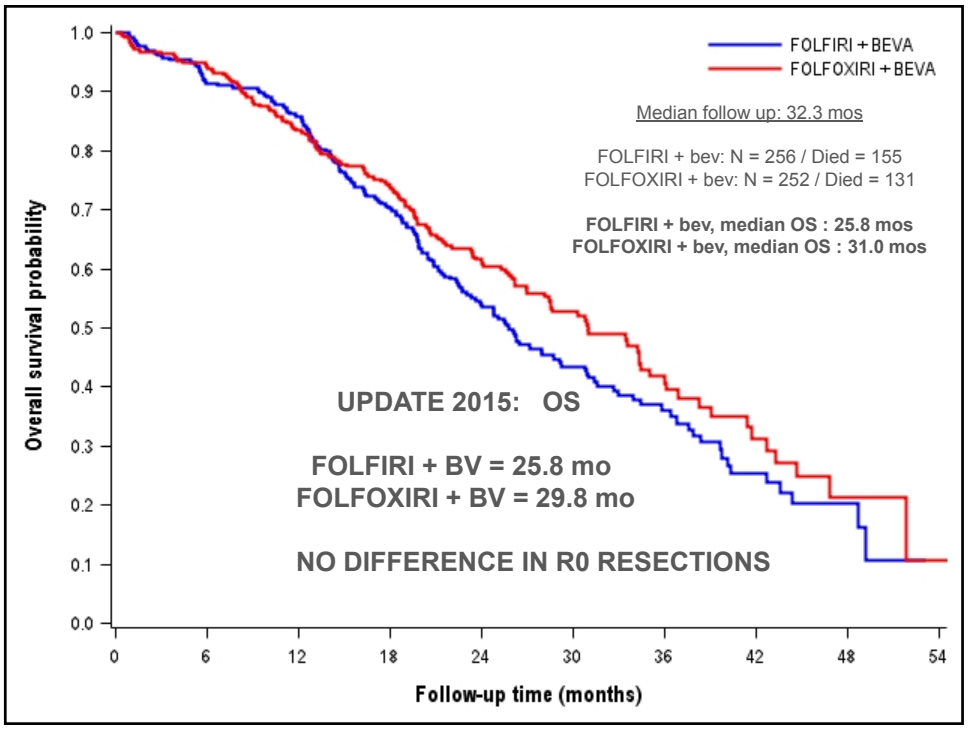


5-YR Survival post-liver metastectomy

↓ OPERATIVE MORTALITY
↑ 5-YEAR SURVIVAL

Authors	Year	Patients	Op. Mort.	5yr Survival
Foster	1981	259	%	22%
Iwatsuki	1986	60	0%	35%
Nordlinger	1987	80	5%	25%
Adson	1987	141	3%	25%
Hughes	1988	859	-	33%
Scheele	1991	219	5%	39%
Rosen	1992	280	4%	25%
Nordlinger - Jaeck	1992	1818	2%	26%
Gayowski	1994	204	0%	32%
Fong	1999	1001	2.8%	37%
Minigawa	2000	235	0%	38%
Ercolani	2002	257	0.8%	34%
Choti	2002	133	-	58%
Adam	2003	615	1%	41%
Abdalla	2004	190	-	58%





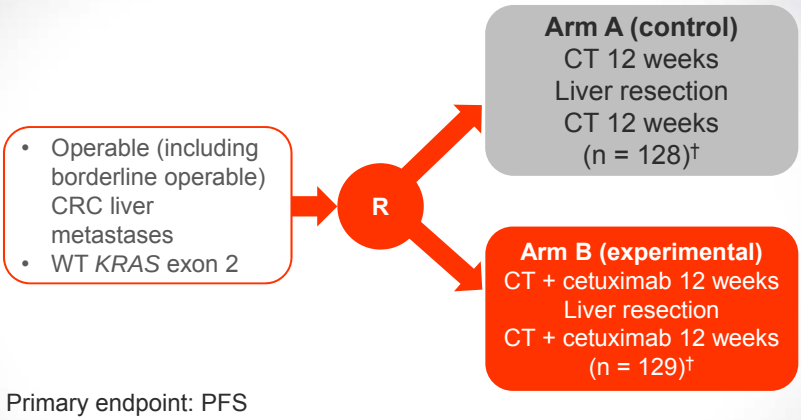
Secondary endpoint: Response rate (updated) - ITT population

NO DIFFERENCE IN R0 LIVER RESECTIONS !!

Best Response, %	FOLFIRI + bev N = 256	FOLFOXIRI + bev N = 252	*p*
Complete Response	3%	5%	
Partial Response	50%	60%	
Response Rate	**53%**	**65%**	***0.006***
Stable Disease	32%	25%	
Progressive Disease	11%	6%	
Not Assessed	4%	4%	

Loupakis et al, N Engl J Med 2014; 371: 1609-1618

New EPOC (E Peri-Operative Chemotherapy)



- Primary endpoint: PFS

Primrose J, et al. Lancet Oncol 2014;15:601–11.

New EPOC: PFS and OS

RR favors Chemo + CETUXIMAB

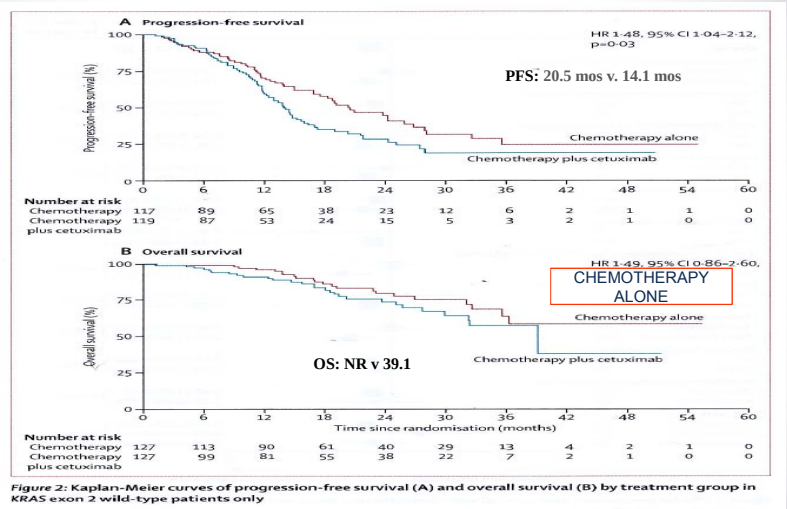
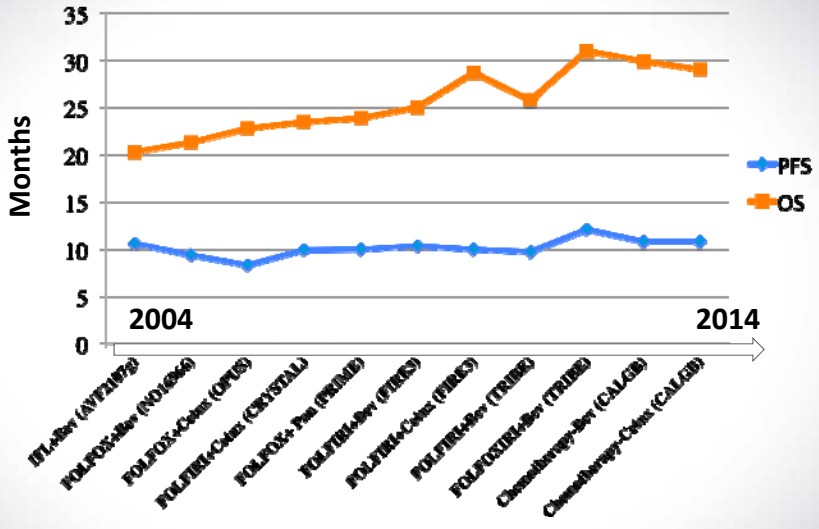


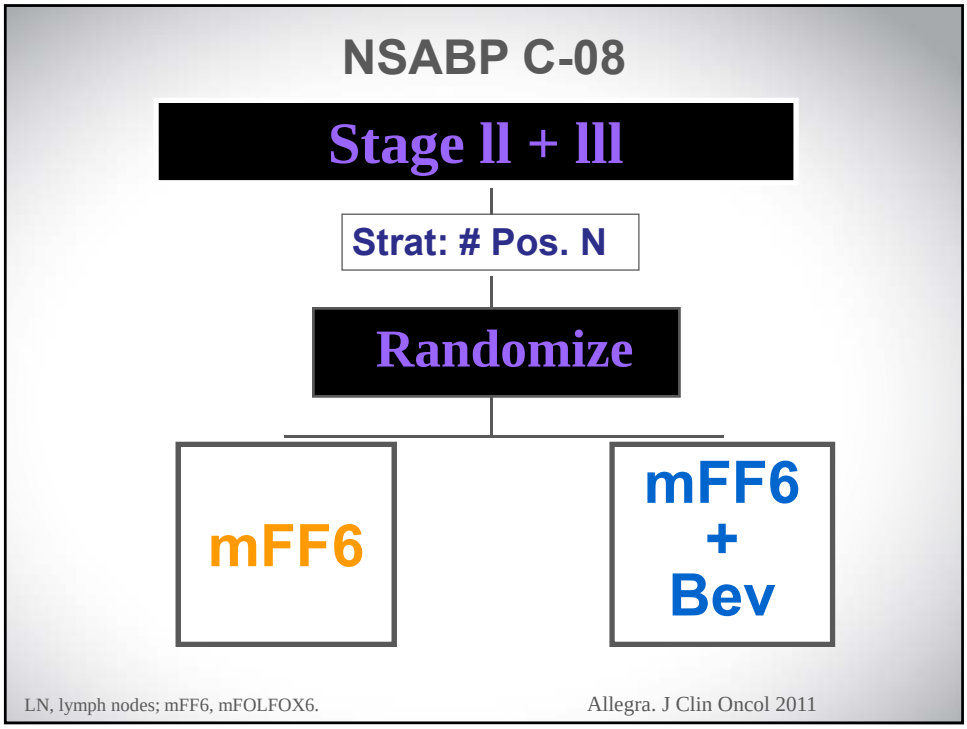
Figure 2: Kaplan-Meier curves of progression-free survival (A) and overall survival (B) by treatment group in *KRAS* exon 2 wild-type patients only

Primrose, et al, Lancet Oncol, 2014.

OS Improving, PFS stays the same

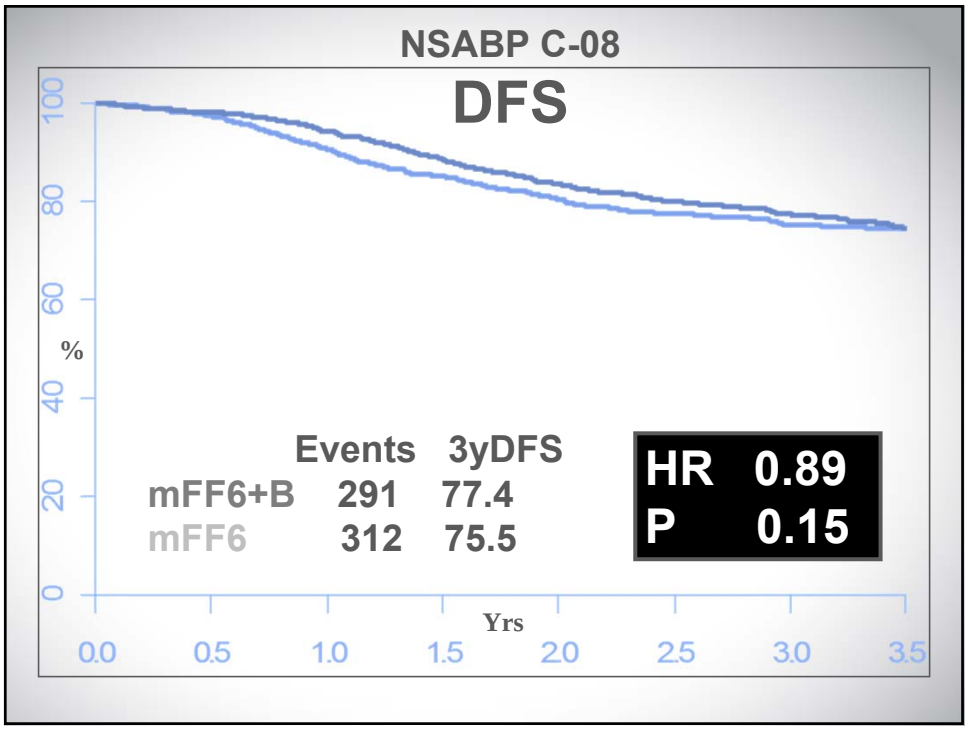


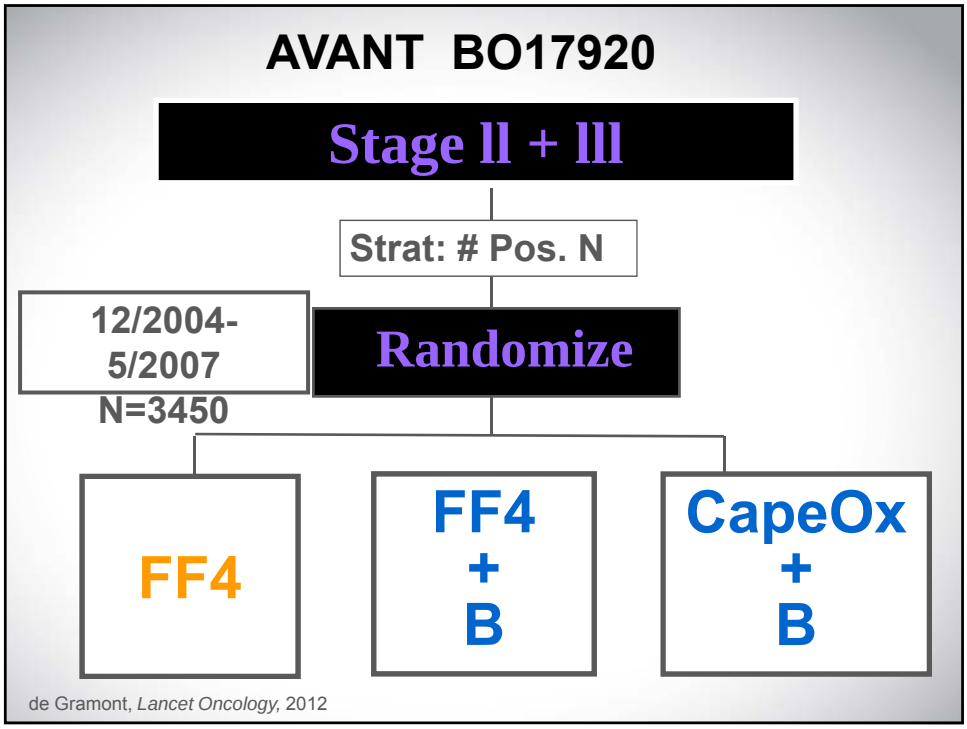
1. Hurwitz. 2004; 2. Saltz. 2008; 3. Bokemeyer. 2011; 4. Van Cutsem. 2011; 5. Douillard. 2011; 6. Heinemann. 2013; 7. Falcone. 2013. 8. Venook, 2014.

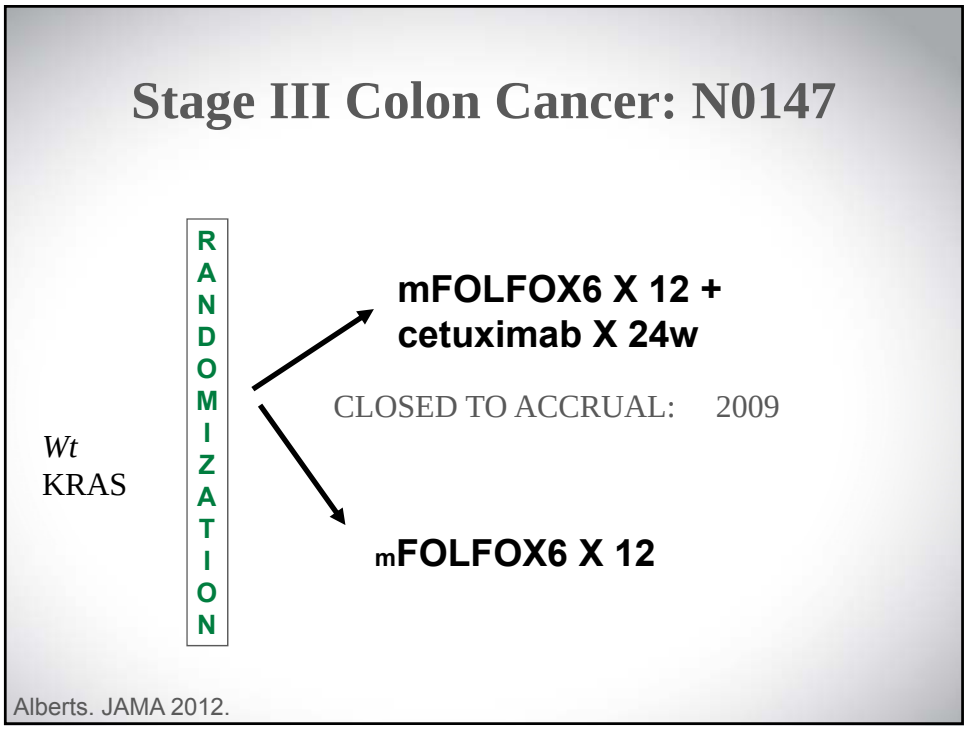


LN, lymph nodes; mFF6, mFOLFOX6.

Allegra. J Clin Oncol 2011



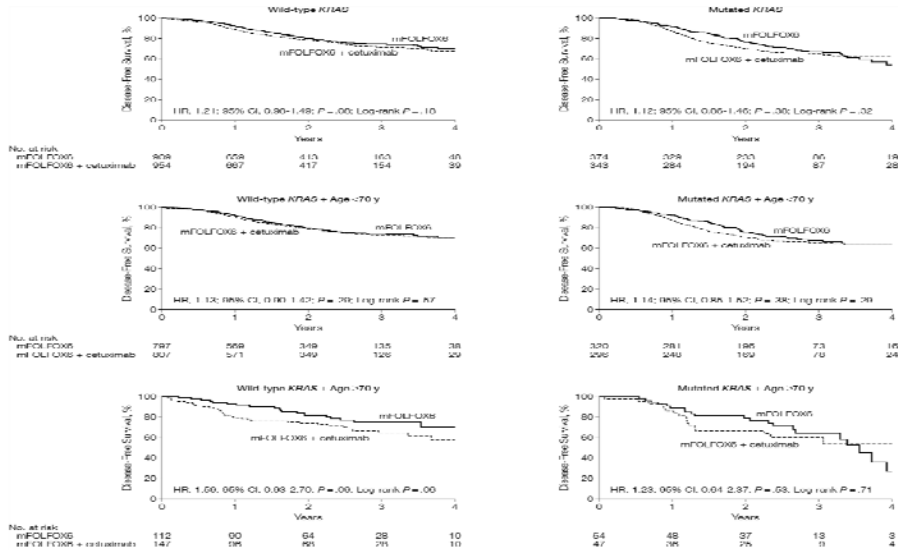




The JAMA Network

From: **Effect of Oxaliplatin, Fluorouracil, and Leucovorin With or Without Cetuximab on Survival Among Patients With Resected Stage III Colon Cancer: A Randomized Trial**

JAMA. 2012;307(13):1383-1393.



Continuum of Care in metastatic CRC: Decisions, Decisions, Decisions

1st Line

- Potential for resection of mets?
- What chemo intensity?
- What biologic (*RAS* status, *BRAF* status)?
- How many cycles?

Is this more important than 1st line?

Maintenance

- Maintenance?
- De-escalation?
- OPTIMOX?

2nd Line

- What chemo (impact of prior exposure)?
- What biologic now, if any?
- Quality versus quantity of life?

3rd Line

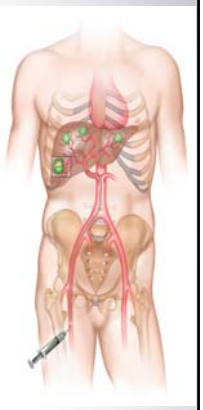
- What is the therapeutic goal?
- How can we maximize declining PS?
- Role of retreatment?

…

Resection, Ablation, Radiosurgery, Radioembolization

Selective Internal Radiation Therapy (SIRT)

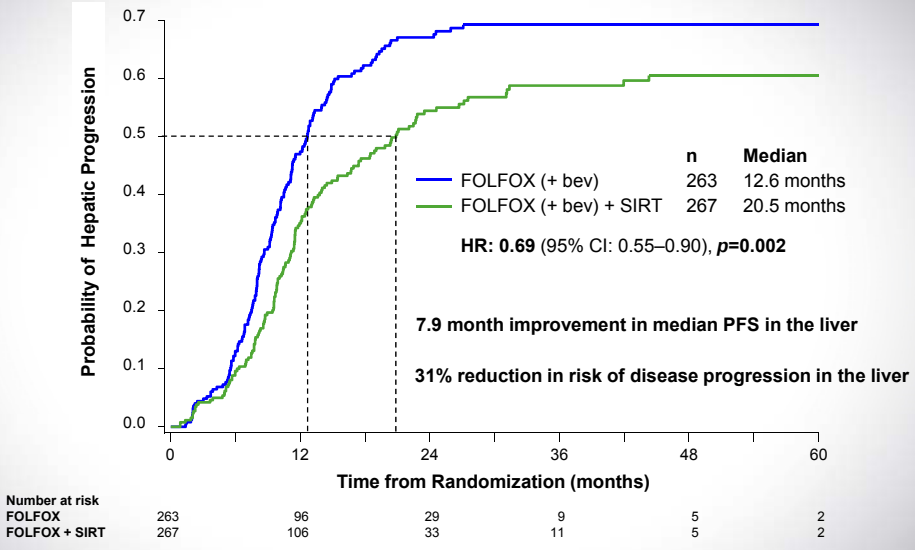
- SIRT employs Yttrium-90 (Y-90) labelled resin microspheres as a liver-directed therapy (1)
  - Hepatic artery injection
  - Delivers a single large radiation dose to liver tumors
  - Radiation deposited over 3 weeks
  - FDA approved in 2002 for unresectable CRCLMs (2)
- Combining SIRT with first-line chemotherapy may improve control of CRC liver metastases and thereby improve overall survival (3, 4)



1. Kennedy A *et al. Int J Radiat Oncol, Biol Phys* 2007;**68**:13–23.
2. Colorectal cancer liver metastases.
3. Van Hazel *et al. J Surg Oncol* 2004;**88**:78–85.
4. Sharma *et al. J Clin Oncol* 2007;**25**:1099–106.

Gibbs P *et al. Presented at 2015 ASCO Annual Meeting; J Clin Oncol* 2015; **33** (Suppl): Abs 3502.

Progression-Free Survival in the Liver



Gibbs P *et al. Presented at 2015 ASCO Annual Meeting; J Clin Oncol* 2015; **33** (Suppl): Abs 3502.

Colorectal Cancer: 20 Years Later

80405 results superimposed

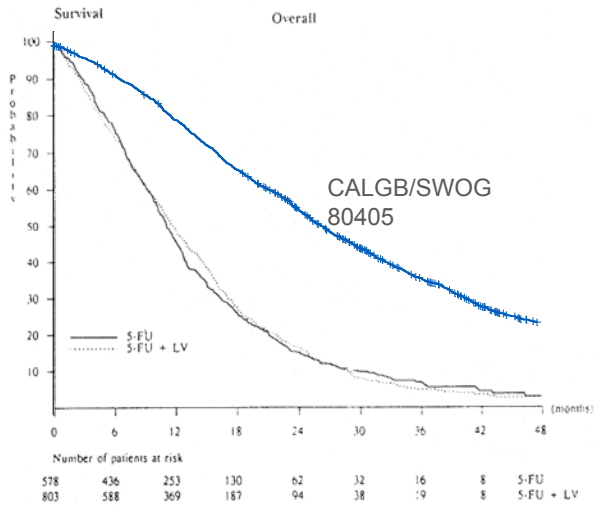


Fig 2. Overall survival. J Clin Oncol, 1992

Colorectal Cancer
Lessons Learned: 1980-2015

- Studies may (often) have conflicting results
  - FIRE-3 v. CALGB/SWOG 80405
  - New EPOC
- Conventional paradigms may be wrong
  - Activity in advanced disease may not translate into efficacy in the adjuvant setting
- Enrichment of patient populations may:
  - Improve survival in a subset of patients
  - But decrease survival (relatively) in the rest

How to Improve Survival in CRC: 1990

MORE EFFECTIVE TREATMENT

- Get beyond 5FU / Develop new therapies
- Ablative / surgical techniques
- Multidisciplinary care / **Lifestyle adjustments**

IMPROVE STAGING

- Find metastatic disease and treat earlier
- **Incorporate tumor biology**

CURE MORE PATIENTS

- Identify and cure "curable" patients
- Move new treatments into earlier setting

Lifestyle questions: FINDINGS

DECREASES risk of recurrence

- EXERCISE
- Aspirin
- NON-Western diet

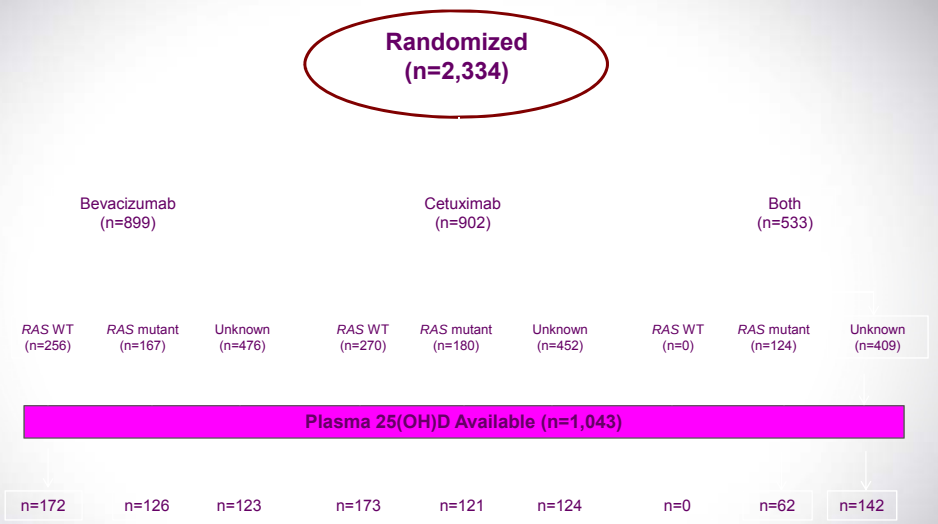
DECREASES RISK OF DEATH

- Aspirin

INCREASES RISK OF RECURRENCE

- SWEETENED BEVERAGES

CALGB 80405 and Vitamin D



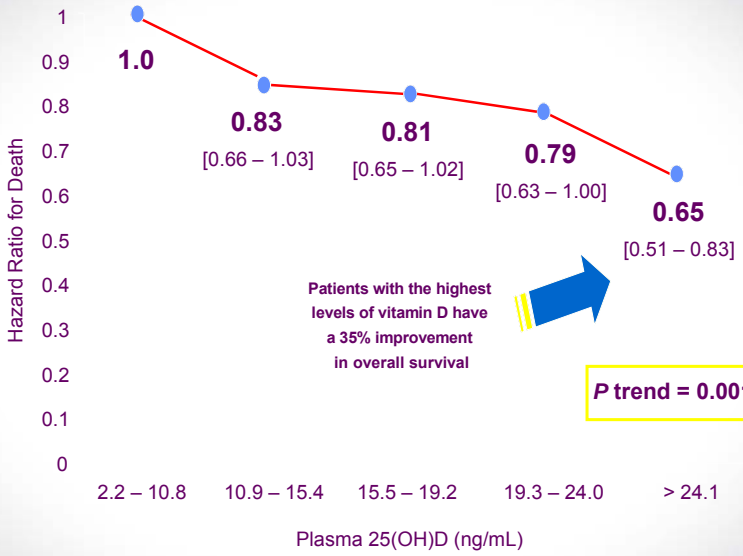
Ng, ASCO, 2105

Multivariate Analysis

- Final model adjusted for:
  - Age
  - Sex
  - Race
  - ECOG performance status
  - Chemotherapy backbone
  - Previous adjuvant therapy
  - Assigned biologic
  - *RAS* mutation status
  - Season of blood draw
  - Geographic region of residence
  - Body-mass index
  - Physical activity

Ng, ASCO, 2105

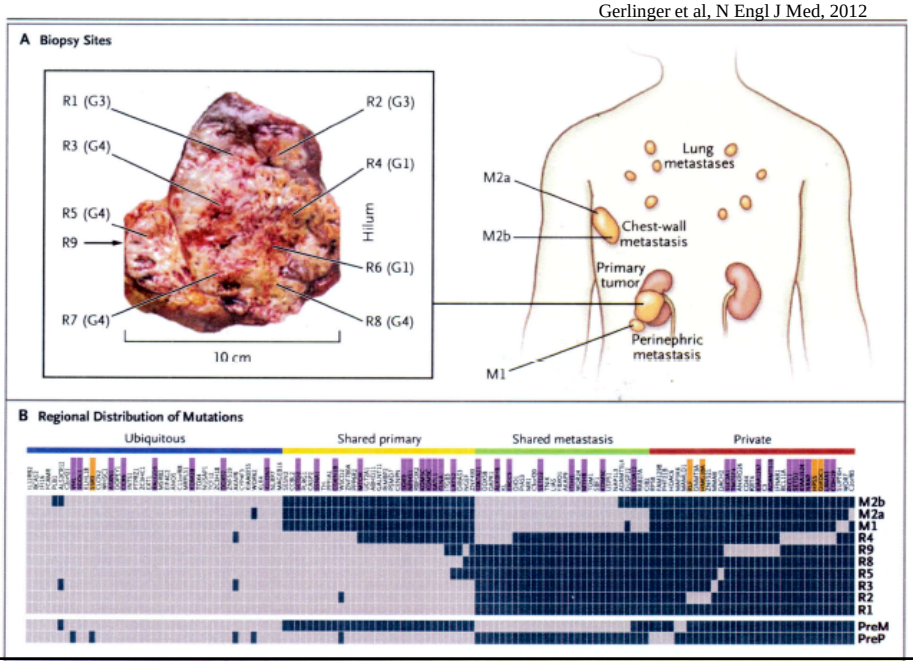
Multivariate Hazard Ratios: Overall Survival



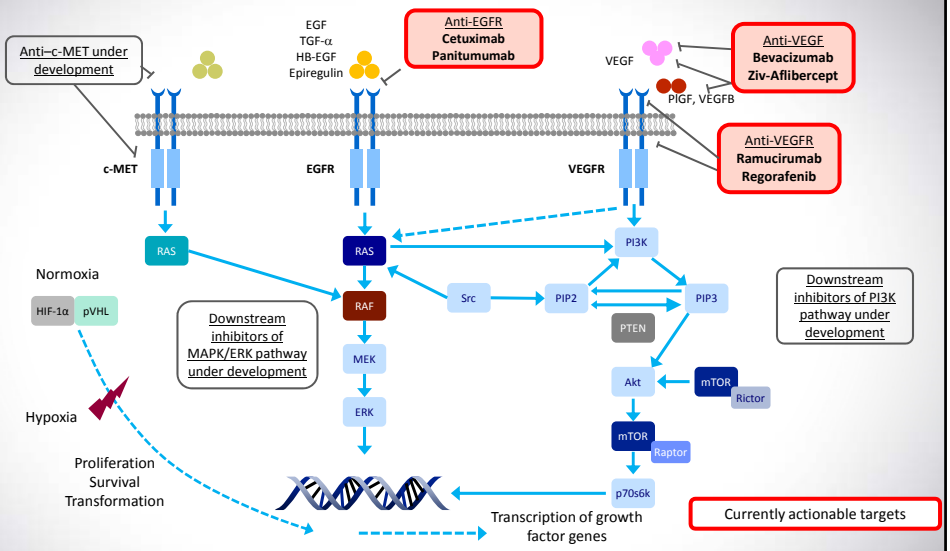
Ng,ASCO, 2105

Intratumor Heterogeneity Revealed by Multiregion Sequencing

Gerlinger et al, N Engl J Med, 2012



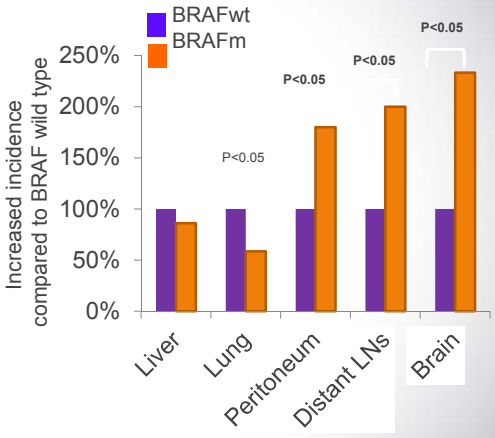
Key Signalling Pathways in CRC Decisions



HB-EGF, heparin-binding epidermal growth factor; HIF, hypoxia-inducible factor; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase; PlGF, phosphatidylinositol-glycan biosynthesis class F protein; PTEN, phosphatase and tensin homolog; pVHL, Von Hippel-Lindau tumour suppressor; TGF, transforming growth factor; VEGF, vascular endothelial growth factor.
Adapted from Siena. 2009.

BRAF mutated Colorectal Cancer (BRAFm CRC): Distinct Biology

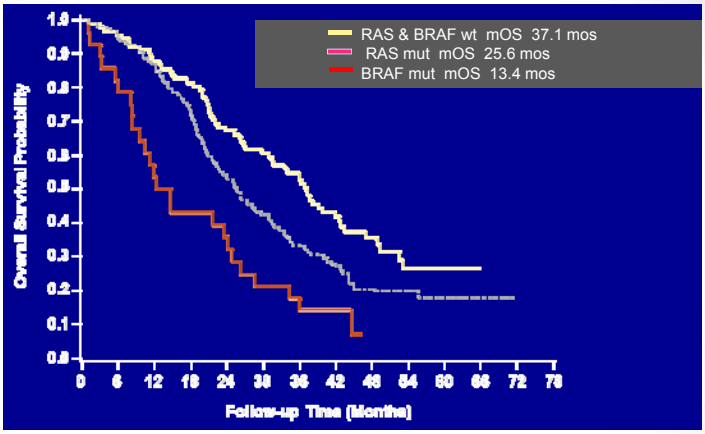
- Origin: serrated adenoma in proximal colon
- Microsatellite unstable
- Hyper-methylated
- RAS wild-type
- Patients: female, peritoneal, LN & brain metastases



Tran et al, *Cancer* 2011

BRAFm CRC: Poor Survival

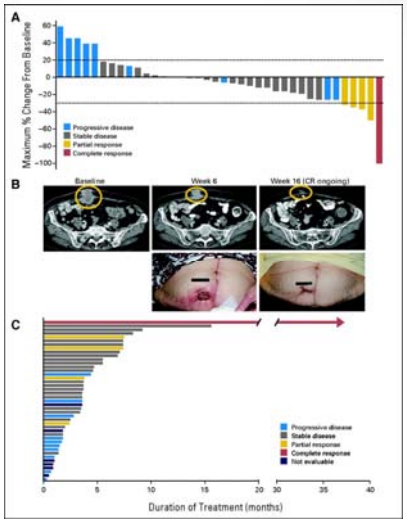
TRIBE



Cremolini, Lancet Oncology, 2015

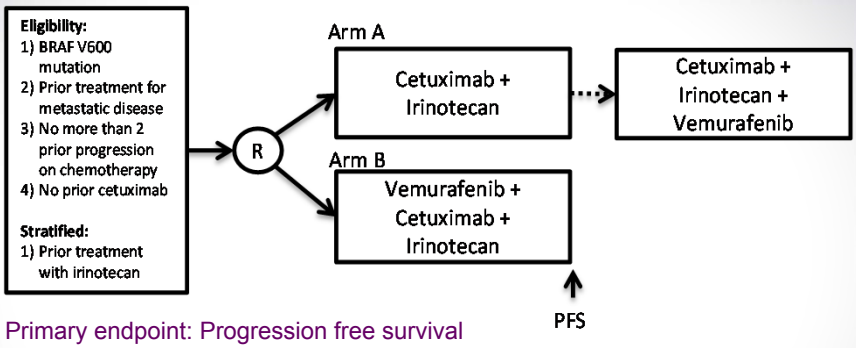
Combined BRAF and MEK inhibition with Dabrafenib and Trametinib in BRAF V600-mutant colorectal cancer

(A) Waterfall plot of maximum percent reduction in target lesion size by RECIST. Horizontal lines at + 20% and − 30% denote boundaries of stable disease.



Ryan B. Corcoran et al. JCO doi:10.1200/JCO.2015.63.2471

S1406: Cetuximab + Irinotecan ± Vemurafenib

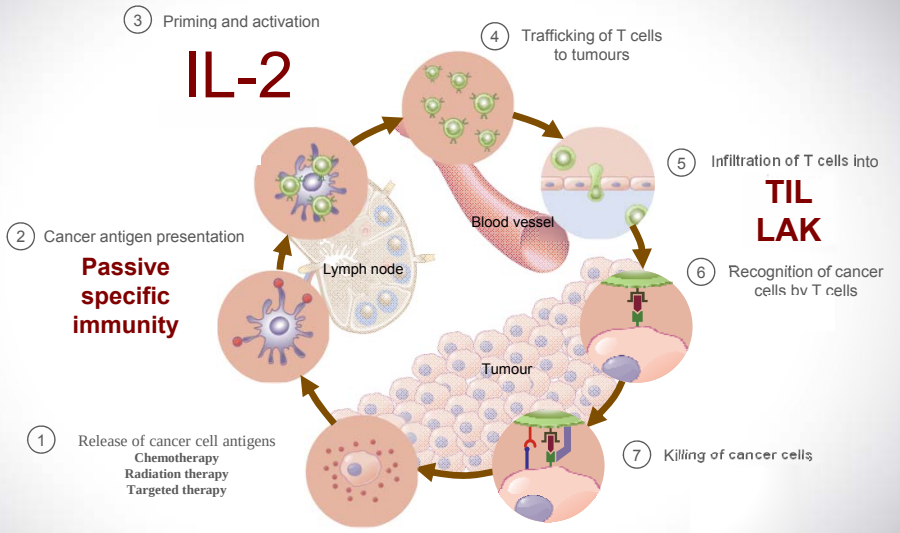


Primary endpoint: Progression free survival
Targeted enrollment: 78 patients

ACCRUAL AMENDED TO >100

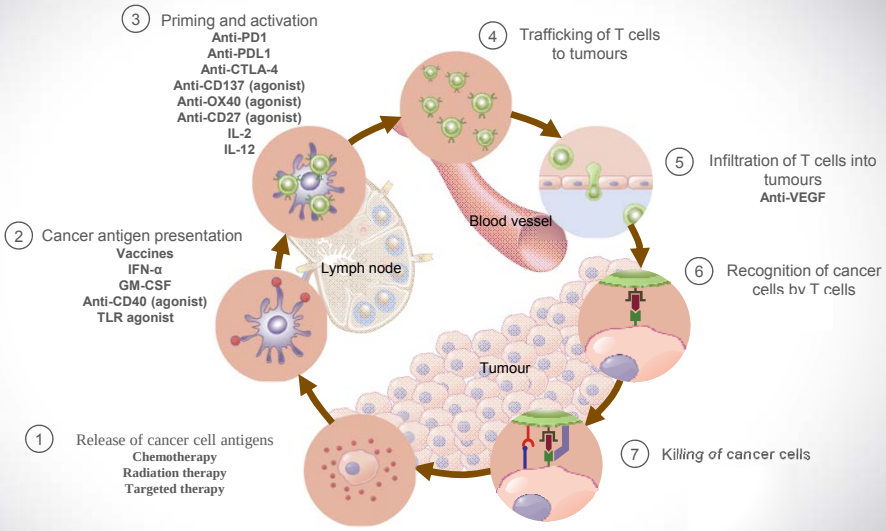
SWOG PI: Scott Kopetz
Alliance PI: Chloe Atreya
ECOG PI: Luis Diaz
NSABP PI: Carmen Allegra

Therapies that might affect the cancer-immunity cycle
circa 1990



Chen & Mellman. Immunity 2013

Therapies that might affect the cancer-immunity cycle



Chen & Mellman. Immunity 2013

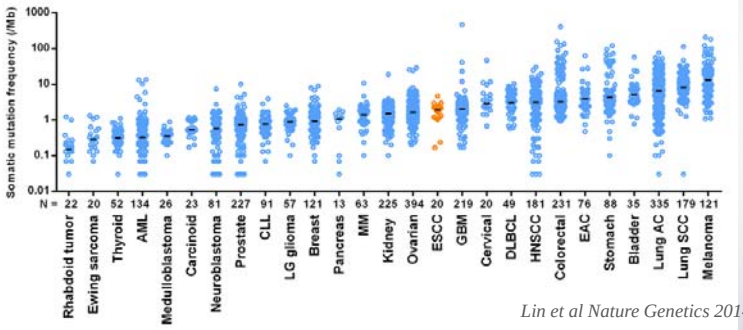
RESEARCH | REPORTS

CANCER IMMUNOLOGY

Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer

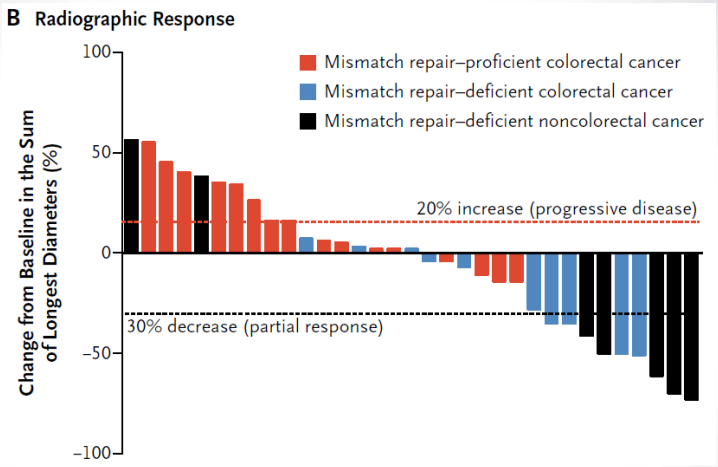
Naiyer A. Rizvi,[1,2*†] Matthew D. Hellmann,[1,2*] Alexandra Snyder,[1,2,3*] Pia Kvistborg,[4] Vladimir Makarov,[3] Jonathan J. Havel,[3] William Lee,[3] Jianda Yuan,[6] Phillip Wong,[6] Teresa S. Ho,[6] Martin L. Miller,[7] Natasha Rekhtman,[8] Andre L. Moreira,[8] Fawzia Ibrahim,[1] Cameron Bruggeman,[9] Billel Gasmi,[10] Roberta Zappasodi,[10] Yuka Maeda,[10] Chris Sander,[7] Edward B. Garon,[11] Taha Merghoub,[1,10] Jedd D. Wolchok,[1,2,10] Ton N. Schumacher,[4] Timothy A. Chan[2,3,5†]

Mutation Rate/neoantigen load may contribute to sensitivity to PD-1



Lin et al Nature Genetics 2014

Anti-PD1 (Pembrolizumab)

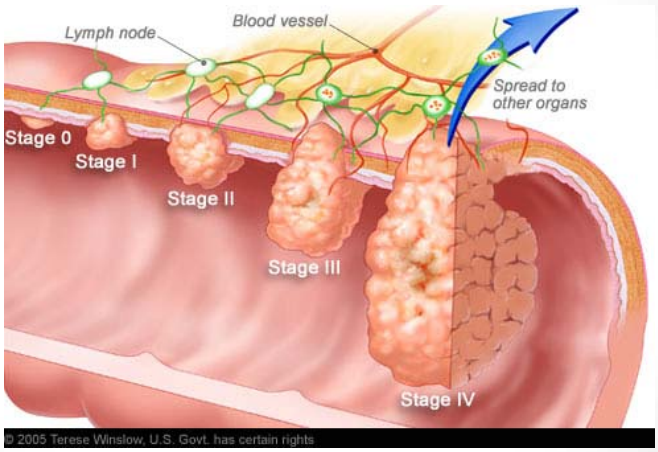


Objective Response Rate
62% MMR-deficient CRC
0% MMR-proficient CRC

Le et al, NEJM 372;26, 2015

CRC Pathophysiology

- Typically [illegible] Early detection [illegible]



ACS. Colon Cancer Facts & Figures website. 2011-2013. Accessed June 12, 2012

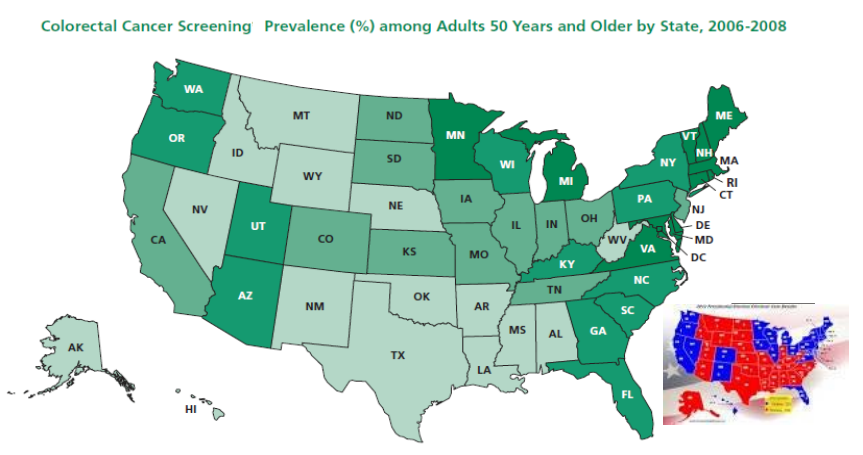
CRC Screening Barriers and Strategies to Improve Screening Rates

Barriers	Potential Improvement Strategies
Lack of access to health care	Home use FOBT cards and instructions
Lack of a healthcare practitioner's recommendation for screening	One-on-one discussions with a HCP regarding the importance of screening for CRC
Differences in physician (colonoscopy) and patient (FOBT) screening preferences	Mailed appointment reminders to patients who are due for screening
Demographics: low levels of educational achievement and income	Involvement of patient navigators to assist patients in managing referrals, navigating the health care system, and facilitating follow-up
Personal barriers: fear and embarrassment	

FOBT, fecal occult blood test

ACS. Colon Cancer Facts & Figures website. 2011-2013. Accessed June 12, 2012.

CRC Screening Prevalence



- **Fecal occult blood test within the past year or sigmoidoscopy or colonoscopy within the past 10 years. Screening and diagnosis exams combined.**

ACS. Colon Cancer Facts & Figures website. 2011-2013. Accessed June 12, 2012.

DELAWARE

SIZE = 2489 SQ MILES

POPULATION = 917,092

SACRAMENTO

SIZE = 995 SQ MILE

POP = 1,420,000

Colorectal cancer: Looking ahead
DELAWARE EXPERIENCE

- STATE / INSURERS / PHYSICIANS
- Guarantee colonoscopy / care regardless of insurance status
- Nurse navigators
- Community outreach

Grubbs, JCO, 2013

Colorectal cancer: Looking ahead
DELAWARE EXPERIENCE

Screening (population, >50): 57% to 74%

(African American, > 50) 48% 74%

Colon cancers stage at diagnosis:

Advanced 79% to 40%; local 16% to 50%

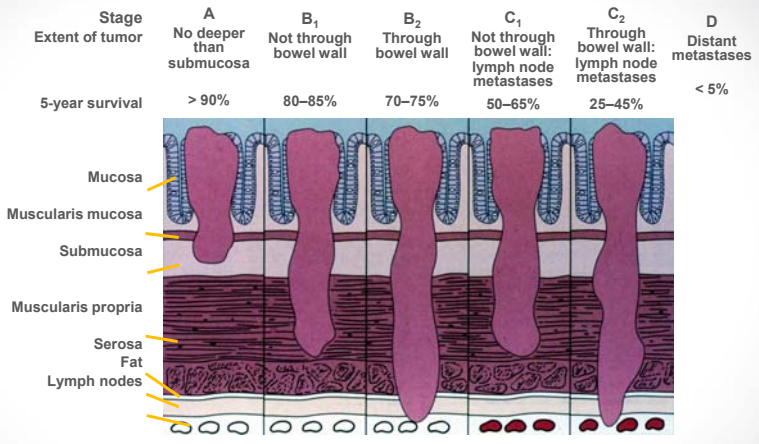
Incidence (per 100000): all, 58 to 45

AA, 67 to 45

Mortality: decrease 41%

Grubbs, JCO, 2013

Staging of Colorectal Cancer



Adapted from Skarin. *Slide Atlas of Diagnostic Oncology*. Gower Medical Publishing; 1997:Fig 5.98.

Consensus Molecular Subtypes of Colorectal Cancer

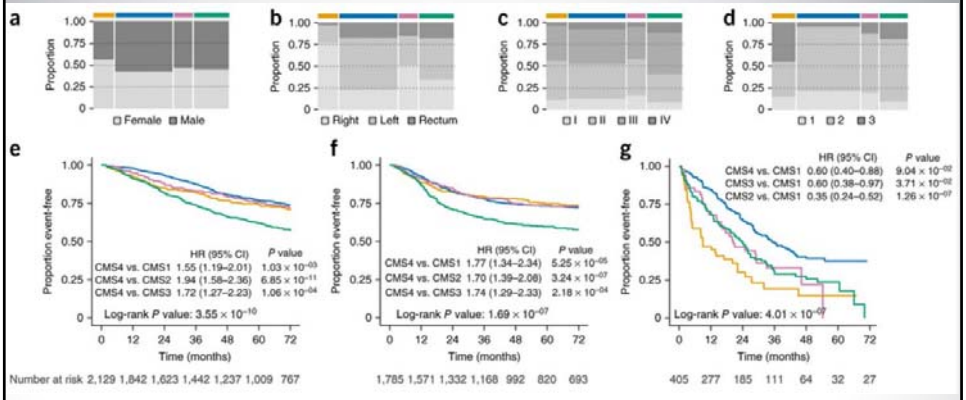


Figure 4: Clinicopathological and prognostic associations of consensus molecular subtype groups.

(**a–d**) Distribution of gender (n = 2,844) (**a**), tumor site location (n = 2,641) (**b**), stage at diagnosis (n = 2,952) (**c**) and histopathological grade (n = 747) (**d**) across consensus subtype samples, represented by the colored bars CMS1, yellow; CMS2, blue; CMS3, pink; CMS4, green. (**e–g**) Prognostic value of CMS1 (yellow), CMS2 (blue), CMS3 (pink) and CMS4 (green) with Kaplan-Meier survival analysis in the aggregated cohort for overall survival (n = 2,129) (**e**), relapse-free survival (n = 1,785) (**f**) and survival after relapse (n = 405) (**g**). The hazard ratios (HR) and 95% confidence intervals (CI) for significant pairwise comparisons in univariate analyses (log-rank test) are displayed in each Kaplan-Meier plot. Numbers below the x axes represent the number of patients at risk at the selected time points. Detailed statistics are in Supplementary Tables 5 and 13.

Consensus Molecular Subtypes of Colorectal Cancer

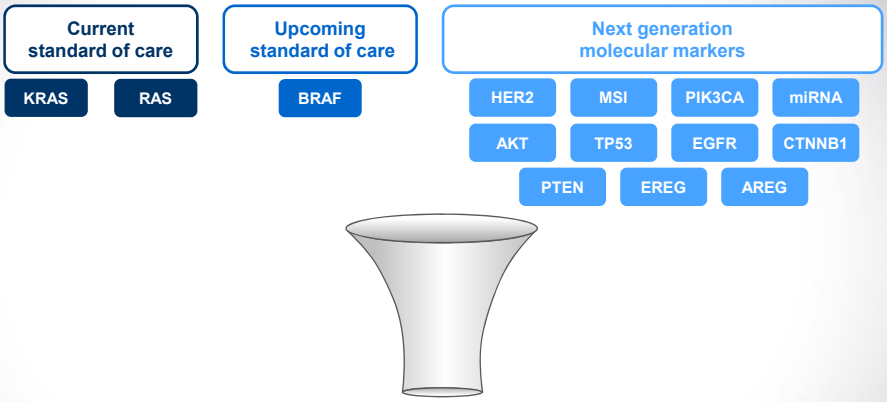
Figure 5: Proposed taxonomy of colorectal cancer, reflecting significant biological differences in the gene expression-based molecular subtypes.

CMS1 MSI immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
14%	37%	13%	23%
MSI, CIMP high, hypermutation	SCNA high	Mixed MSI status, SCNA low, CIMP low	SCNA high
BRAF mutations		*KRAS* mutations	
Immune infiltration and activation	WNT and MYC activation	Metabolic deregulation	Stromal infiltration, TGF-β activation, angiogenesis
Worse survival after relapse			Worse relapse-free and overall survival

CIMP, CpG island methylator phenotype; MSI, microsatellite instability; SCNA, somatic copy number alterations.

Guinney, et al. Nature Med, 2015

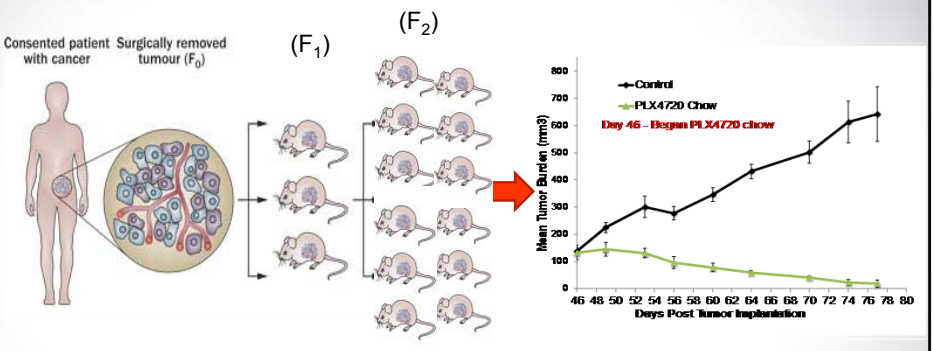
Finding Actionable Targets



Therapy tailored according to molecular status

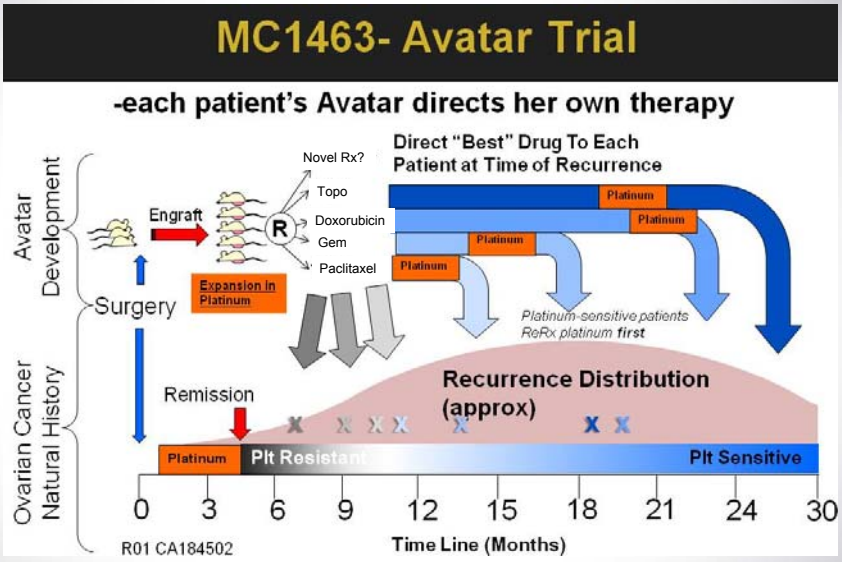
Caiazza, et al. Biomark Med 2015

Patient-derived Xenografts



Adapted from: Tentler, *et al.* (2012) *Nat. Rev. Clin. Oncol*

Using PDX Models to *Guide* Treatment



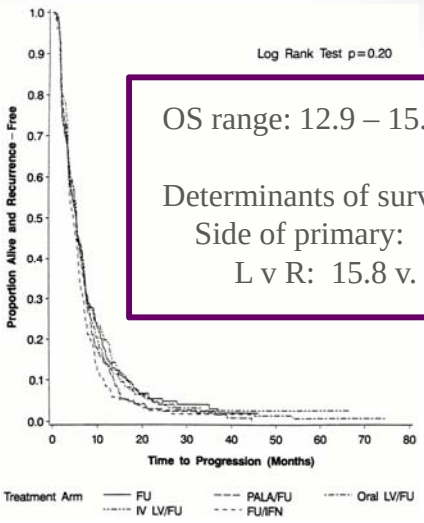
Haluska et al, ASCO 2014

Colorectal Cancer
Lessons Learned: 1980-2015

- Studies may (often) have conflicting results
  - FIRE-3 v. CALGB/SWOG 80405
  - New EPOC
- Conventional paradigms may be wrong
  - Activity in advanced disease may not translate into efficacy in the adjuvant setting
- Enrichment of patient populations may:
  - Improve survival in a subset of patients
  - But decrease survival (relatively) in the rest

- **We do not know as much as we thought we knew**

ECOG 2290 / CALGB 9092



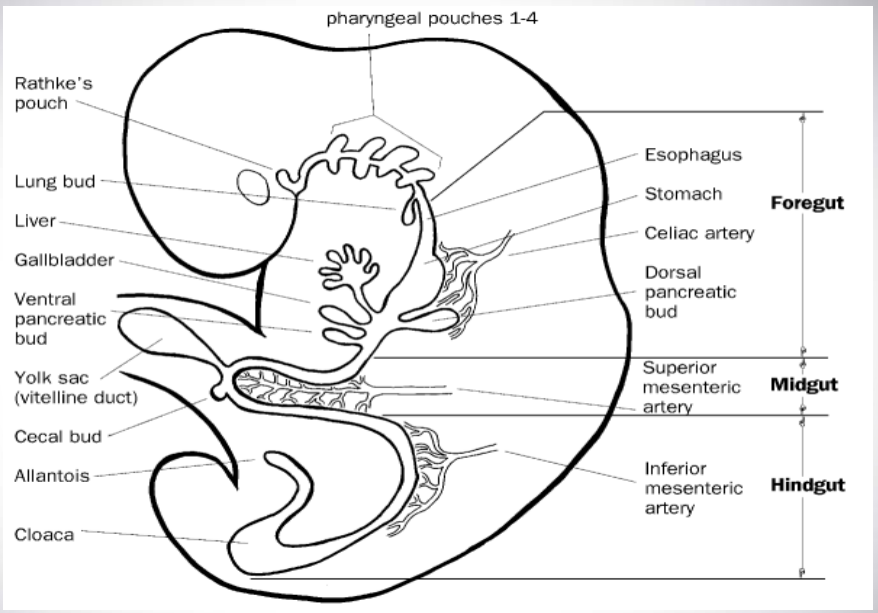
OS range: 12.9 – 15.2 months

Determinants of survival:
Side of primary:
L v R: 15.8 v. 10.9 p <.001

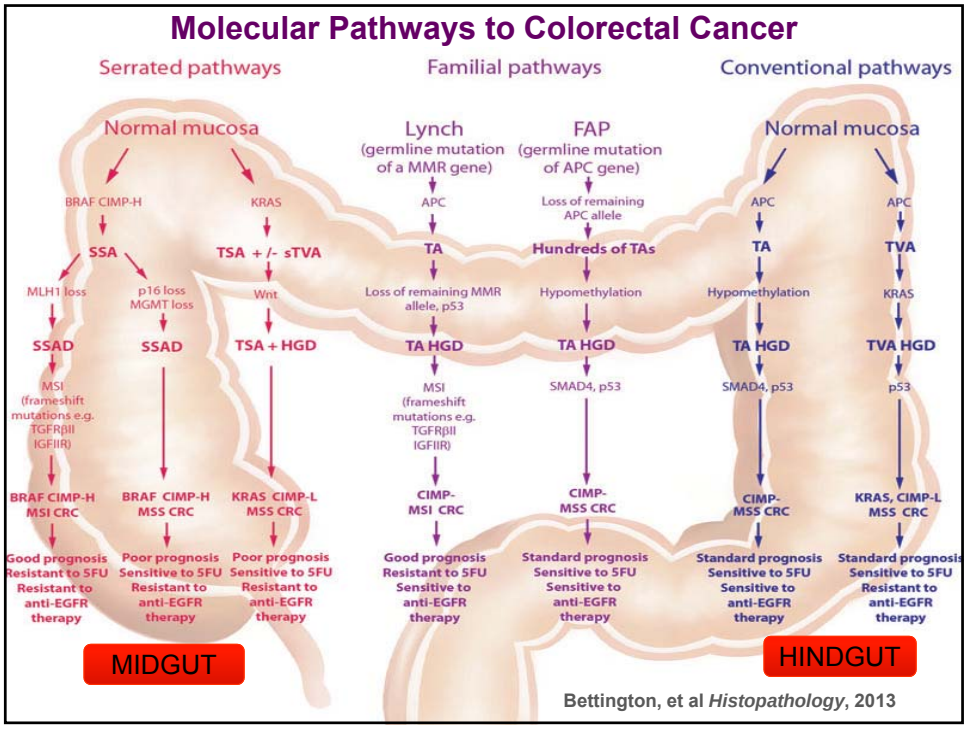
Peter J. O'Dwyer et al. JCO 2001;19:2413-2421

JOURNAL OF CLINICAL ONCOLOGY ASCO

Embryology: The origin of the colon



Bettington, et al. *Histopathology*. 2013.



Taking Sides: Metastatic Colorectal Cancer

PUBLICATION	Patients	Molecular Selection	Treatment	OS: RIGHT v. LEFT (Months)
O'Dwyer JCO, 2001	N = 1120 (E2290)	NONE	5FU VARIATIONS	10.9 v 15.8
Heinemann, ASCO, 2014 (ABS)	N = 333 (FIRE-3)	ALL RAS wt BRAF	FOLFIRI / BEV / CET	22.7 v. 28.0 16.1 v. 38.7
Brule, JAMA, 2014	N = (CO.17)	KRAS wt	BSC v. BSC + CET	R: L:
Von Einem, J Res Clin Oncol, 2014	N = 146 (AIO)	KRAS wt (95) KRAS mut (51)	CAPIRI/CAPOX/ CET	Wt: 13.0 v. 29.0 Mut: 18.9 v. 19.7
Loupakis, JNCI, 2015	N = 2053	NONE	FOLFIRI/BEV (200) FuOX/BEV (1268) IFL/BEV (559)	24.8 v 42.0 18.0 v. 23.0 14.6 v. 24.0

FIRE-3: Impact of Sidedness

Heinemann, et al, ASCO, 2014

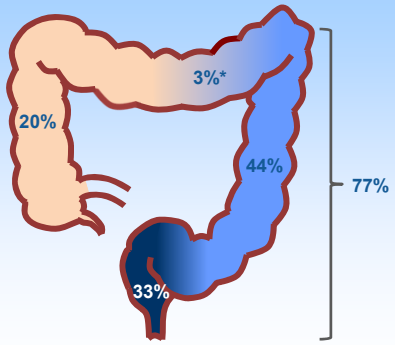
Definition of primary tumor location

- **Right sided** CRC (”midgut”): coecum to hepatic flexure
- **Left sided** CRC (“hindgut”): splenic flexure to rectum
- **Colon transversum** tumors (n=9) were excluded

Statistics

- Differences in response (ORR) and survival (PFS/OS) within both treatment arms were calculated using ***two-sided Fisher´s exact*** and ***log-rank test***, respectively.
- Using a backward elimination design, ***COX regression analysis*** was performed taking baseline characteristics plus BRAF and PIK3CA mutations into account.

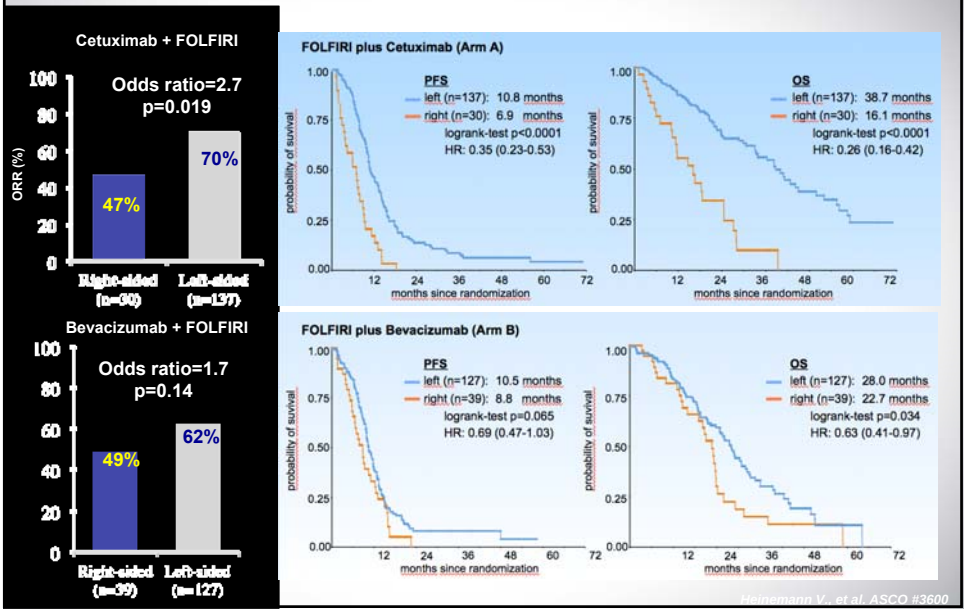
Distribution of right- and left-sided primaries in FIRE-3



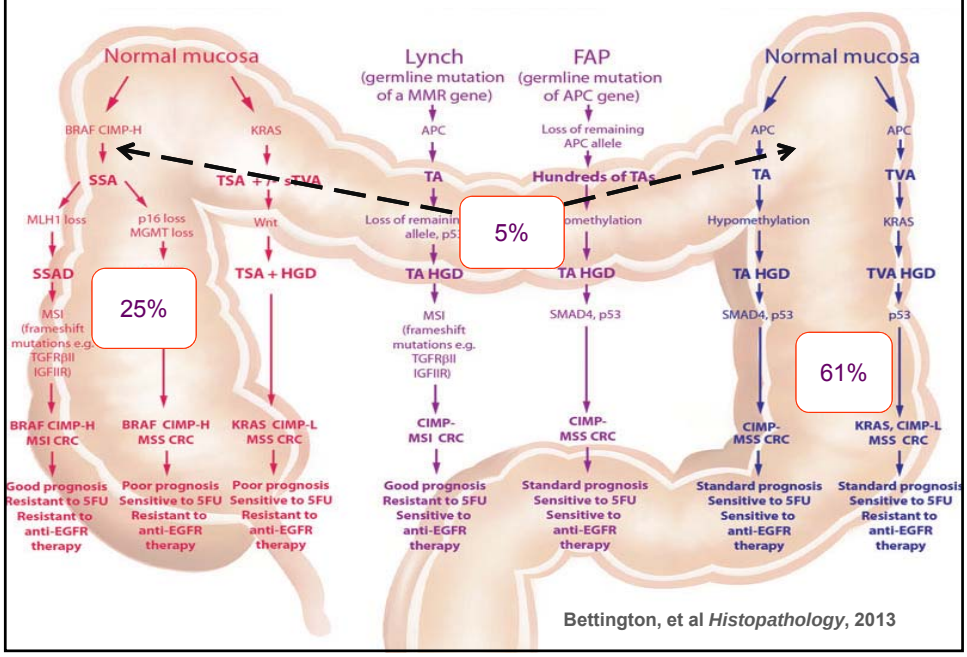
*tumors of the transversum were excluded from further analysis

FIRE-3:

Effect of Tumor localization on PFS and OS



Distribution of Primary Tumors in 80405



Bettington, et al *Histopathology*, 2013

C80405: Overall Survival by Sidedness

Sunday June 5th ASCO, Chicago

Colorectal Cancer: 2015 - 2025

- Screening
- Optimize inhibition of “actionable” targets
- Harness the immune system
- Make “non-actionable” targets actionable
- Find new targets that are actionable
- Refine staging / clinical correlations
- Maximize standard treatments
- Understand biology