Registry/ Observational study data- what we can believe and what we can't believe!

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Disclosure

- Advisory Board: Sanofi Oncology, Eli-Lilly, Bristol Meyers Squibb, Merck Serono, Gilead Science
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- Honorarium: Taiho, Pfizer, Amgen, Eli-Lilly, Bayer

Registry/ observation studies

- Observation cohort studies allows
  - access to innovation prior to marketing authorisation
  - further safety data collection in less stringent “real world” setting
  - combination with alternative standard of care treatment
  - much larger study sample sizes
- Limitations[1]
  - Unable to randomly assign patient to treatment and control groups
  - Lead to imbalances between patients groups
  - Selection bias
  - Confounding variables correlating both the independent variable (treatment) and dependent variable (outcome); can be measured or unmeasured (such as patient or physician’s choice)
  - Although various statistical methodologies to limit selection bias and confounding, this can never be fully controlled

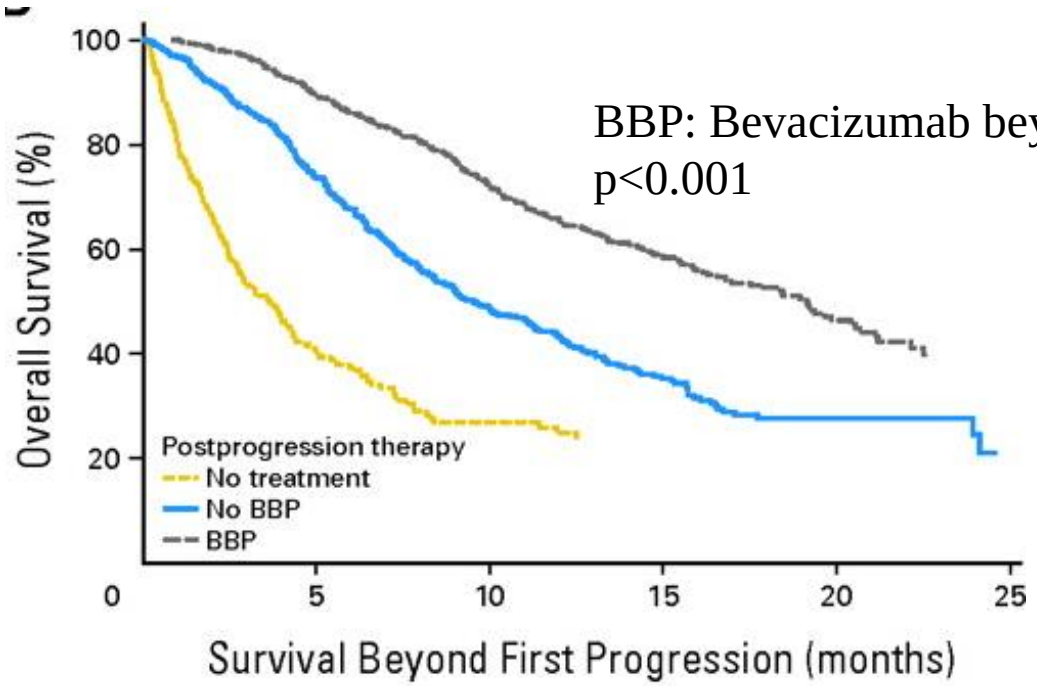
[1]Hershman and Wright J Clin Oncol 2012

Post authorisation studies

- Post authorisation safety study (PASS)
  - carried out after a medicine has been authorised
  - to identify, characterise or quantify a safety hazard
  - to confirm the safety profile of a medicine
  - to measure the effectiveness of risk-management measures
- Post authorisation efficacy study (PAES)
  - conducted within authorised therapeutic indication to complement available efficacy data in the light of well-reasoned scientific uncertainties on aspects of the evidence of benefits that should be, or can only be, addressed post-authorisation
  - may be initiated, managed or financed by a marketing authorisation holder (MAH) voluntarily
  - or pursuant to an obligation imposed by a competent authority

European Medicines Agency
Accessed 4 December 2015

BRiTE study: continuing bevacizumab beyond disease progression

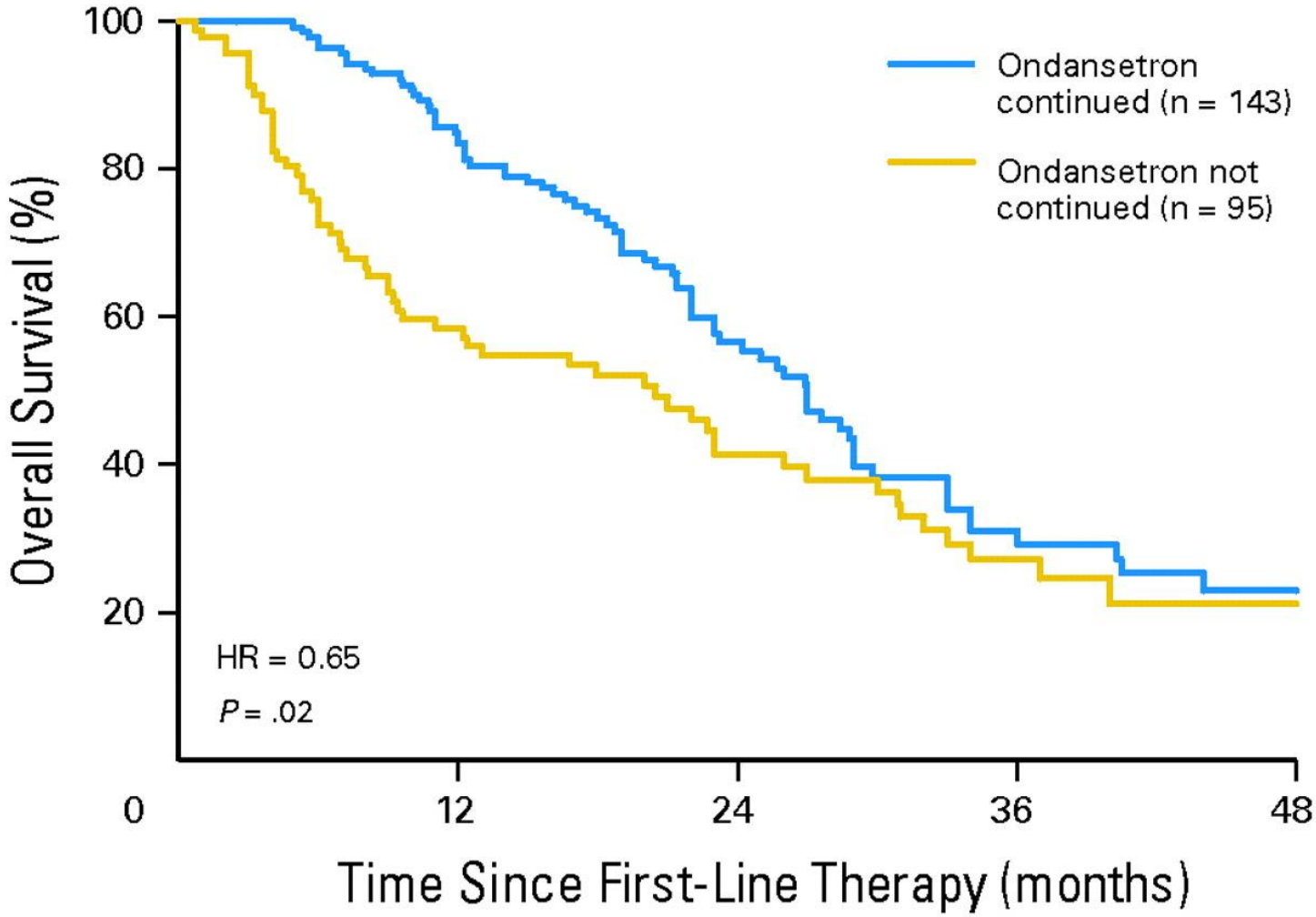


BBP: Bevacizumab beyond disease progression
p<0.001

	All pts	No post-progression Rx	No BBP	BBP
1-yr OS	74.7%	52.5%	77.3%	87.7%
Median OS beyond first progression	12.0m	3.6m	9.5m	19.2m

Grothey et al. J Clin Oncol 2008

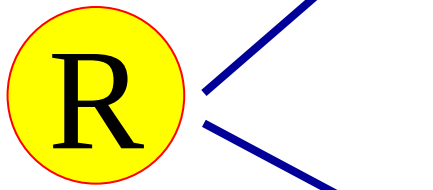
Ondansetron beyond disease progression



Kopetz et al. J Clin Oncol 2009

German AIO/Intergroup ML18147/TML trial design

1st line oxaliplatin /irinotecan/ fluoropyridimines + BEV
Disease progression ≥3 months



n=411

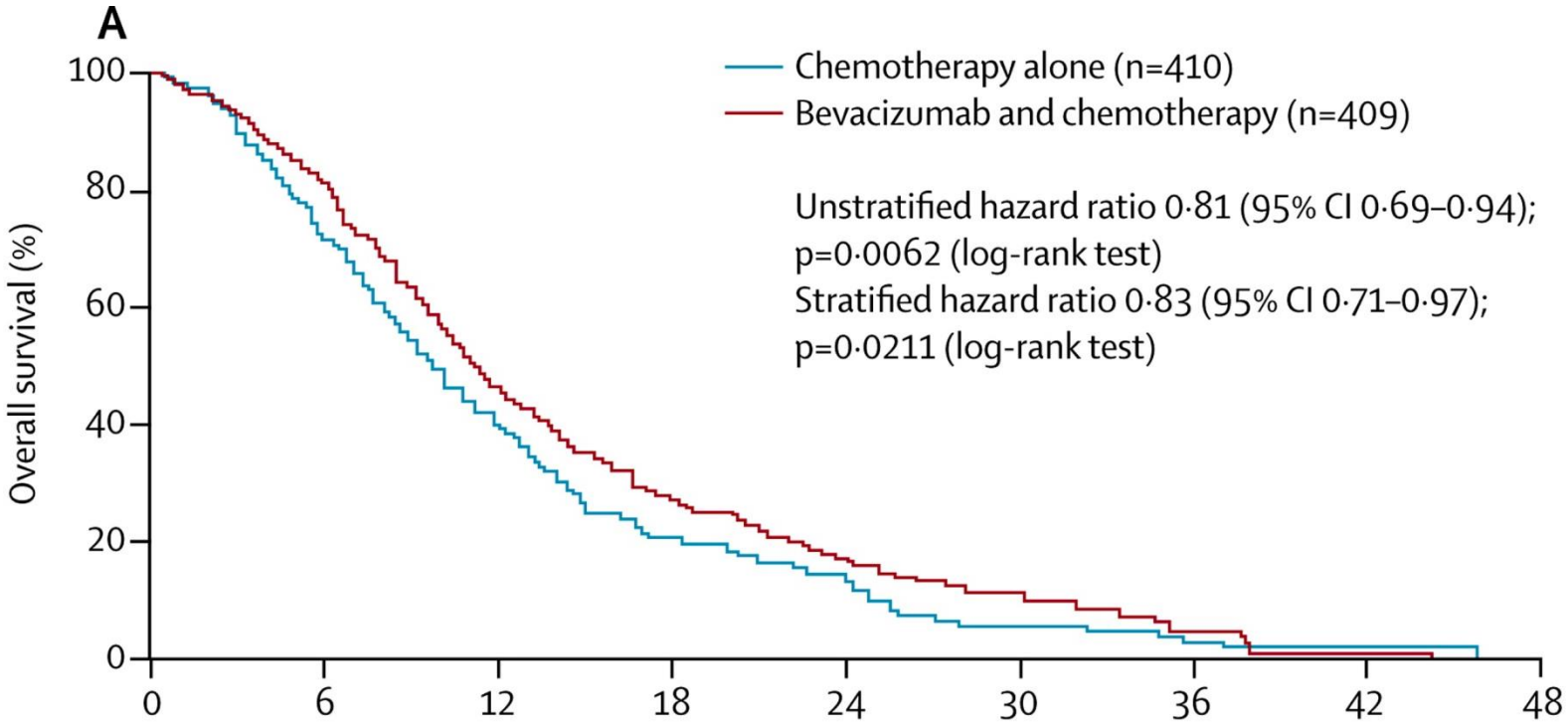
Chemo + BEV
Ox or Iri depending on first line chemotherapy

n=410

Chemo alone
Ox or Iri depending on first line chemotherapy

Bennouna et al Lancet Oncol 2013

ML18147/TML
Overall survival



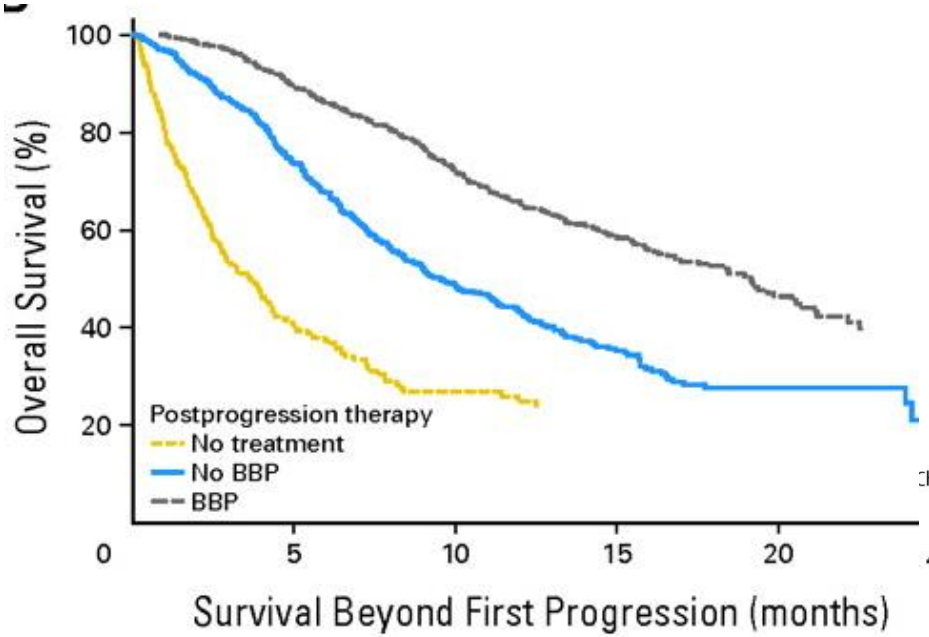
Number at risk

Chemotherapy alone	410	293	162	51	24	7	3	2	0
Bevacizumab and chemotherapy	409	328	188	64	29	13	4	1	0

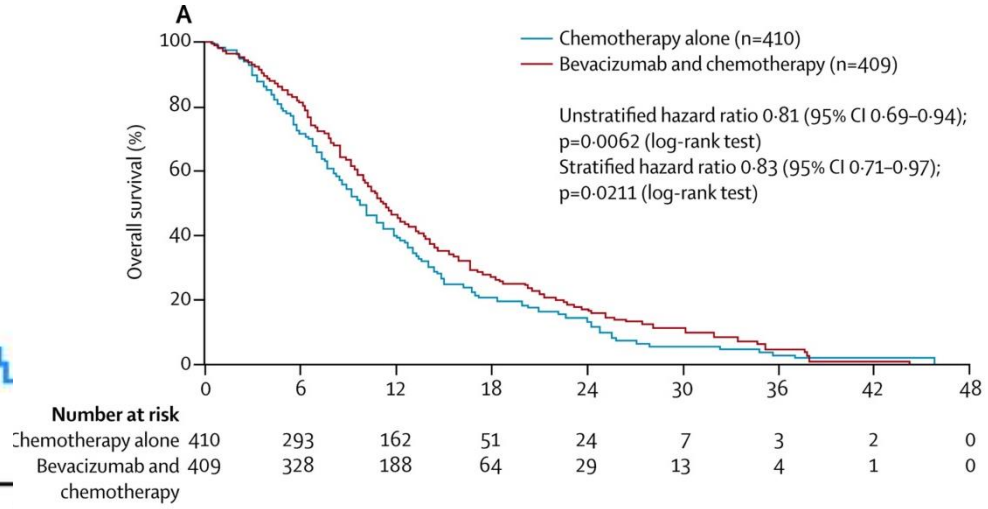
Bennouna et al Lancet Oncol 2013

Bevacizumab beyond first progression: Registry vs. RCT

BRiTE[1]



ML18147[2]



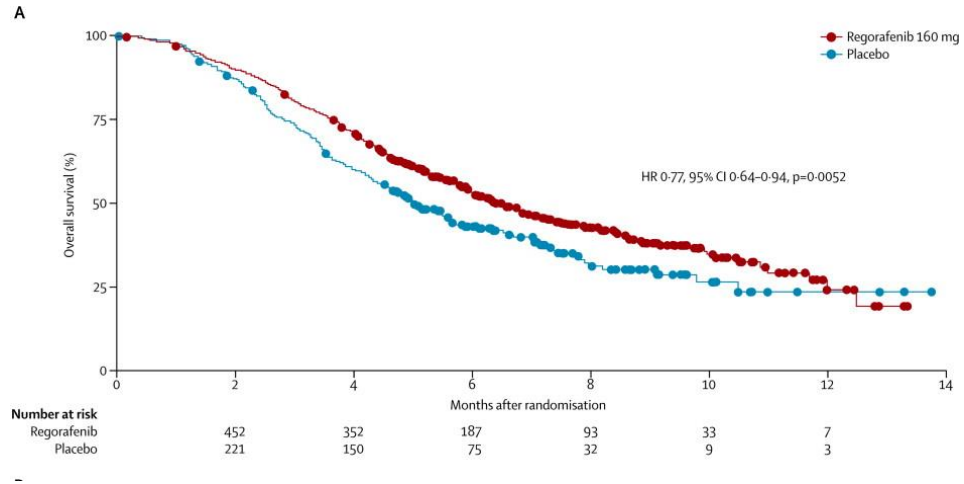
	mOS beyond 1st progression
BBP	19.2months
No BBP	9.5 months
	HR: 0.49

	mOS beyond 1st progression
BBP	11.2months
No BBP	9.8 months
	HR: 0.81

[1]Grothey et al. J Clin Oncol 2008;
[2]Bennouna et al Lancet Oncol 2013

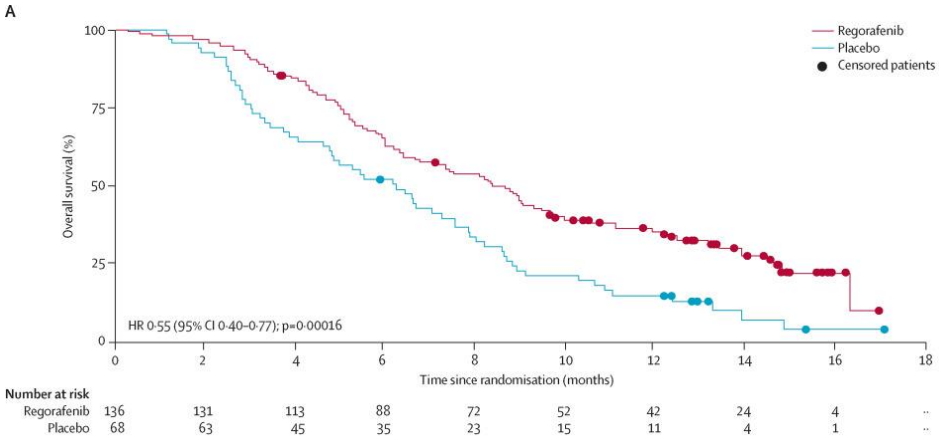
Randomised controlled trials of regorafenib in mCRC

CORRECT[1]



	n	mOS
Regorafenib	505	6.4months
Placebo	255	5.0 months
	HR: 0.77	

CONCUR[2]



	n	mOS
Regorafenib	136	8.8 months
Placebo	68	6.3 months
	HR: 0.55	

[1]Grothey et al Lancet 2013;
[2]Li et al Lancet Oncol 2015

CONSIGN study

- Phase 3B study
- Purpose
  - To characterise safety of regorafenib
  - To allow patients with mCRC to receive regorafenib prior to market authorisation
- Population
  - Planned recruitment ~ 3000 patients
  - Actual recruitment = 2,872
  - Safety population = 2,864
  - Similar population to CORRECT (i.e. progression after biological therapy)
- PFS only efficacy variable (investigator-determined interval and assessed cf every 8 weeks in CORRECT and CONCUR)

Van Cutsem et al ESMO Asia 2015

Baseline characteristics of patients receiving regorafenib

Studies	CORRECT	CONCUR	CONSIGN
N	505	136	2,872
Median age	61	57.5	62
Male	62%	63%	59%
ECOG PS 0/1	52%/48%	26%/74%	47%/53%
KRAS mutation	54%	34%*	51%
Prior treatment			
1-2	27%	35%	26%
3	25%	24%	27%
≥4	49%	38%	46%

*29% had unknown KRAS status

Van Cutsem et al ESMO Asia 2015

Drug delivery of patients receiving regorafenib

Studies	CORRECT	CONCUR	CONSIGN
N	505	136	2,872
Median duration of treatment	2.8 months	2.4 months	2.5 months
Mean percentage of planned dose	78.9%	91%	75%

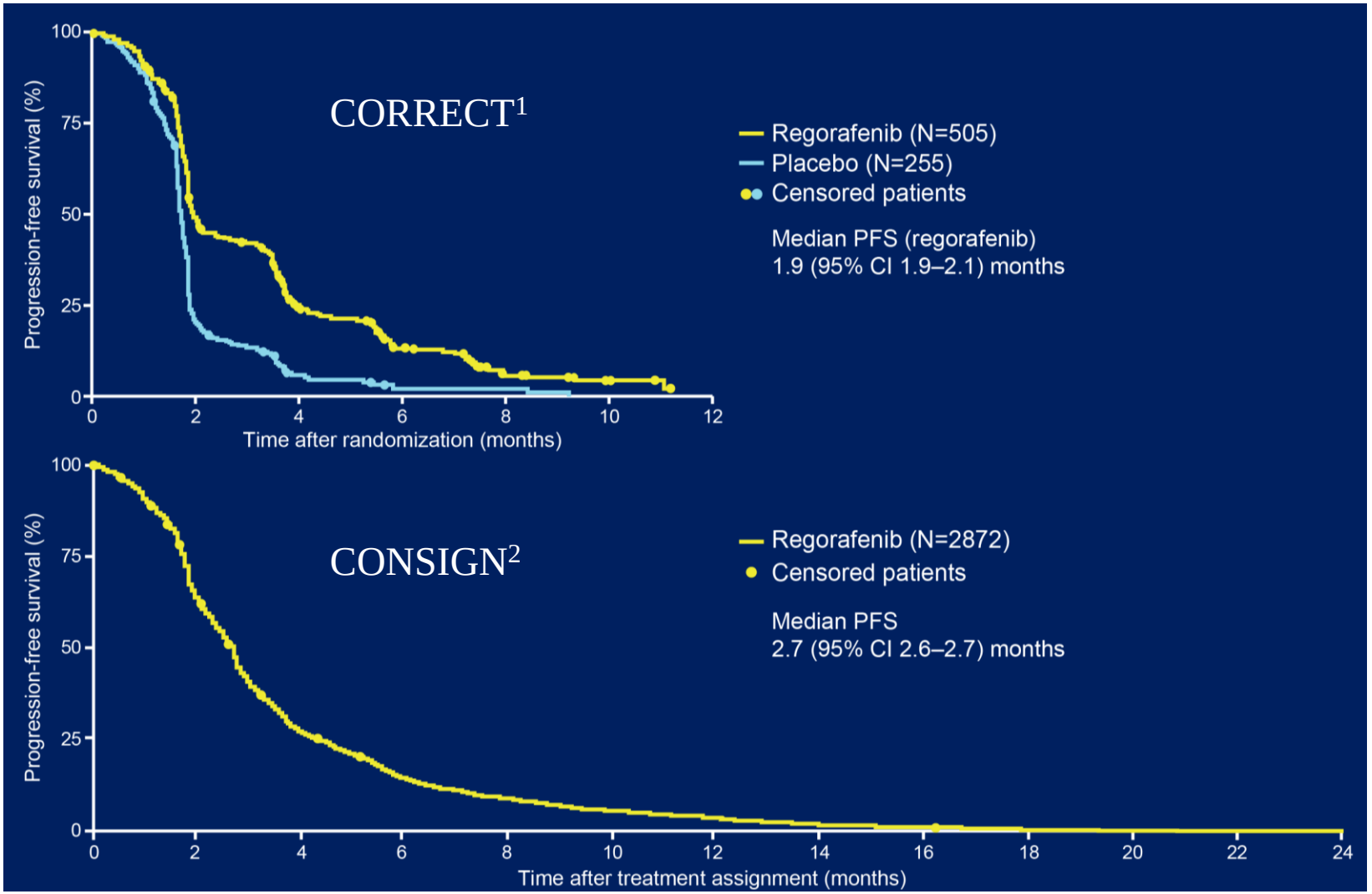
Van Cutsem et al ESMO Asia 2015

Adverse events of patients receiving regorafenib

Studies	CORRECT	CONCUR	CONSIGN
N	500	136	2,864
Any grade	93%	97%	91%
Grade ≥3	54%	54%	57%
Grade 5	<1%	1%	<1%
Grade 3 /4 toxicities			
Hypertension	7%	11%	15%
Hand foot syndrome	17%	16%	14%
Fatigue	10%	3%	13%
Diarrhoea	7%	1%	5%
↑bilirubin	2%	6%	13%
↑AST	NR	6%	7%
↑ALT	NR	7%	6%
Anaemia	3%	2%	4%
Thrombocytopenia	3%	3%	2%
Neutropenia	NR	2%	1%

Van Cutsem et al ESMO Asia 2015

Progression free survival



[1]Grothey et al Lancet 2013;
[2]Van Cutsem ESMO Asia 2015

Comments

- CONSIGN patient population more similar to CORRECT
- Safety broadly similar to pivotal CORRECT study
  - Incidences of AEs estimated with much greater precision
- Progression free survival similar to CORRECT study, but schedule of assessment imaging not pre-determined
  - Why was overall survival not an efficacy outcome in this phase 3B study?
- Still cannot be clear about efficacy or safety in real world population

Patients' age on recruitment into phase III mCRC trials

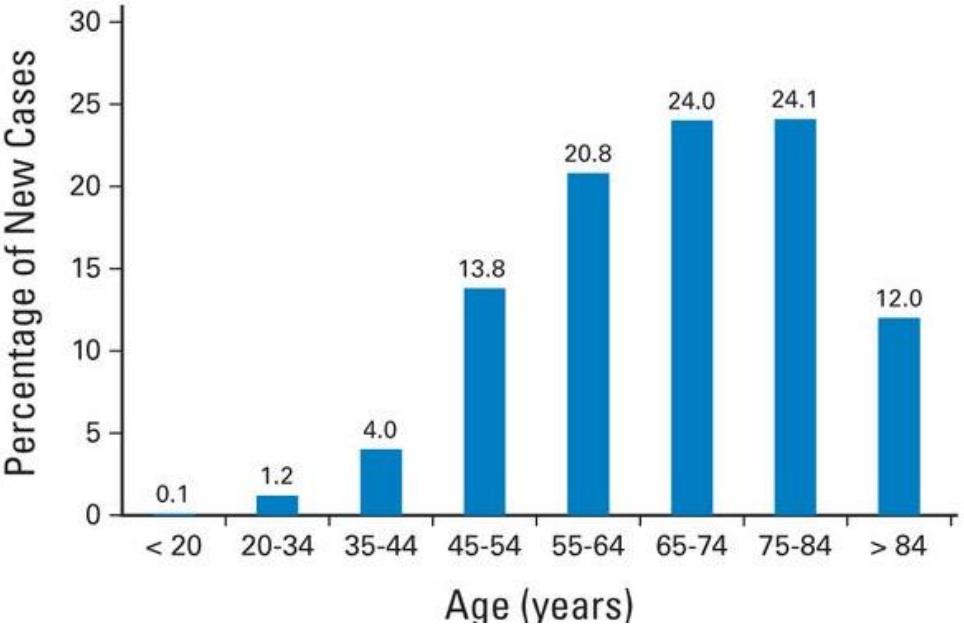
Trials	Treatment arms	n	Median age in years (range)
FIRE 3[1]	FOLFIRI + cetuximab	297	64 (38-79)
	FOLFIRI + bevaciuzmab	295	65 (27-76)
CALGB/SWOG 80405[2]	Chemo + cetuximab	578	59 (20-89)
	Chemo + bevacizumab	559	59 (21-85)
TRIBE[3]	FOLFIRI + bevacizumab	256	60 (29-75)
	FOLFOXIRI + bevacizumab	252	60.5 (29-75)
CORRECT[4]	Regorafenib	505	61 (54-67)*
	Placebo	255	61 (54-68)*
RECOURSE[5]	TAS-102	534	63 (27-82)
	Placebo	266	63 (27-82)

*IQR

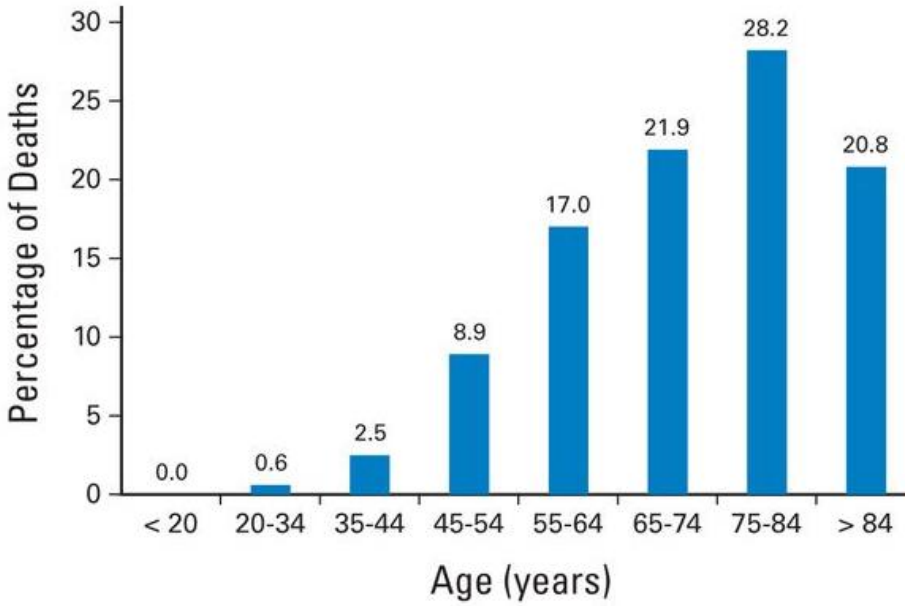
[1]Heinemann et al Lancet Oncol 2014; [2]Venook et al ASCO 2014; [3]Loupakis et al N Engl J Med 2014; [4]Grothey et al Lancet 2013; [5]Mayer et al N Engl J Med 2015

SEER data on CRC by age

Incidence of new CRC

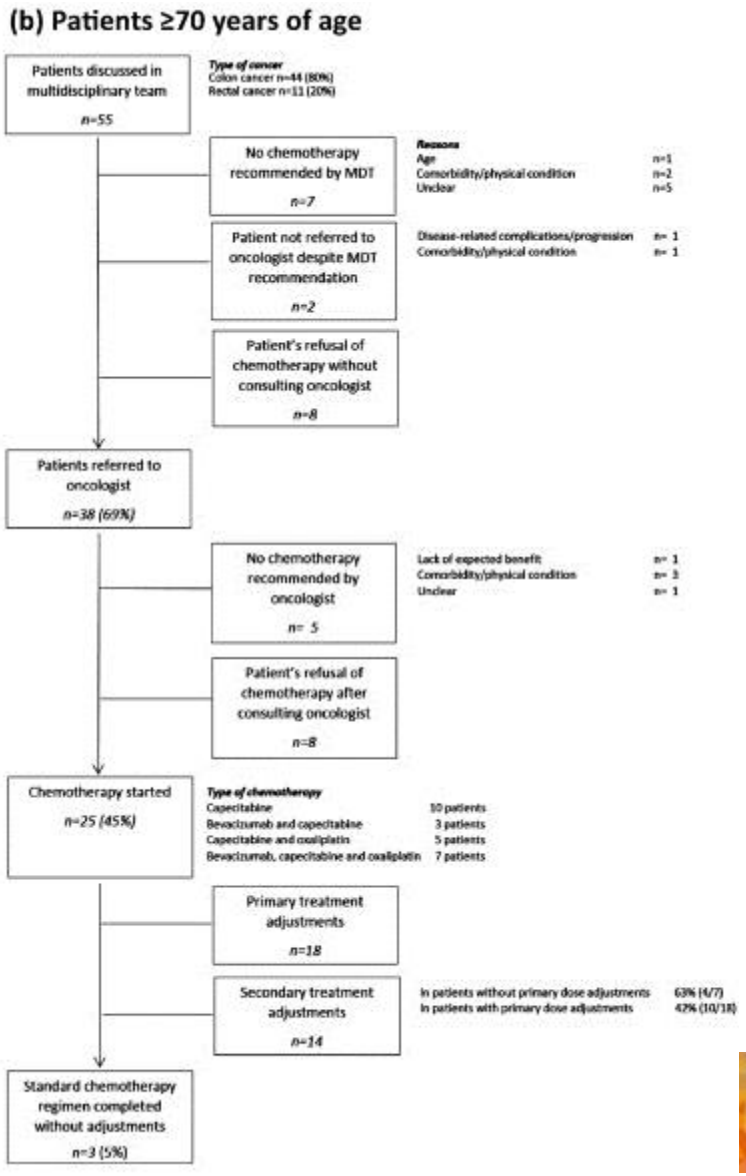


CRC–related deaths



McCleary et al J Clin Oncol 2014

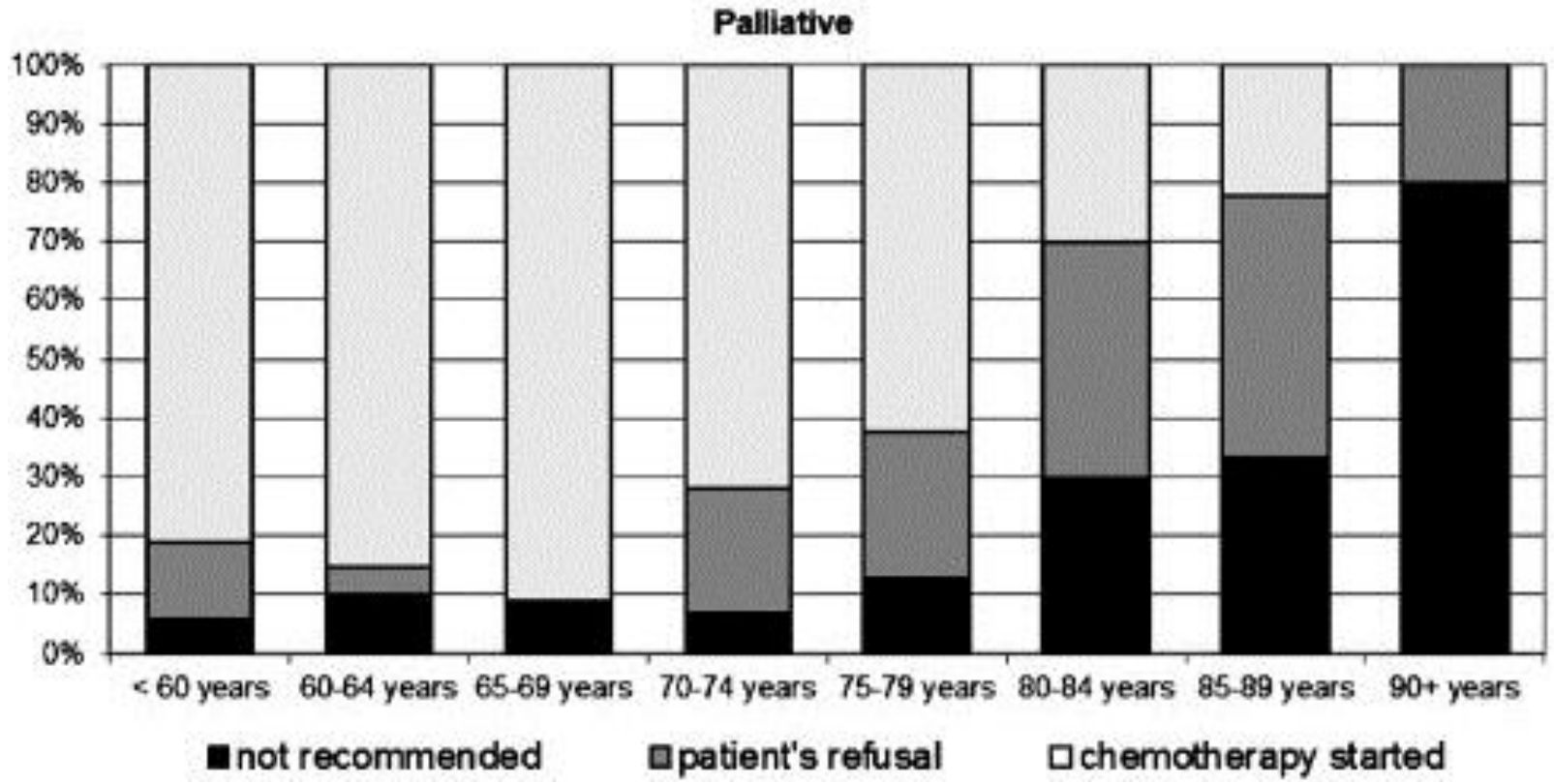
Multidisciplinary decision-making on palliative chemotherapy for mCRC



- 157 MDT meetings over 3 years in a large teaching hospital in Utrecht, Netherlands
- 98% of young patients referred to oncologist to discuss chemotherapy vs. 69% for the older (aged ≥70 years) patients

Hamaker et al J Geriatr Oncol 2015

Multidisciplinary decision-making on chemotherapy for colorectal cancer



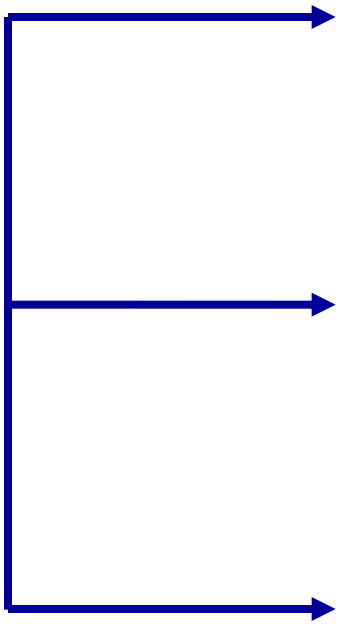
Hamaker et al J Geriatr Oncol 2015

French ThInDiT national cohort

N	Aged <75 3588	Aged ≥75 2724	p
Rx of mCRC			
Primary tumour resection	68%	57%	<0.0001
Liver resection	17%	7%	<0.0001
1st line chemotherapy	85%	48%	<0.0001
5-FU/Capecitabine mono	10%	30%	<0.0001
Oxaliplatin-5FU	34%	31%	0.1
Irinotecan-5FU	6%	11%	<0.00001
Irinotecan-Oxaliplatin-5FU	5%	2%	<0.0001
Bevacizumab + chemo	35%	20%	<0.0001
Cetuximab ± chemo	9%	4%	<0.0001
Median OS	22.3 months	8.4 months	

Doat et al Eur J Cancer 2014

Evidence for treating mCRC in older patients



Randomised controlled trials

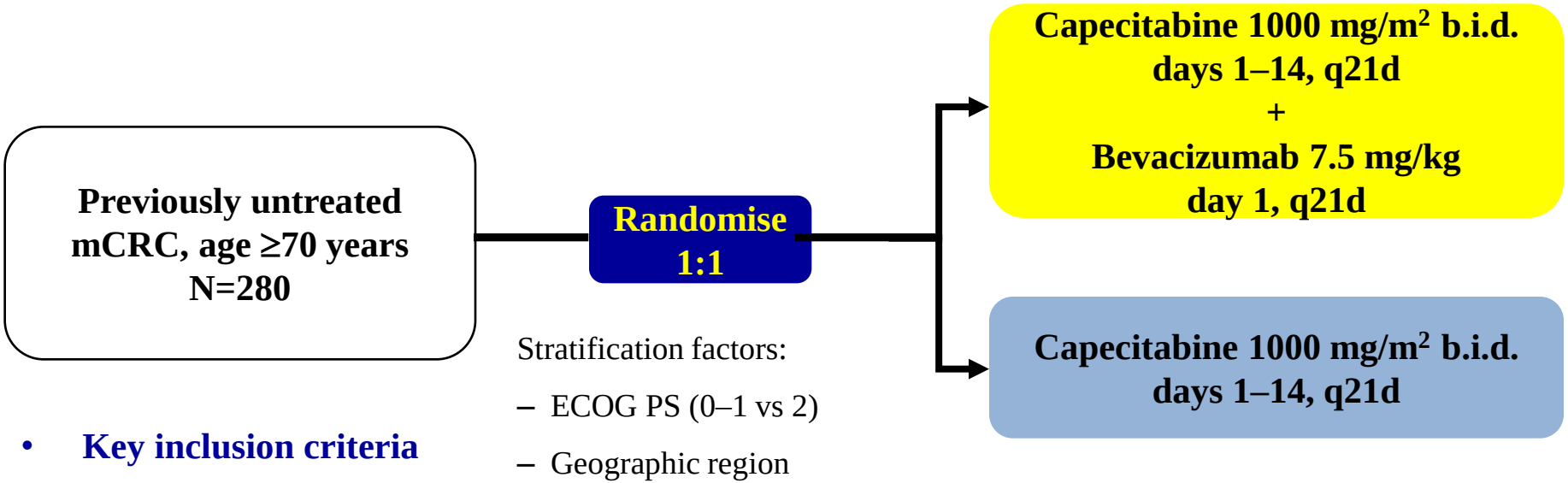
Prospective uncontrolled studies

Registry studies

Evidence for treating mCRC in older patients

- Randomised controlled trials
  - FOCUS 2
  - FFCD 2001-02
  - AVEX
  - MAX
  - N016966, AVF2107, AVF2192 & E3200 Pooled analysis

AVEX Study design



- **Key inclusion criteria**
  - **ECOG PS 0–2**
  - **Prior adjuvant chemotherapy allowed if completed >6 month before inclusion**
  - **Not optimal candidates for a combination chemotherapy with irinotecan or oxaliplatin**

- **Key exclusion criteria**
  - **Prior chemotherapy for mCRC or prior adjuvant anti-VEGF treatment**
  - **Clinically significant cardiovascular disease**
  - **Current or recent use of aspirin (>325 mg/day) or other NSAID**
  - **Use of full-dose anticoagulants or thrombolytic agents**

Cunningham et al Lancet Oncol 2013

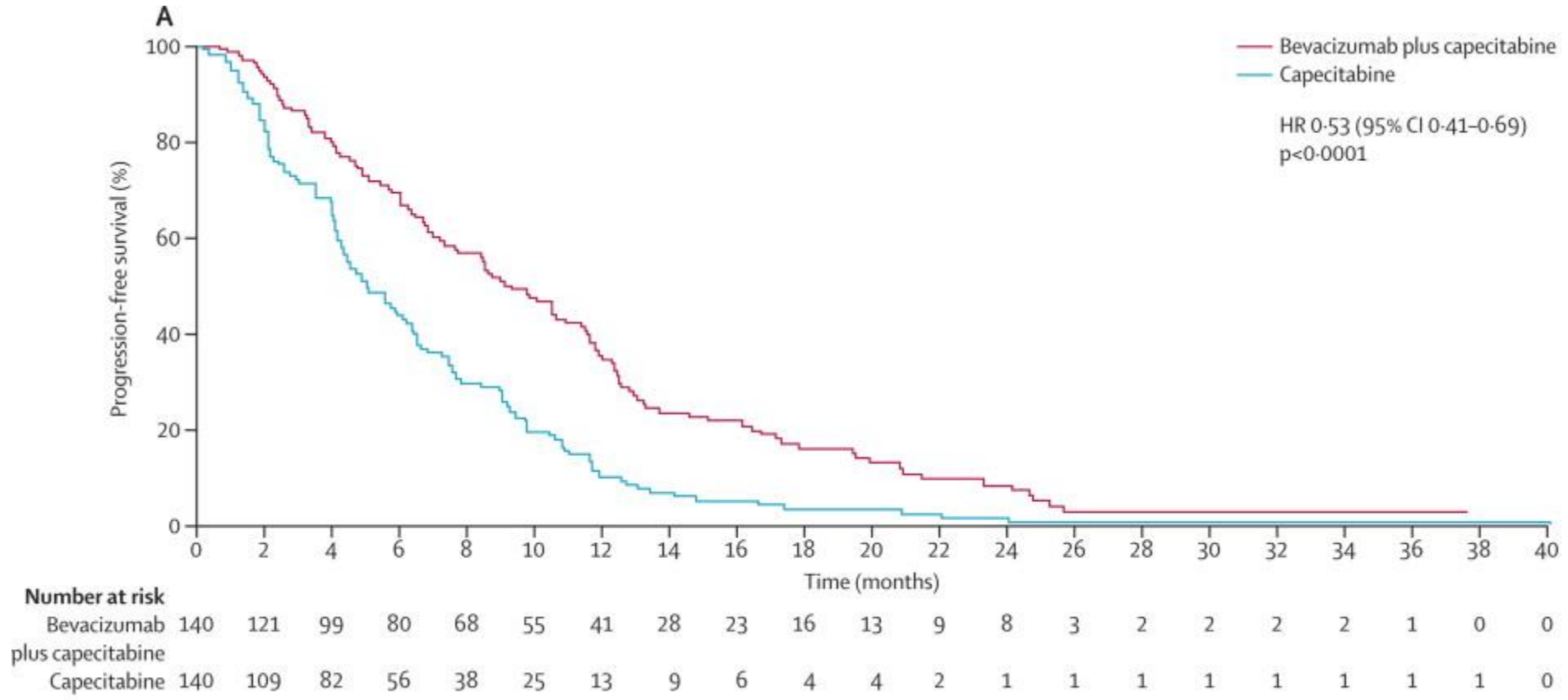
Baseline patient characteristics

		Cape + BEV (n=140)	Cape (n=140)
Sex, %	Female	40.0	40.0
Median age, years (range)		76 (70–87)	77 (70–87)
	<75 years, %	39	33
	≥75 years, %	61	67
ECOG performance status, %	0	50	43
	1	41	48
	2	7	8
Prior adjuvant therapy, %	Yes	32	19
Site of metastatic disease, %	Liver	63	68
	Lung	36	41
	Other	35	23
	Liver only	37	39
Surgical resection, %	Yes	74	64
Location of primary disease, %	Colon only	58	54
	Rectum	31	25
	Colon and rectum	11	19

e: ECOG PS = Eastern Cooperative Grou

Cunningham et al Lancet Oncol 2013

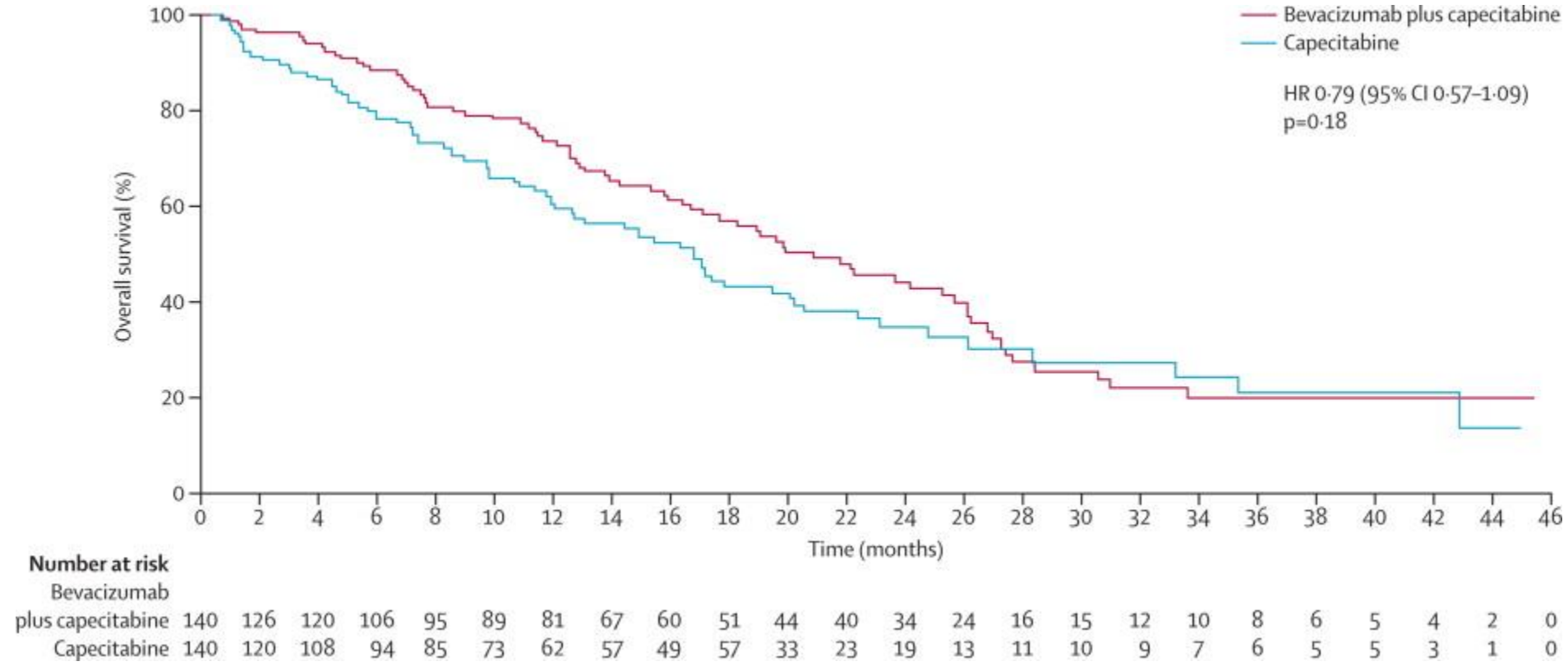
AVEX Progression-free survival



	CAP + BEV	CAP
Median PFS	9.1 months	5.1 months

Cunningham et al Lancet Oncol 2013

AVEX Overall survival



	CAP + BEV	CAP
Median OS	20.7 months	16.8 months

Cunningham et al Lancet Oncol 2013

Subsequent therapies

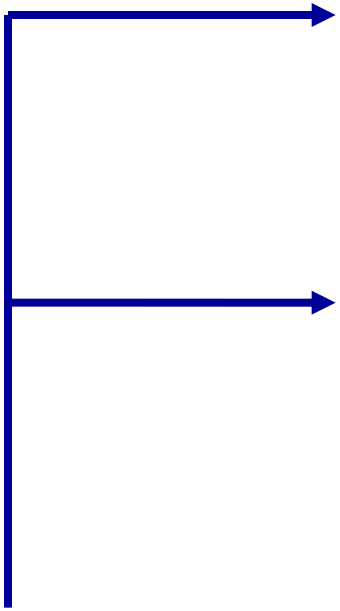
Subsequent therapy (selected), %	Cape + BEV (n=140)	Cape (n=140)
Any additional treatment for malignancy	37	37
Fluoropyrimidine monotherapyl	17	18
Oxaliplatin-doublet	2	1
Irinotecan-doublet	6	3
Bevacizumab	6	8
Cetuximab	3	1
Panitumumab	1	4

ITT population.

Selected adverse events of special interest for bevacizumab and chemotherapy

	Bevacizumab plus capecitabine (n=134)				Capecitabine (n=136)			
	All grades	Grade 3	Grade 4	Grade 5	All grades	Grade 3	Grade 4	Grade 5
Selected adverse events of special interest for bevacizumab								
Bleeding/haemorrhage	34 (25%)	0	0	0	9 (7%)	0	0	1 (1%)
Hypertension	26 (19%)	3 (2%)	0	0	7 (5%)	2 (1%)	0	0
Venous thromboembolic events	16 (12%)	3 (2%)	7 (5%)	1 (1%)	7 (5%)	4 (3%)	2 (1%)	0
Proteinuria	10 (7%)	2 (1%)	0	0	1 (1%)	0	0	0
Arterial thromboembolic events	6 (4%)	2 (1%)	1 (1%)	2 (1%)	3 (2%)	1 (1%)	0	0
Wound-healing complications	2 (1%)	0	0	0	0	0	0	0
Pulmonary haemorrhage or haemoptysis	1 (1%)	0	0	0	1 (1%)	1 (1%)	0	0
Congestive heart failure	0	0	0	0	1 (1%)	0	0	1 (1%)
Fistulae	1 (1%)	0	0	0	0	0	0	0
Gastrointestinal perforation	1 (1%)	0	0	0	0	0	0	0
Reversible posterior leukoencephalopathy syndrome	0	0	0	0	0	0	0	0
Selected adverse events of special interest for chemotherapy*								
Hand-foot syndrome	66 (49%)	21 (16%)	0	0	54 (40%)	9 (7%)	0	0
Diarrhoea	54 (40%)	8 (6%)	1 (1%)	0	48 (35%)	7 (5%)	2 (1%)	0
Asthenia	30 (22%)	6 (4%)	1 (1%)	0	22 (16%)	4 (3%)	1 (1%)	0
Fatigue	32 (24%)	4 (3%)	1 (1%)	0	37 (27%)	1 (1%)	0	0
Nausea	32 (24%)	1 (1%)	0	0	37 (27%)	0	0	0
Vomiting	28 (21%)	3 (2%)	0	0	16 (12%)	2 (1%)	0	0
Stomatitis	20 (15%)	0	0	0	11 (8%)	1 (1%)	0	0
Neutropenia	7 (5%)	0	1 (1%)	0	2 (1%)	1 (1%)	0	0

Evidence for treating mCRC in older patients



Randomised controlled trials

Prospective uncontrolled studies

Prospective studies of first line bevacizumab-containing regimens in older population

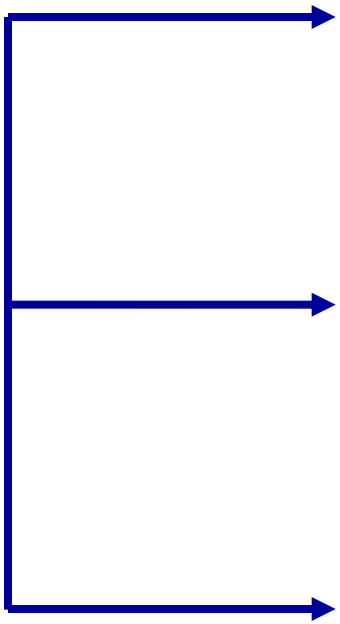
Author	Country	n	Treatment	Median age	PS2	ORR	mPFS	mOS
Naeim et al[1]	USA	45	CAP + Bev	79	62%	35.5%	6.87	12.7
Yoshida et al[2]	Japan	56	S-1 + Bev	75	0%	43%	9.9	25
Vamvakas et al[3]	Greece	48	CAPOX + Bev	76	8.3%	46.8%	7.9	20.1
Feliu et al[4]	Spain	68	CAPOX + Bev	75.6	0%	45.6%	11.1	20.4

[1]Naeim et al J Geriatr Oncol 2013; [2]Yoshida et al Eur J Cancer 2015;
[3]Vamvakas et al BMC Cancer 2014; [4]Feliu et al Br J Cancer 2014

Toxicities

- Toxicities in these four prospective studies in the elderly appeared to be comparable to other RCTs involving all age groups.
- Grade 3 toxicities are mainly in diarrhoea and fatigue
- BEV-related adverse events did not appear to be more pronounced than expected

Evidence for treating mCRC in older patients



Randomised controlled trials

Prospective uncontrolled studies

Registry studies

Pooled analysis of registry data

- Five phase 4/ observational cohort studies
- N=7,688
- Allowed analyses of the very young (aged <25) and the very old (aged >85) – both under-represented in RCTs
- Somewhat worse OS in the very young (n=13) and the very old (n=67), although small sample sizes means large 95% confidence intervals; thus overlapped with other age groups
- PFS similar trend in the very young, but not the very old
- Toxicities not quantified in these extreme age group due to small sample sizes, but probably safe in the elderly

Hubbard et al ESMO Asia 2015

BUT: Cautionary notes to generalise results from these registry data to routine clinical practice

- Exclusion criteria of BEAT:
  - Uncontrolled hypertension;
  - clinically significant cardiovascular disease,
  - haemorrhagic diathesis or coagulopathy;
  - use of full-dose anticoagulants or thrombolytics;
  - serious non-healing wounds or ulcers and treatment with aspirin (>325 mg/day) or other medications predisposing to GI ulceration
- However BRiTE and ARIES did not have such exclusion criteria
- Other studies encouraged clinicians to treat patients that fulfil the criteria of bevacizumab treatment based on the summary of product characteristics (SPC)
  - SPC cautions the use of bevacizumab in all the above situation

Conclusions

- What we can believe
  - Safety of regorafenib was generally in line with what observed in RCTs
  - ↑ incidence of hypertension and hyperbilirubinaemia with regorafenib in CONSIGN compared to RCT
  - Bevacizumab could be combined with different chemotherapy backbones in the elderly
- What we can't believe
  - Missing safety data on less common VEGF-related side effects (fistula/fissures, reversible posterior leucoencephalopathy syndrome)
  - Selection bias in patients entering into observation studies
  - Comparative data are at best hypothesis-generating
  - Efficacy of bevacizumab in the very elderly age groups - care should be exercised when registry data go beyond their original purpose and attempt to answer effectiveness questions

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