المستجدات في علاج سرطان الكولون

د.نورس نبيل جعفر
أخصائية في علم الأورام
طبيبة مشرفة في مشفى ابن النفيس

Colorectal Cancer: Epidemiology

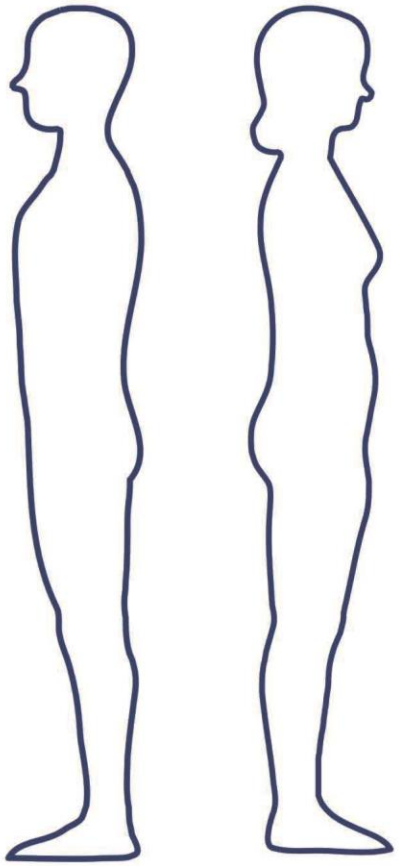
- Colorectal cancer (CRC) remains a major public health problem.
- Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the third leading cause of disease mortality in the United States.
- Worldwide, it is estimated that more than 1 million new cases of CRC will be diagnosed each year.

James J. Lee, Edward Chu, E lsevier Inc. Vol. 13, No. 3, 135-44 ª 2014.
Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. CA Cancer J Clin 2014; 64:9-29.

2016 Estimated US Cancer:

New GI Cases

Men		Women	
Prostate	21%	29%	Breast
Lung & bronchus	14%	13%	Lung & bronchus
Colorectal	**8%**	**8%**	**Colorectal**
Urinary bladder	7%	7%	Uterine corpus
Melanoma	6%	6%	Thyroid
NHL	5%	4%	NHL
Kidney	5%	3%	Melanoma
Leukemia	4%	3%	Leukemia
H&N	4%	**3%**	**Pancreas**
Liver/Cholangio	**3%**	3%	Kidney
All Other Sites	23%	21%	All Other Sites

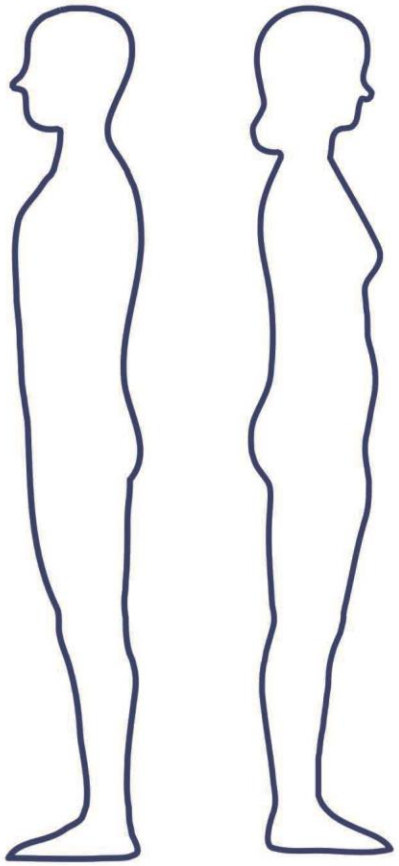


ACS – Surveillance Research 2015

2016 Estimated US Cancer:

GI Cancer Deaths

Men		Women	
Lung & bronchus	27%	26%	Lung & bronchus
Prostate	8%	14%	Breast
Colorectal	**8%**	**8%**	**Colorectal**
Pancreas	**7%**	**7%**	**Pancreas**
Liver/Cholangio	**6%**	5%	Ovary
Leukemia	4%	4%	Uterine corpus
Esophagus	**4%**	4%	Leukemia
Urinary bladder	4%	**3%**	**Liver/Cholangio**
NHL	4%	3%	NHL
Brain/CNS	3%	2%	Brain/CNS
All other sites	25%	24%	All other sites



ACS – Surveillance Research 2015

Epidemiology In Syria

2016Estimated Syrian Cancer Cases (multi-centre study)

		Men	Women		
Lung & bronchus	**18%**	**9631**	**8827**	**32%**	**Breast**
Colon & rectum	13%			12%	Colon & rectum
Leukemia	12 %			9%	Leukemia
Lymphoma	8%			8 %	Thyroid
C.N.S	7%			5%	Uterine Corpus
Urinary bladder	6%			5%	Lymphoma
Prostate	6%			4%	Ovary
Bone&ST	5%			4%	C.N.S
Stomach	5%			3%	Bone&ST
Larynx	3%			3%	Lung & bronchus
Liver	3%			3%	**Stomach**
Skin	3%			2%	Cervix
Thyroid	2%			2%	Liver
All Other Sites	9%			8%	All Other Sites

Source: Syrian National Cancer Registry,2016.(hospital Based)

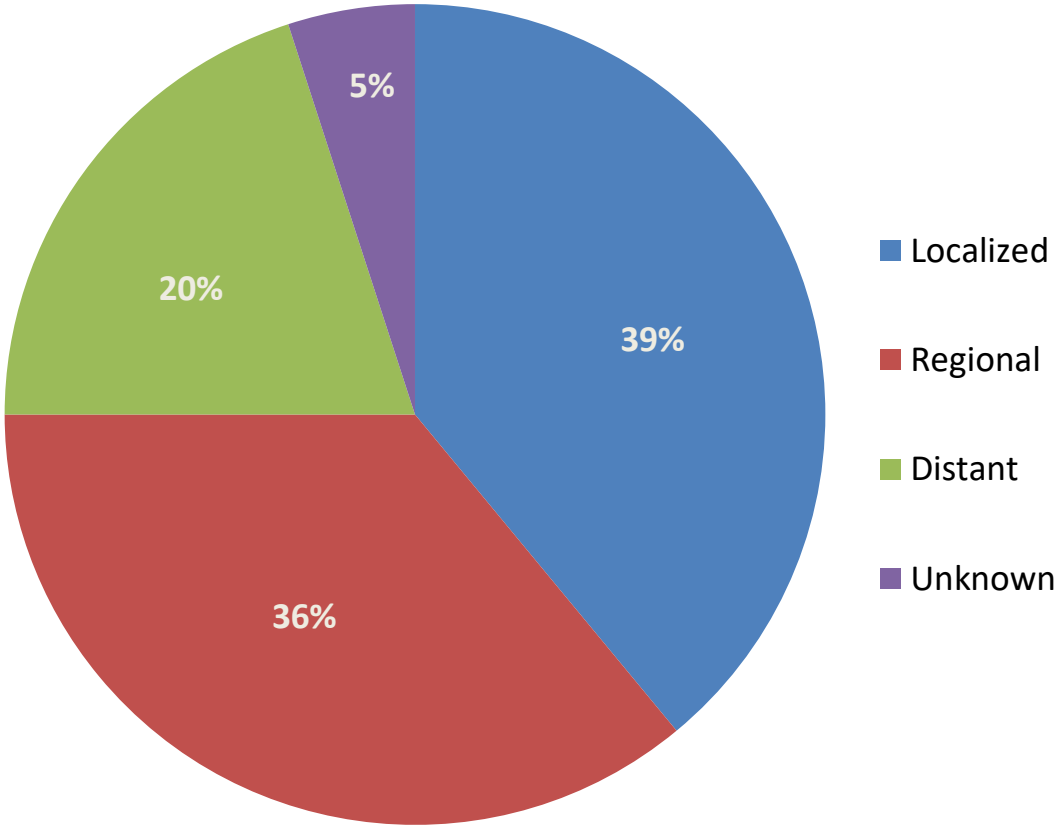
Colorectal Cancer: Epidemiology

- Approximately 20% of newly diagnosed CRC is metastatic at the time of initial presentation.

- More than 50-60% of patients diagnosed with CRC develop colorectal metastases, and 80-90% of these patients have unresectable metastase liver disease.

James J. Lee, Edward Chu, E lsevier Inc. Vol. 13, No. 3, 135-44 ª 2014.
Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. CA Cancer J Clin 2014; 64:9-29.

CRC stage at diagnosis



1. SEER. 2011. Available at seer.cancer.gov.
2. 2. American Cancer Society. 2011. Available at www.cancer.org.

Colorectal Cancer: Epidemiology

- Despite significant progress in the treatment of metastatic CRC (mCRC), the prognosis of mCRC is still quite poor.

- Although median overall survival (OS) has improved to the point where it is now in the range of 24 to 28 months, 5-year OS remains less than 10%.

James J. Lee, Edward Chu, Elsevier Inc. Vol. 13, No. 3, 135-44 ª 2014 .

Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. CA Cancer J Clin 2014; 64:9-29.

Risk Factors for CRC

- Age >50 (average risk)
- Racial, ethnic factors
  - African-Americans have increased risk
- Dietary factors
  - high animal fat, low fiber diet
- Lifestyle
  - Obesity
  - Smoking
  - Alcohol
- Family or personal history of CRC
- HNPCC – Lynch syndrome I, II
- Polyposis syndromes
- IBD

Vitamin D Status and Survival of Metastatic Colorectal Cancer Patients: Results from CALGB/SWOG 80405 (Alliance)

Kimmie Ng[1], Alan P. Venook[2], Kaori Sato[1], Chen Yuan[1], Bruce W. Hollis[3], Donna Niedzwiecki[4], Cynthia Ye[4], I-Wen Chang[5], Bert H. O'Neil[6], Federico Innocenti[7], Heinz-Josef Lenz[8], Charles D. Blanke[9], Robert J. Mayer[1], Charles S. Fuchs[1], Jeffrey A. Meyerhardt[1]

[1]Dana-Farber Cancer Institute, [2]University of California San Francisco, [3]Medical University of South Carolina, [4]Alliance Statistics and Data Center, [5]Wayne Memorial Hospital, [6]Indiana University Hospital, [7]University of North Carolina at Chapel Hill, [8]University of Southern California, [9]Oregon Health and Science University

DANA-FARBER CANCER INSTITUTE

Alliance for Clinical Trials in Oncology

SWOG Leading cancer research. Together.

HARVARD MEDICAL SCHOOL

Presented By Kimmie Ng at 2015 ASCO Annual Meeting

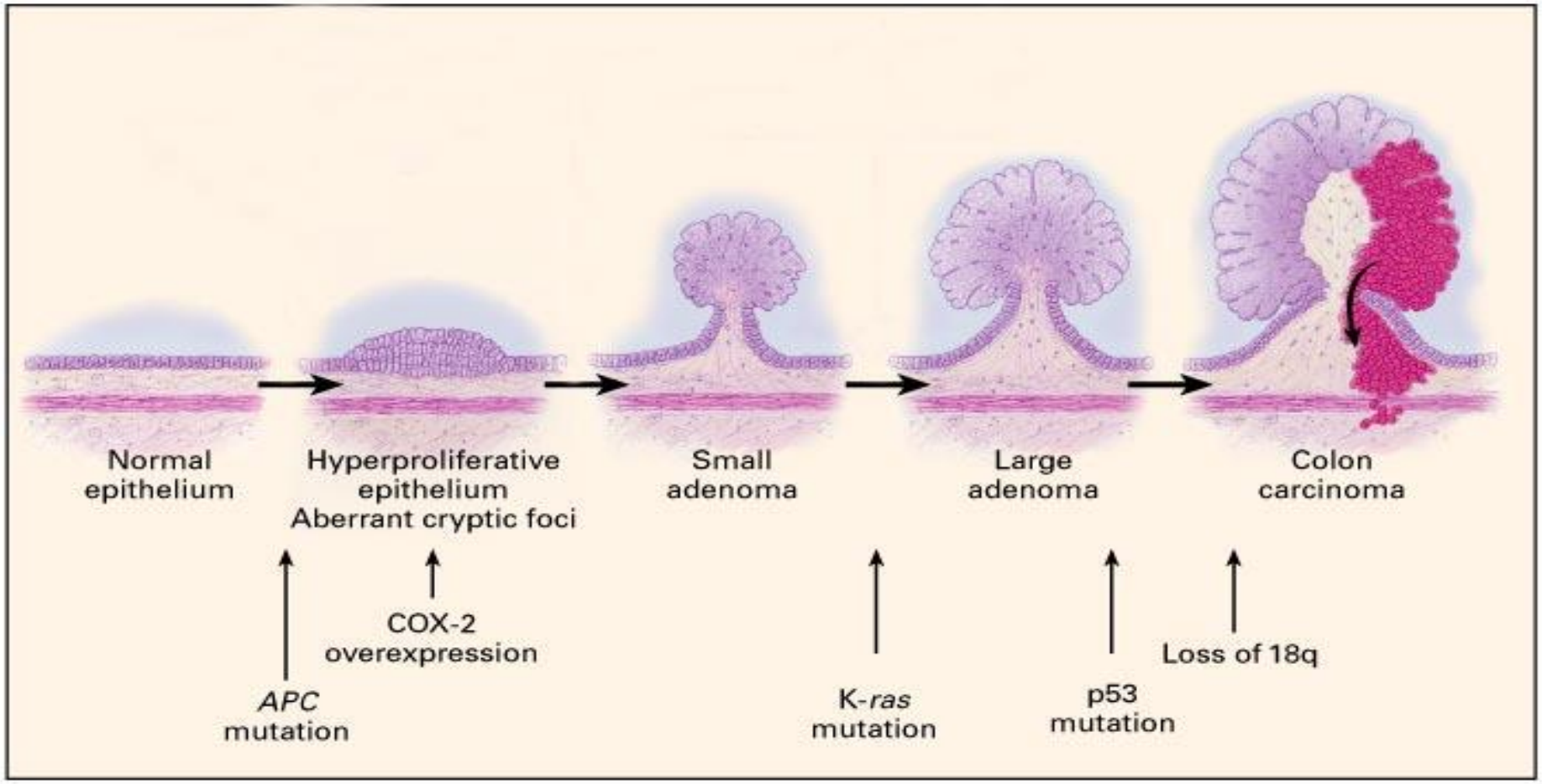
Impact of aspirin as secondary prevention in an unselected cohort of 25,644 patients with colorectal cancer: A population-based study

Simer Bains, MD
Centre for Molecular Medicine Norway,
University of Oslo

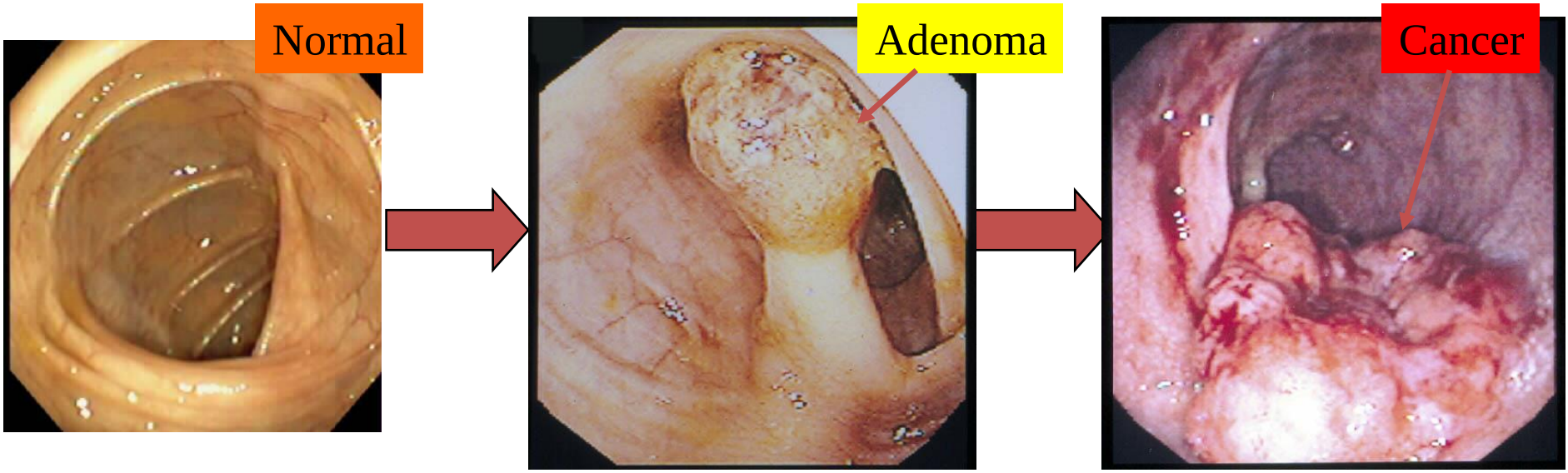
NCMM

PRESENTED AT: ASCO Annual '15 Meeting

Pathogenesis:



Adenoma to Carcinoma Pathway



APC loss

K-ras mutation

Chrom 18 loss

p53 loss

Normal Epithelium → Hyper-proliferation → Early Adenoma → Intermediate Adenoma → Late Adenoma → Cancer

Table 1. Definitions for T, N, M

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria[a]
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into the pericolorectal tissues
T4a	Tumor penetrates to the surface of the visceral peritoneum[b]
T4b	Tumor directly invades or is adherent to other organs or structures[b,c]

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-3 regional lymph nodes
N1a	Metastasis in one regional lymph node
N1b	Metastasis in 2-3 regional lymph nodes
N1c	Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
N2	Metastasis in four or more regional lymph nodes
N2a	Metastasis in 4-6 regional lymph nodes
N2b	Metastasis in seven or more regional lymph nodes

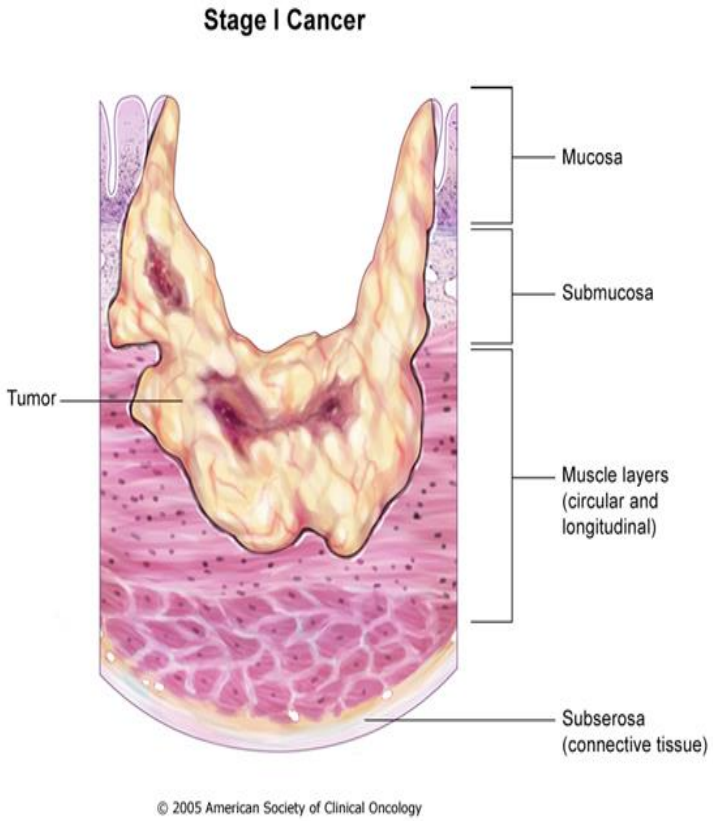
Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to one organ or site (eg, liver, lung, ovary, nonregional node)
M1b	Metastases in more than one organ/site or the peritoneum

Staging

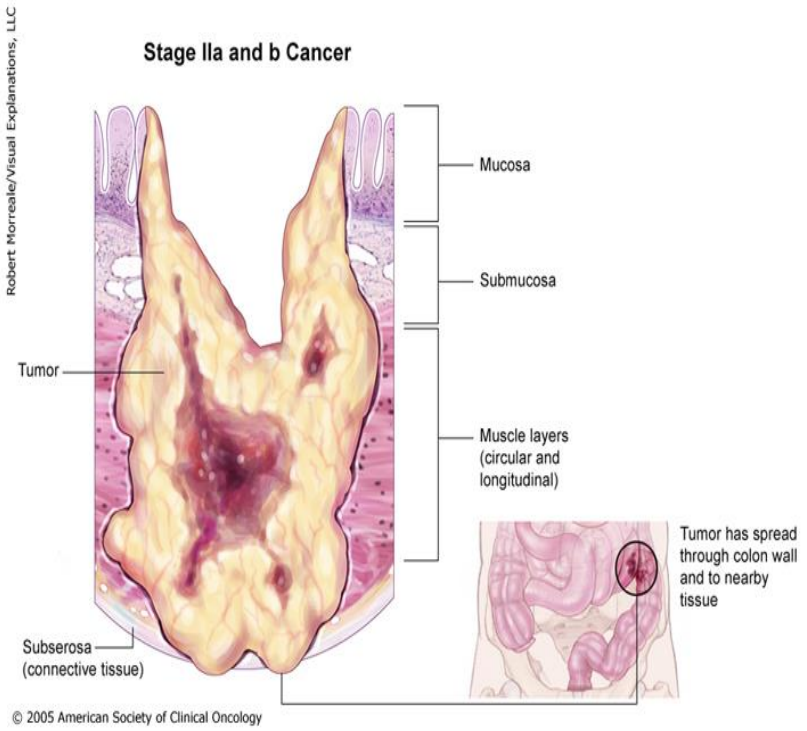
	T	N	M	
Stage I	1,2	0	0	Invades Muscularis propria
Stage II	3,4	0	0	Through the Muscularis propria
Stage III	Any	1,2	0	Lymph node Mets
Stage IV	Any	Any	1	Distant Mets

Stage I Colorectal Cancer



- The cancer has grown through the mucosa and invaded the muscularis (muscular coat)
- Treatment is surgery to remove the tumor and some surrounding lymph nodes

Stage II Colorectal Cancer



- The cancer has grown beyond the muscularis of the colon or rectum but has not spread to the lymph nodes

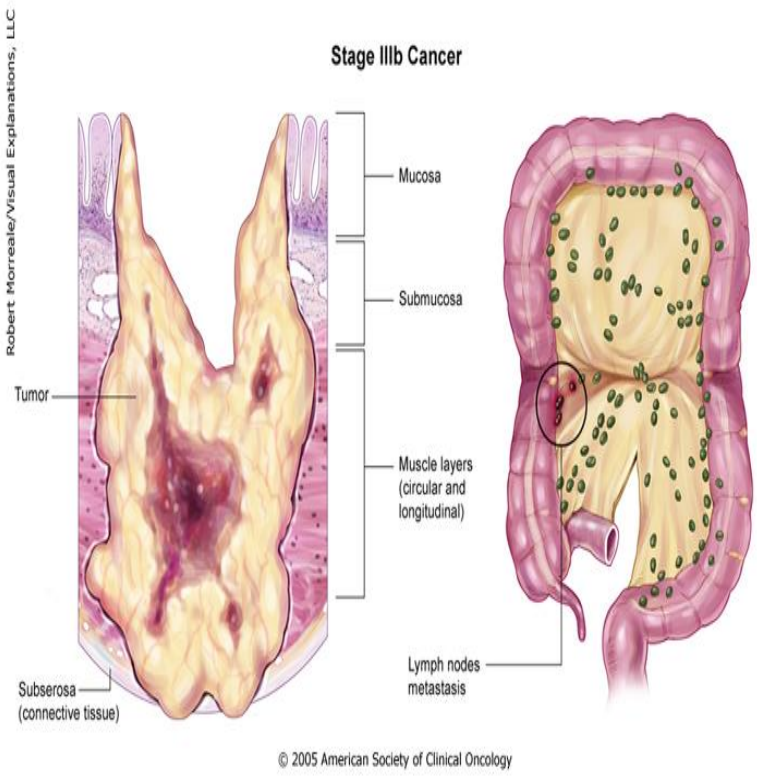
- Stage II colon cancer is treated with surgery and, in some cases(H.R), chemotherapy after surgery

High-risk stage II (T3-T4, N0, M0)

1. Poor prognostic features including T4 tumors (stage IIB)
2. poor histologic grade (grade 3 or 4 lesions)
3. peritumoral lymphovascular involvement
4. bowel obstruction at presentation
5. T3 lesions with localized perforation or close
6. Indeterminate, or positive margins
7. Inadequately sampled nodes(less than 12 lymph nodes)

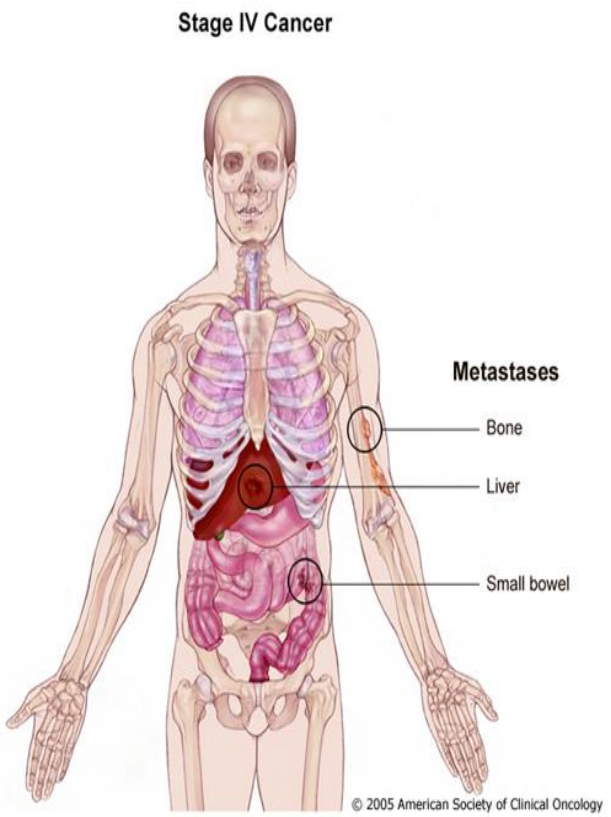
should be considered for adjuvant chemotherapy.

Stage III Colorectal Cancer



- The cancer has spread to the regional lymph nodes (lymph nodes near the colon and rectum)
- Stage III colon cancer is treated with surgery and chemotherapy

Stage IV Colorectal Cancer



- The cancer has spread outside of the colon to other areas of the body
- Stage IV cancer is treated with chemotherapy. Surgery to remove the colon may or may not be done
- Additional surgery to remove metastases may also be done in carefully selected patients

Stage III Adjuvant Chemotherapy

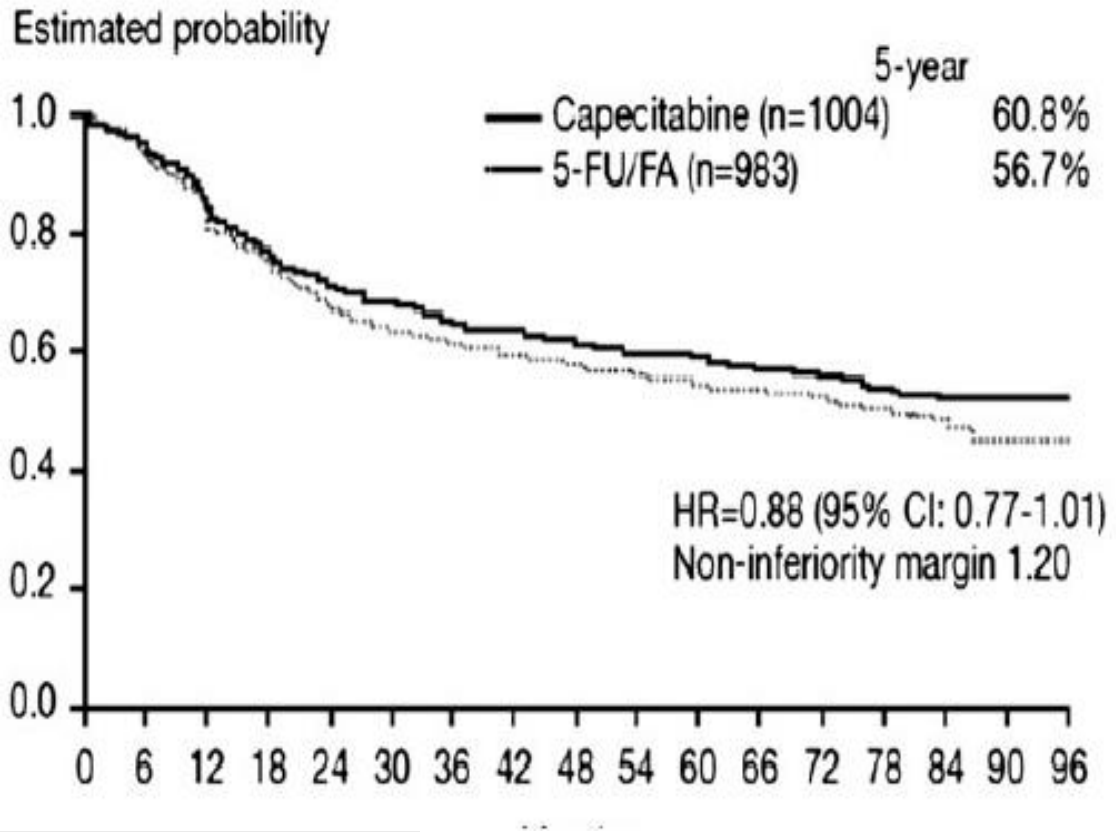
Trial	FU schedule	% 3-year DFS	HR (95% C1)
X-ACT			
■ FU/LV	Bolus	60.6	0.87
■ Capecitabine	Oral	64.2	(0.75-1.00)
MOSAIC			
■ FU/LV	Infusion	65.3	0.76
■ FOLFOX	Infusion	72.2	(0.62-0.92)
NSABP C07			
■ FU/LV	Bolus	65.3	0.77
■ FLOX	Bolus	72.2	(0.65-0.92)
PETACC-3			
■ FU/LV	Infusion	59.9	0.87
■ FU/LV/I	Infusion	62.9	(0.76-0.99)

Allegra C, Sargent DJ. *N Engl J Med*. 2005;352:2746-2748.

Stage III

X-ACT: Overall Survival Capecitabine vs. 5-FU/FA

Overall Survival

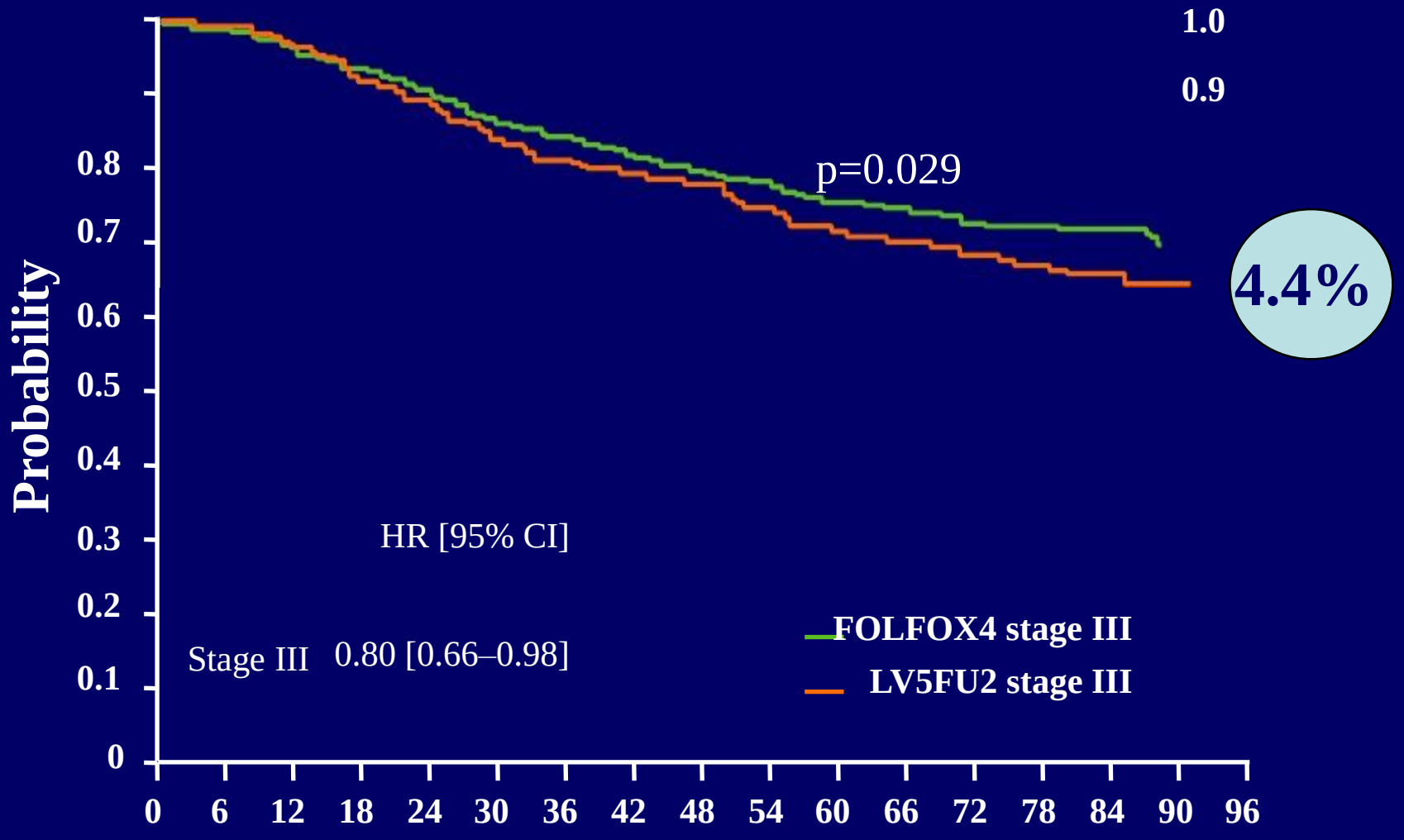


Cape 2500mg/m² d1-14

Dose modifications in ~60% of patients

Twelves et al. Ann Oncol 2012

MOSAIK Study Survival: Stage III infusional 5-FU/LV vs. FOLFOX

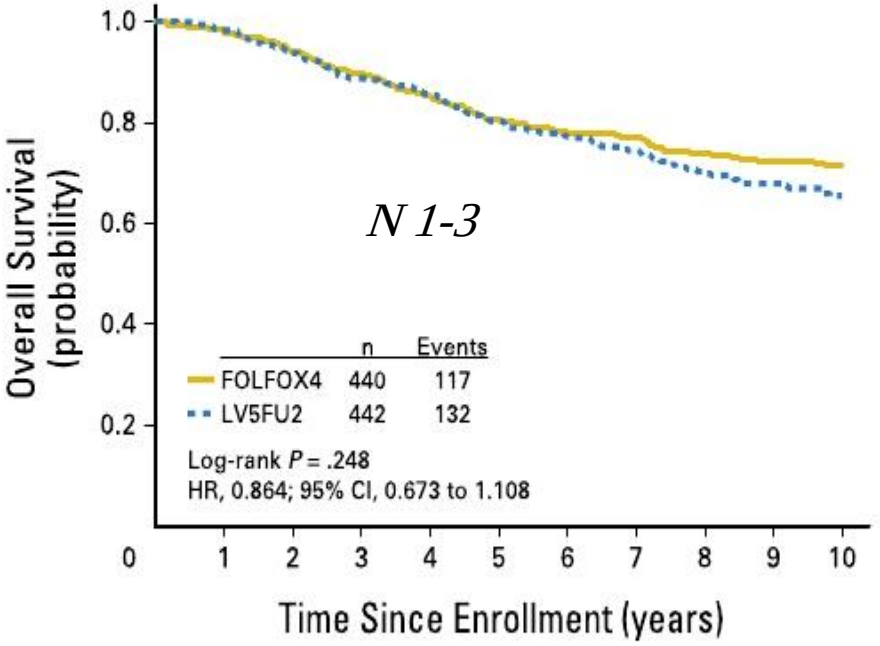


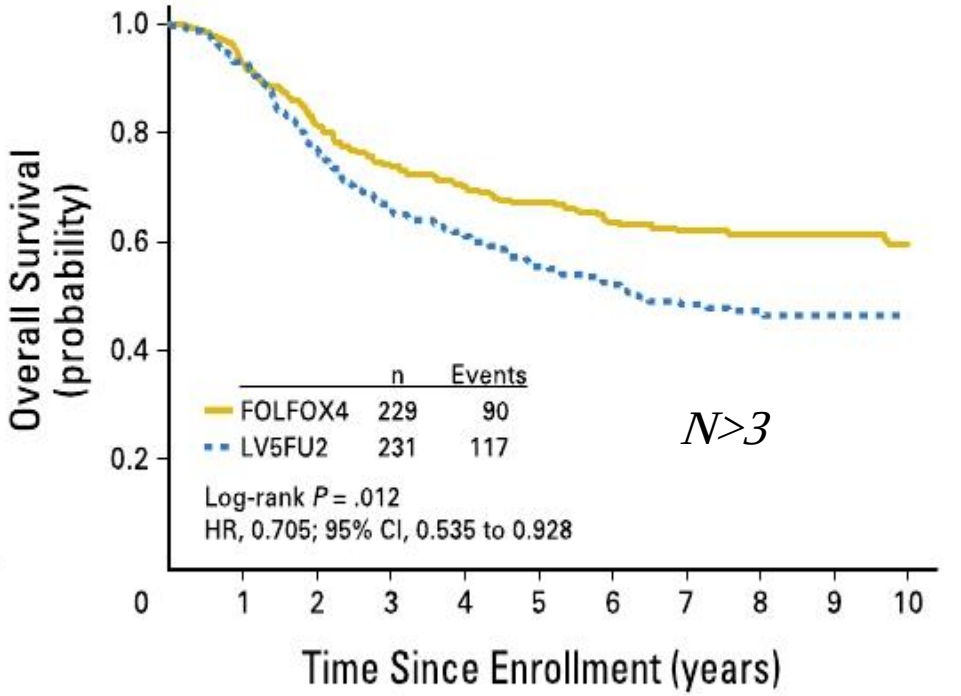
Data cut-off: January 2007

De Gramont et al. ASCO 2007

How to decrease long term toxicity by maintaining efficacy?

Adjuvant therapy with 6 months 5FU/LV +/- Oxaliplatin Colon Cancer Stage III pT3-4 N+

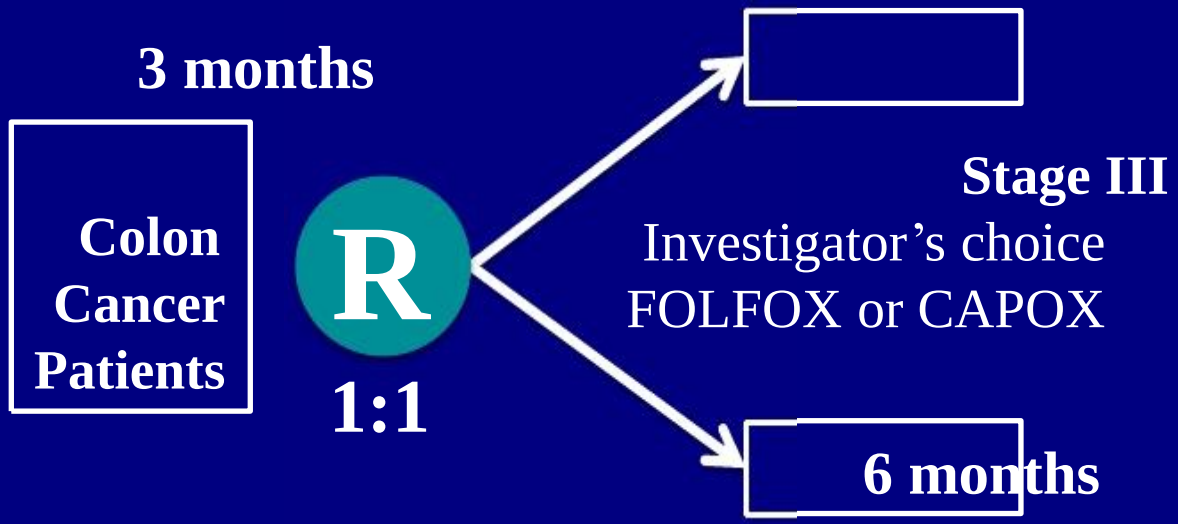




Andre et al. JCO 2015

IDEA Study Schema

Total planned accrual ≥ 10,500
Stage III Patients from 6 studies included in analysis: 12,834



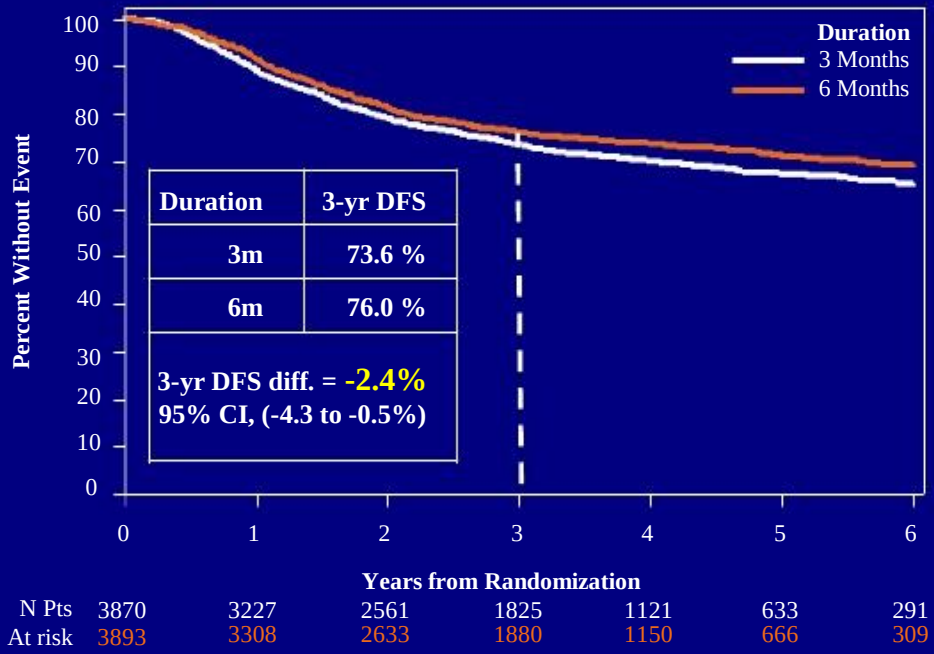
FOLFOX: 5FU/LV + Oxaliplatin

CAPOX: Capecitabine + Oxaliplatin

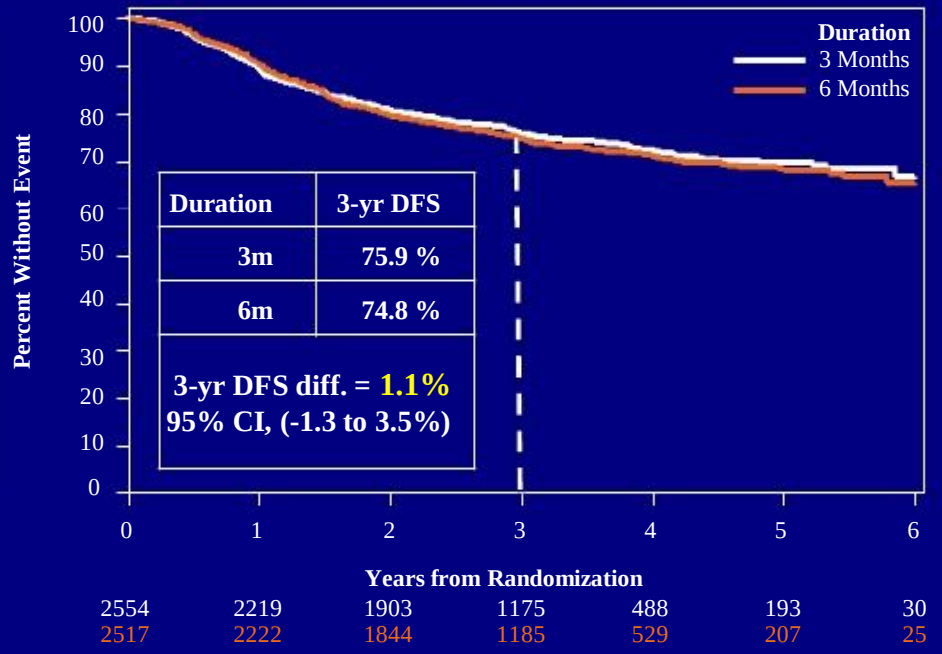
Presented by: Qian Shi, PhD on behalf of IDEA collaborators

DFS Comparison by Regimen

FOLFOX



CAPOX



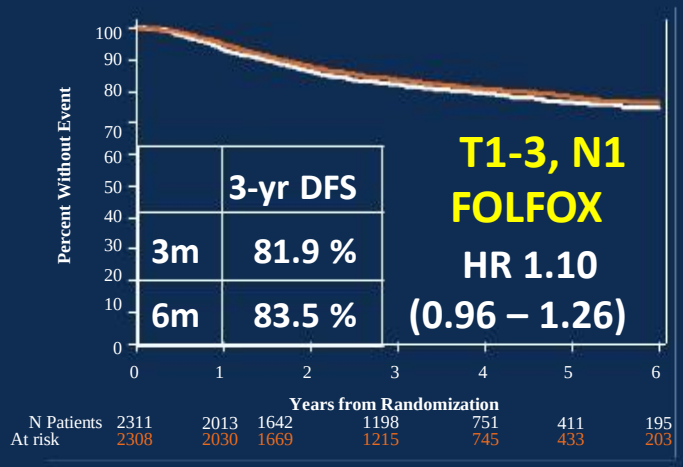
DFS HR = 1.16
95% CI, 1.06 to 1.26

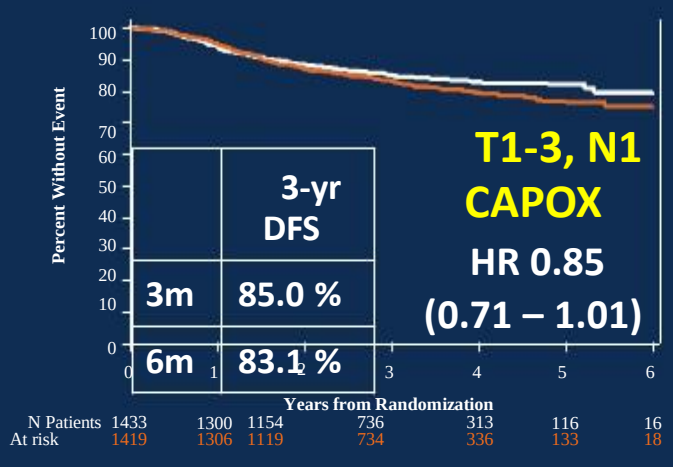
Interaction p-value = 0.0051

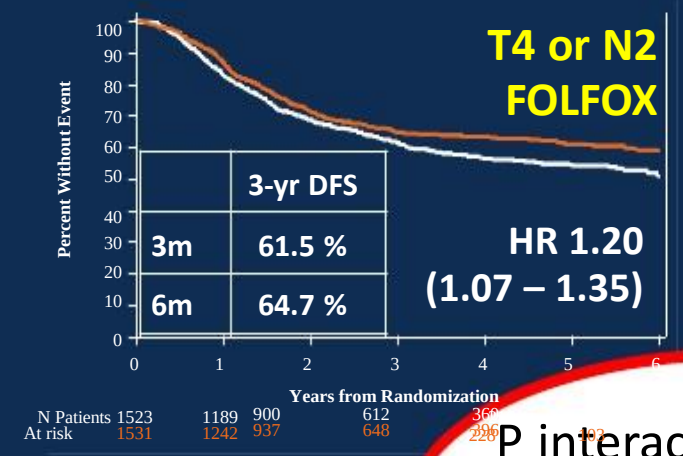
DFS HR = 0.95
95% CI, 0.85 to 1.06

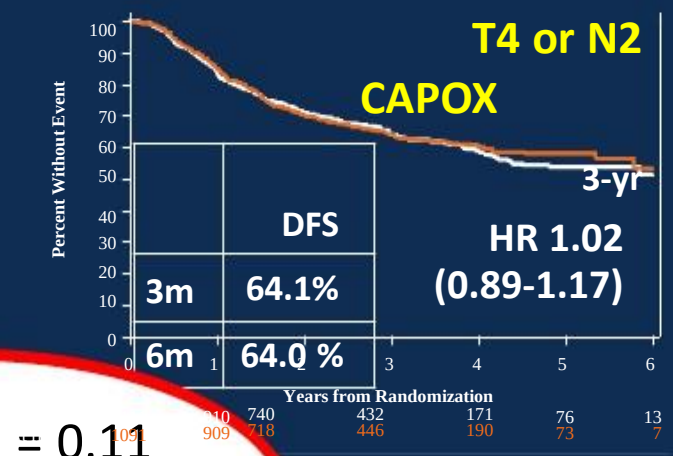
Presented by: Qian Shi, PhD on behalf of IDEA collaborators

DFS Comparison by Risk Group and Regimen in IDEA









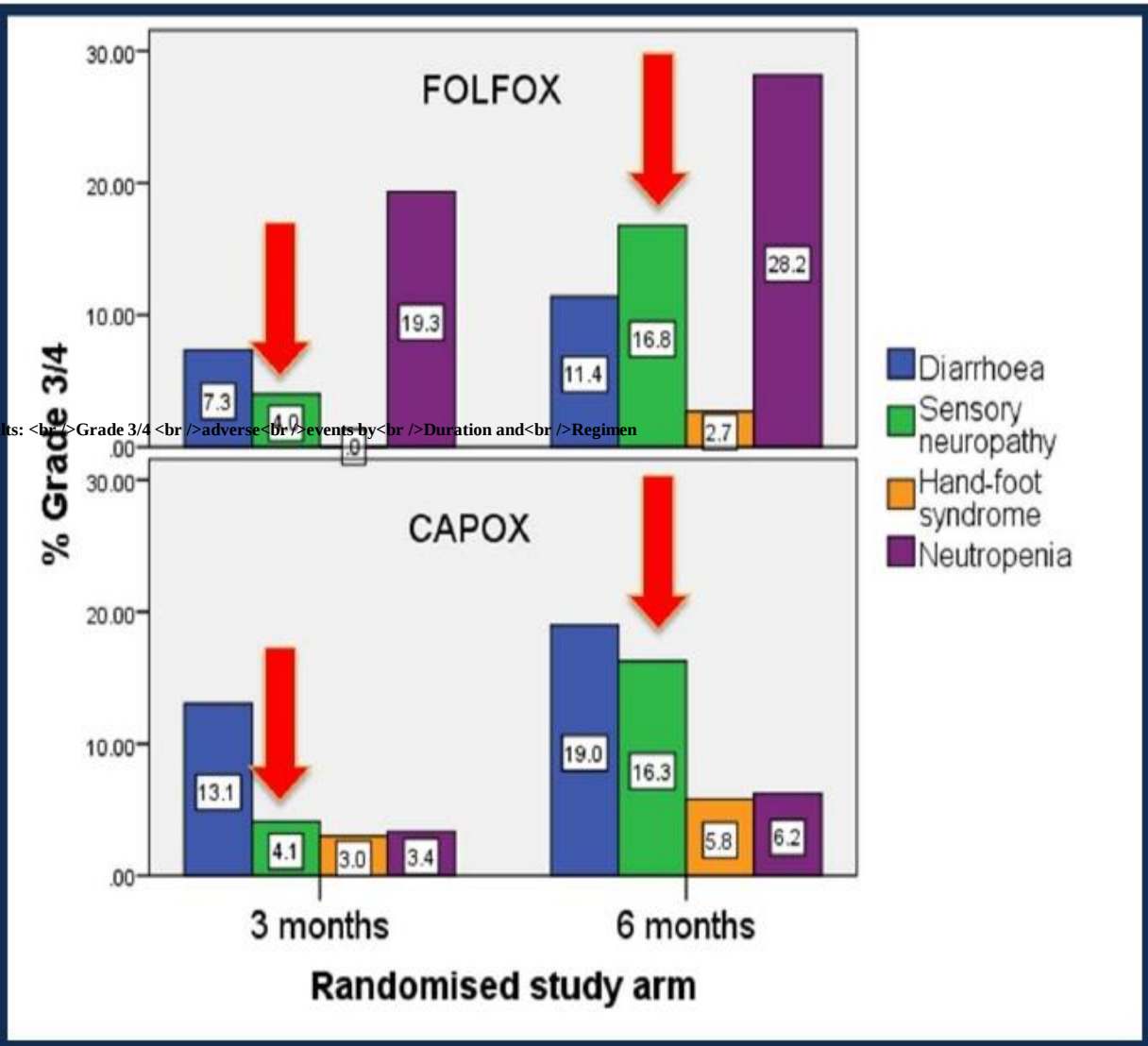
Shi et al ASCO 2017

Duration
3 Months
6 Months

P interaction = 0.11 comparing T1-3 N1 to T4 or N2

Presentedby: JeffreyMeyerhardt,MD, MPH

Results: Grade 3/4 adverse events by Duration and Regimen



Results:
Grade 3/4
adverse
events by
Duration and
Regimen

Specifically, the NCCN's stage III colon cancer treatment recommendations are differentiated on the basis of risk status:

- Low-risk stage III is defined as pathologic stages T1-3N1. For these patients, the preferred treatments are CAPEOX for 3 months or FOLFOX for 3 to 6 months.
- High-risk stage III disease is defined as pathologic stages T4N1-2 and AnyTN2. For these patients, the preferred treatments are CAPEOX for 3 to 6 months or FOLFOX for 6 months.

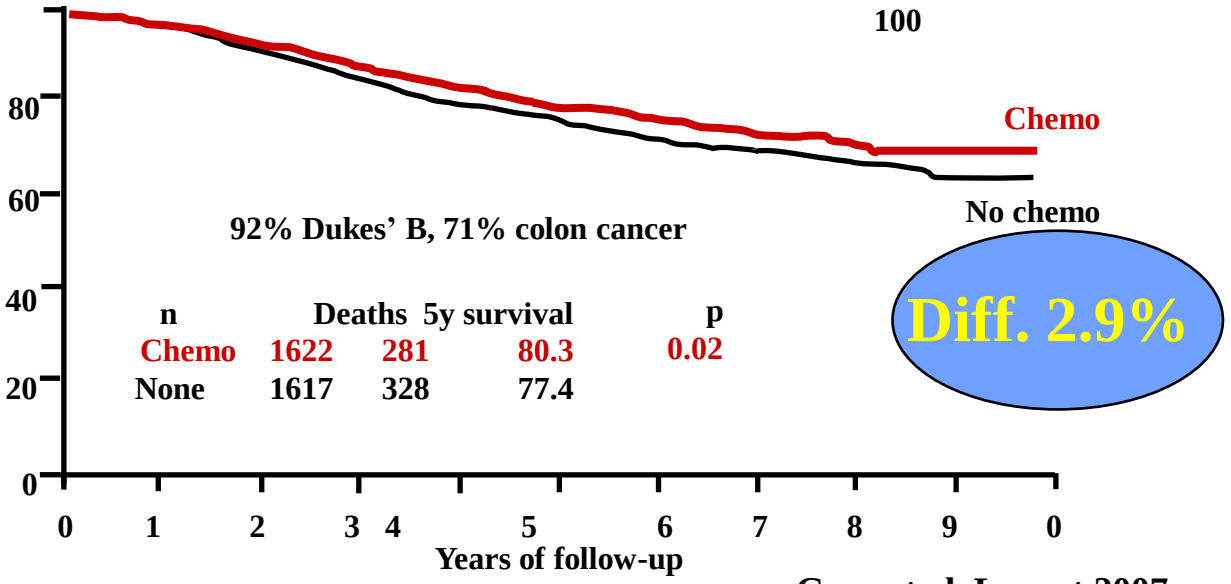
The guidelines note that rates of neurotoxicity of grade 3+ are lower for patients who receive 3 months vs 6 months of treatment (3% vs 16% for FOLFOX; 3% vs 9% for CAPEOX).

Clinical Data in Stage II Colon Cancer

- Randomized trials: Stage II subsets

Study	N	Arms	5y OS
Intergroup 0035	935	5FU/LV vs. Obs.	72% vs. 72%
QUASAR	3238	FU vs. Obs.	80% vs. 77%
IMPACT B2	1016	5FU vs. Obs.	82% vs. 80%

- **QUASAR-1:superior OS with adjuvant therapy for stage II disease**



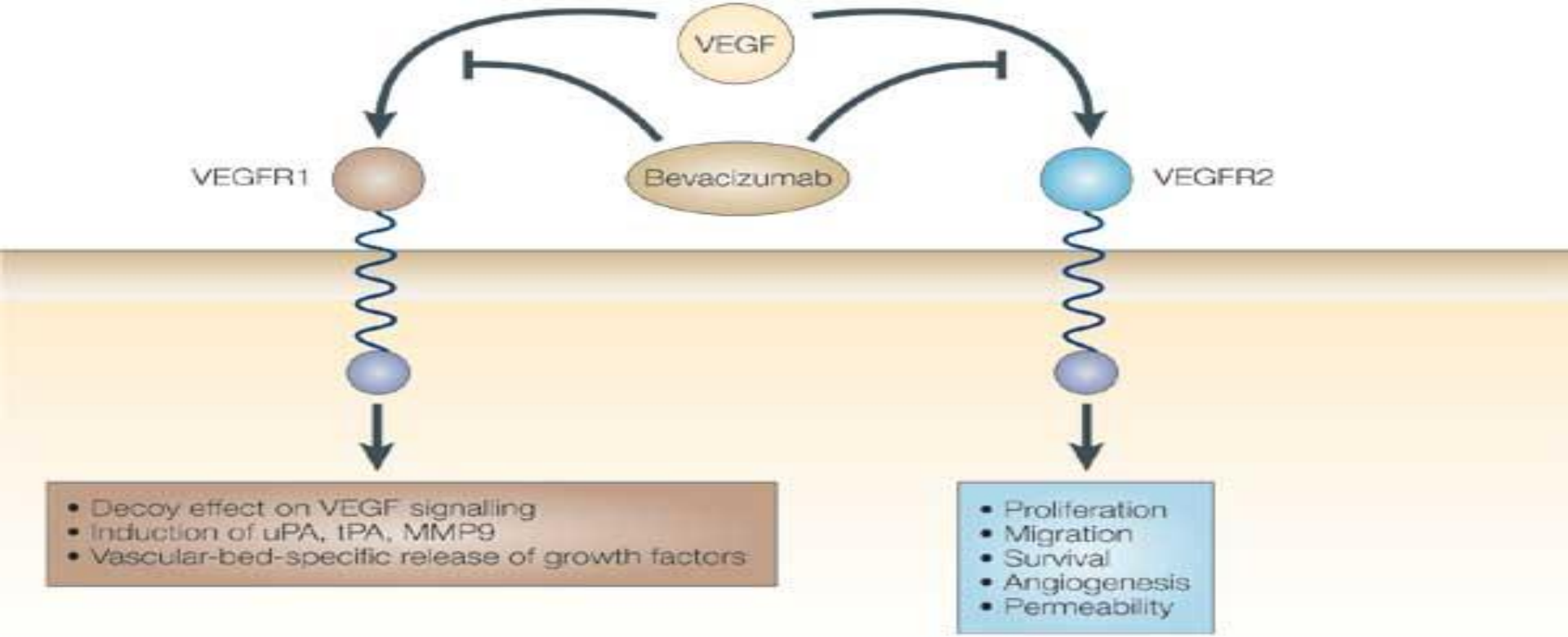
Gray et al. Lancet 2007

WHY Targeted Therapy

- According to NCCN guidelines , the repeated use of chemotherapy (oral or IV) beyond the 2nd line has not been clinically shown to have a survival benefit in any large , randomized study.

Bevacizumab
in adjuvant setting

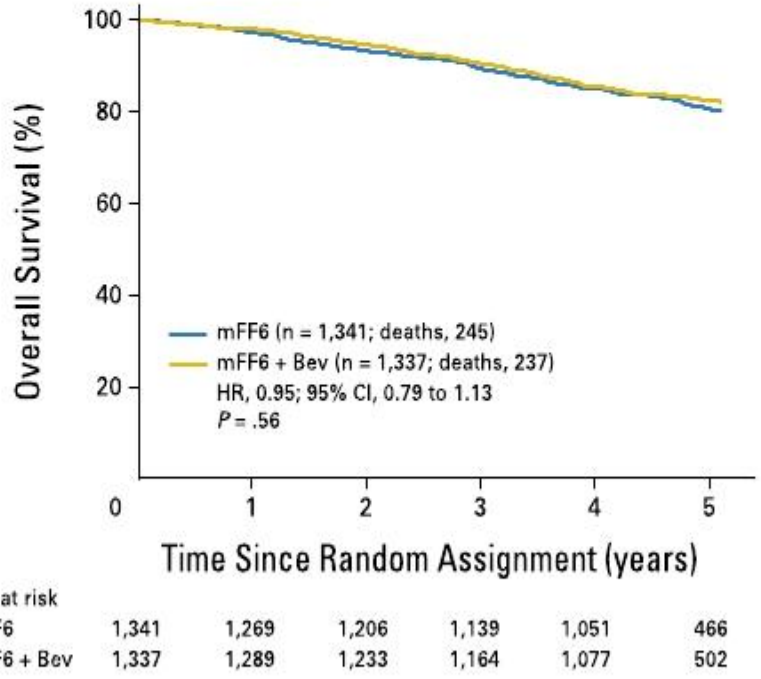
- Bevacizumab is a humanized monoclonal antibody that inhibits vascular endothelial



Nature Reviews | Drug Discovery

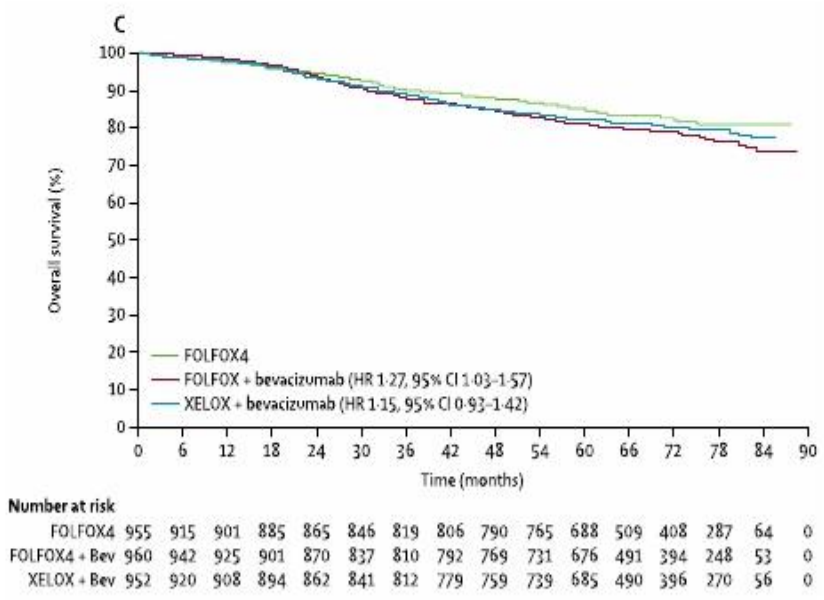
Bevacizumab for adjuvant therapy in Colon Cancer
- negative data -

NSABP C-08
2673 pts. stage II and III



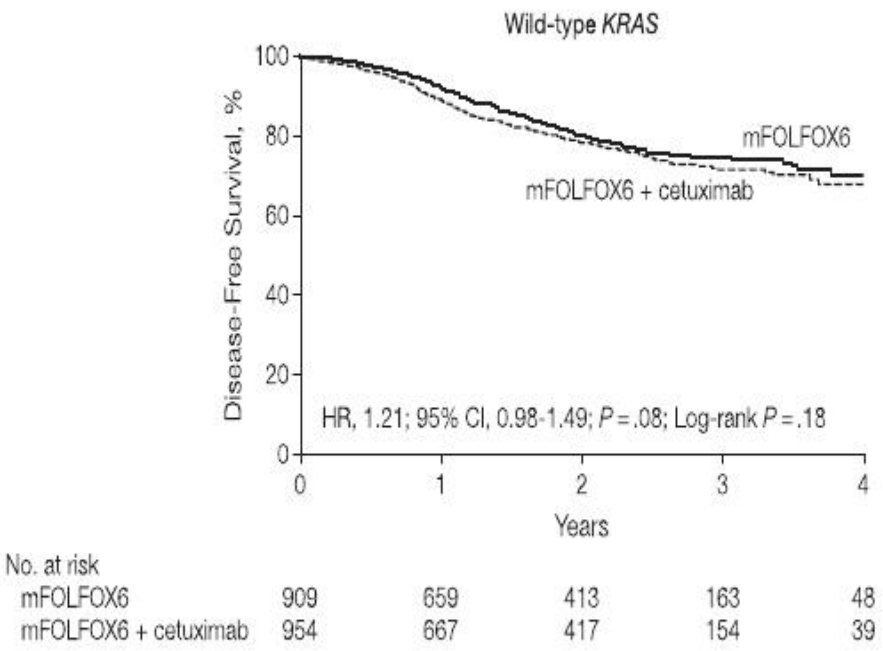
Allegra et al. JCO 2013

AVANT
3451 pts. stage II and III

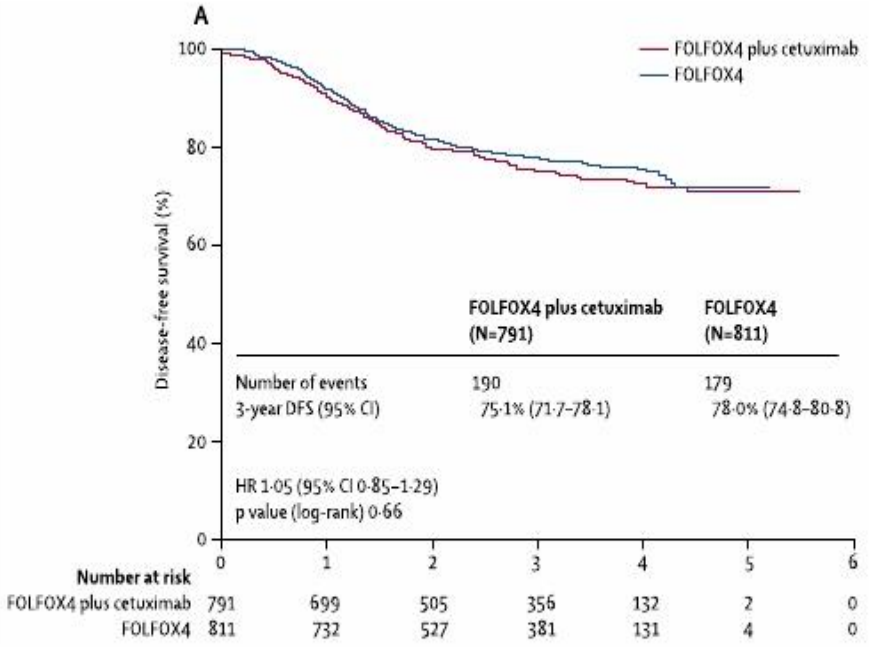


De Gramont et al. Lancet Oncol 2012

FOLFOX +/- Cetuximab in stage III colon cancer



Albers et al. JAMA 2012



Taieb et al. Lancet Oncol 2014

mCRC – Targeted Therapy……

- **EGFR-targeted therapy:**
  - Cetuximab.
  - Panitumumab.
- **Anti angiogenic agents:**
  - Bevacizumab.
  - Ziv-aflibercept.
  - Ramucirumab.
- **Regorafenib.** (multikinase small molecule inhibitor)

EGFR-targeted therapy

Cetuximab & Panitumumab

Anti-EGFR Therapy in the 1st Line Treatment of MCRC

	First-Line (KRAS-WT)			
	PRIME (n = 512)		CRYSTAL (n = 666)	
	FOLFOX PMAB	FOLFOX	FOLFIRI CMAB	FOLFIRI
PFS *KRAS*-WT	9.6m* HR=0.8	8m	9.9 m* HR = 0.69	8.4m
PFS *RAS* WT	10.1m* HR=0.78	7.9m	11.4 m* HR = 0.56	8.4m
OS *KRAS*-WT	23.8m* HR=0.83	19.4m	23.5m* HR = 0.8	20m
OS *RAS* WT	25.8* HR=0.77	20.2	28.4* HR = 0.69	20.2
OS *RAS/RAF* WT	28.3* HR = 0.74	20.9	-	-

Prime Study: Anti-EGFR therapy associated with a negative impact on PFS and OS in *KRAS*-MT or *RAS*-MT CRC in the setting of FOLFOX

CRYSTAL Study: Anti-EGFR therapy associated with no improvement in PFS and OS in *KRAS*-MT or *RAS*-MT CRC in the setting of FOLFIRI

Douillard JY, et al. *N Engl J Med.* 2103;369(11):1023-34. Ciardiello F, et al. *J Clin Oncol.* 2014;32:5s abstr3506.

Anti-EGFR Therapy in the 2nd Line Treatment of MCRC

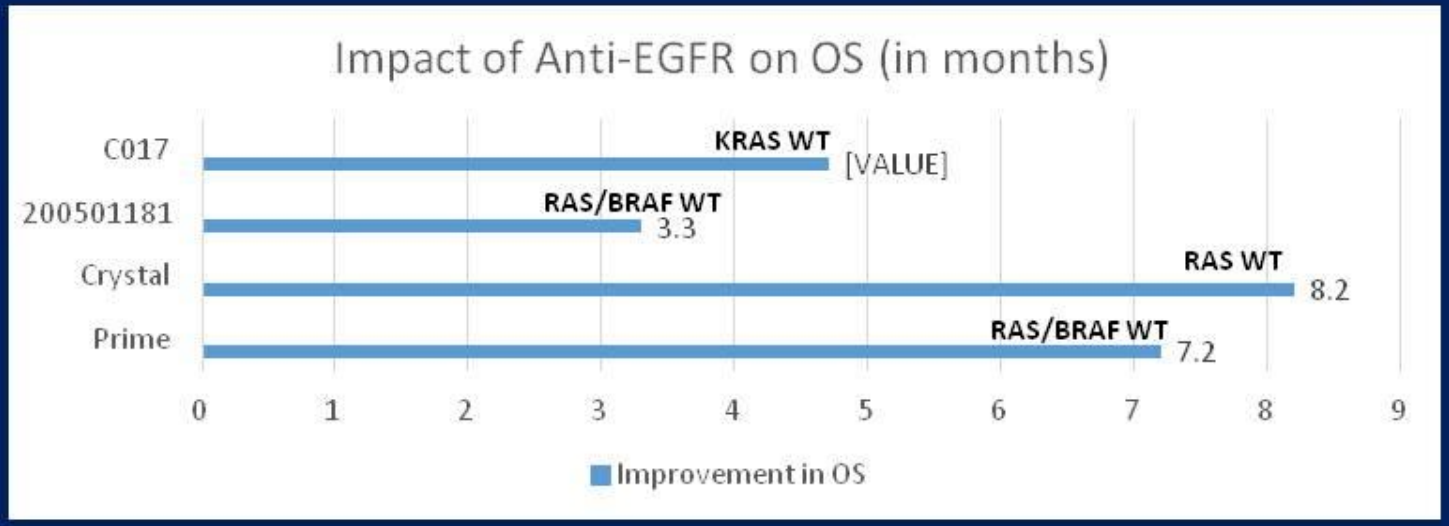
	Second-Line (KRAS-WT)			
	200501181 (n = 597)		PICCOLO (n = 460)	
	FOLFIRI PMAB	FOLFIRI	IRI PMAB	IRI
PFS *KRAS*-WT	5.9m* HR = 0.73	3.9m	HR = 0.78*	
PFS *RAS* WT	6.4m* HR = 0.7	4.6m		
OS *KRAS*-WT	14.5m HR = 0.85	12.5m	10.4m HR = 1.01	10.9m
OS *RAS* WT	16.2m HR = 0.81	13.9m	-	-
OS *RAS/RAF* WT	18.7m HR = 0.83	15.4m	-	-

Peeters M. *J Clin Oncol.* 2014;32:5s abstr3568. Seymour MT. Lancet Oncol 2013; 14: 749-59

Anti-EGFR Therapy in MCRC

Anti-EGFR Therapy

- **RAS mutation** — NO ROLE
- **BRAF mutation** — Questionable
- **RAS/BRAF WT** — Definite



Douillard JY, et al. *N Engl J Med*. 2103;369(11):1023-34. Van Cutsem E. J Clin Oncol. 2015 (33): 692-700. Peeters M, et al. *J Clin Oncol*. 2014;32:5s abstr3568; Karapetis, C. NEJM 2008 Oct 23;359(17):1757-65.

Anti angiogenic Agents

- Bevacizumab.
- ziv- aflibercept.
- Ramucirumab.

Bevacizumab in mCRC
First-line Chemotherapy

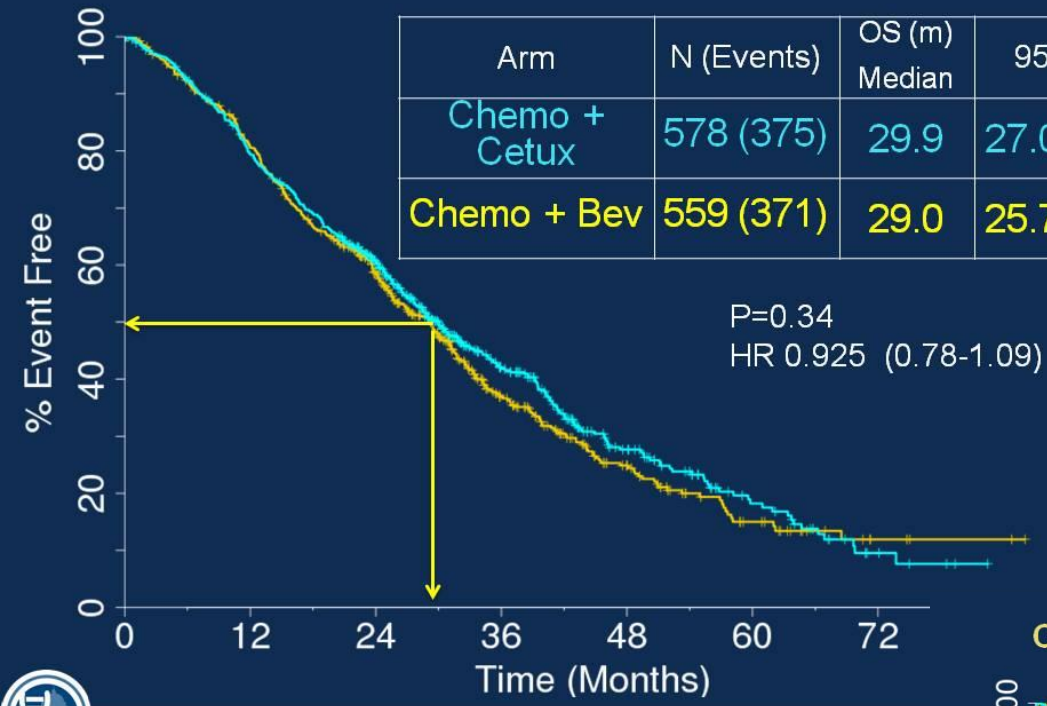
Comparative Regimens, Mos	PFS	OS
IFL/Bev vs IFL[1]	10.6 vs 6.2	20.3 vs 15.6
FOLFOX4/XELOX/Bev vs FOLFOX4/XELOX[2]	9.4 vs 8.0	21.3 vs 19.9
FOLFOX/Bev vs FOLFIRI/Bev[3]	10.3 vs 10.2	23.7 vs 25.5

1. Hurwitz H, et al. N Engl J Med. 2004;350:2335-2342. 2. Saltz LB, et al. J Clin Oncol. 2008;26:2013-2019. 3. Bendell JC, et al. Oncologist. 2012;17:1486-1495.

CALGB/SWOG 80405: Overall Survival

Arm	N (Events)	OS (m) Median	95% CI
Chemo + Cetux	578 (375)	29.9	27.0-32.9
Chemo + Bev	559 (371)	29.0	25.7-31.2

P=0.34
HR 0.925 (0.78-1.09)



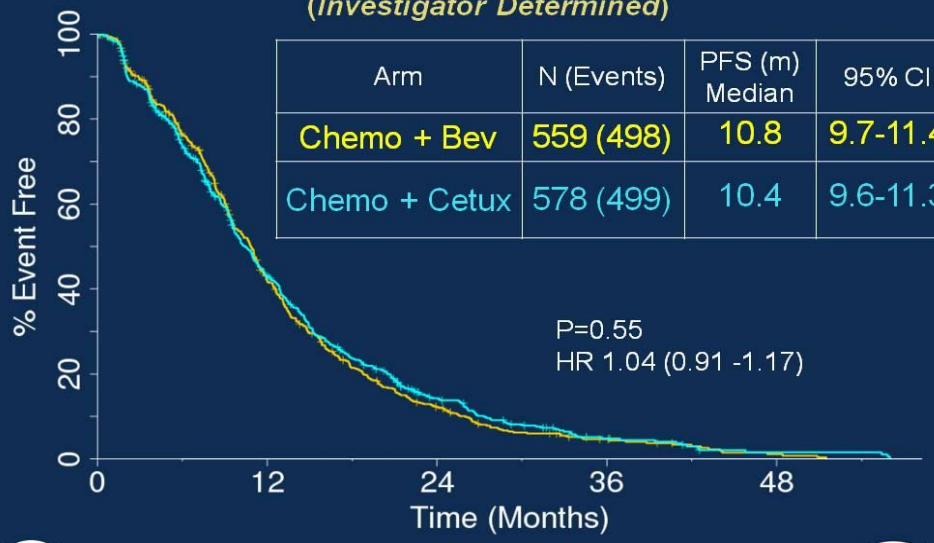
Presented by:

Whish To Start?

CALGB/SWOG 80405: Progression-Free Survival
(Investigator Determined)

Arm	N (Events)	PFS (m) Median	95% CI
Chemo + Bev	559 (498)	10.8	9.7-11.4
Chemo + Cetux	578 (499)	10.4	9.6-11.3

P=0.55
HR 1.04 (0.91 -1.17)

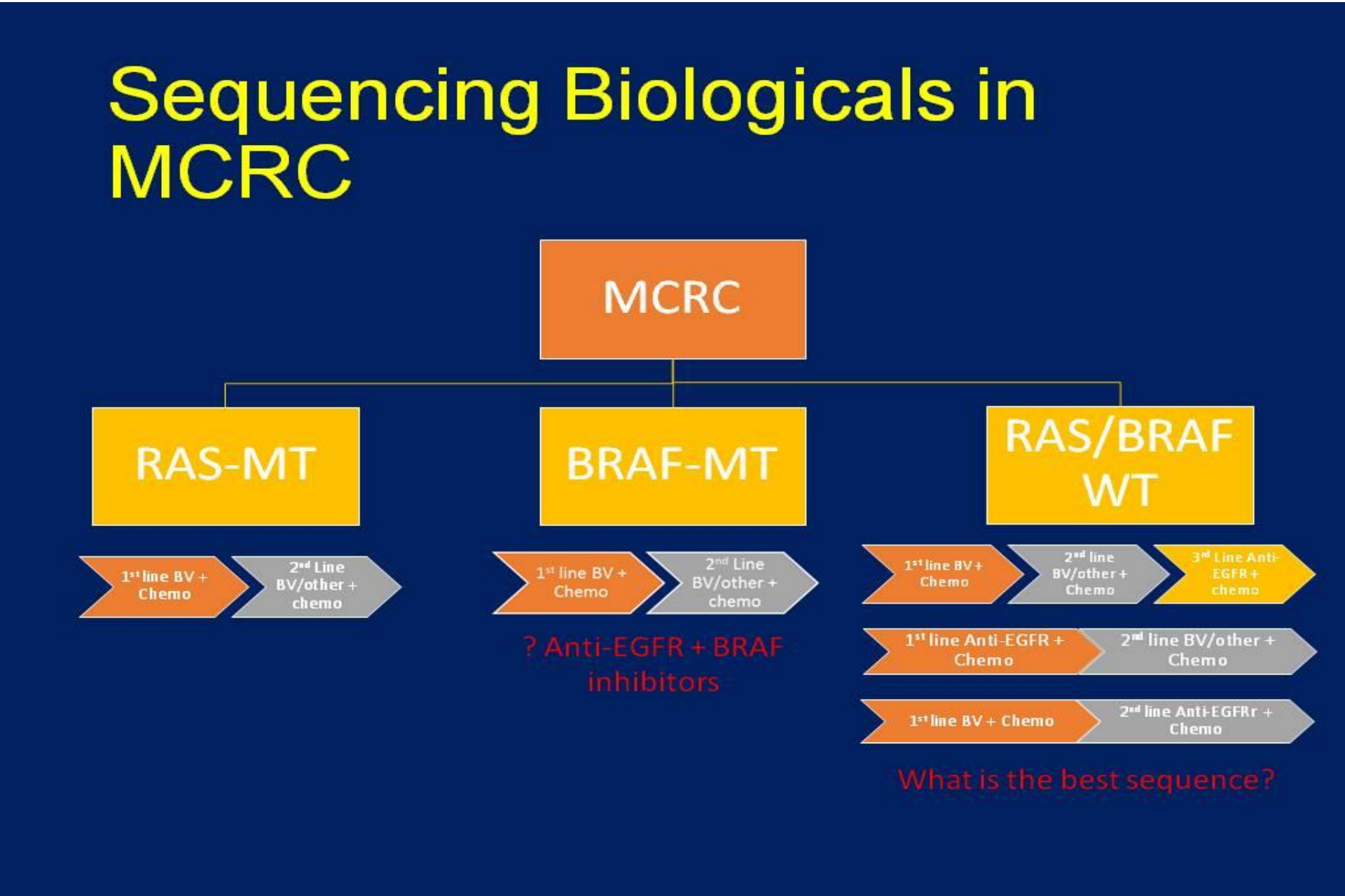


Presented by:

PRESENTED AT:

ASCO 50 ANNUAL MEETING SCIENCE & SOCIETY

Whish To Start?



First line biological: BV or anti-EGFR

- No definitive better sequence when anti-EGFR or anti-angiogenic agents are contemplated!

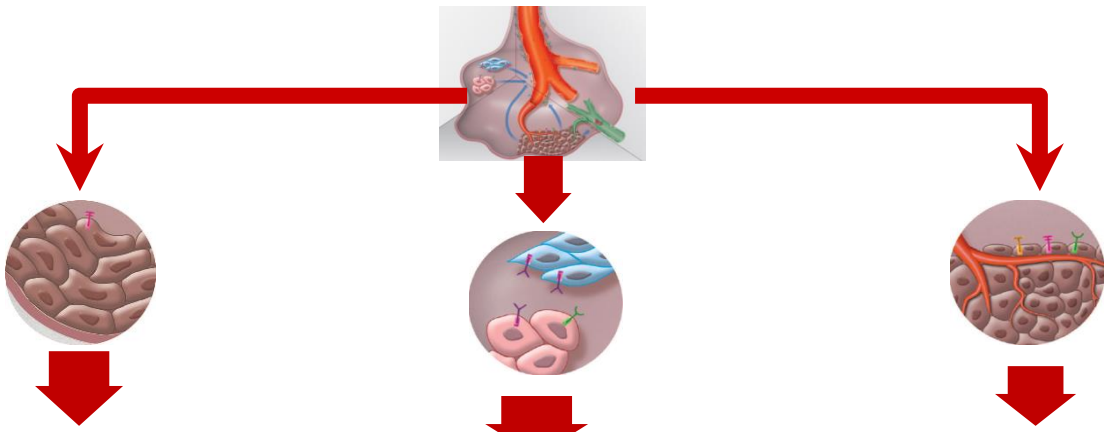
Favor anti-EGFR

- Patients with risk of perforation
- Patients with risk of ATE
- Patients with active wound
- Patients with uncontrolled HTN
- Patients in need of maximum down-staging

Favor Bevacizumab

- Avoid skin toxicity/ cosmetic concerns
- Avoid electrolyte imbalance

Regorafenib



Inhibition of proliferation

tumor microenvironment signaling

Inhibition of neoangiogenes

Zopf D, et al. AACR 2010; abstract 1666

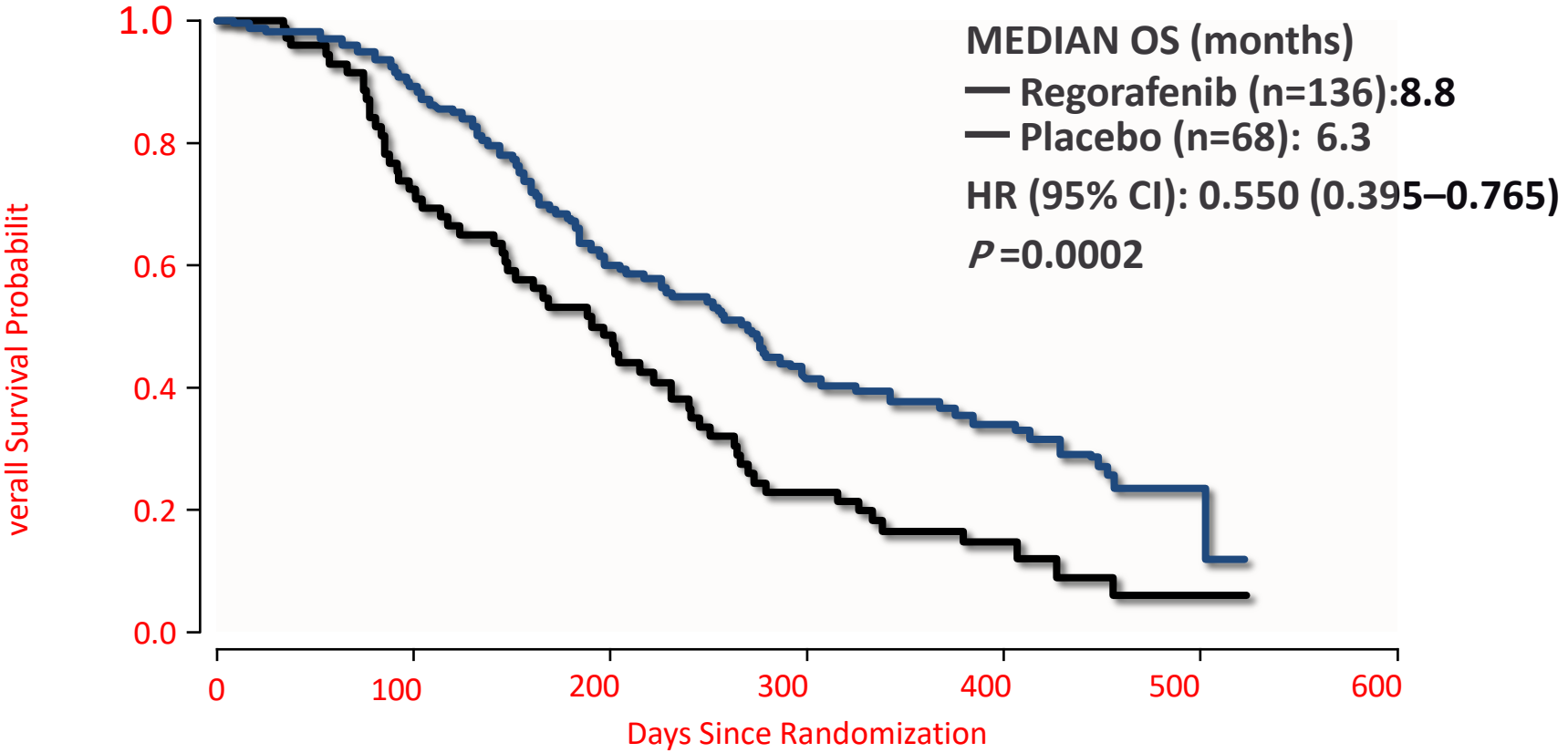
Regorafenib

Regorafenib is an oral multikinase inhibitor with a distinct profile targeting:

– Angiogenic (VEGFR-1–3, TIE-2)
– Tumor microenvironment (PDGFR-b, FGFR)
– Oncogenic (KIT, PDGFR, RET) receptor tyrosine kinases

Wilhelm SM et al. Int J Cancer 2011.
Mross K et al. Clin Cancer Research 2012.
Strumberg D et al. Expert Opin Invest Drugs 2012

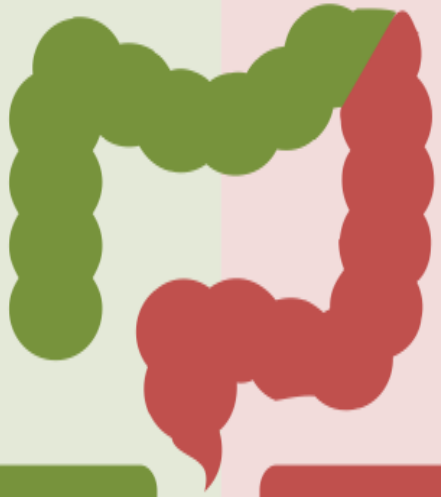
CONCUR



Overall survival defined as time from randomization to death.
Comparison using a stratified log-rank test with a one-sided alpha = 0.2.

Cut-off date for the analysis was 29 November 2013. Dots represent censored observations

Primary tumor location
Predictive or Prognostic?



Right-sided tumors

- Older patients
- Higher incidence in female patients
- Microsatellite instability (MSI)
- *BRAF, PI3KCA, KRAS* mutations
- Worse prognosis

Left-sided tumors

- Younger patients
- Predominantly wild type
- HER2 gain
- High AREG, EREG
- Better prognosis

WHAT ABOUT IMMUNOTHERAPY?

Pembrolizumab.

- Is a programmed death receptor-1 (PD-1)-blocking antibody indicated for the treatment of:
- patients with unresectable or metastatic melanoma.
- patients with metastatic NSCLC whose tumors have high PD-L1 expression.
- patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy

Pembrolizumab.

- Nov. 2, 2015, The FDA has granted a breakthrough therapy designation to Pembrolizumab (Keytruda) as a potential therapy for patients with microsatellite instability-high (MSI-H)
- Ongoing studies to confirm benefit including 1st line Pembro vs. chemo (KEYNOTE-177; NCT02563002) in MSI-H or mismatch repair(MMR-D) mCRC

Silas Inman @silasinman Published Online: Monday, November 2, 2015.
http://www.onclive.com/web-exclusives/pembrolizumab-granted-breakthrough-status-for-microsatellite-instability-high-mcrc#sthash.ChsXeQhb.dpuf.
New England Journal of Medicine.

ASCO-GI 2018 — Nivolumab + ipilimumab shows strong benefit in mCRC subtype

- Nivolumab (NIVO) + ipilimumab (IPI) may represent a new standard of care for previously treated patients with DNA mismatch repair (dMMR) -deficient/microsatellite instability-high (MSI-H) metastatic colorectal cancer (mCRC).

Nivolumab plus ipilimumab led to a 1-year overall survival rate of 85% in previously treated metas tatic colorectal cancer patients with DNA mismatch repair–deficient or microsatellite instability–high tumors. These data were reported in the first report of the full cohort of CheckMate-142. #GI18 #nivolumab #ipilimumab #colorectalcancer #MMRdeficient #MSIH #CheckMate142

Questions?

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لاستماعكم