Systemic and targeted therapy in CRC- locally advanced and metastatic

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- Introduction
- Adjuvant
- Neoadjuvant
- Metastatic

- 43/ M, diagnosed to have bowel obstruction , after evaluation, underwent a emergency right hemicolectomy and
- post op HPE – adenocarcinoma , pT3 N0 ,
- no. of nodes 0/6 nodes negative

Colon cancer

History

- Earliest clinical trials of adjuvant chemotherapy in colon cancer were conducted in the 1950s .
- In 1986, large meta-analysis of controlled randomized trials of adjuvant therapy
- Nonsignificant trend toward an OS benefit, with a mortality OR of 0.83 in favor of therapy (95% CI = 0.70 to 0.98).

Adjuvant 5 FU

- NSABP C 01 [1988]
- Between 1977 and 1983,
- 1,166 patients with colon ca
- Randomized into the Observation, MOF and BCG
- MOF had a significantly better DFS and OS than the control group (P = .02 and P = .05, respectively)

Wolmark N, Fisher B, Rockette H, et al: Postoperative adjuvant chemotherapy or BCG for colon cancer: Results from NSABP protocol C-01. J Nat1 Cancer Inst 80:30x36, 1988

Survival Results of NSABP C-07

Patients with stage II or III carcinoma of the colon stratified by number of positive lymph nodes

N = 2,409

FULV

5-FU 500 m^2 IV bolus weekly x 6; LV 500 mg/m^2 IV weekly x 6, each 8-week cycle x 3

(N = 1,209)

FLOX

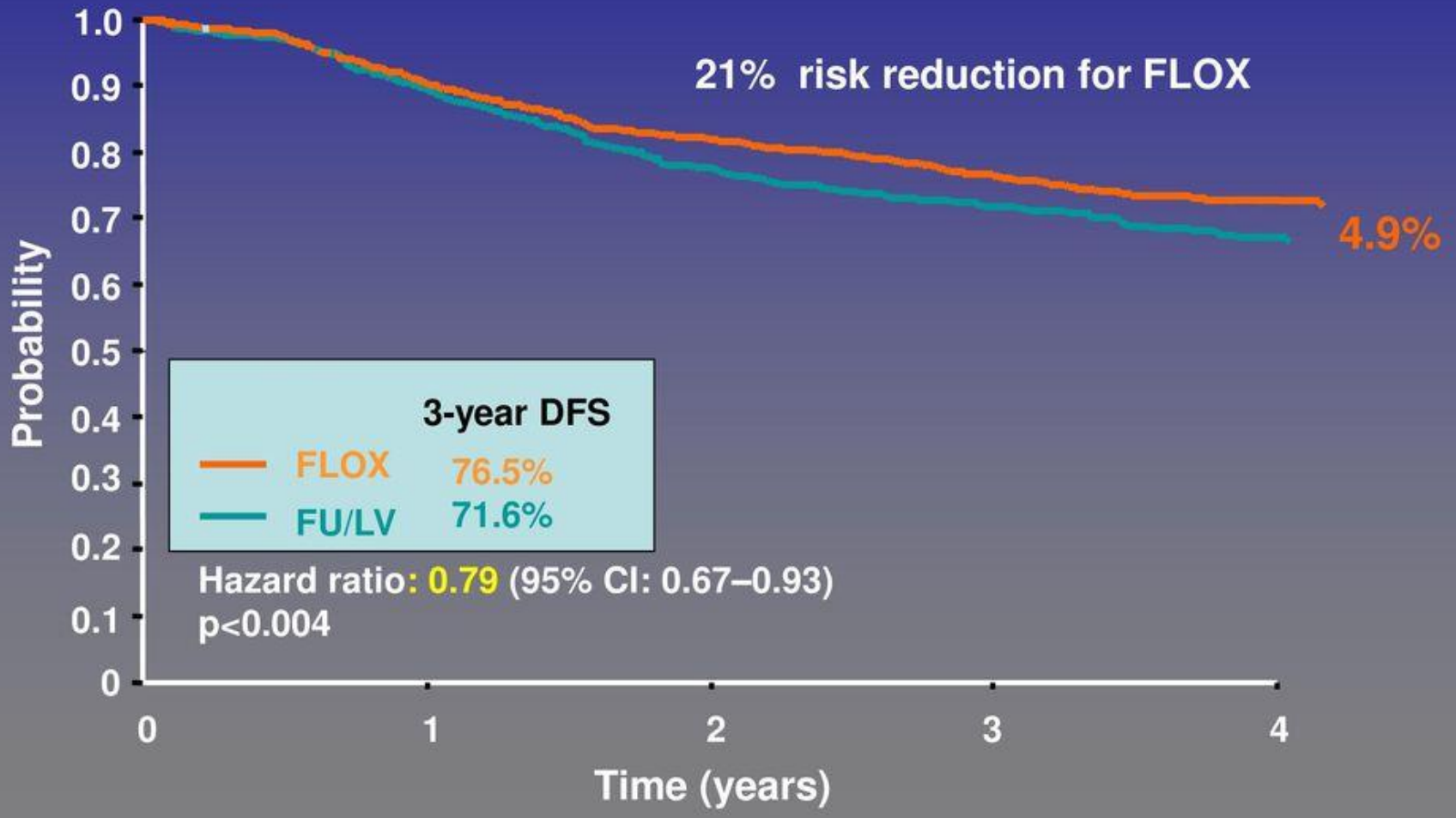
FULV + oxaliplatin 85 mg/m^2 IV on Weeks 1, 3, and 5 of each 8-week cycle x 3

(N = 1,200)

- Primary endpoint: DFS

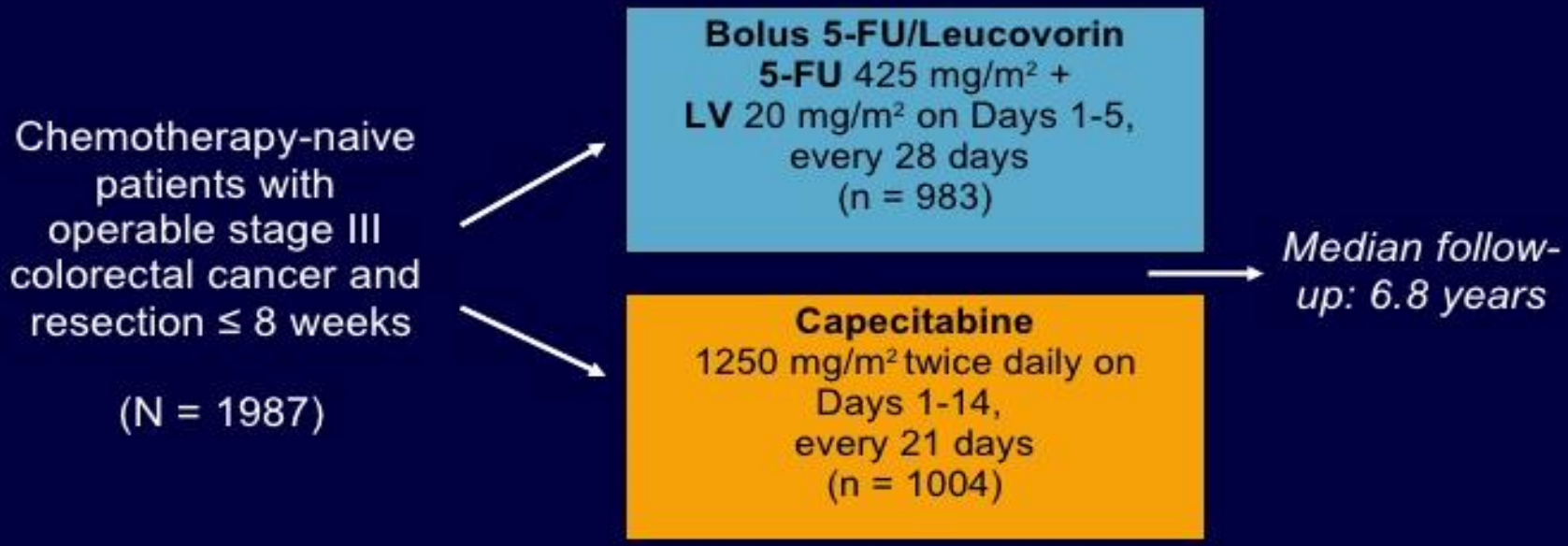
Wolmark N, et al. ASCO 2008. Abstract LBA4005.

Eloxatin combinations: NSABP C-07 3-year DFS



P.Kuebler et al. JCO,June 2007,2198-2204

X-ACT Trial Design



X-ACT Trial Key Findings

- Trend toward superior 5-year DFS and OS with capecitabine treatment
  - DFS: 60.8% vs 56.7% (*P* = .0682)
  - OS: 68.4% vs 71.4% (*P* = .06)
- Hand-foot syndrome common toxicity with capecitabine
  - Associated with higher DFS and OS
  - Possible clinical marker for optimal capecitabine exposure

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Capecitabine Plus Oxaliplatin Compared With Fluorouracil and Folinic Acid As Adjuvant Therapy for Stage III Colon Cancer

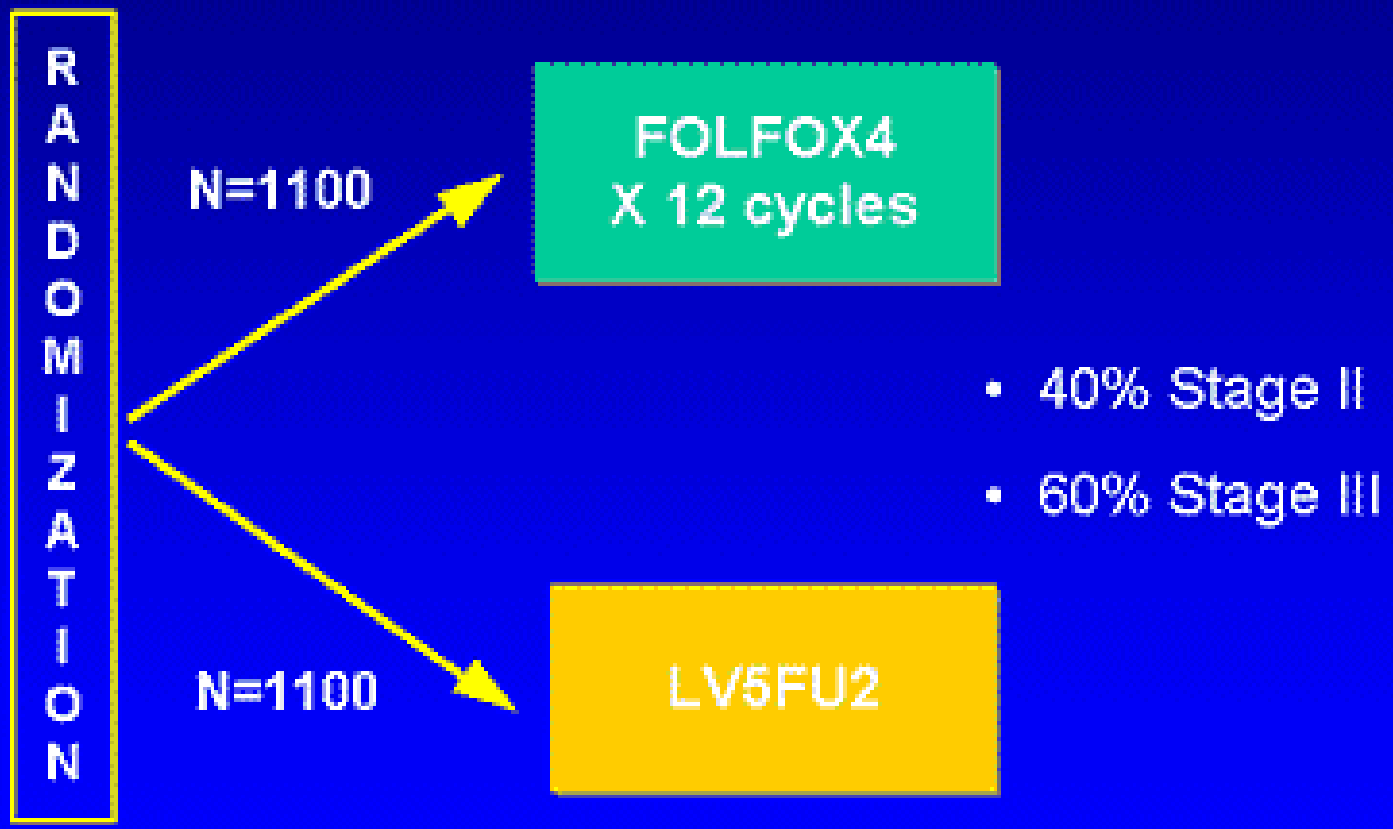
Daniel G. Haller, Josep Tabernero, Jean Maroun, Filippo de Braud, Timothy Price, Eric Van Cutsem, Mark Hill, Frank Gilberg, Karen Rittweger, and Hans-Joachim Schmoll

- Multicenter, randomized trial
- 1,886 patients.
- 57 months of follow-up,
- RR 31.3%(XELOX) Vs 37.5% FU/FA
- The 5-year OS for XELOX and FU/FA were 77.6% and 74.2%, respectively.
- Addition of oxaliplatin to capecitabine improves DFS in patients with stage III colon cancer. XELOX is an additional adjuvant treatment option for these patients.

Daniel G, JCO 29 2011

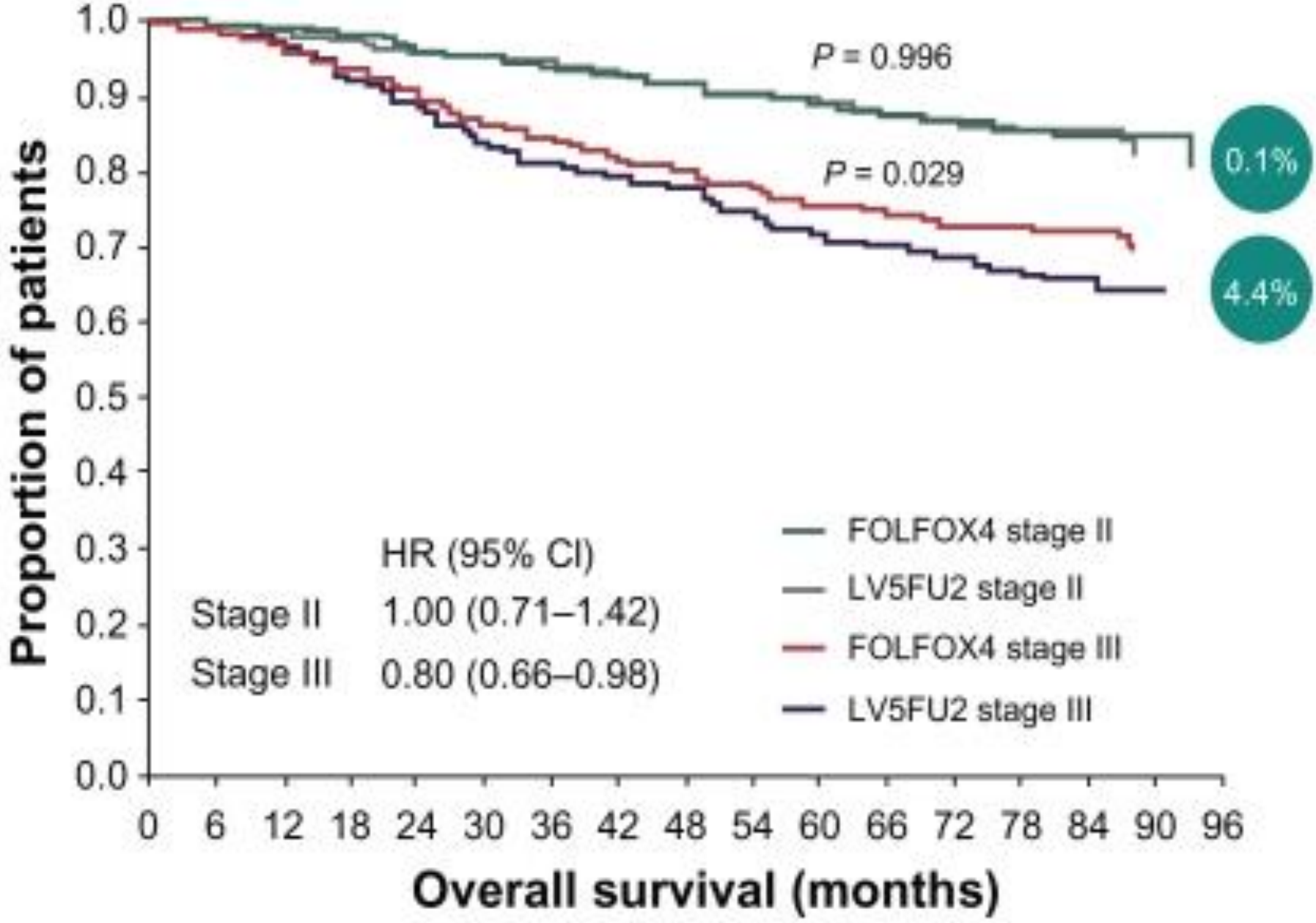
MOSAIC Phase III Trial

Schema



- 40% Stage II
- 60% Stage III

de Gramont A et al. *Proc ASCO*. 2003;23 (abstr 1015).


1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Proportion of patients
P = 0.996
P = 0.029
0.1%
4.4%
HR (95% CI)
Stage II 1.00 (0.71–1.42)
Stage III 0.80 (0.66–0.98)
FOLFOX4 stage II
LV5FU2 stage II
FOLFOX4 stage III
LV5FU2 stage III
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90 96
Overall survival (months)

After a median follow-up of 9.5 years,

10-year OS among all 2,246 patients was 71.7% (FOLFOX4 group) vs 67.1% (5-FU/leucovorin group) (hazard ratio [HR] = 0.85, *P* = .043),

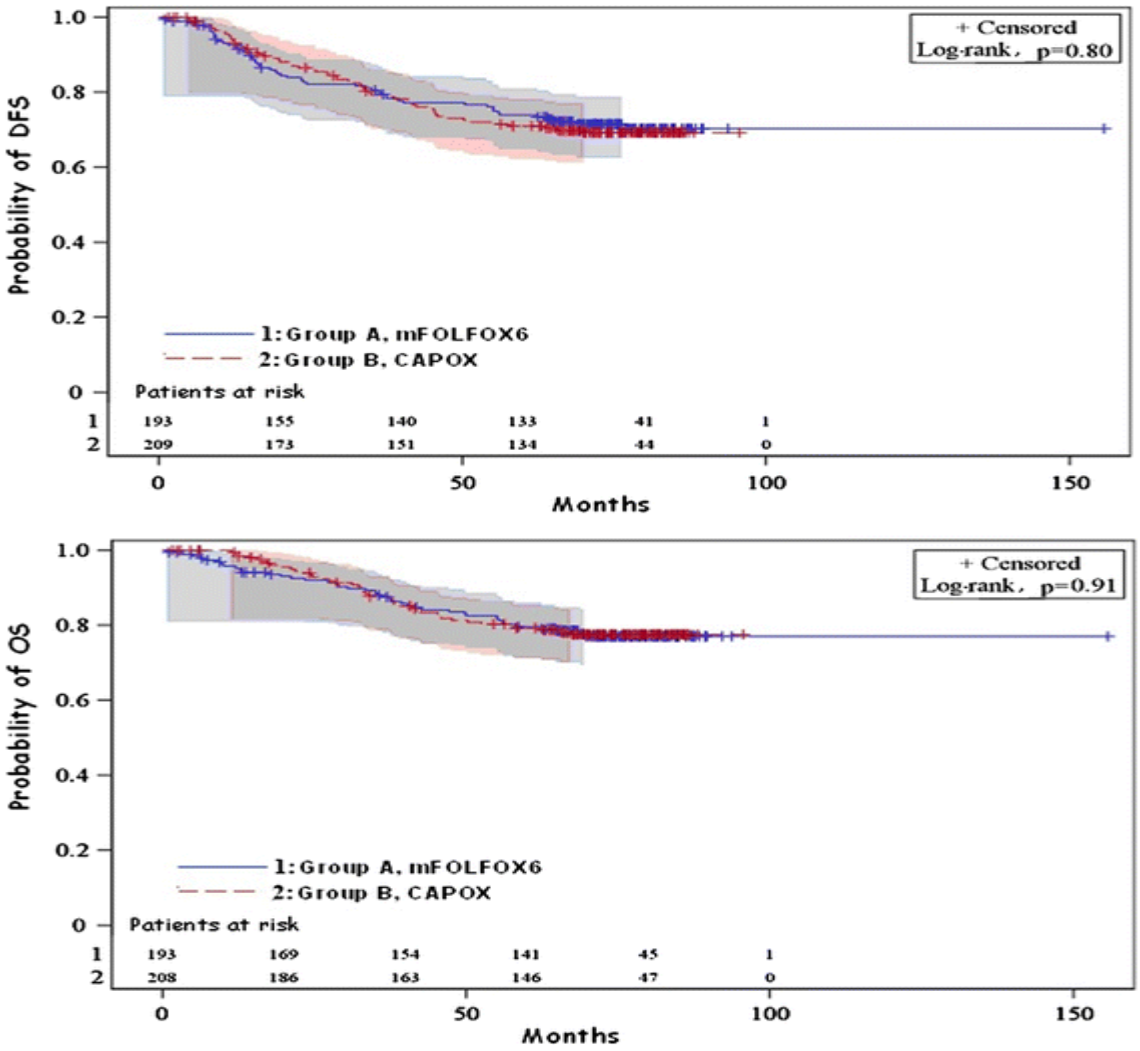
78.4% vs 79.5% in those with stage II disease (HR = 1.00, *P* = .980),

67.1% vs 59.0% in those with stage III disease (HR = 0.80, *P* = .016).

Matthew Stenger et al., Colorectal Cancer, 2015

- CAPEOX Vs FOLFOX

Randomized phase III clinical trial comparing the combination of capecitabine and oxaliplatin (CAPOX) with the combination of 5-fluorouracil, leucovorin and oxaliplatin (modified FOLFOX6) as adjuvant therapy in patients with operated high-risk stage II or stage III colorectal cancer



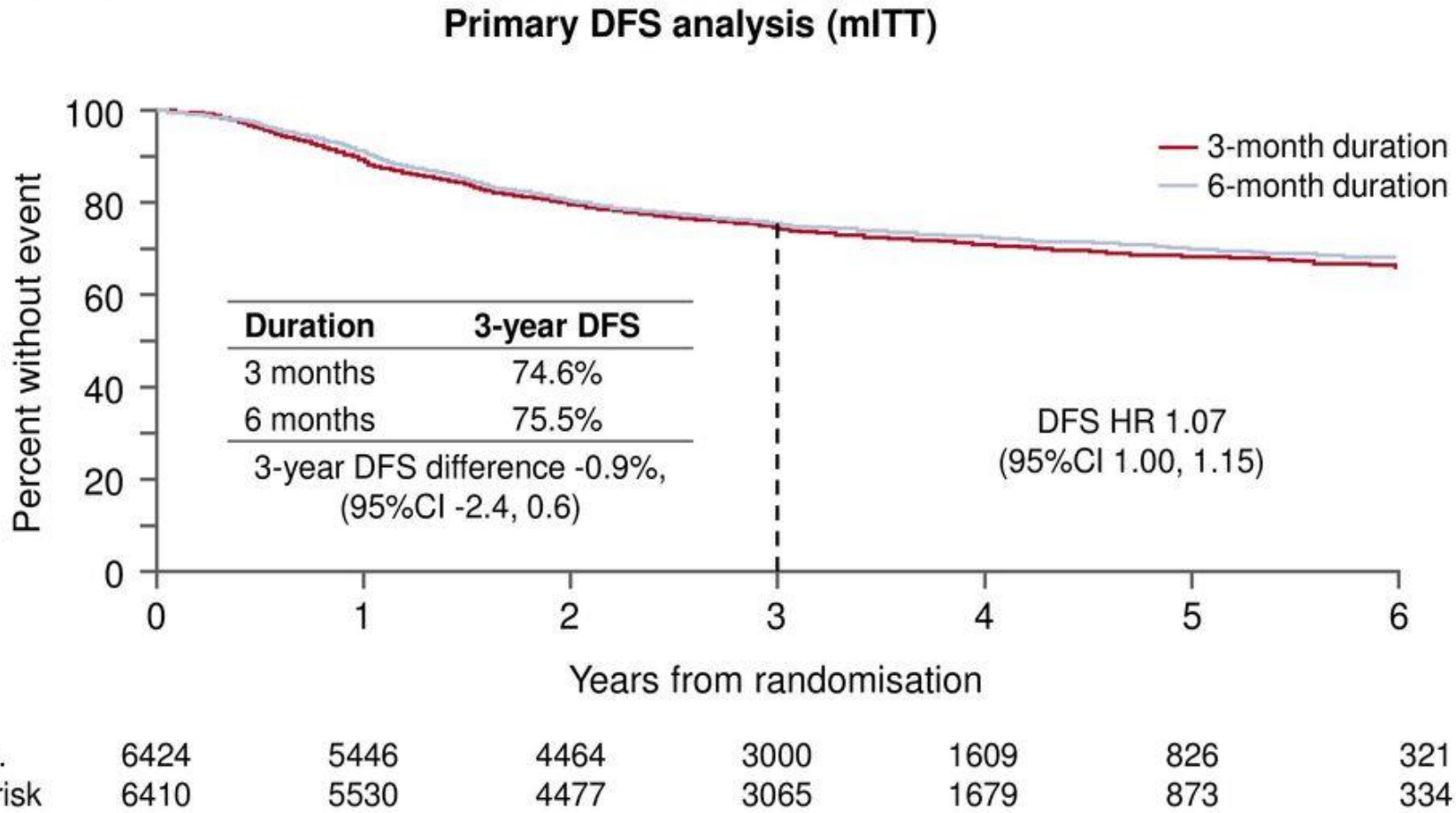
No significant difference in 3yr DFS and 3yr OS

Dimitrios Pectasides, *BMC Cancer*2015**15**:384

- 3 months or 6 months of adjuvant?
- Stage III - Low risk or high risk?

LBA1: Prospective pooled analysis of six phase III trials investigating duration of adjuvant (adjuv) oxaliplatin-based therapy (3 vs 6 months) for patients (pts) with stage III colon cancer (CC): The IDEA (International Duration Evaluation of Adjuvant chemotherapy) collaboration – Shi Q, et al

Key results



Shi Q, et al. J Clin Oncol 2017;35(Suppl):Abstr LBA1

IDEA Consensus: Risk-based approach to adjuvant chemotherapy in stage III colon cancer

Risk group	Recommended duration of adjuvant therapy
T1-3 N1 (~60% of stage III)	3 months
T4 and/or N2 (Or other high-risk factors)	6 months

Duration of therapy determined by

- tolerability of therapy
- patient preference
- assessment of risk of recurrence
- Regimen (CAPOX vs FOLFOX)

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

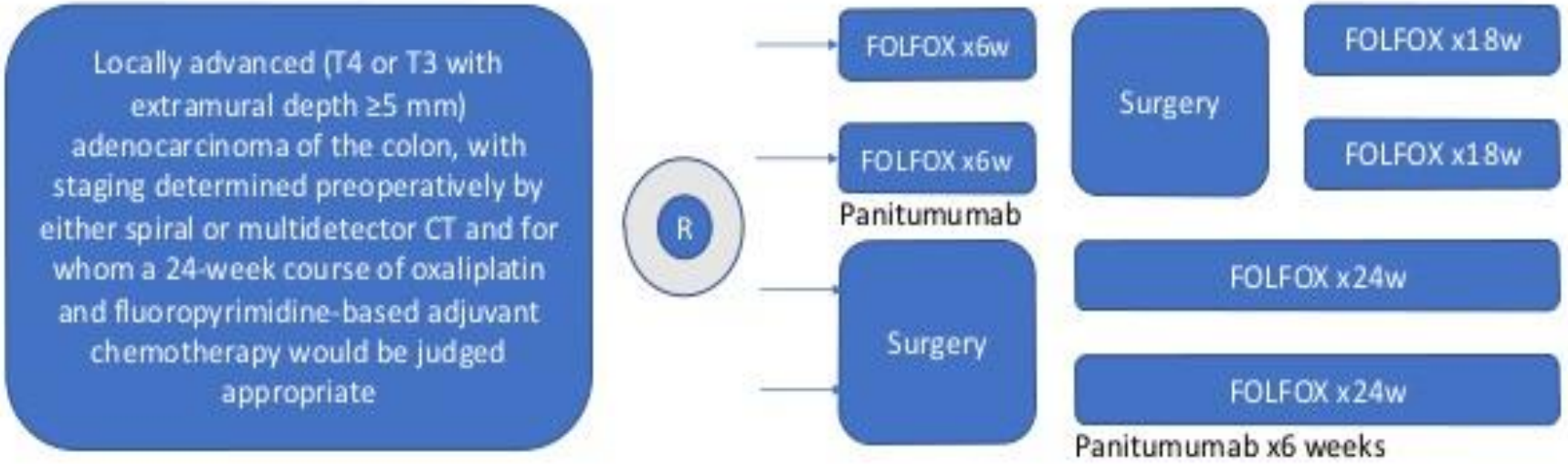
- Timing of adjuvant chemotherapy?

- Each 4 week delay in chemotherapy after surgery resulted in 14% decrease in OS [Biagi JJ et al, JAMA 2011].
- > 6 weeks delay in adjuvant chemo resulted in reduced survival [Sun et al, Dis colon rectum 2016]

- Neoadjuvant?

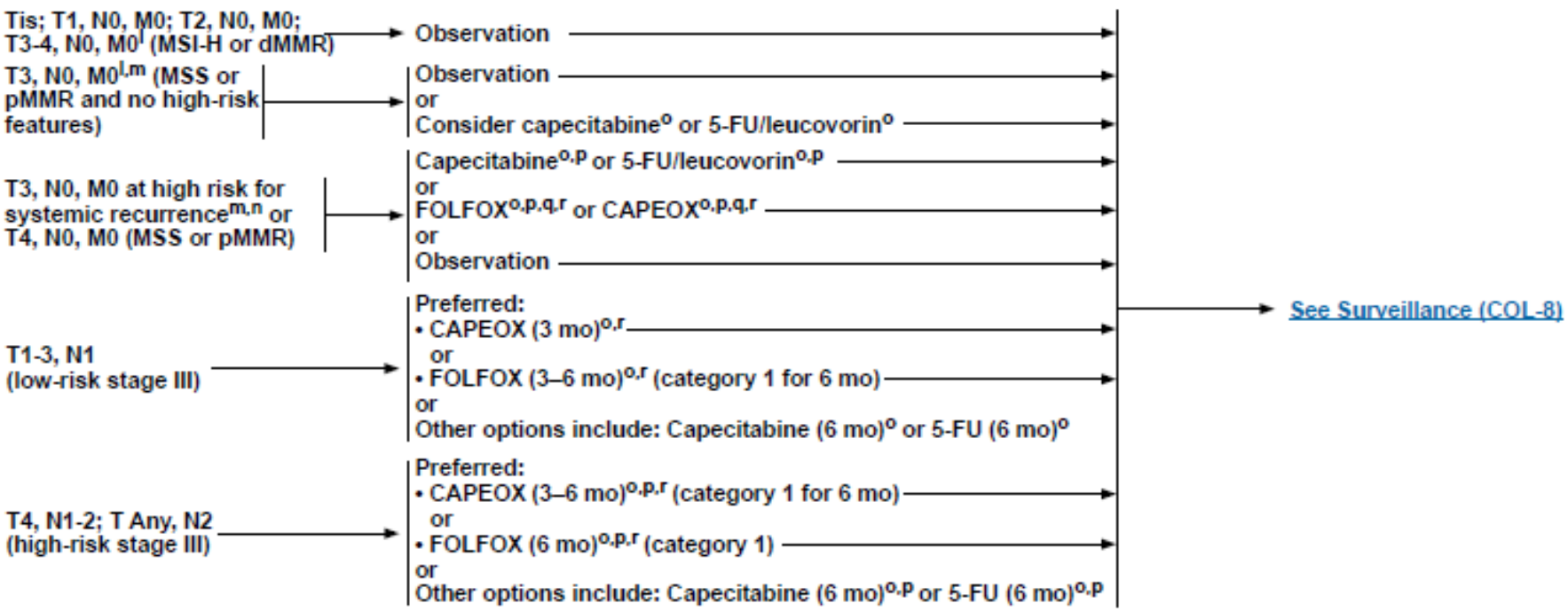
FOxTROT trial design

Feasibility of preoperative chemotherapy for locally advanced, operable colon cancer: the pilot phase of a randomised controlled trial.



Primary outcome measures of the pilot phase were feasibility, safety, and tolerance of preoperative therapy, and accuracy of radiological staging.

FOxTROT Collaborative Group, ***Lancet Oncol***, 2012



[b] See Principles of Imaging (COL-A).
[e] See Principles of Pathologic Review (COL-B).
[l] See Principles of Risk Assessment for Stage II Disease (COL-F).
[m] High-risk factors for recurrence: poorly differentiated histology (exclusive of those cancers that are MSI-H), lymphatic/vascular invasion, bowel obstruction, <12 lymph nodes examined, perineural invasion, localized perforation, or close, indeterminate, or positive margins. In high-risk stage II patients, there are no data that correlate risk features and selection of chemotherapy.
[n] There are insufficient data to recommend the use of multi-gene assay panels to determine adjuvant therapy.
[o] See Principles of Adjuvant Therapy (COL-G).
[p] Consider RT for T4 with penetration to a fixed structure. See Principles of Radiation Therapy (COL-E).
[q] A survival benefit has not been demonstrated for the addition of oxaliplatin to 5-FU/leucovorin in stage II colon cancer. Tournigand C, et al. J Clin Oncol 2012; 30:3353-3360.
[r] A benefit for the addition of oxaliplatin to 5-FU/leucovorin in patients age 70 and older has not been proven.
[s] In patients staged as T1-3, N1 (low-risk stage III), 3 months of CapeOX is non-inferior to 6 months of CapeOX for disease-free survival; non-inferiority of 3 vs. 6 months of FOLFOX has not been proven. In patients staged as T4, N1-2 or T any, N2 (high-risk stage III), 3 months of FOLFOX is inferior to 6 months of FOLFOX for disease-free survival, whereas non-inferiority of 3 vs. 6 months of CapeOX has not been proven. Grade 3+ neurotoxicity rates are lower for patients who receive 3 months vs. 6 months of treatment (3% vs. 16% for FOLFOX; 3% vs. 9% for CapeOX). Shi Q, et al. J Clin Oncol 2017;35 (suppl):LBA1.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Rectum

Background

- Use of adjuvant radiation therapy is based on the substantial incidence of local-regional failure with surgical therapy alone.
- local failure rates with surgery alone for up to 50% in patients with T3-4 or N+ disease[1,2]
- local-regional failure is decreased by the use of radiation therapy and is further decreased by the use of concurrent 5-FU-based chemotherapy

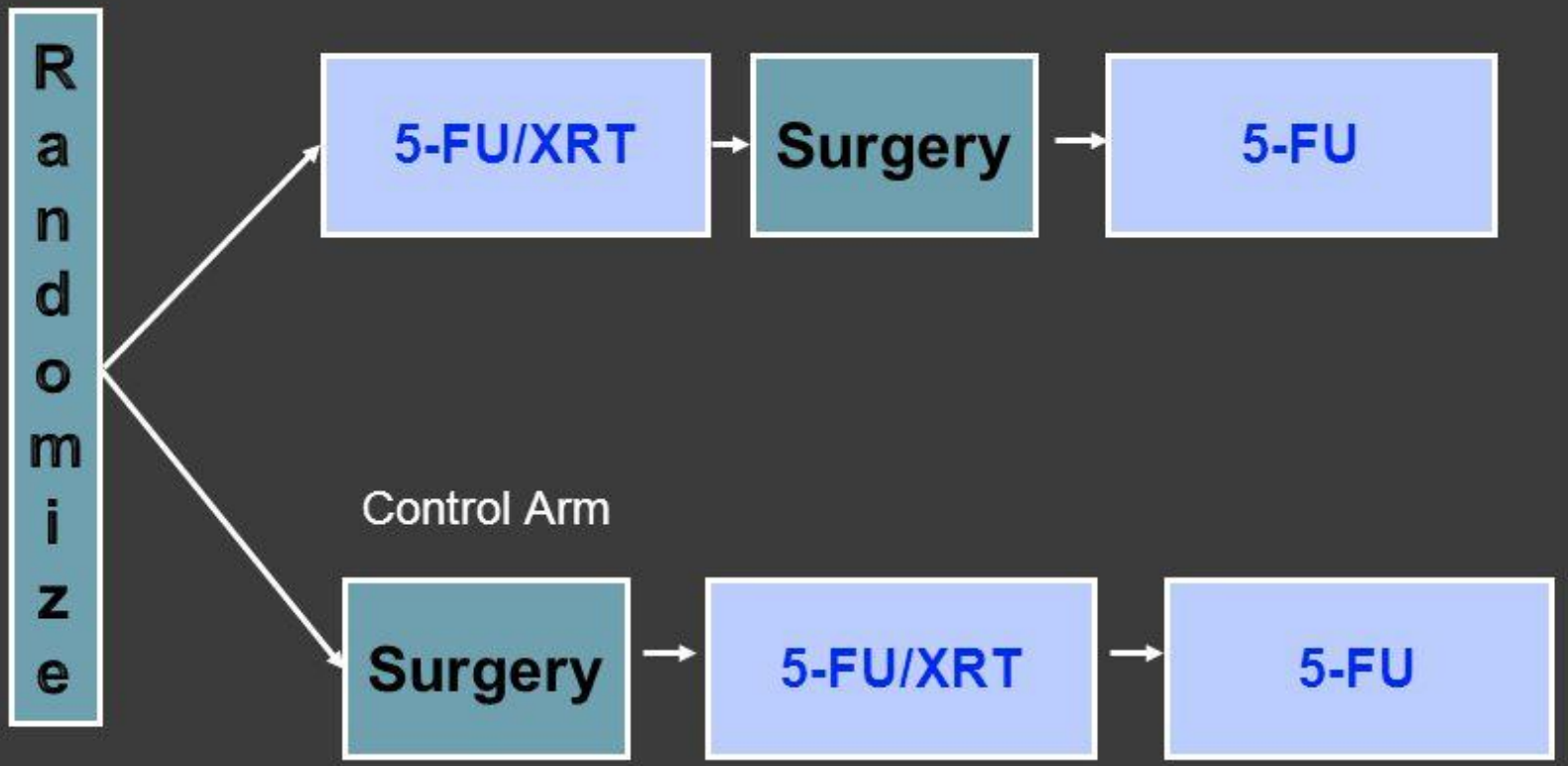
1. Pilipshen S, Cancer 1984;53:1354.
2. Martling A, Cancer 2001;92(4):896.

- Use of adjuvant chemotherapy has centered on the use of 5-FU chemotherapy.
- Initial trials – bolus 5 FU during weeks 1 and 5 of the RT.
- NCCTG- use of long-term continuous infusion 5-Fu[1].

1. O'Connell MJ, N Engl J Med 1994;331(8):502.

Neoadjuvant Vs Adjuvant?

Neoadjuvant Chemoradiotherapy for Rectal Cancer: CAO/ARO/AIO-94



Primary endpoint: DFS

Sauer et al NEJM, 2004:

German Trial – CAO/ARO/AIO-94

800+ pts – T3/T4, N+ rectal cancer(CI 5-FU + 50.4 Gy)

	Pre-Op	Post-Op	p-value
5-yr Local Recurrence	6%	12%	p=.02
5-yr Distant Relapse	35%	39%	p=.52
5-yr DFS	59%	55%	p=.23
5 –yr Overall Survival	78%	73%	p=.38
Acute Grade 3/4 Tox	30%	30%	NS
Anastomotic Stenosis	2.7%	8.5%	p=.001
Sphincter preserved (188 – low lying tumors)	39% (pCR 8%)	19%	p=.004

U Penn Oncolink Report on Plenary Session Presentation – ASTRO 45th Annual Meeting – Oct. 2003 - R. Sauer et al – German Rectal Cancer Group

- The 10-year cumulative incidence of local relapse was 7.1% and 10.1% in the pre- and postoperative arms, respectively (P = .048).
- No significant differences were detected for 10-year cumulative incidence of distant metastases (29.8% and 29.6%; P = 0.9) and disease-free survival

Sauer R, J Clin Oncol. 2012 Jun 1;30(16):1926-33.

3500: A multi-center randomized controlled trial of mFOLFOX6 with or without radiation in neoadjuvant treatment of local advanced rectal cancer (FOWARC study): Preliminary results – Deng Y, et al

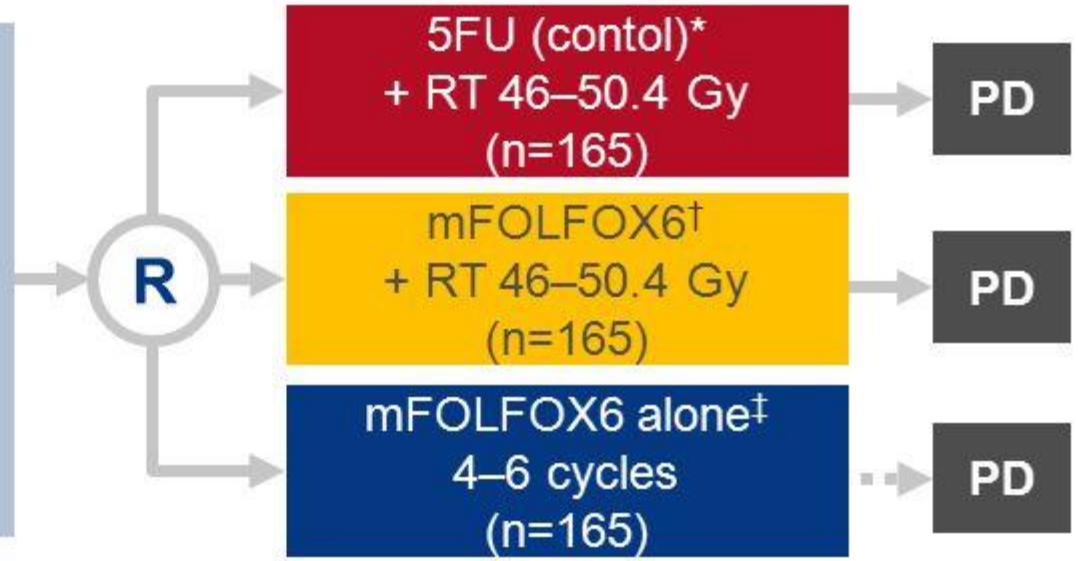
Study objective

- To determine whether perioperative mFOLFOX6 CT improves DFS in locally advanced rectal cancer

Key patient inclusion criteria

- Rectal cancer ≤12 cm from the anal verge
- T3/4 and/or N+; R0/1
- Staged by MRI
- ECOG PS 0–1

(n=495)



PRIMARY ENDPOINT

- DFS

SECONDARY ENDPOINTS

- pCR, R0 resection, sphincter preservation, local recurrence, OS, QoL, toxicity (*follow-up ongoing for recurrence/OS*)

*Leucovorin 0.4 mg/m^2 D1, 5FU 0.4 mg/m^2 bolus IV then 2.4 mg/m^2 continuous IV 48 h; †As above but with initial oxaliplatin 85 mg/m^2 2 h IV infusion. ‡Postoperative radiation permitted (physician's decision)

Deng et al. J Clin Oncol 2015; 33 (suppl): abstr 3500

3500: A multi-center randomized controlled trial of mFOLFOX6 with or without radiation in neoadjuvant treatment of local advanced rectal cancer (FOWARC study): Preliminary results – Deng Y, et al

Key results

n (%)	5FU + RT (n=133)	mFOLFOX6 + RT (n=143)	mFOLFOX6 alone (n=148)
R0 resection	120 (90.2)	128 (89.5)	132 (91.2)
pCR*	19 (14.3)	40 (28.0)	9 (6.1)
Anastomotic leakage†	28 (21.1)	26 (18.2)	10 (6.8)
Infection of incision‡	30 (22.6)	24 (16.8)	9 (6.1)
Grade 3/4 AEs, n (%)	**5FU + RT (n=155)**	**mFOLFOX6 + RT (n=158)**	**mFOLFOX6 alone (n=163)**
Leucopenia	19 (12.9)	29 (19.0)	9 (5.7)
Nausea/vomiting	4 (2.6)	9 (5.7)	4 (2.5)
Diarrhoea	12 (7.7)	23 (14.5)	12 (7.3)
Radiodermatitis	22 (14.1)	32 (20.3)	-

Conclusions

- **mFOLFOX + RT as a neoadjuvant treatment had a higher pCR rate, increased response and slightly increased toxicity vs. 5FU in patients with locally advanced rectal cancer**
- **mFOLFOX alone had a similar R0 resection rate, similar good response rate and fewer surgical complications vs. 5FU**
- **mFOLFOX6 + RT may replace 5FU as a standard treatment in this setting**
- **~35% of the patients may not need RT to create a good excision plane for surgery**

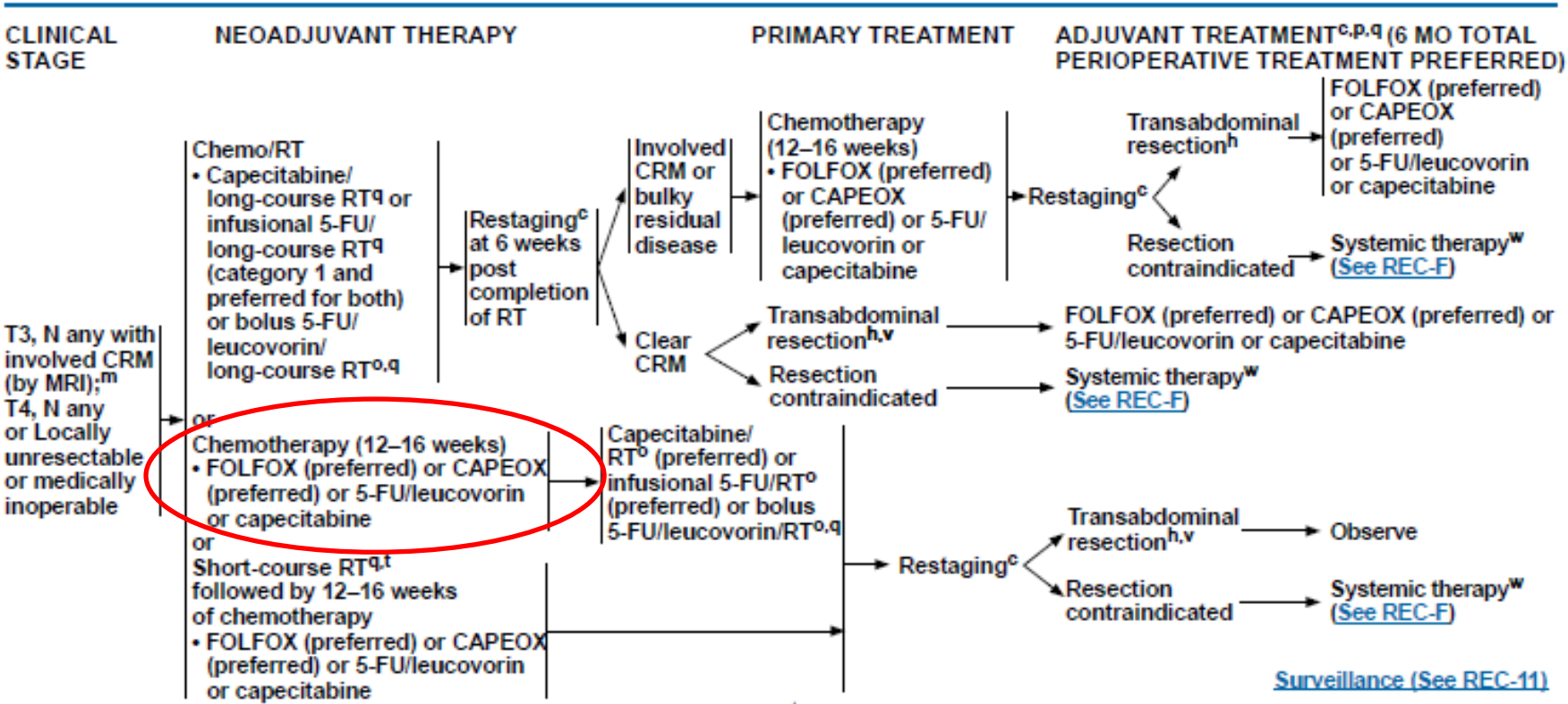
*p=0.001; †p=0.02; ‡p=0.009

Deng et al. J Clin Oncol 2015; 33 (suppl): abstr 3500

Table 2. Studies of Neoadjuvant Chemotherapy Alone in Rectal Cancer

	Study	No. Patients	Inclusion Criteria	Chemotherapy	pCR	Outcomes
HIGH RISK	Uehara et al (2013)[51]	32	MRI-defined poor risk	Oxaliplatin + capecitabine + bevacizumab × 12 wks	13%	R0 resection rate = 90% Postoperative complication rate = 43%
HIGH RISK	Hasegawa et al (2014) [48]	25	T4 or lymph node–positive	XELOX (4 cycles) plus bevacizumab (3 cycles)	4%	R0 resection rate = 92% Postoperative complication rate = 26%
	Ishii et al (2010)[49]	26	T3 or T4 and N0–2	IFL (2 cycles)	3.8%	5-yr DFS = 74% 5-yr OS = 84% LR = 11%
	Schrag et al (2014)[50]	32	Clinical stages II to III	FOLFOX (6 cycles) + bevacizumab (cycles 1–4)	25%	R0 resection rate = 100% 4-yr LR = 0% 4-yr DFS = 84%

DFS = disease-free survival; FOLFOX = leucovorin + fluorouracil + oxaliplatin; IFL = irinotecan + fluorouracil + leucovorin; LR = local recurrence; MRI = magnetic resonance imaging; OS = overall survival; pCR = pathologic complete response; XELOX = capecitabine + oxaliplatin.



[c] See Principles of Imaging (REC-A).
[h] See Principles of Surgery (REC-C).
[m] CRM measured at the closest distance of the tumor to the mesorectal fascia. Involved CRM: within 1 mm of mesorectal fascia; or, for lower third rectal tumors, within 1 mm from levator muscle; or, for anal canal lesions, invasion into or beyond the intersphincteric plane.
[o] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
[p] See Principles of Adjuvant Therapy (REC-D).
[q] See Principles of Radiation Therapy (REC-E).
[t] Evaluation for short-course RT should be in a multidisciplinary setting, with a discussion of the need for downstaging and the possibility of long-term toxicity. Short-course RT is not recommended for low-lying tumors, <5 cm from anal verge.
[v] In those patients who achieve a complete clinical response with no evidence of residual disease on digital rectal examination, rectal MRI, and direct endoscopic evaluation, a "watch and wait," nonoperative management approach may be considered in centers with experienced multidisciplinary teams. The degree to which risk of local and/or distant failure may be increased relative to standard surgical resection has not yet been adequately characterized. Decisions for non-operative management should involve a careful discussion with the patient of his/her risk tolerance.
[w] FOLFOXIRI is not recommended in this setting.

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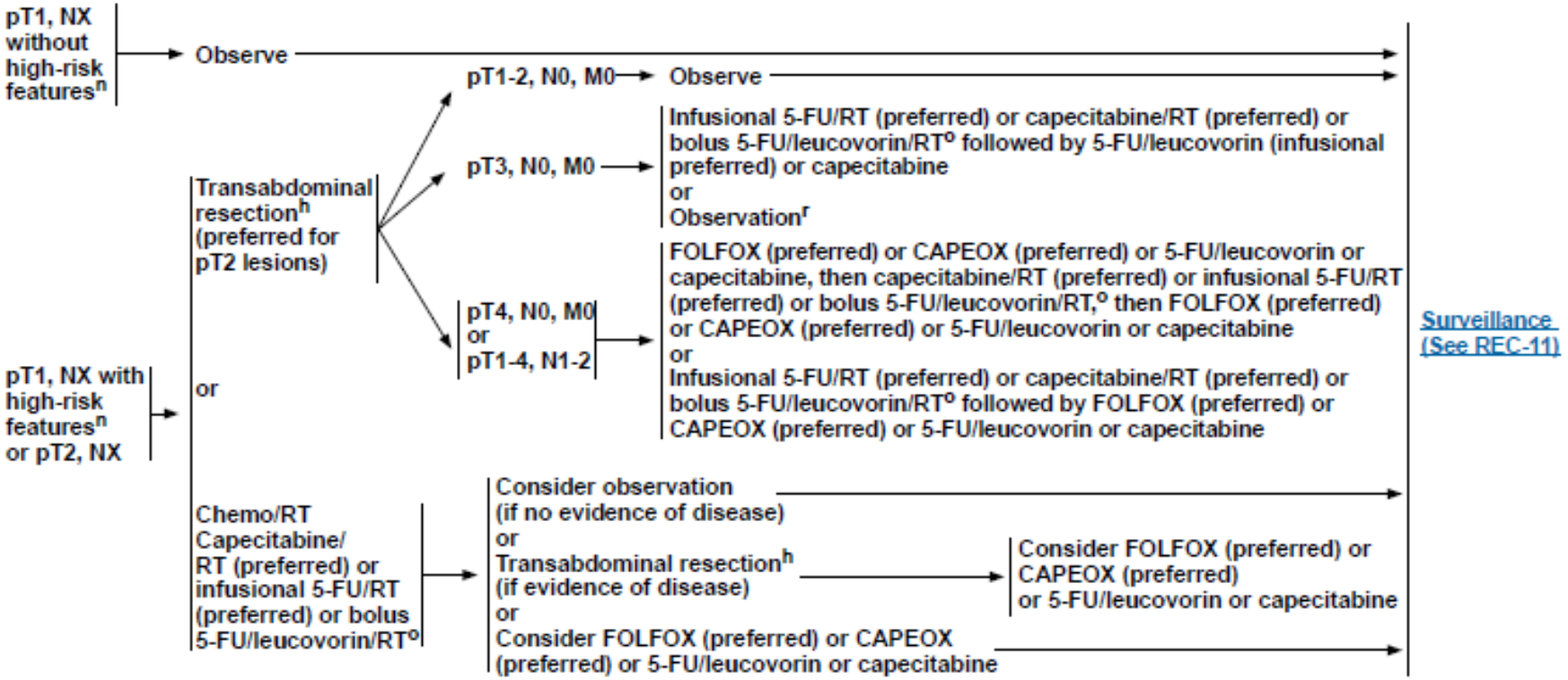

[c] See Principles of Imaging (REC-A).
[h] See Principles of Surgery (REC-C).
[n] High-risk features include positive margins, lymphovascular invasion, poorly differentiated tumors, or sm3 invasion (submucosal invasion to the lower third of the submucosal level).
[o] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
[p] See Principles of Adjuvant Therapy (REC-D).
[q] See Principles of Radiation Therapy (REC-E).

[r] Observation following transabdominal resection can be considered in patients with pT3N0 rectal cancer if the tumor was well-differentiated or moderately well-differentiated carcinoma invading less than 2 mm into the mesorectum, without lymphatic or venous vessel involvement and was located in upper rectum. Willett CG, Badizadegan K, Ancukiewicz M, Shellito PC. Prognostic factors in stage T3N0 rectal cancer: do all patients require postoperative pelvic irradiation and chemotherapy? Dis Colon Rectum 1999;42:167-173.
[s] A benefit for the addition of oxaliplatin to 5-FU/leucovorin in patients aged 70 years or older has not been proven.

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Phase III: CAO/ARO/AIO-04

Best arm of CAO/ARO/AIO-94:

RT 50.4 Gy + 5-FU
1000 mg/m² days 1-5 + 29-33

5-FU
500 mg/m² d 1-5, q29
4 cycles (4 months)

T
M
E

Based on phase I/II trials:

RT 50.4 Gy + 5-FU/OX
Ox: 50 mg/m² d 1, 8, 22, 29
5-FU: 250 mg/m² d 1-14 + 22-35

Note: Chemo gap 3rd week of RT !

mFOLFOX6
Oxaliplatin: 100 mg/m² d1,q15
Folinic Acid: 400 mg/m² d1
5-FU: 2400 mg/m² d1-2
8 cycles (4 months)

- The use of adjuvant chemotherapy was associated with a significant reduction in the risk of disease relapse (hazard ratio [HR] for relapse 0.75, 95% CI 0.68-0.83) and death (HR for death 0.83, 95% CI 0.76-0.91).
- A survival benefit for the addition of adjuvant chemotherapy after potentially curative resection of rectal cancer was shown in a 2012 meta-analysis of 21 trials

Petersen SH, Postoperative adjuvant chemotherapy in rectal cancer operated for cure. Cochrane Database Syst Rev. 2012;

Infusional versus bolus fluorouracil?

- Both bolus and infusional FU alone represent appropriate choices.
- PVI FU was associated with a significant reduction in distant metastases (31 Vs 40 %) and improvements in 4yr RFS as well as OS (70 Vs 60 %), but there was no difference in LR, higher risk of severe diarrhea.
- Int 0144 revealed no diff in 3yr DFS or OS or side effects except that the PVI FU arm had less hematologic toxicity

Capecitabine Vs 5 FU?

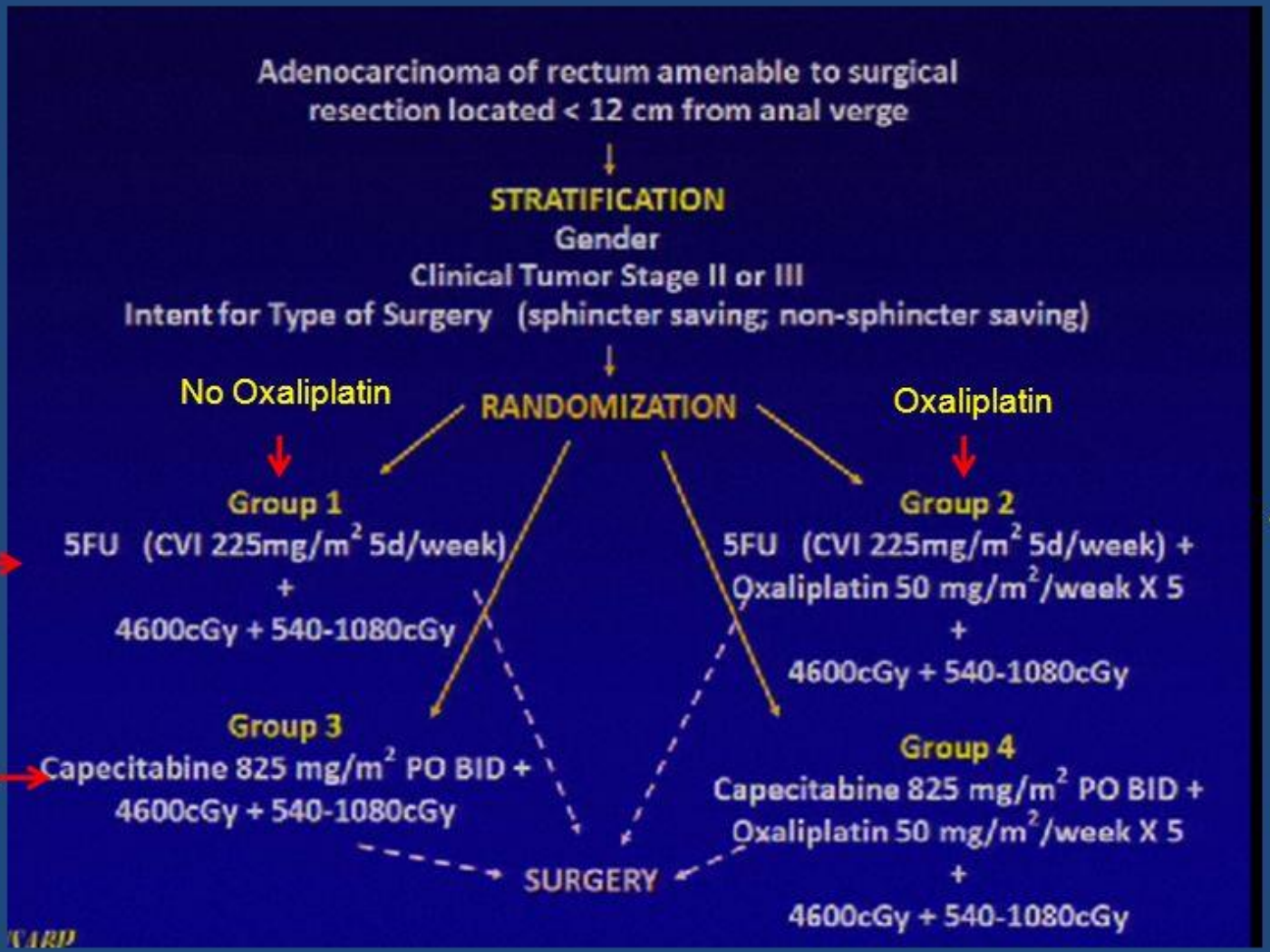
- Thymidine phosphorylase is present in higher concentrations in tumors (particularly colorectal cancers) than in normal tissue
- Higher tumor to plasma ratios of FU are achievable with capecitabine than with intravenous FU

Schuller J, Cassidy J, Dumont E, et al. Preferential activation of capecitabine in tumor following oral administration to colorectal cancer patients. Cancer Chemother Pharmacol 2000;45(4):291.

- 5-yr OS in the capecitabine group was non-inferior to that in the fluorouracil group (76% vs 67%; p=0·0004). [Hofheinz RD, Lancet Oncol. 2012]

- Postresection use of adjuvant chemotherapy based on the results in colon cancer.
- Use of FOLFOX is reasonable, albeit unproven, extrapolation from

NSABP-R04



5FU →

Capecitabine →

1200 pts

***Capecitabine is 825 mg /m2 bid for 5/7(Rad days)

Roh et al ASCO 2011

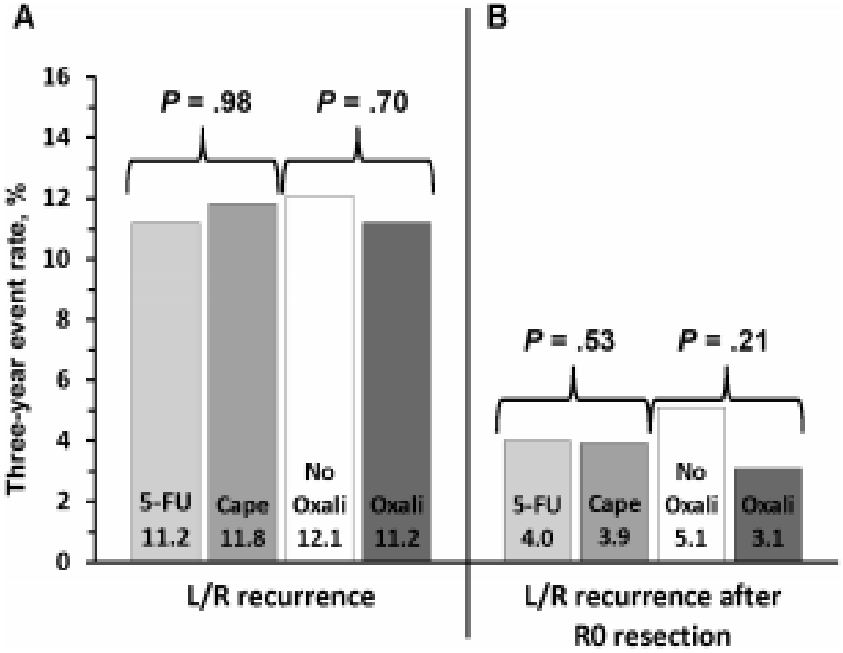
NSABP-R04 results

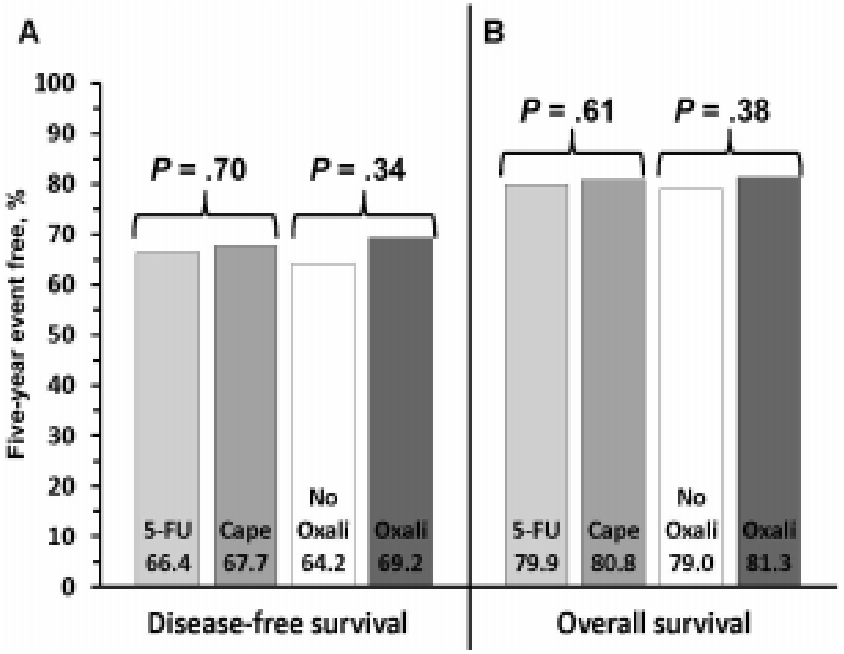
5-FU versus Capecitabine (Cape)			
	5-FU (± Oxaliplatin)	Capecitabine (± Oxaliplatin)	*p*-value
pCR rate, (n=719, 707)	18.8%	22.2%	0.12
SSS, (n=727, 710)	61.2%	62.7%	0.59
SD, (n=188, 187)	20.7%	23.0%	0.62

Oxaliplatin (Ox) versus None			
	(5-FU or Capecitabine) Oxaliplatin	(5-FU or Capecitabine) No Oxaliplatin	*p*-value
pCR rate, (n=578, 580)	20.9%	19.1%	0.46
SSS, (n=584, 582)	60.4%	63.6%	0.28
SD, (n=151, 152)	19.2%	23.0%	0.48

pCR, pathologic complete response; SSS, sphincter-saving surgery; SD, surgical downstaging

Roh MS et al. *Proc ASCO* 2011;Abstract 3503.


A
B
Three-year event rate, %
16
14
12
10
8
6
4
2
0
P = .98
P = .70
P = .53
P = .21
5-FU
11.2
Cape
11.8
No Oxali
12.1
Oxali
11.2
5-FU
4.0
Cape
3.9
No Oxali
5.1
Oxali
3.1
L/R recurrence
L/R recurrence after R0 resection


A
B
Five-year event free, %
100
90
80
70
60
50
40
30
20
10
0
P = .70
P = .34
P = .61
P = .38
5-FU
66.4
Cape
67.7
No Oxali
64.2
Oxali
69.2
5-FU
79.9
Cape
80.8
No Oxali
79.0
Oxali
81.3
Disease-free survival
Overall survival

- **Oxaliplatin** — Given the lack of benefit and the enhanced toxicity when oxaliplatin is added as a component of neoadjuvant concomitant chemoradiotherapy, it should not be used concurrently with RT in the adjuvant setting.

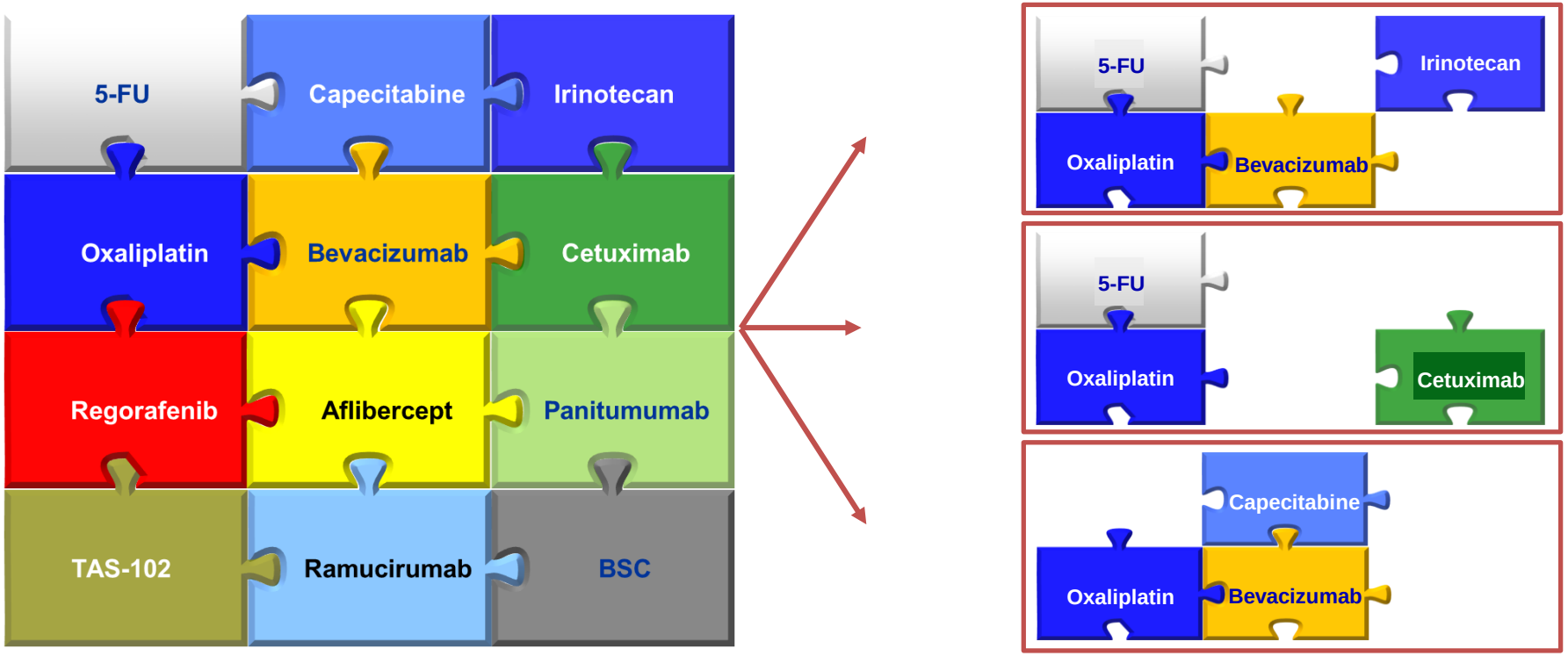
- Addition of irinotecan, but because of the overlapping toxicity of diarrhea with radiation therapy, 5-FU and irinotecan, this has not been heavily pursued[1].

Mitchell EP. Irinotecan in preoperative combined-modality therapy for locally advanced rectal cancer. Oncology (Williston Park) 2000;14(12 Suppl 14):56.

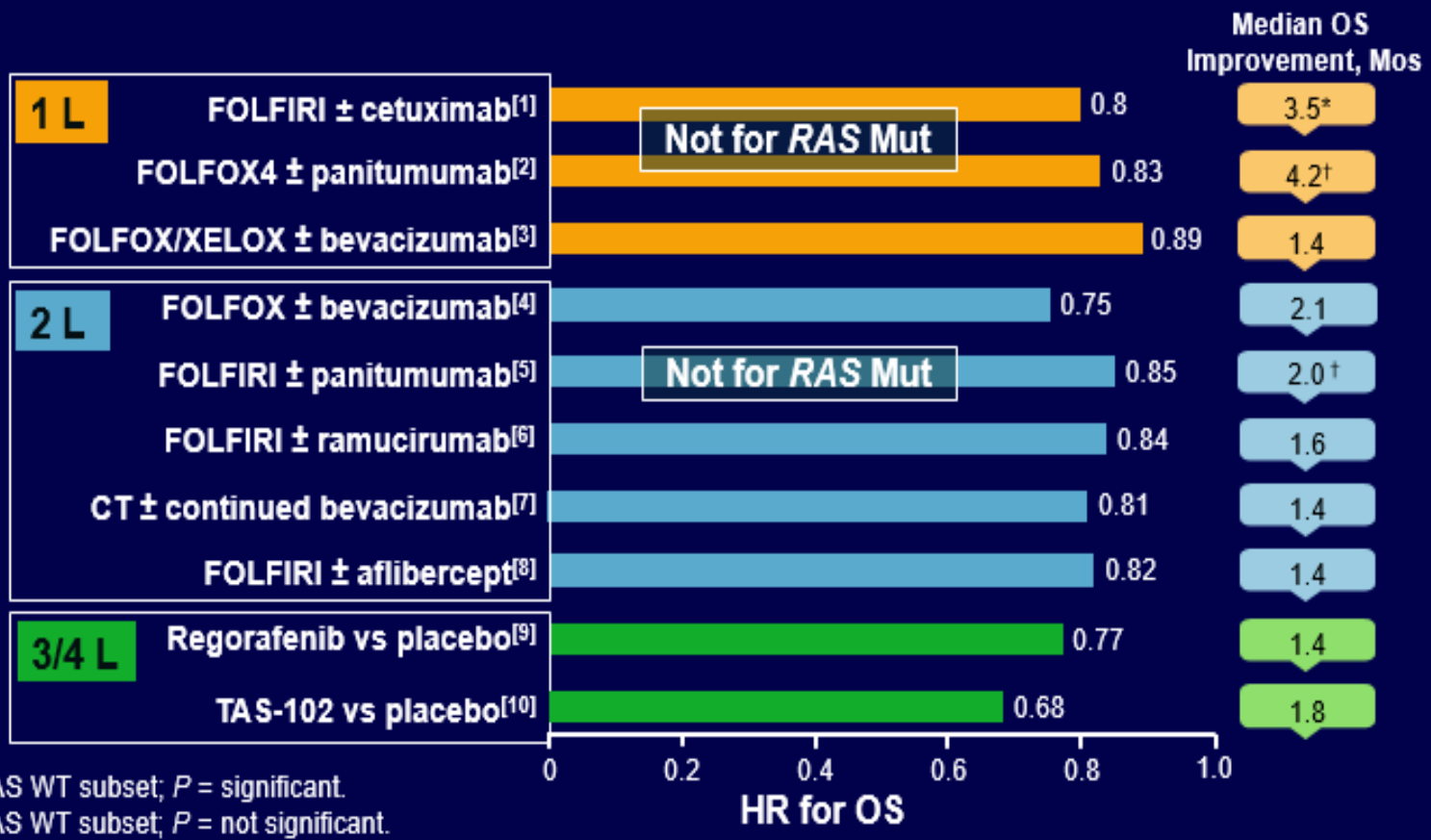
Metastatic disease

- Cure?
- Prolong overall survival and maintain quality of life (QOL) for as long as possible.
- For decades, fluorouracil (FU) was the sole active agent for advanced colorectal cancer (CRC).

The Luxury of So Many Options: How Do We Personalize Therapy?



Proportional Impact on Magnitude of OS Benefit Achieved Across Lines of Therapy



*KRAS WT subset; *P* = significant.
†KRAS WT subset; *P* = not significant.

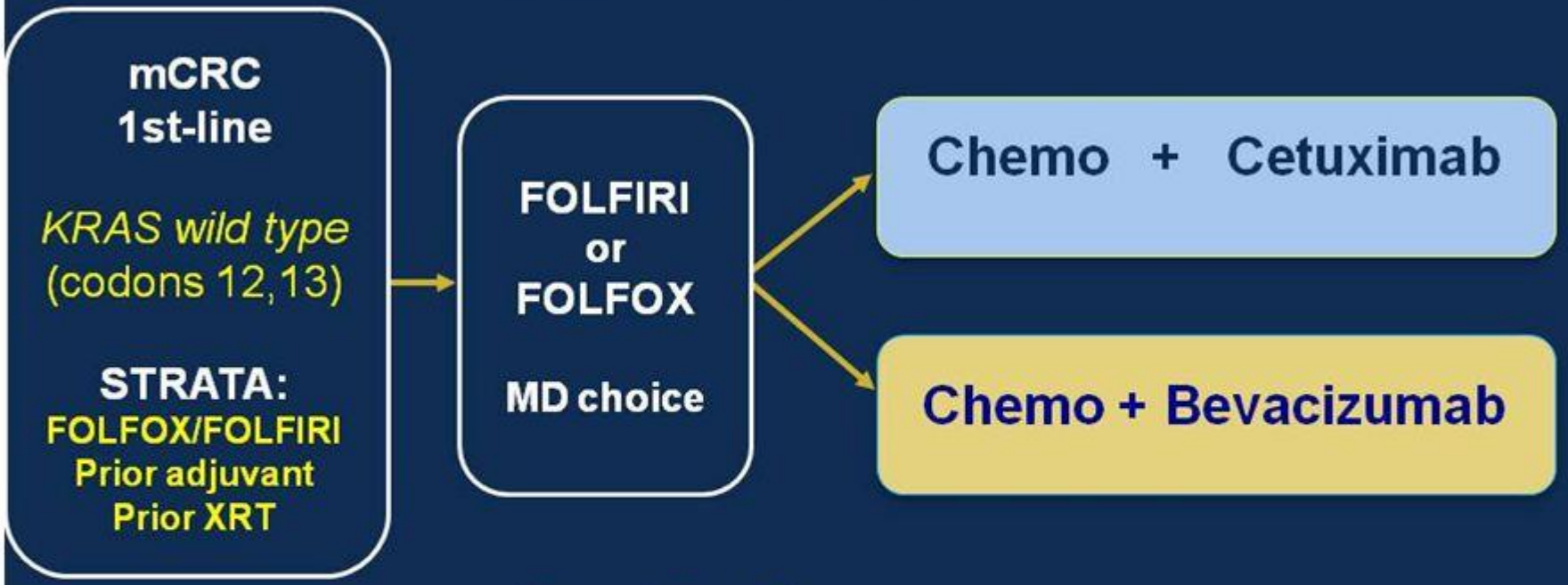
References in slidenotes.

1. Van Cutsem E, et al. J Clin Oncol. 2011;29:2011-2019.
2. Douillard JY, et al. J Clin Oncol. 2010;28:4697-4705.
3. Saltz LB, et al. J Clin Oncol. 2008;26:2013-2019.
4. Giantonio BJ, et al. J Clin Oncol. 2007;25:1539-1544.
5. Peeters M, et al. J Clin Oncol . 2010;28:4706-4713.
6. Tabernero J, et al. Lancet Oncol. 2015;16:499-508.J
7. Bennouna J, et al. Lancet Oncol. 2013;14:29-37.
8. Van Cutsem E, et al. J Clin Oncol. 2012;30:3499-3506.
9. Grothey A, et al. Lancet. 2013;381:303-312.
10. Mayer RJ, et al. N Engl J Med. 2015;372:1909-1919.

- Accumulating data suggest that long-term survival may also be improving.[1-2]
- North Center Cancer Treatment Group (NCCTG) trials conducted in the FU plus leucovorin (LV) era, 5 yr survival rate 1.1% [3].
- Phase III FIRE-3 trial (first-line irinotecan with short-term infusional FU plus LV [FOLFIRI] plus
either bevacizumab or cetuximab), the 5yr SR for patients with RAS wild-type tumors treated with FOLFIRI plus cetuximab was ~ 20 %. [4]

1. Renouf DJ, Clin Colorectal Cancer. 2011;10(2):97. Epub 2011 Apr 22.
2. Sanoff HK, J Clin Oncol. 2008;26(35):5721. Epub 2008 Nov 10.
3. Dy GK, Clin Colorectal Cancer. 2009 Apr;8(2):88-93.
4. Heinemann V, Lancet Oncol. 2014;15(10):1065. Epub 2014 Jul 31.

CALGB/SWOG 80405: FINAL DESIGN



N = 1140

1° Endpoint: Overall Survival

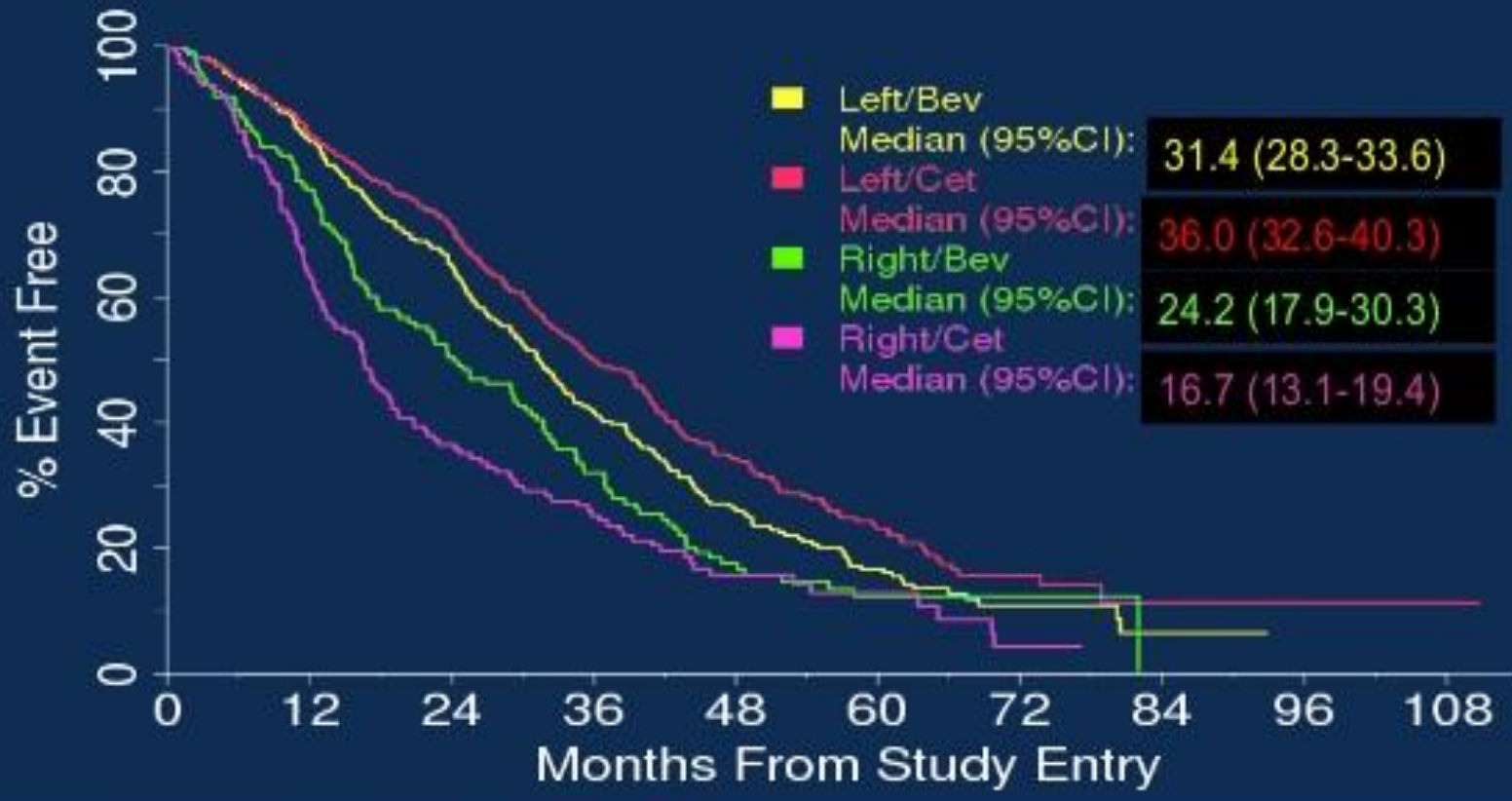
PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Presented By Alan Venook at 2014 ASCO Annual Meeting

Three Takeaways in Colorectal Cancer From ASCO 2014

- For first-line therapy, either cetuximab or bevacizumab offer improved median survival and long-term responses in patients with *KRAS* wild-type metastatic disease.
- For maintenance therapy, switching to either 5-FU with or without bevacizumab, or bevacizumab alone—but not to a treatment holiday—appears appropriate.
- Extended RAS analysis—not just KRAS screening—should be performed for all patients.

80405: Overall Survival by Sidedness and Biologic



CALGB/SWOG 80405 Substudy: Tumor Sidedness Prognostic for OS by Therapy

- OS for pts with left-sided tumors is 19.3 mos longer than for right-sided tumors treated with cetuximab[1]

Median OS, Mos (N = 1025)	Primary Tumor Side		HR (95% CI)	*P* Value*
	Right (n = 293)	Left (n = 732)		
All pts	19.4	33.3	1.55 (1.32-1.82)	< .0001
Cetuximab	16.7	36.0	1.87 (1.48-2.32)	< .0001
Bevacizumab	24.2	31.4	1.32 (1.05-1.65)	.01

*Adjusted for biologic, protocol chemotherapy, previous adjuvant therapy, previous radiotherapy, age, sex, synchronous disease, in place primary, liver metastases.

- Findings consistent with FIRE-3 trial in pts with all *RAS* wt[2,3]

1. Venook AP, et al. ASCO 2016. Abstract 3504.
2. Stintzing S, et al. ESMO 2013. Abstract E17-7073.

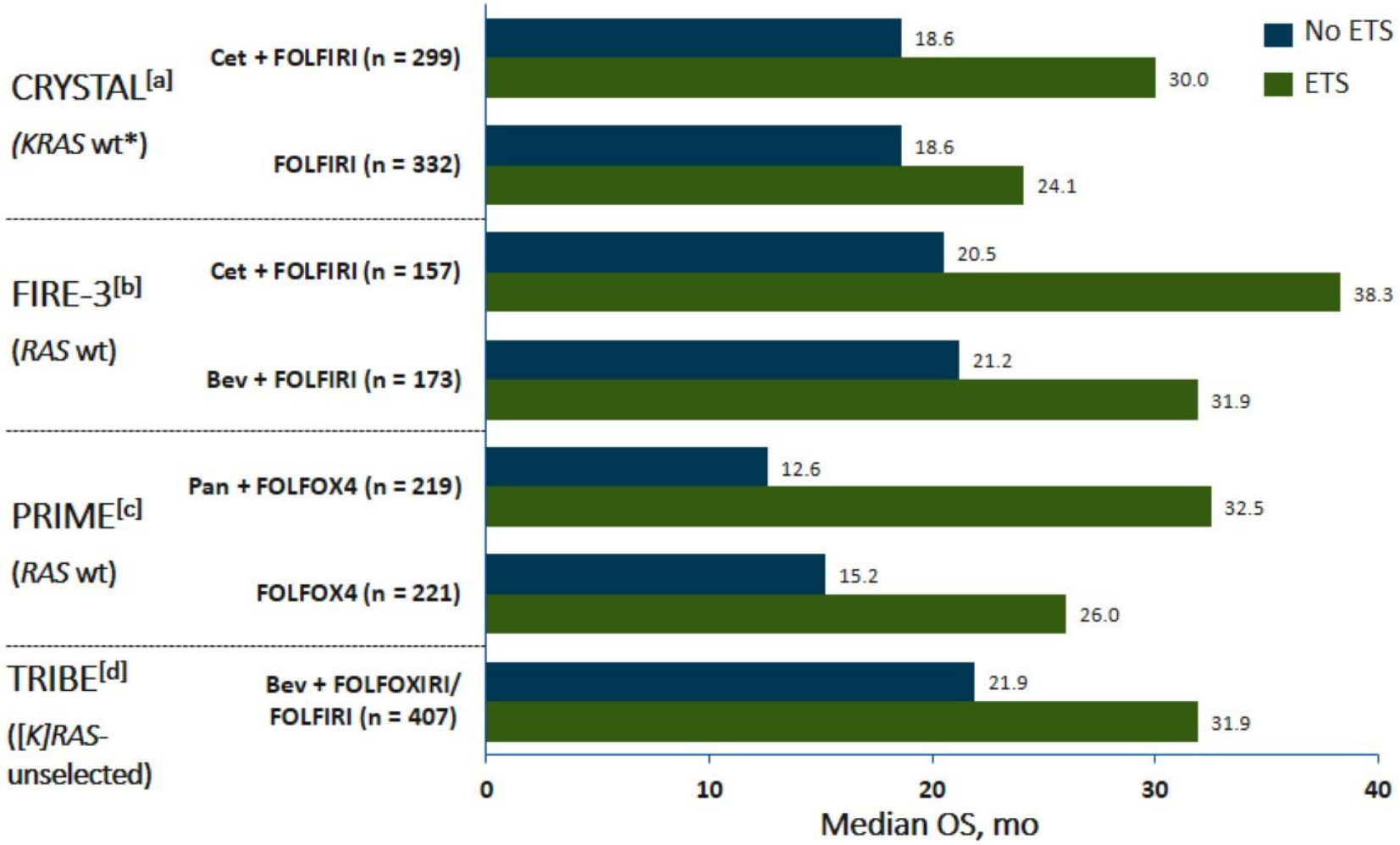
Conclusions

- OS and PFS were superior in patients with KRAS WT mCRC with left- vs right-sided 1° tumours
- Efficacy with 1L cetuximab vs bevacizumab differ according to 1° tumour location
- More precise biomarkers are needed to replace left- or right-sided tumour location in order to individualise patient care
  - However, for now mCRC studies should stratify patients by tumour sidedness
- These data support 1L bevacizumab in patients with mCRC and right-sided 1° tumours

*Corresponds to a 19.3-month increase in mOS when the primary is on the left.

Venook et al. J Clin Oncol 2016; 34 (suppl): abstr 3504

Consistent OS Benefit of Attaining ETS in More Recent Phase 3 Studies With Targeted Agents

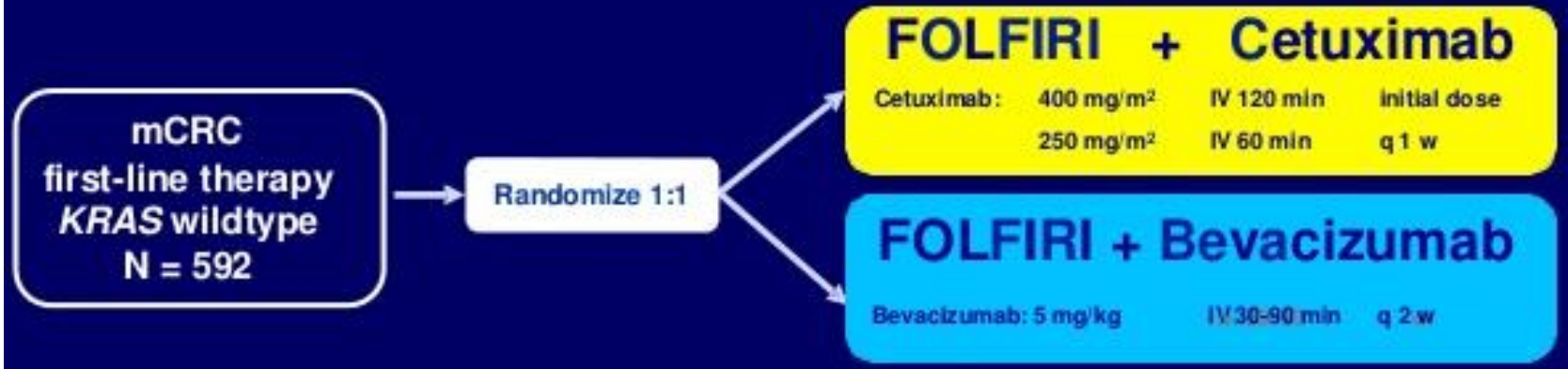


a. Piessevaux H, et al. *J Clin Oncol.* 2013;31:3764-3775; b. Stintzing S, et al. *Ann Oncol.* 2014;25:1-41. Abstract LBA11; c. Douillard JY, et al. *Eur J Cancer.* 2015;51:1231-1242; d. Cremolini C, et al. Ann *Oncol.* 2015;26:1188-1194.

Evidenced-Based First-Line Options Today

- FOLFOX, XELOX, or FOLFIRI + bevacizumab or anti-EGFR therapy
- FOLFOXIRI + bevacizumab
- 5-FU or capecitabine + bevacizumab

FIRE-3 Phase III Study Design

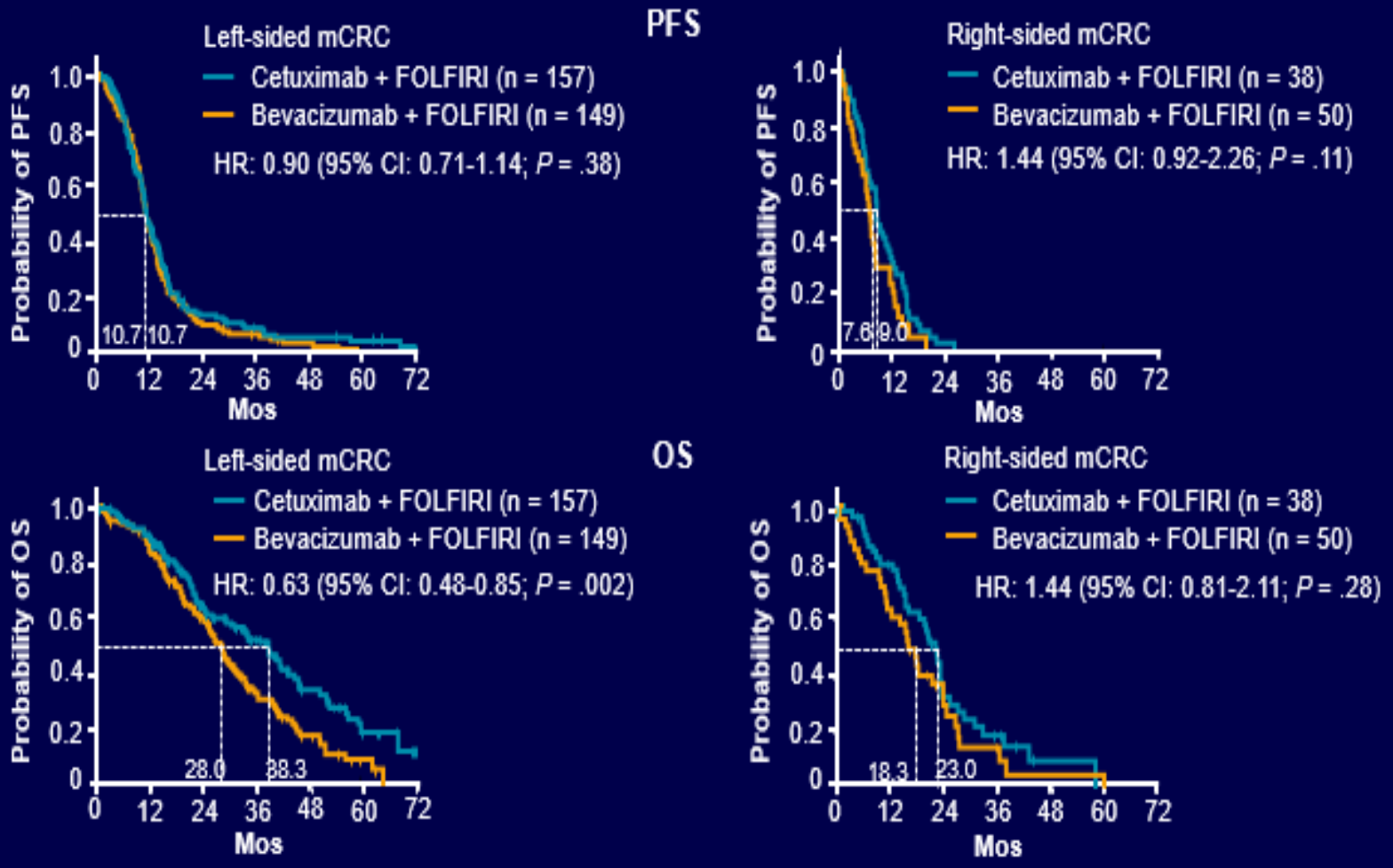


FOLFIRI: 5FU: 400 mg/m² (IV bolus); folinic acid: 400 mg/m²
irinotecan: 180 mg/m²
5FU: 2400 mg/m² (IV 46h)

- Primary objective: ORR (investigator assessed)
- Designed to detect a difference of 12% in ORR induced by FOLFIRI + cetuximab (62%) as compared to FOLFIRI + bevacizumab (50%)
- 284 evaluable patients per arm needed to achieve 80% power for an one-sided Fisher's exact test at an alpha level of 2.5%

Heinemann V, et al. *J Clin Oncol.* 2013;31(Suppl): Abstract LBA3506.

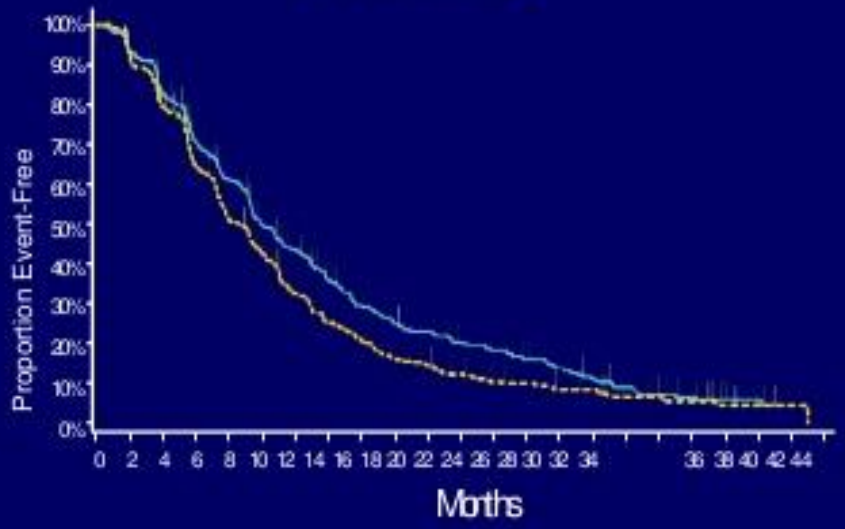
FIRE-3 (FOLFIRI + Bevacizumab or Cetuximab): PFS and OS by Tumor Location



Tejpar S, et al. JAMA Oncol. 2016;3:194-201.

PRIME (FOLFOX +/- Panitumumab)
PFS by *KRAS* Mutation Status
"Final Analysis"

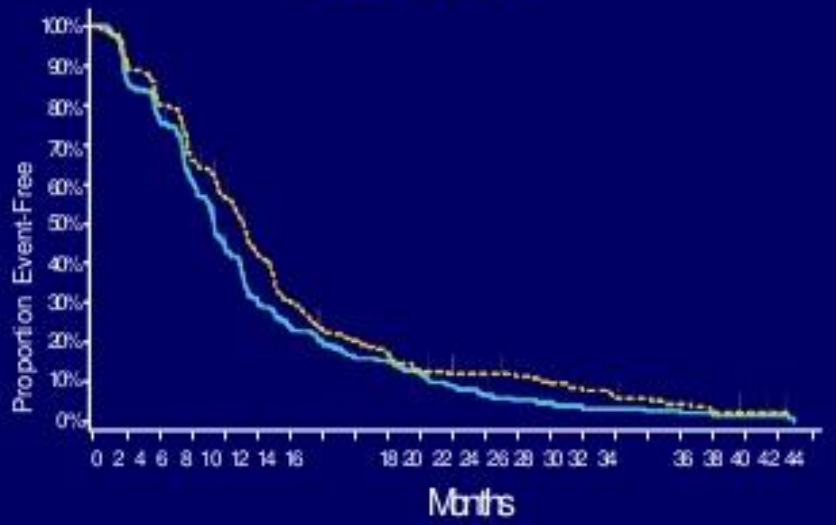
WT *KRAS*



	Median, months (95% CI)
Panitumumab + FOLFOX4	10.0 (9.3 – 11.4)
FOLFOX4	8.6 (7.5 – 9.5)

HR = 0.80 (95% CI: 0.67 – 0.95)
Log-rank *P* value = .01

MT *KRAS*



	Median, months (95% CI)
Panitumumab + FOLFOX4	7.4 (6.9 – 8.1)
FOLFOX4	9.2 (8.1 – 9.9)

HR = 1.27 (95% CI: 1.04 – 1.55)
Log-rank *P* value = .02

Douillard J, et al. *J Clin Oncol.* 2011;29(Suppl): Abstract 3510.

Pan-Asian ESMO Consensus Guidelines Now Published

ACCEPTED MANUSCRIPT

Pan-Asian adapted ESMO consensus guidelines for the management of patients with metastatic colorectal cancer; A JSMO – ESMO initiative endorsed by CSCO, KACO, MOS, SSO and TOS

T Yoshino ✉, D Arnold, H Taniguchi, G Pentheroudakis, K Yamazaki, R-H Xu, T W Kim, F Ismail, I B Tan, K-H Yeh ... Show more

Annals of Oncology, mdx738, https://doi.org/10.1093/annonc/mdx738
Published: 16 November 2017

The European Perspective on the ESMO Position Paper on Tumor Sidedness

- European guidelines and practices have been traditionally more focused on treatment goal
- By comparison, Asian guidelines have perhaps been more based on molecular markers
- Both viewpoints recommend that anti-EGFR antibodies be used in RASwt and BRAFwt left-sided primary tumors
- Benefit of anti-EGFR antibodies not clear in right-sided tumors even when RASwt and BRAFwt
- In first-line combination approaches, both FOLFOX and FOLFIRI provide similar benefit

First-Line Treatment Choice for *RAS* and *BRAF* Wild-Type Right-Sided Tumors

- Selection of first-line therapy for right-sided tumors is very challenging
- Prognosis of right-sided tumors is very poor
- Selection of standard therapy depends on treatment goal:

Tumor shrinkage not required

- **Doublet or triplet chemo + bevacizumab**

Tumor shrinkage required

- **Triplet chemo + bevacizumab**

or

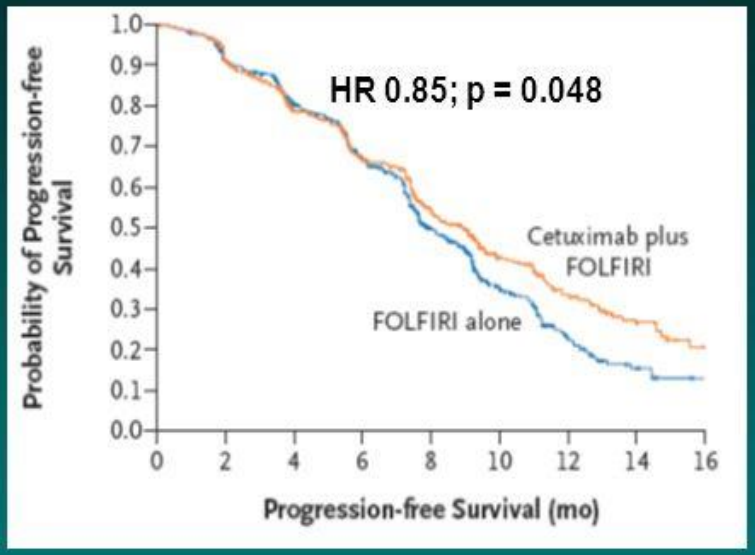
- **Chemo + cetuximab/ panitumumab**

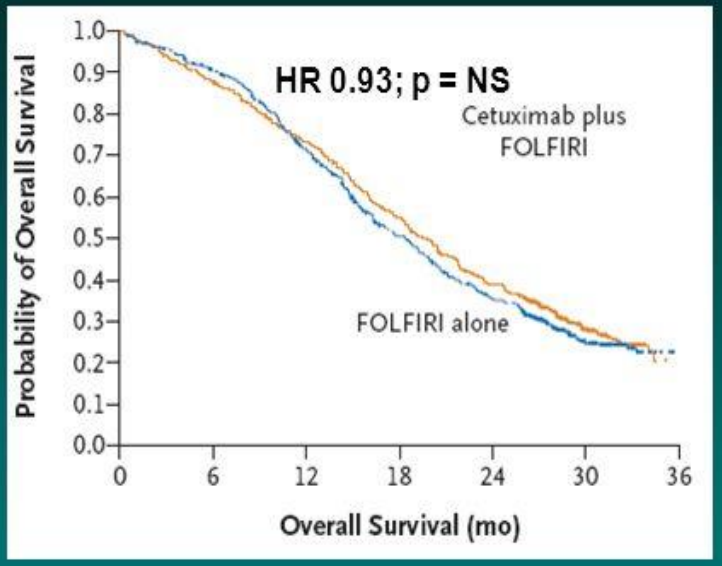
Discussion Summary: Key Points

- Left and right-sided primary tumors differ in terms of biology, pathophysiology, the development of cancer, and the genes involved
  - This information is important in guiding selection of the best treatment for the individual patient in terms of the chemotherapy backbone and molecularly targeted agent
- Chemotherapy + anti-EGFR antibody is the most appropriate treatment choice for the patient with a *RAS*wt and *BRAF*wt left-sided tumor

The CRYSTAL trial

Cetuximab + FOLFIRI vs FOLFIRI in first line mCRC





Van Custen E, N Engl J Med 2009, 360: 1408-17

The addition of cetuximab improved response rate and PFS.

Despite the statistically significant decrease in the risk of disease progression (HR, 0.85), the absolute benefit was modest (8,9 mo *vs* 8).

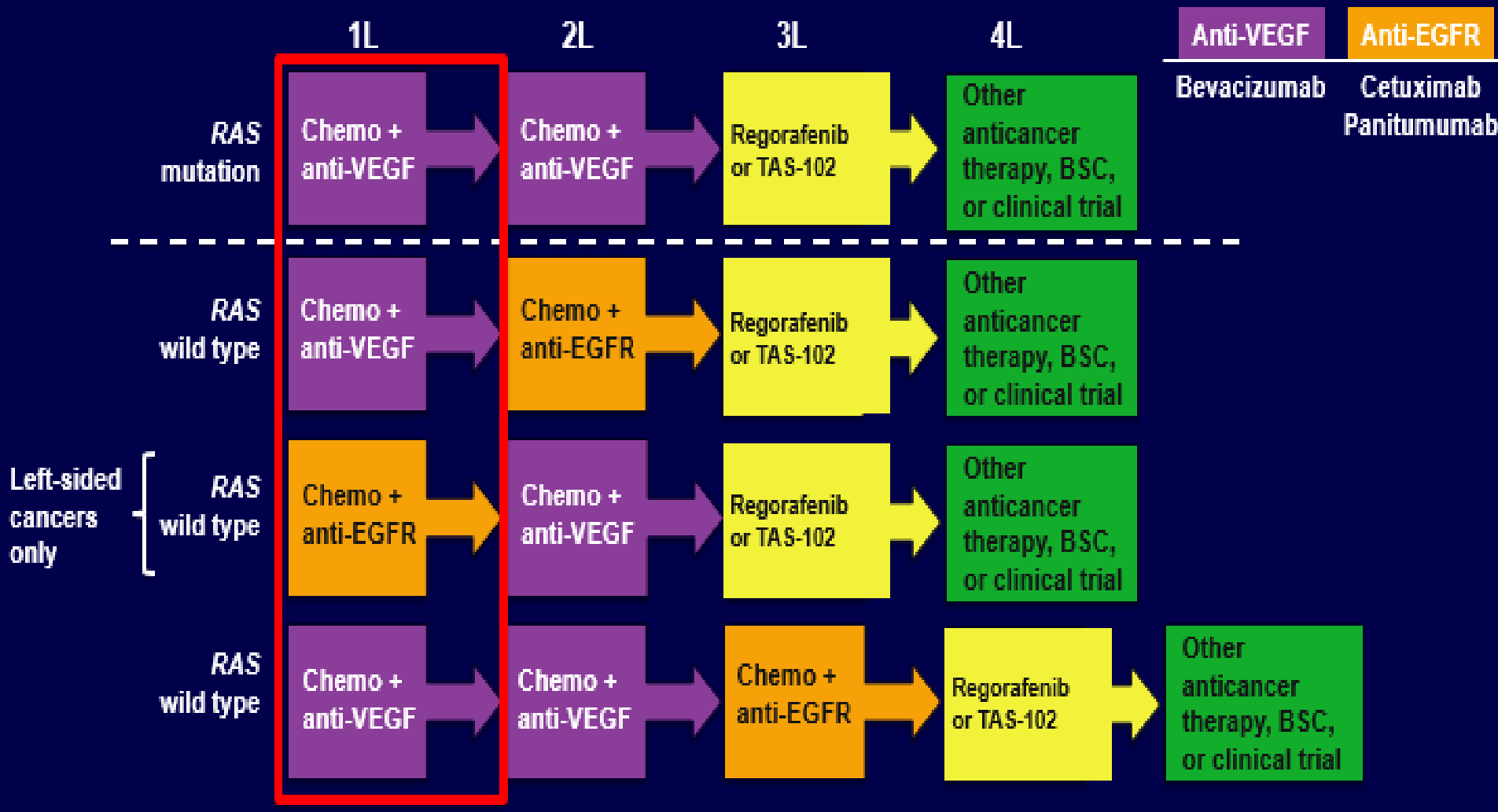
Mutant *RAS* and Outcome With EGFR Inhibitors

	PRIME[1,2]			OPUS[3,4]			CRYSTAL[5,6]		
	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 = 38)	12.0	19.8	Cetuximab + FOLFIRI (n = 178)	11.4	28.4
	FOLFOX4 (n = 253)	7.9	20.2	FOLFOX4 (n = 49)	5.8	17.8	FOLFIRI (n = 189)	8.4	20.2
		HR 0.72*	HR 0.77*		HR 0.53*	HR 0.94*		HR 0.56*	HR 0.69*
Any *RAS* MT	Panitumumab + FOLFOX4 (n = 272)	7.3	15.5	Cetuximab + FOLFOX4 (n = 92)	5.6	13.5	Cetuximab + FOLFIRI (n = 246)	7.4	16.4
	FOLFOX4 (n = 276)	8.7	18.7	FOLFOX4 (n = 75)	7.8	17.8	FOLFIRI (n = 214)	7.5	17.7
		HR 1.31*	HR 1.21*		HR 1.54*	HR 1.29		HR 1.10	HR 1.05

*Statistically significant.

References in slide notes.

mCRC Treatment Decision Recommendations: First Line



van Cutsem E, et al. Ann Oncol. 2016;27:1386-1422.

Slide credit: clinicaloptions.com

Second-line *RAS*-Mutated mCRC

Factors in Choosing Second-line Treatment

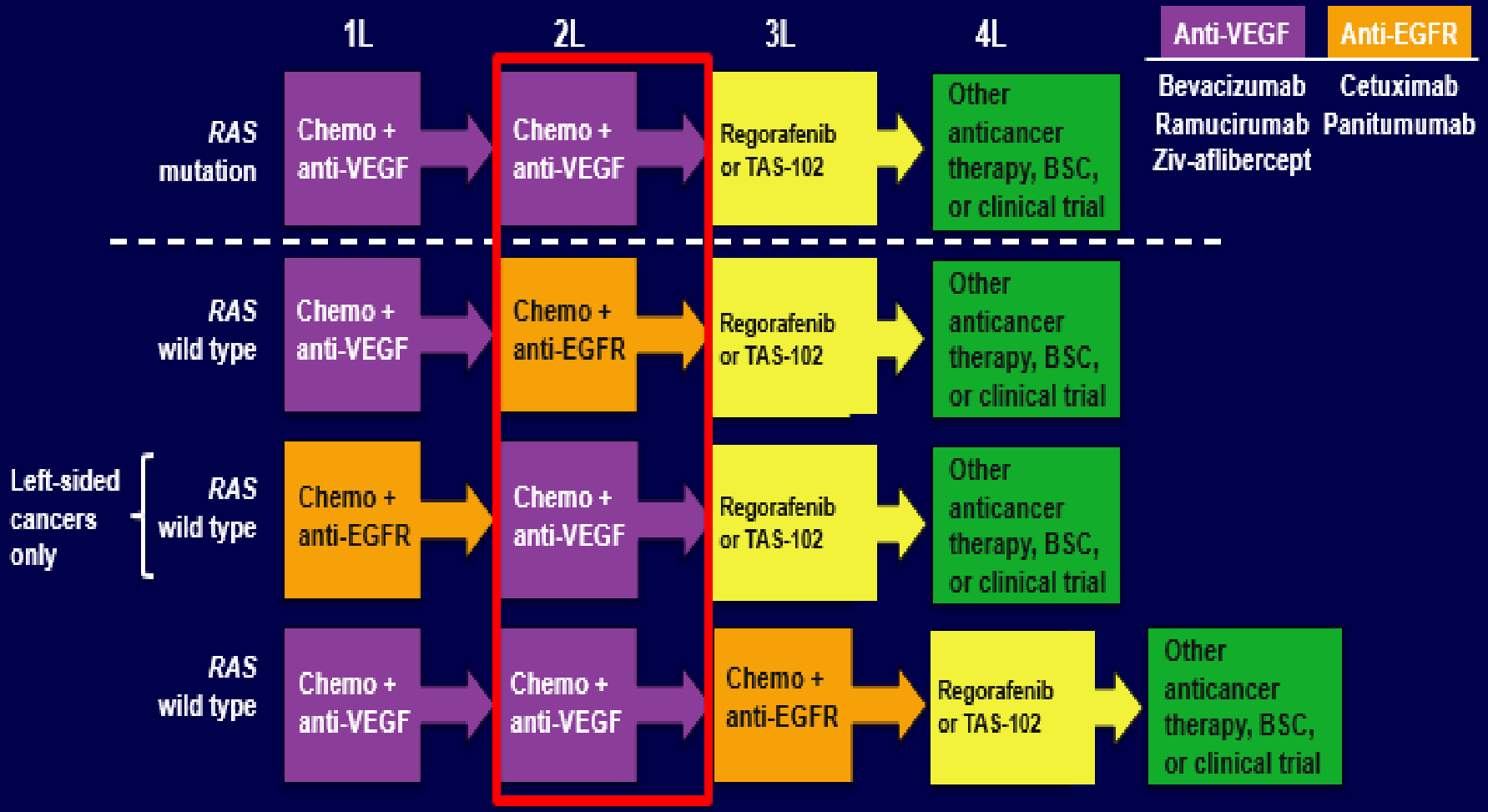
- Prior treatment with VEGF or EGFR inhibitor
- Progression within 6 months on prior VEGF inhibitor
- If received prior VEGF, > 3 months after maintenance
- Molecular and genetic phenotype of tumor (including MSI, *BRAF*, *HER2* status)
- Toxicity considerations

VEGF Inhibition After Progression on Bevacizumab

Agent	Bevacizumab		Ziv-aflibercept		Ramucirumab	
Trial	TML[1]		VELOUR[2]		RAISE[3]	
1st Line	Chemo + BEV		FP + Oxali ± BEV		FP + Oxali + BEV	
2nd Line	Chemo + BEV (n = 409)	Chemo (n = 410)	FOLFIRI + AFL (n = 612)	FOLFIRI + PL (n = 614)	FOLFIRI + RAM (n = 536)	FOLFIRI + PL (n = 536)
mOS, mo	11.2	9.8	13.5	12.1	13.3	11.7
	HR 0.81 *P* = .0062		HR 0.82 *P* = .0032		HR 0.84 *P* = .022	
mPFS, mo	5.7	4.1	6.9	4.7	5.7	4.5
	HR 0.68 *P* < .0001		HR 0.76 *P* < .0001		HR 0.79 *P* = .0005	
RR, %	5.4	3.9	19.8	11.1	13.4	12.5

1. Bennouna J, et al. Lancet Oncol. 2013;14:29-37. 2. van Cutsem E, et al. J Clin Oncol. 2012;30:3499-3506.
3. Tabernero J, et al. Lancet Oncol. 2015;16:499-508.

mCRC Treatment Decision Recommendations: Second Line



van Cutsem E, et al. Ann Oncol. 2016;27:1386-1422.

Slide credit: clinicaloptions.com

HER2 Amplification as a Negative Predictive Biomarker for EGFR Targeting: Outcomes

Cohort	*HER2* Amplified	*HER2* Not Amplified	*P* value
Anti-EGFR in 2L/3L			
Median PFS, mo			
▪ Testing cohort 1	2.9	8.1	< .001
▪ Validation cohort 2	2.9	9.3	< .001
No anti-EGFR in 1L			
Median PFS, mo			
▪ Testing cohort 1	9.7	10.1	.848
▪ Validation cohort 2	13.7	11.3	.616
OS, HR (95% CI)			
▪ Testing cohort 1		1.13 (0.5-2.3)	.78
▪ Validation cohort 2		1.09 (0.4-2.7)	.86

Raghav KPS, et al. ASCO 2016. Abstract 3517.

EGFR Targeting: Key Points

- Cetuximab and panitumumab may be interchangeable[1]
- Molecular markers identify patients unlikely to benefit from EGFR therapy[2,3]
  - *RAS (KRAS/NRAS)* mutations
  - *BRAF* mutation (likely)
  - *HER2* amplification (needs to be validated)
- Tumor location may affect chance of benefit[4,5]
  - No benefit from EGFR mAbs in right-sided cancers (at least in first-line)
- Patient subset considered candidates for EGFR antibody therapy becoming more refined

1. Price TJ, et al. Lancet Oncol. 2014;15:569-579. 2. Pietrantonio F, et al. Eur J Cancer. 2015;51:587-594. 3. Raghav KPS, et al. ASCO 2016. Abstract 3517. 4. Venook A, et al. ESMO 2016. Abstract XXX. 5. Tejpar S, et al. JAMA Oncol. 2016;3:194-201.

VEGF-Targeted Therapies: Key Points

- Duration of VEGF inhibition matters
  - Treatment to progression
  - Maintenance strategies
  - Treatment beyond progression
- Clinical synergism between fluoropyrimidine and bevacizumab[1,2]
- Prolonged VEGF inhibition beyond progression supported by 3 positive phase III trials[1-3]
  - No compelling arguments for aflibercept or ramucirumab over bevacizumab
- Bevacizumab can be combined with FOLFOXIRI (phase III TRIBE)[4]

1. van Cutsem E, et al. J Clin Oncol. 2012;30:3499-3506. 2. Tabernero J, et al. Lancet Oncol. 2015;16:499-508.
3. Bennouna J, et al. Lancet Oncol. 2013;14:29-37. 4. Cremolini C, et al. Lancet Oncol. 2015;16:1306-1315.

Salvage Therapy

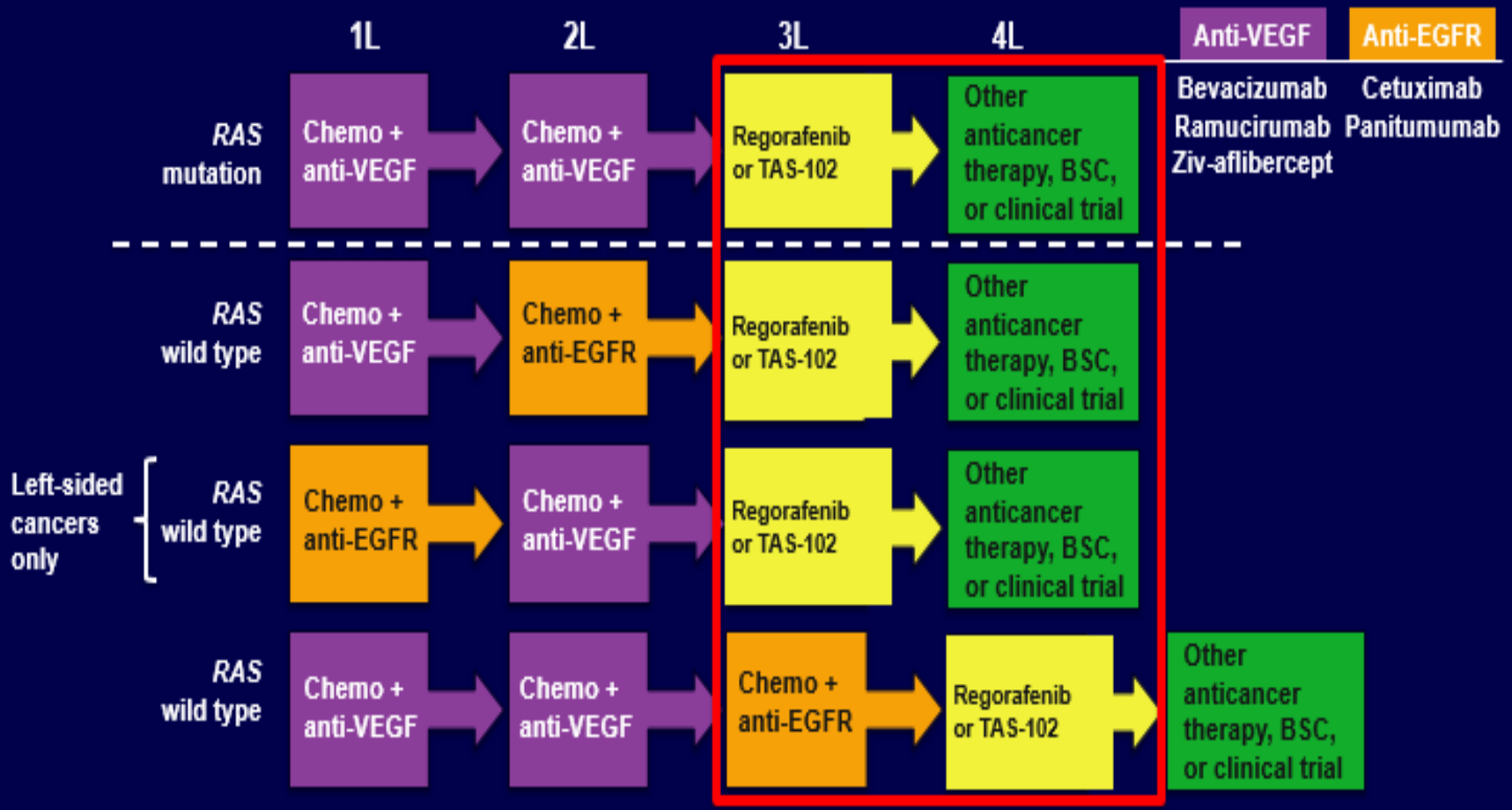
Comparison of Regorafenib, TAS-102 After mCRC Progression

Agent	Regorafenib				TAS-102			
Trial	CORRECT[1]		CONCUR[2]		RECOURSE[3]		TERRA[4]	
Prior biologics	100% BEV 100% EGFR mAbs		60%		100% BEV 53% EGFR mAbs 18% Prior Rego		20% BEV 18% EGFR mAbs	
	Rego (n = 505)	BSC+PL (n = 255)	Rego (n = 136)	BSC+PL (n = 68)	TAS-102 (n = 534)	BSC+PL (n = 266)	TAS-102 (n = 271)	BSC+PL (n = 135)
mOS, mo	6.4	5.0	8.8	6.3	7.1	5.3	7.8	7.1
	HR 0.77 *P* = .0052		HR 0.55 *P* = .0002		HR 0.68 *P* <.0001		HR=0.79 *P* = .0035	
mPFS, mo	1.9	1.7	3.2	1.7	2.0	1.7	2.0	1.8
	HR 0.49 *P* < .0001		HR 0.31 *P* < .0001		HR 0.48 *P* < .0001		HR=0.43 *P* < .0001	
RR, %	1.0	0.4	4.4	0	1.6	0.4	1.1	0

- Main adverse events: hand-foot skin reaction, fatigue (regorafenib); neutropenia, GI toxicities, fatigue (TAS-102)

1. Grothey A, et al. Lancet. 2013;381:303-312. 2. Li J, et al. Lancet Oncol. 2015;16:619-629. 3. Meyer RJ, et al. New Engl J Med. 2015;372:1909-1919. 4. Kim TW, et al. ESMO 2016. Abstract 465PD.

mCRC Treatment Decision Recommendations: Third Line



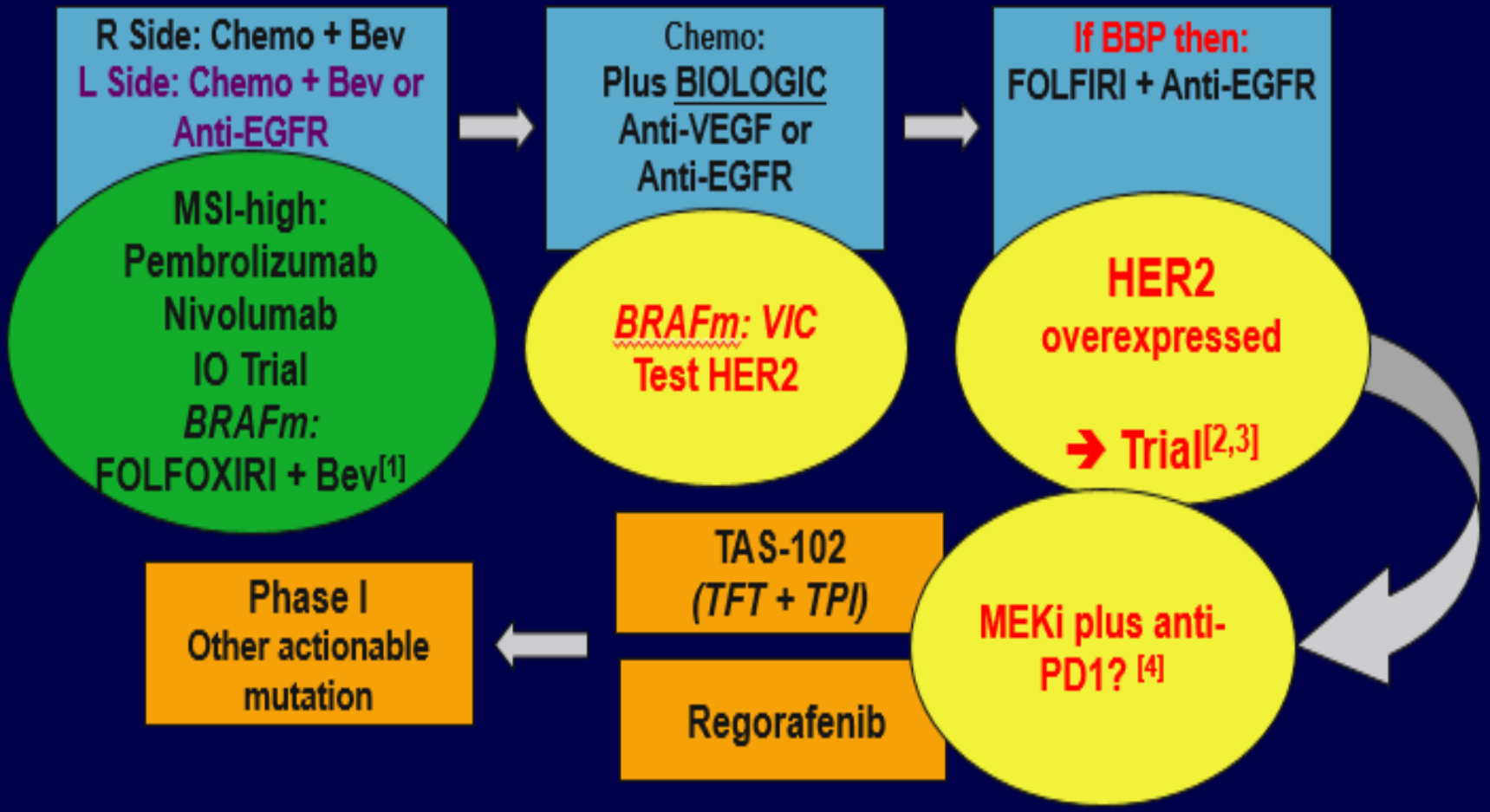
van Cutsem E, et al. Ann Oncol. 2016;27:1386-1422.

BRAF V600E Mutation: Treatment Outcomes

Regimen	RR, %	mPFS, mo
Single/Doublet BRAF/MEK		
Vemurafenib[1]	5	2.1
Dabrafenib[2]	11	NR
Encorafenib[3]	6	4
Dabrafenib + Trametinib[4]	12	3.5
Doublet with EGFR		
Vemurafenib + Panitumumab[5]	13	3.2
Vemurafenib + Cetuximab[6]	20	3.2
Encorafenib + Cetuximab[7]	19	3.7
Dabrafenib + Panitumumab[8]	10	3.4
Triplet with EGFR		
Vemurafenib + Cetuximab + Irinotecan[9]	35	7.7
Dabrafenib +Trametinib + Panitumumab[8]	26	4.1
Encorafenib + Cetuximab + Alpelisib[7]	18	4.2

References in slide notes.

Treatment Paradigm for mCRC



1. Cremolini C, et al. Lancet Oncol. 2015;16:1306-1315. 2. ClinicalTrials.gov. NCT03225937.
3. ClinicalTrials.gov. NCT03043313 . 4. ClinicalTrials.gov. NCT02788279.

Conclusions

- Survival of patients with mCRC has significantly improved in the last decade
- Survival gains are not driven by advances in first-line therapy, but by incremental additional effects of subsequent treatment lines
- To maximize outcomes, patients should receive all active agents
- Identification of patient subgroups is increasing individualization of treatment
- Promising immunotherapeutic strategies include development of improved methods to deliver key antigens to make the tumor environment more receptive to immune infiltration of effector T-cells

KEEP LEARNING

thank u

New ideas make work INTERESTING!

Thank you!

Questions

Comments