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Treatment of elderly cancer patients

Focus on colorectal cancer

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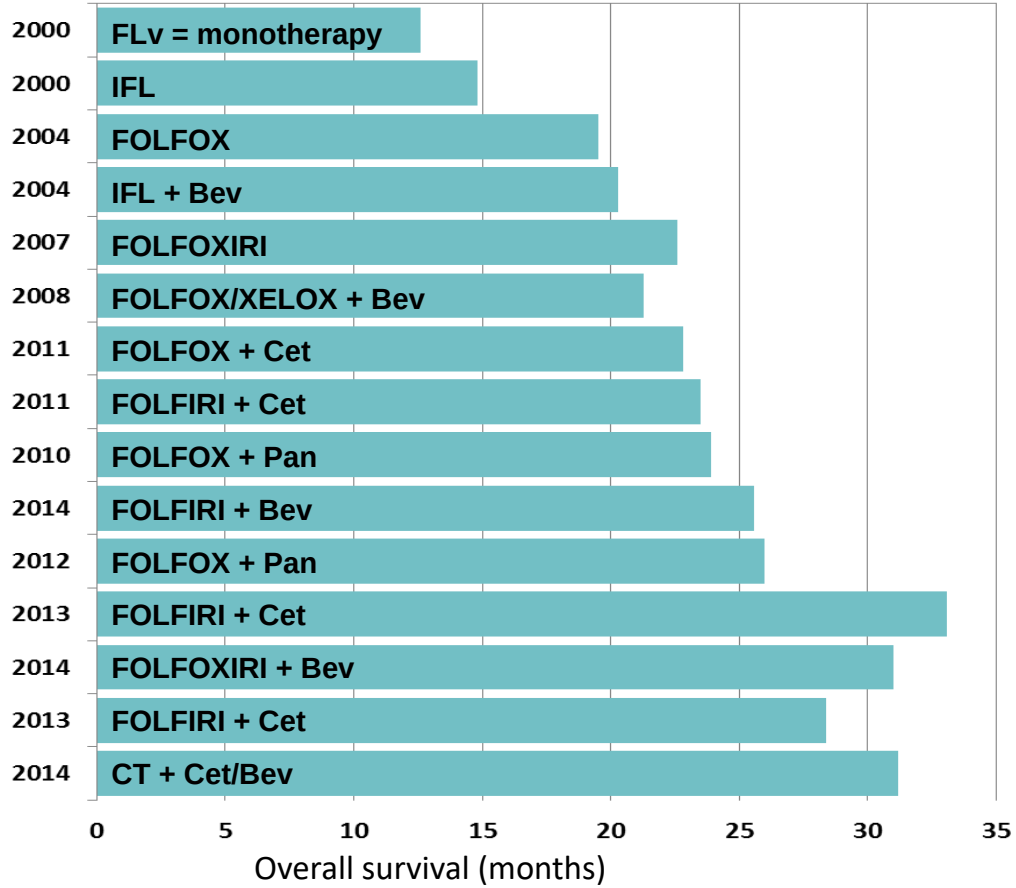
Data from most important mCRC phase III trials since 2000
Combination better than mono therapy

PS 0	PS 1	PS 2	Age	
41	45	13	61	
39	46	15	62	Saltz
50	43	5	61	Goldberg
58	41	0	60	Hurwitz
61	37	2	62	Falcone
58	42	0	60	Saltz
39	54	7	62	Bokemeyer
58	38	4	62	Van Cutsem
50	44	6	62	Douillard
52	47	1	65	Heinemann
50	44	6	62	Douillard
48	50	2	64	Heinemann
90	10	0	60	Cremolini
54	43	3	60	Van Cutsem
58	42	0	59	Lenz



Assessment of elderly cancer patients

- NCCN, SIOG, and EORTC recommend that some form of **geriatric assessment** (GA) should be conducted for all elderly patients for whom chemotherapy is considered
- No solid evidence regarding either the best type of GA for use in the oncology setting or how outcomes are improved as a result of GA

SIOG: International Society of Geriatric Oncology
NCCN: US National Comprehensive Cancer Network
EORTC: European Organisation for Research and Treatment of Cancer

Puts et al. An update on a systematic review of the use of geriatric assessment for older adults in oncology, Ann Oncol 2014

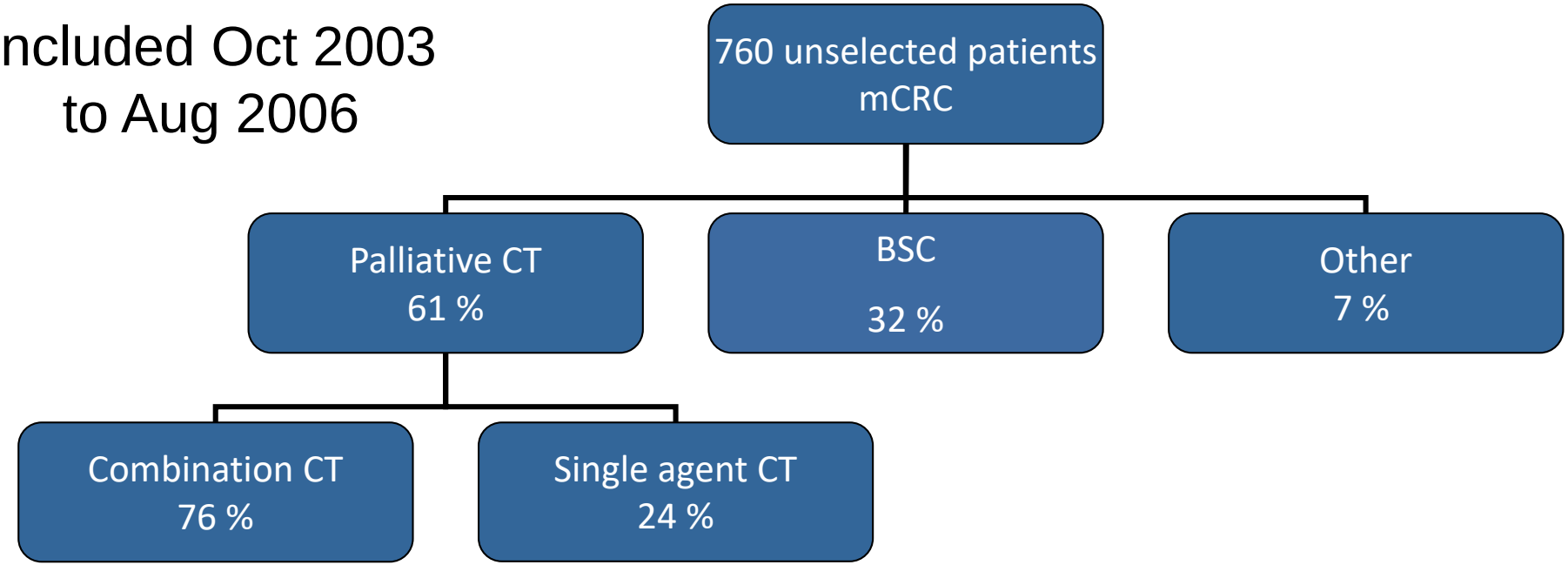
What do we know in CRC ?

- Metastatic CRC
  - median age ~ 70 years, 40% of patients are over 75 years (and increasing)
- Geriatric factors (like MMSE, IADL, G8 and/or VES13) can predict for severe toxicity and unexpected hospitalisation
- However, the evidence so far as how to use the information generated to offer chemotherapy or not or which regimen to use has been limited

Papamichael et al, EJC 2017 (Editorial)
Papamichael et al, Treatment of colorectal cancer in older patients: International Society of Geriatric Oncology (SIOG) consensus recommendations. Ann Oncol 2015

Can efficay from phase III data be translated to all patients ?

Included Oct 2003 to Aug 2006



Sørbye, Pfeiffer….Glimelius. Cancer 2009

Can efficay from phase III data be translated to all patients ?

Age	CT	Comb CT vs Single	BSC	mOS CT
< 65 y	86 %	92 vs. 8 %	11 %	18.0 mo
66-70 y	74 %	93 vs. 7 %	20 %	15.1 mo
71-75 y	63 %	71 vs. 29 %	32 %	18.0 mo
76-80 y	40 %	13 vs. 87 %	50 %	10.2 mo
> 80 y	13 %	0 vs. 100 %	72 %	8.7 mo

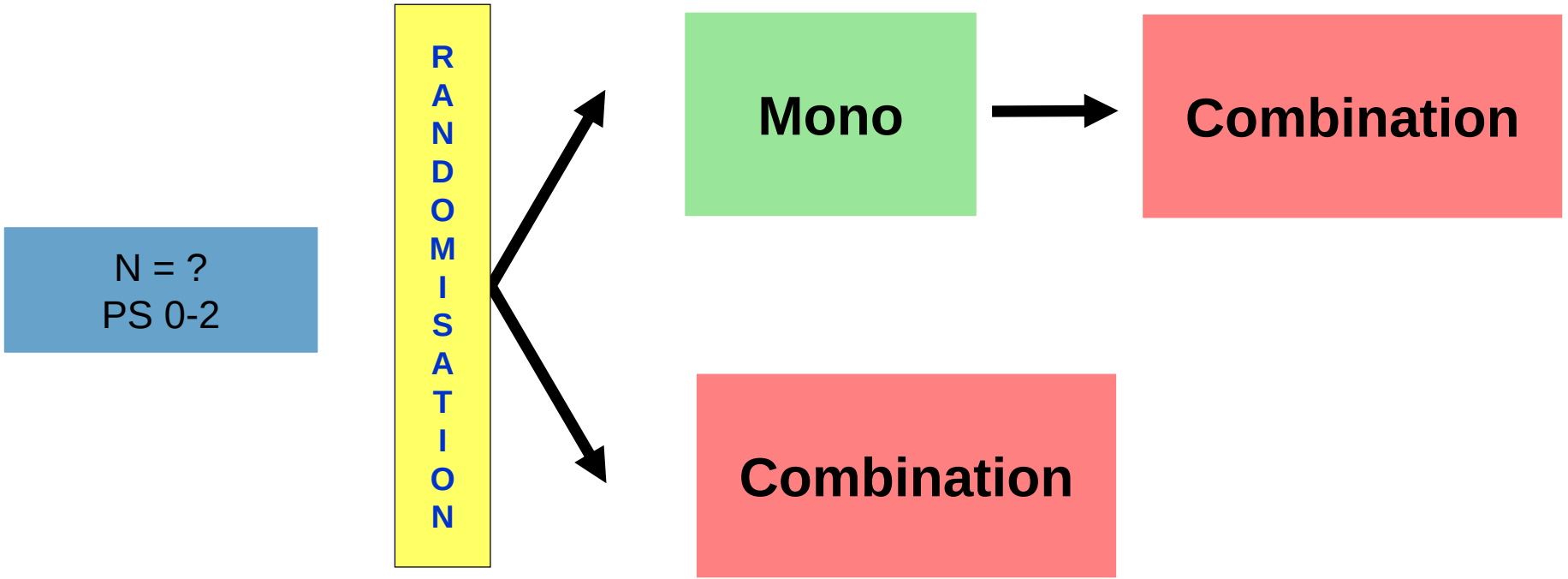
Sørbye, Pfeiffer….Glimelius. Cancer 2009

Treatment of elderly mCRC patients

- Full dose monotherapy ?
- Reduced dose combination ?
- How to select frail/elderly for therapy ?

Randomized trials in elderly mCRC patients

mCRC - 1st line therapy



MRC FOCUS2

mCRC - 1st line therapy

Inclusion
2004-6
61 institutions (3/y)

459 patients
Elderly OR frail

PS 0-2
PS0 21%
PS2 29%
+70 75%

Endpoints
PE: PFS

RANDOMISATION

Comprehensive health assessment

A: FOLF	Mono iv
B: FOLFOX	Combo iv
C. Capecitabine	Mono oral
D: CapOx	Combo

All 80%, escalation possible (37%)

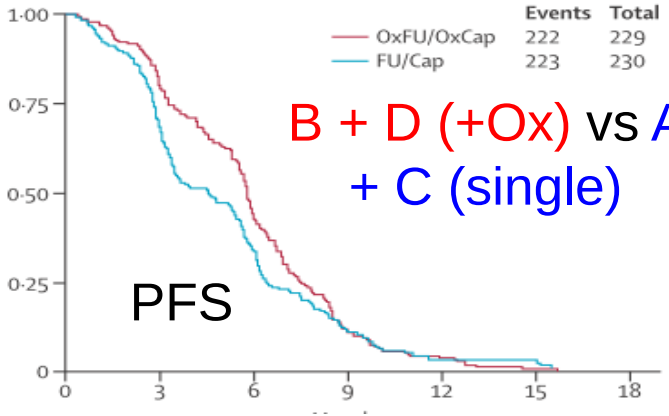
Only 14% sustained full dose to week 12

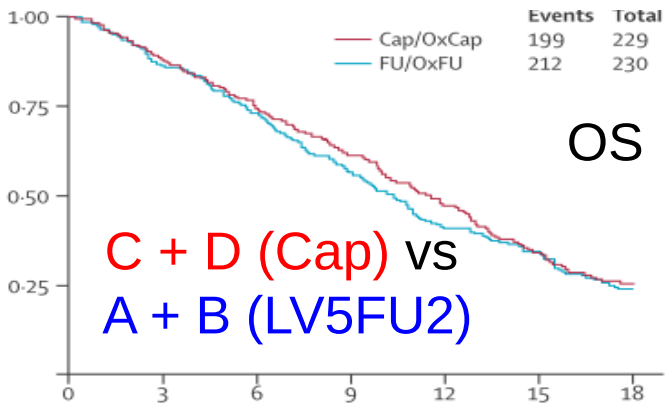
Seymour et al, Lancet 2011; 377: 1749-59

MRC FOCUS2

mCRC - 1st line therapy

Seymour; Lancet 2011	A	B	C	D
No of pts	115	115	115	114
Response rate	11 %	38 %	8 %	32 %
PFS (months)	3.5	5.8	5.2	5.8
Median OS (months)	10.1	10.7	11.0	12.4





Seymour et al, Lancet 2011; 377: 1749-59

MRC FFCD 2001-02

mCRC - 1st line therapy

Inclusion
2003-10
50 institutions (.5/y)

282 patients
+ 75 years
PS 0-2
(KFS ≥ 60)
100: 14%
80-90: 55%
60-70: 31%

Endpoints
PE: PFS

RANDOMISATION

- A: FOLF
- B: FOLFIRI
- C. mFOLF
- D: mFOLFIRI

CGA (123/282=44%)

- QoL
- MMSE (91)
  - Mini-Mental State Examination
- IADL (87/282=31%)
  - Instrumental Activities of Daily Living
- GDS
  - Geriatric Depression Scale
  - cognitive function, dependence, and depression

Irinotecan 150 ⇨ 180 if no tox G3+

68% had dose-reduction >33% during first 4 months

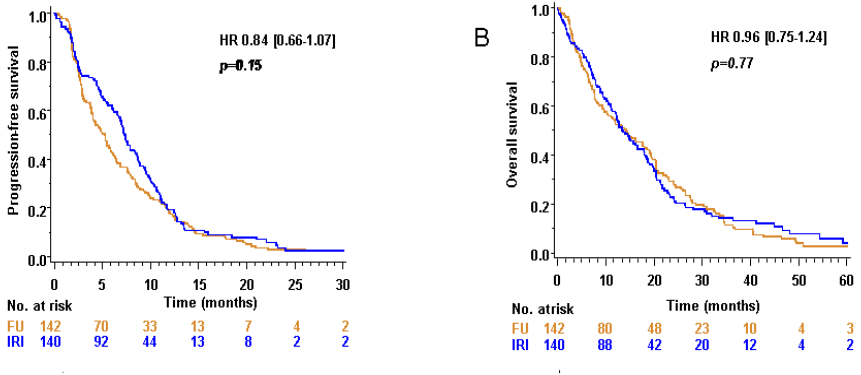
Aparicio et al, Ann Oncol 2016; 1: 121-7

MRC FFCD 2001-02

mCRC - 1st line therapy - 2 x 2 comparison

Aparicio; Ann Oncol 2016	FOLF	FOLFIRI
No of pts	142	140
Response rate	21%	42%
PFS (months)	5.2	7.3
Median OS (months)	14.2	13.3

Mono vs "FLIRI"



Aparicio et al, Ann Oncol 2016; 1: 121-7

MRC FFCD 2001-02

mCRC - 1st line therapy - 2 x 2 comparison

- Almost 90% of patients with impaired cognitive function (MMSE) or impaired autonomy (IADL) treated with FOLFIRI experienced severe toxicity.

- Multivariate analyses revealed that no geriatric parameter was predictive for RR or PFS

- Normal IADL was independently associated with prolonged OS

Aparicio et al, JCO 2013
Aparicio et al, EJC 2017

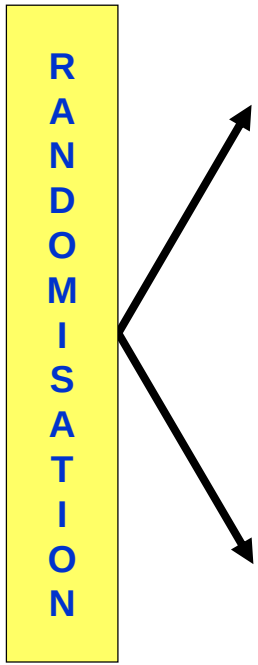
AVEX

mCRC - 1st line therapy - International

Inclusion
2007-10
40 institutions (2/y)

280 patients
Non-resectable
≥ 70 years
PS 0-2

PE: PFS



Capecitabine

No geriatric and comorbidity assessments

Capecitabine + Bev

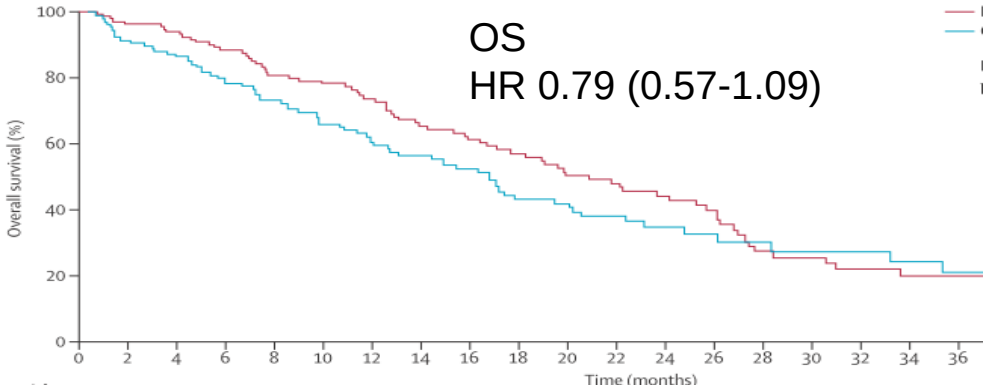
Cunningham et al, ASCO GI 2013; abs 337 & Lancet Onc 2013

AVEX

mCRC - 1st line therapy

Cunningham, ASCO GI 2013	Cap	Cap + Bev
No pts	140	140
Response rate	10 %	19 %
Median PFS (months)	5.1	9.1
Median survival (months)	16.8	20.7

In a subgroup analysis, all patients benefitted from bevacizumab
An equal benefit for those <75 years and those ≥75 years.



Cunningham et al, ASCO GI 2013; abs 337 & Lancet Onc 2013

Double vs mono in elderly mCRC patients

	FOCUS 2		FFCD		AVEX		PRODIGE	
Year	2004-6		2003-10		2007-10		2011-3	
Variable	**FOLF n = 230**	**FOLFOX n = 229**	**FOLF n = 142**	**FOLFIRI n = 140**	***Cap n = 140***	***Cap Bev n = 140***	***CT n = 51***	***CT Bev n = 51***
Age, median	75	75	80	81	76	77	80	81
70+, %	75%	75%	100%	100%	100%	100%	100%	100%
PS 0, %	22%	20%	12%	15%	50%	43%	22%	26%
RR, %	13 %	35 %	21 %	42 %	10	19	33	37
PFS, mo	4.5	5.8	5.2	7.3	5.1	9.1	7.8	9.7
OS, mo	10.5	11.0	14.2	13.3	16.8	20.7	19.8	21.7

Combination: Higher response rate - longer PFS

Seymour et al, Lancet 2011; Cunningham et al , Lancet Onc 2013; Aparicio et al, Ann Oncol 2016; Aparicio et al, Ann Oncol 2018

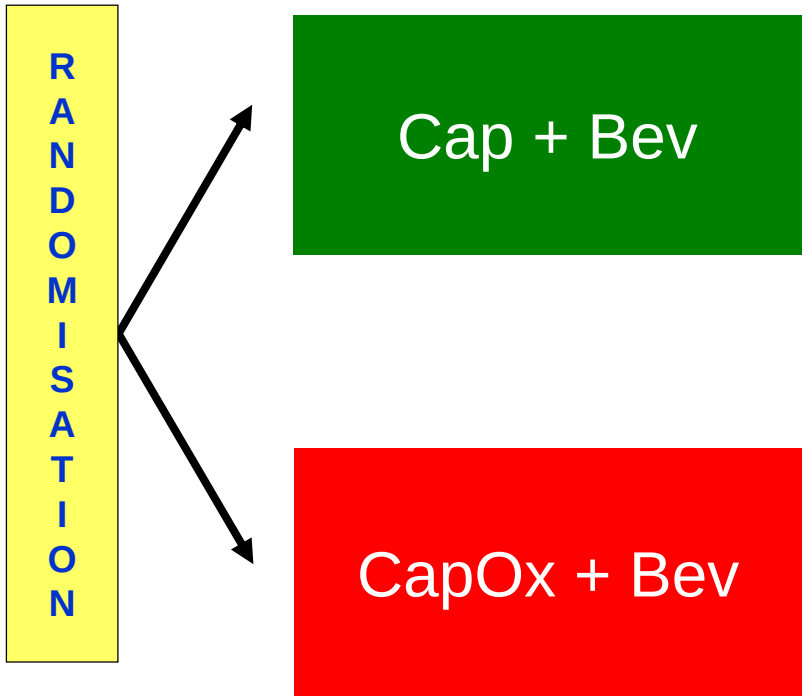
NCCTG N0949

mCRC - 1st line therapy

Inclusion
2011-12

31/380 patients
Non-resectable
PS 0-2
Age ≥ 70 years
315 sites

PE: TFS

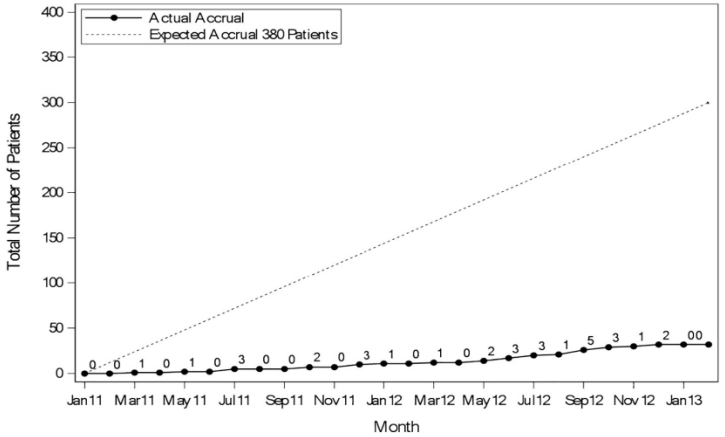


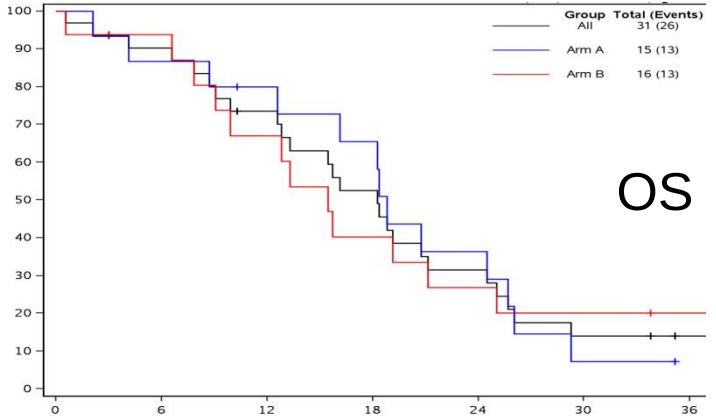
McCleary, Hubbard, Mahoney, Meyerhardt, Sargent, Venook, Grothey. Challenges of conducting a prospective clinical trial for older patients: Lessons learned from NCCTG N0949 (alliance). JGO 2017

NCCTG N0949

mCRC - 1st line therapy

McCleary; JGO 2017	Cap + Bev	CapOx + Bev
No pts	15	16
Median PFS1 (months)	6.7	6.7
Median survival (months)	18.8	15.4





Why did it fail ? Discomfort with randomizing frail patients to oxaliplatin or fit patients to non-oxaliplatin based regimen as barriers to enrollment

McCleary et al JGO 2017

Why did NCCTG N0949 fail ?

- CGA to predict treatment-related toxicity, hospitalization, dose delay or reduction or discontinuation of chemotherapy
- Patient-centered
  - PRO-CTAE, Neurotoxicity Symptom Experience Diary, quality of life [Fatigue/Uniscale assessment, Linear Analog Self-Assessment, Was It Worth It questionnaire, EQ-5D].
  - Pharmacokinetic and pharmacogenetic studies
  - Two frailty assessments - Rockwood Canadian Study of Health and Aging Clinical Frailty Scale and NCCTG Brief Frailty Inventory

- 18-page booklet with 7 questionnaires (92 questions prior to each cycle)
- Most respondents noted discomfort with randomizing frail patients to combination or fit patients to monotherapy as barriers to enrollment.

McCleary, Hubbard, Mahoney, Meyerhardt, Sargent, Venook, Grothey. Challenges of conducting a prospective clinical trial for older patients: Lessons learned from NCCTG N0949 (alliance). JGO 2017

Conclusion

- Elderly and frail patients are under-represented in trials
  - Especially a problem in 75+
- There is a need to:
  - Develop randomized trials for older/frail adults
  - Improve recruitment for older/frail patients into trials
  - Incorporate geriatric principles in oncology trial design
- For many elderly patients a less intensive regimen is a good treatment choice

Final slide

Thank you for your attention

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