Metastatic Colorectal Cancer

What to do after progression?

JY Douillard MD, PhD

Professor of Medical Oncology

Integrated Center of Oncology R Gauducheau

Nantes France

UNIVERSITÉ DE NANTES

ESMO

Institut de Cancérologie de l'Ouest

mCRC: what to do after progression

- Most of patients with mCRC will progress under treatment or after a treatment break
- Several drugs and drug combination are available
- Anti EGFR have single agent activity and in combination with chemotherapy. They work in all lines in RAS wt mCRC
- Bevacizumab has no activity as single agent but improve outcome in comnination with chemotherapy.
- Most patients will receive multiple lines of treatment

mCRC: what to do after progression

- Several factors should be considered if an additional line is needed:
  - Patient's desire to continue treatment
  - Patient's condition (PS) and comorbidities
  - Tolerance to last line or residual toxicity
  - Safety of the planned combination
  - Drugs previously used
  - Strategy/schedule use in previous lines

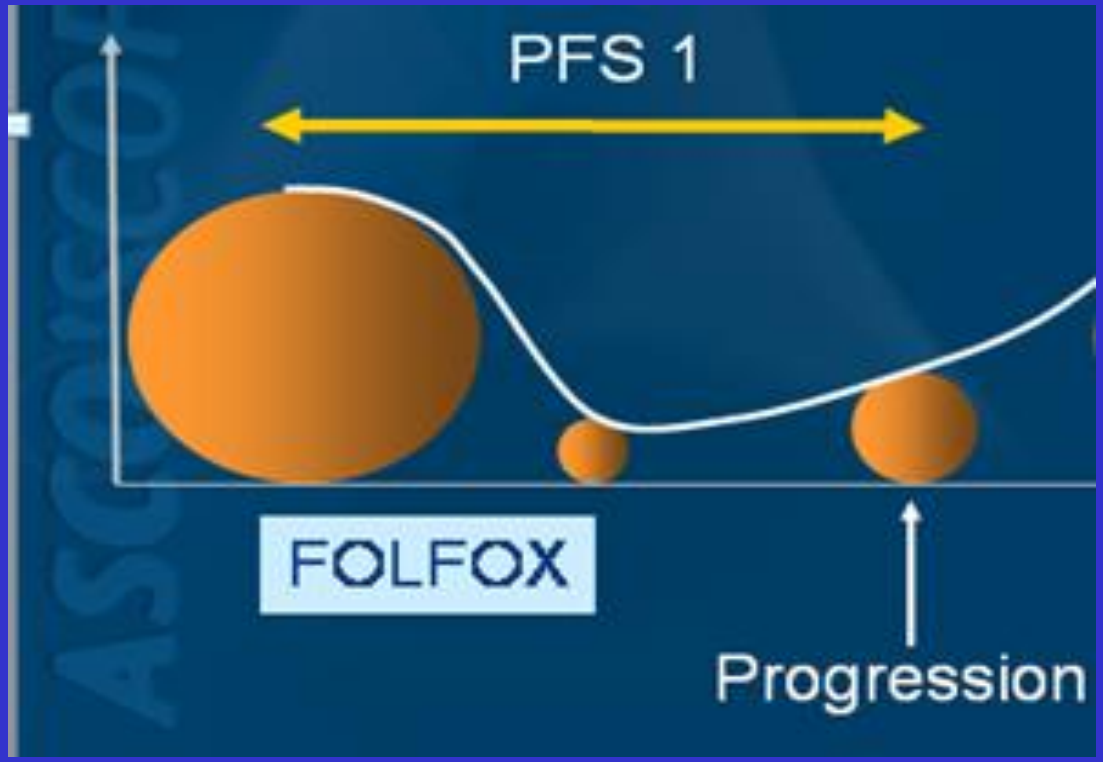
mCRC: what to do after progression

- The concept of lines should be revised:
  - Drug re-introduction
  - Drug continuation
  - Intercalating other treatment method
    - Surgery (even palliative)
    - Radiation
    - Radio-frequency
    - Radio-immunotherapy

- Adding several tretment modality illustrate tne concept of Continuum of care

mCRC: what to do after progression

- **HOW TO DEFINE PROGRESSION?**
  - **In clinical trials: RECIST is the Gold Standard**



RECIST criteria 1.2

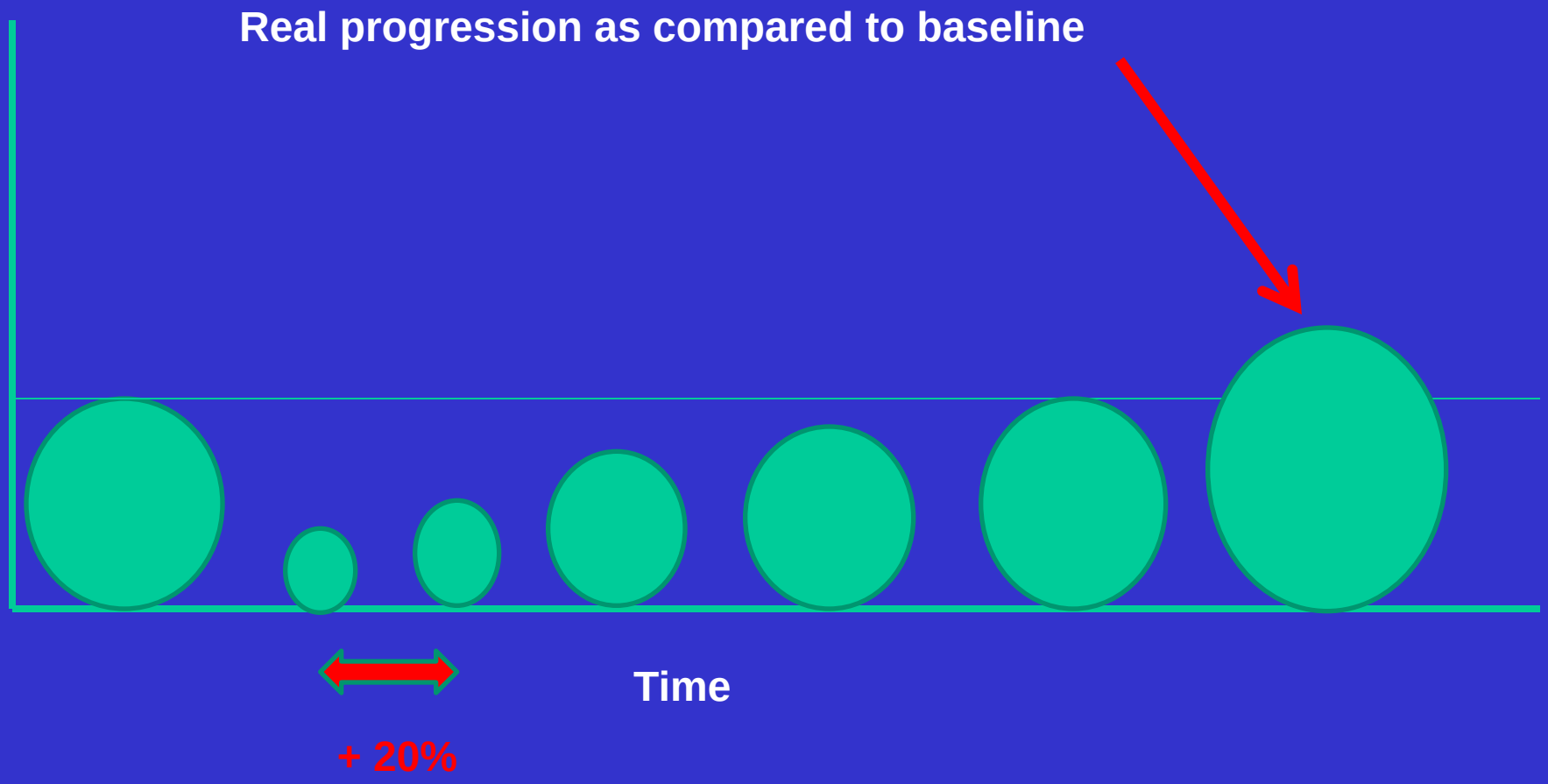
Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study* (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Eisenhauer et al EJC 2009; 45: 228

RECIST

- Essentially used for evaluation of new drugs/regimen in clinical trials
- A tool to measure efficacy in a standardized manner
  - To obtain a Response Rate
  - To evaluate Progression-Free Survival
- Not always easy to use
  - Bone lesions
  - Pleural, peritoneal, pericardial effusion
  - Best for round-shaped lesions
- Is it reliable for treatment modification/decision in clinical practice?

RECIST 1.2



Definition of progression in clinical practice

- Target lesion size should be considered

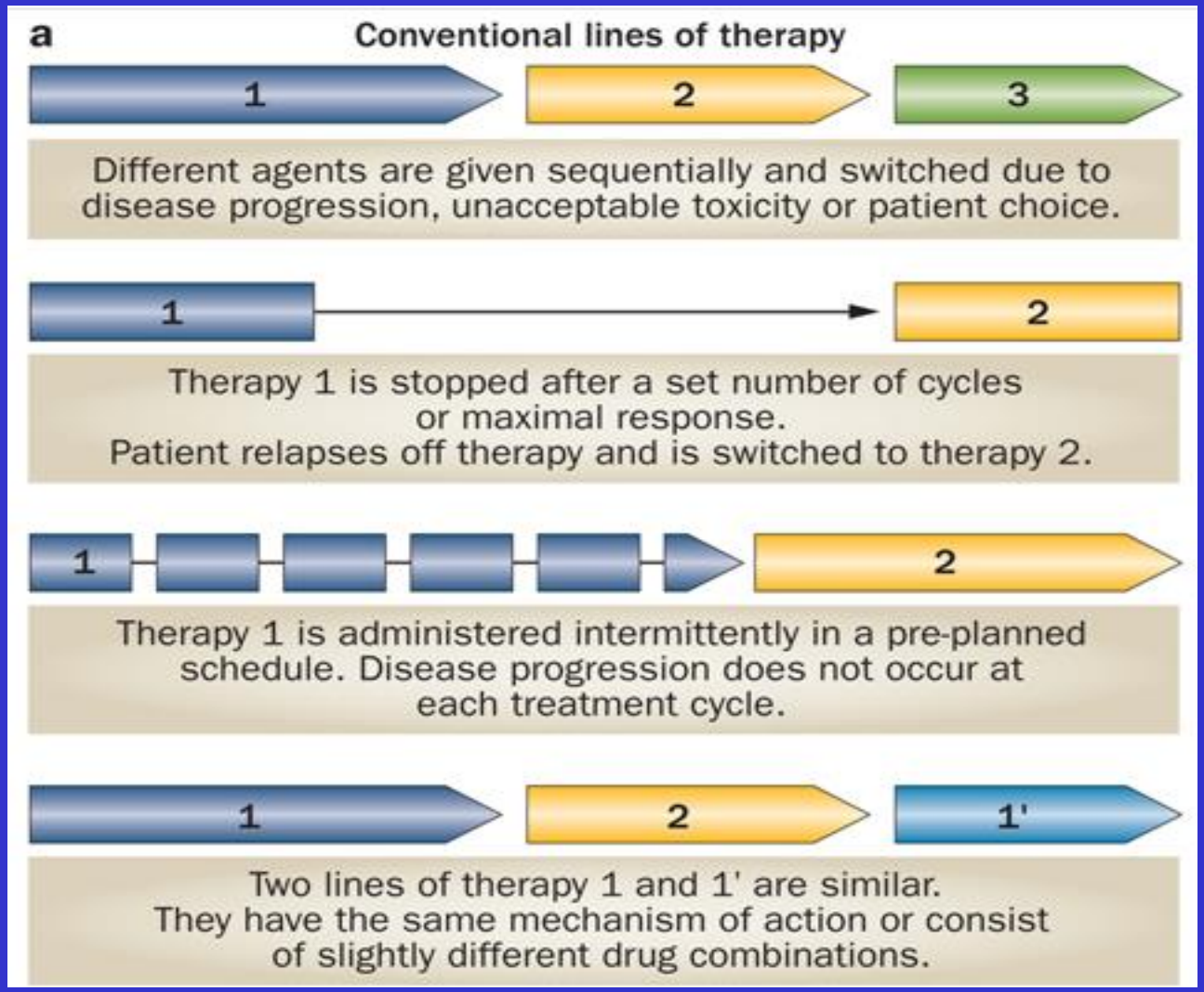
- Other parameters are important as well:
  - Symptoms/quality of life
  - Clinical examination
  - Tolerance to treatment/acceptability
  - Patient opinion
  - Growth rate
  - Tumor markers (CEA, Ca 19.9)

- Daily clinical practice is not clinical research practice

What to do after progression?

- Progression may be established on multiple parameters
- Once established:
- Multiple options are available

Conventional and nonconventional (drug rechallenge and treatment beyond progression) therapy regimens in medical oncology

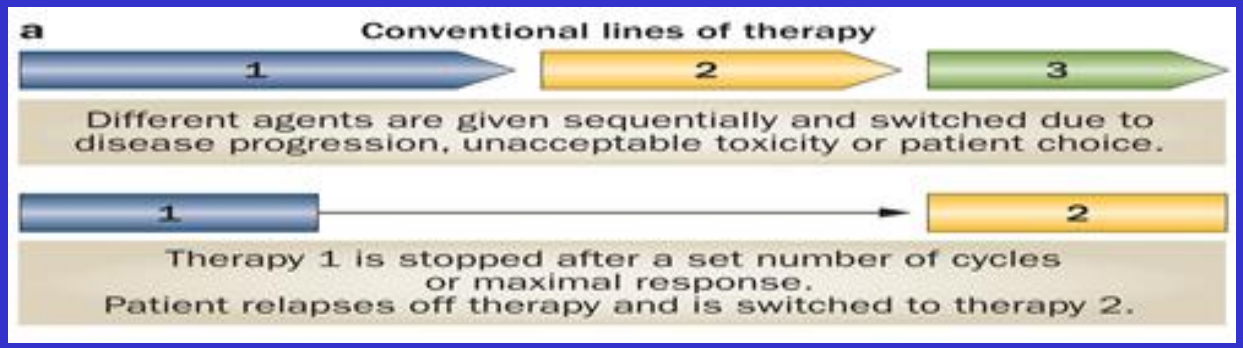


Kuczynski, E. A. *et al.* (2013) Drug rechallenge and treatment beyond progression—implications for drug resistance
***Nat. Rev. Clin. Oncol.* Oct 2013;10: 571-87**

nature REVIEWS CLINICAL ONCOLOGY

Sequential 1st and 2nd Line Combinations

Randomized, multicentric, open-label, prospective, phase III trial



Arm A: FOLFIRI (until progression) → FOLFOX6 (until progression)

R

CPT-11 180 mg/m^2 IV
+ simplified LV5FU

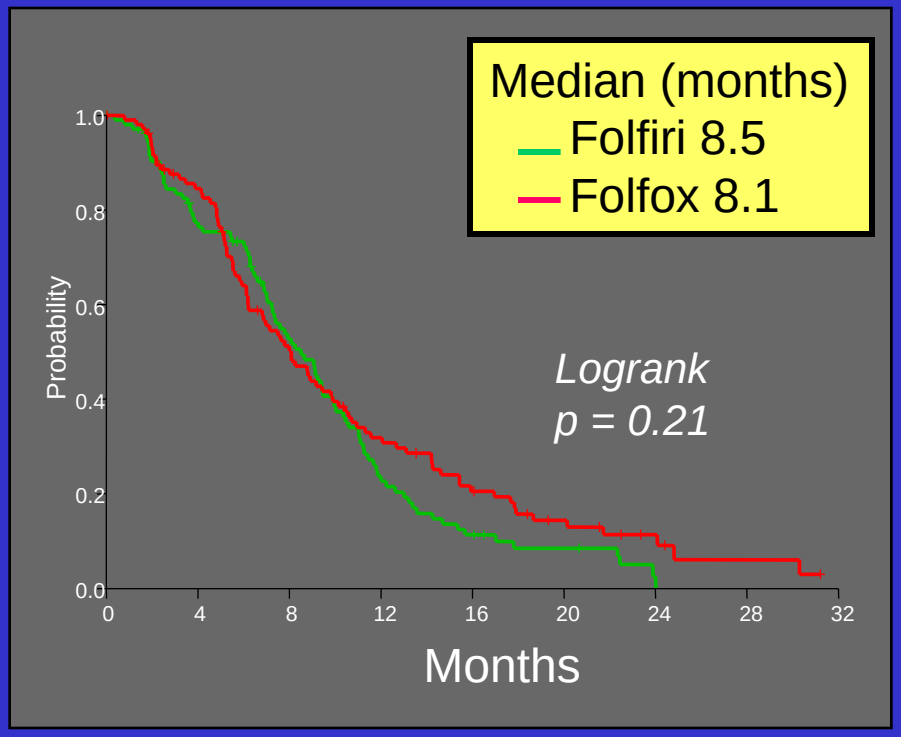
Arm B: FOLFOX6 (until progression) → FOLFIRI (until progression)

Oxaliplatin 100 mg/m^2 IV
+ simplified LV5FU

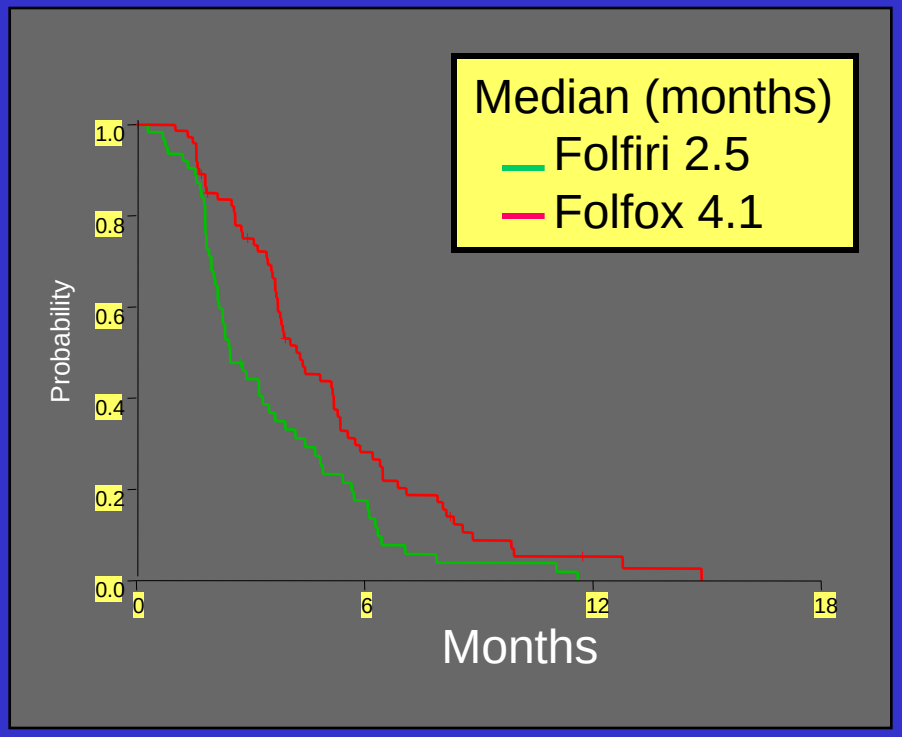
Tournigand at al. J Clin Oncol 2004; 22: 23-30

Efficacy Endpoints

Time to progression in 1st line



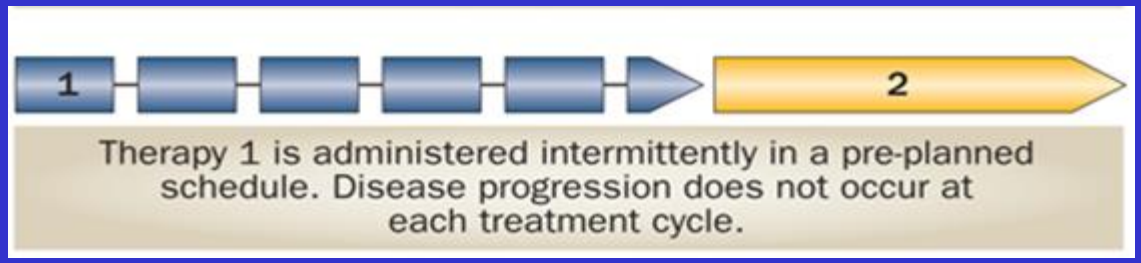
Time to progression in 2nd line

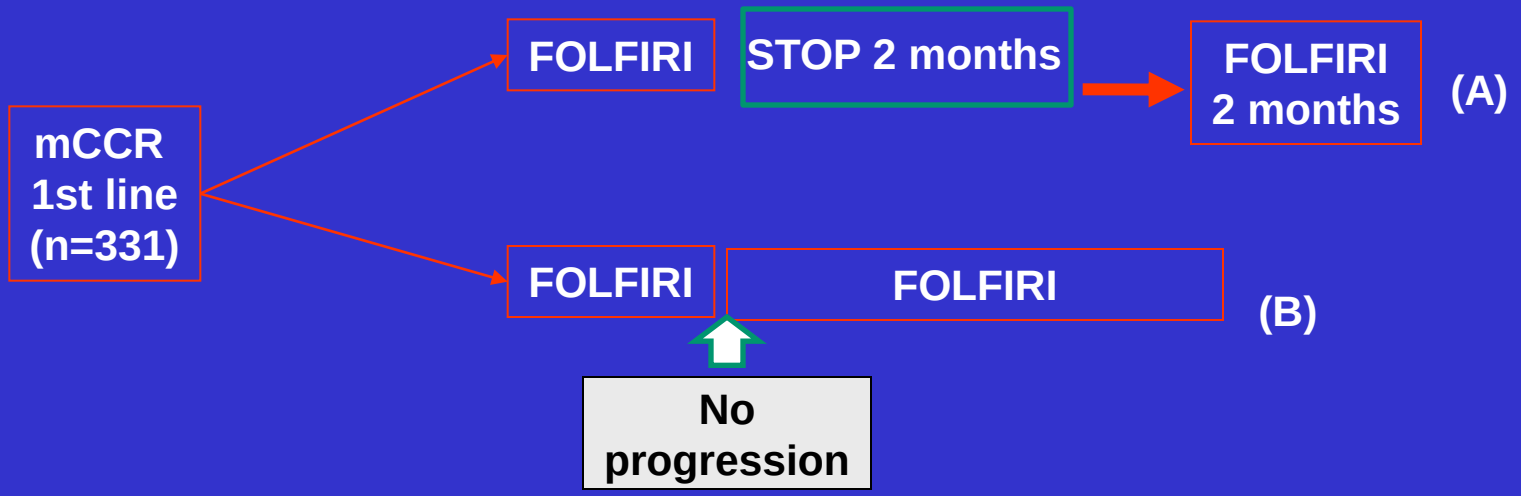


Efficacy

	Arm A		Arm B		
	FOLFIRI	FOLFOX	FOLFOX	FOLFIRI	*P*
n	109	81	111	69	
ORR (CR) %	53 (3)	15	54 (5)	4	0.68
ORR+SD %	79	63	81	35	
Median TTP	14.4		11.5		0.65
Median surv	20.4		21.5		0.90
Progression-free at 15 mo	49		40		

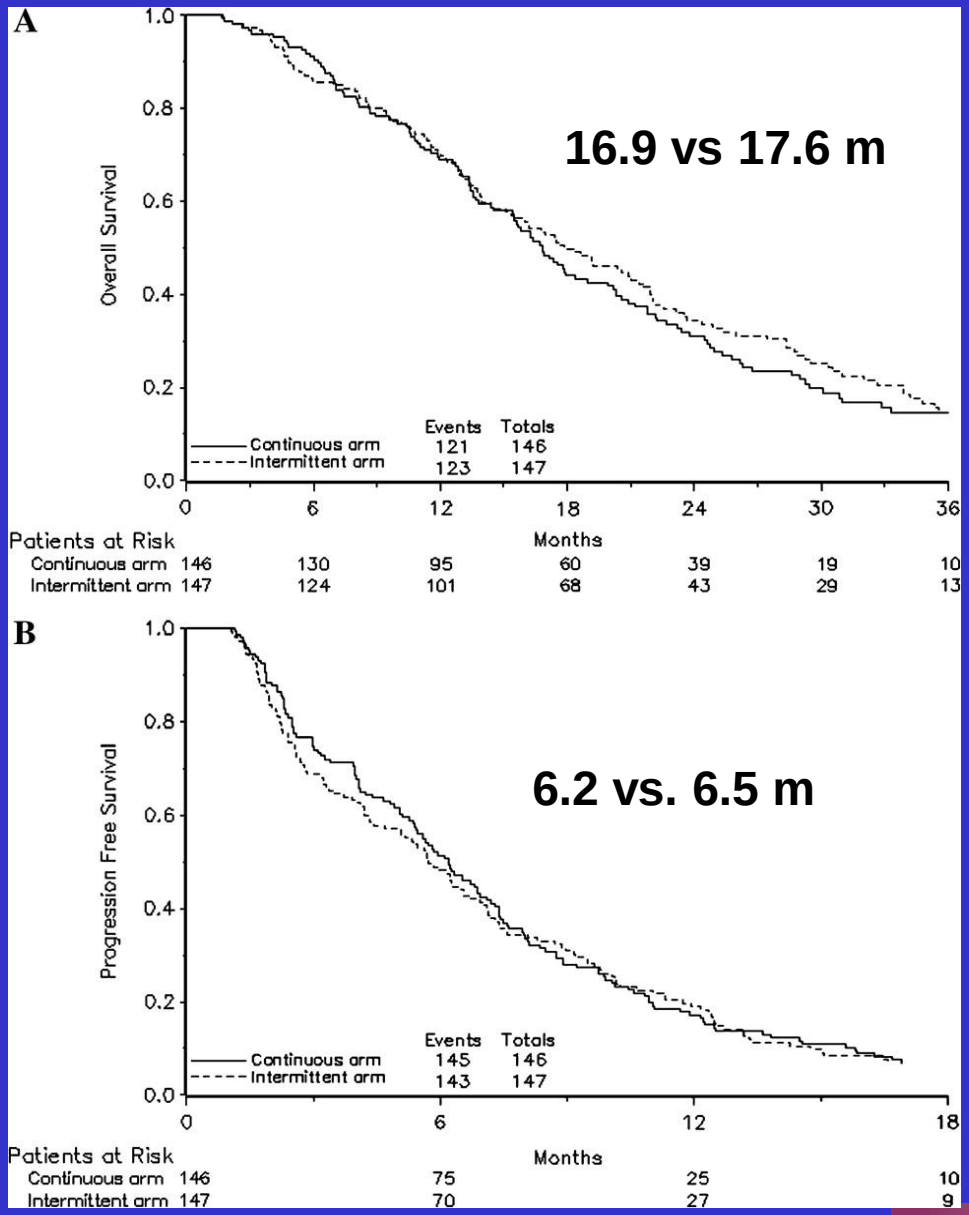
« stop and go » strategy (GISCAD)





Labianca R et al. Ann Oncol 2011;22:1236-1242

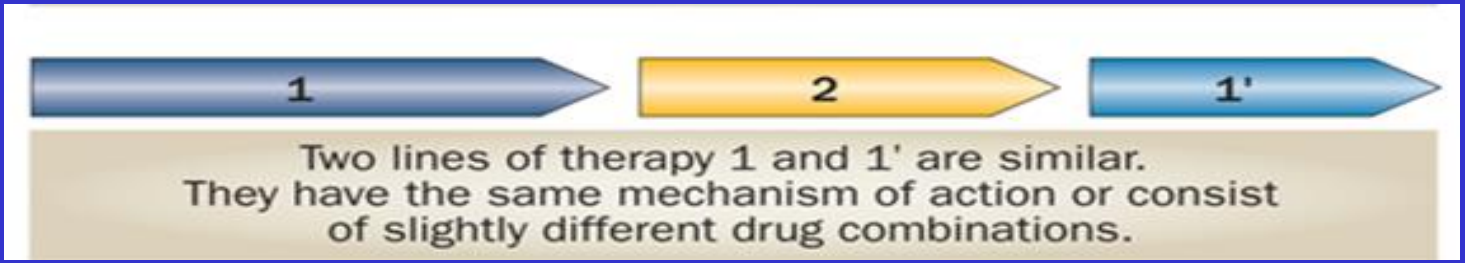
Kaplan–Meier curves for overall survival (A) and progression-free survival (B).



Labianca R et al. Ann Oncol 2011;22:1236-1242

Annals of Oncology

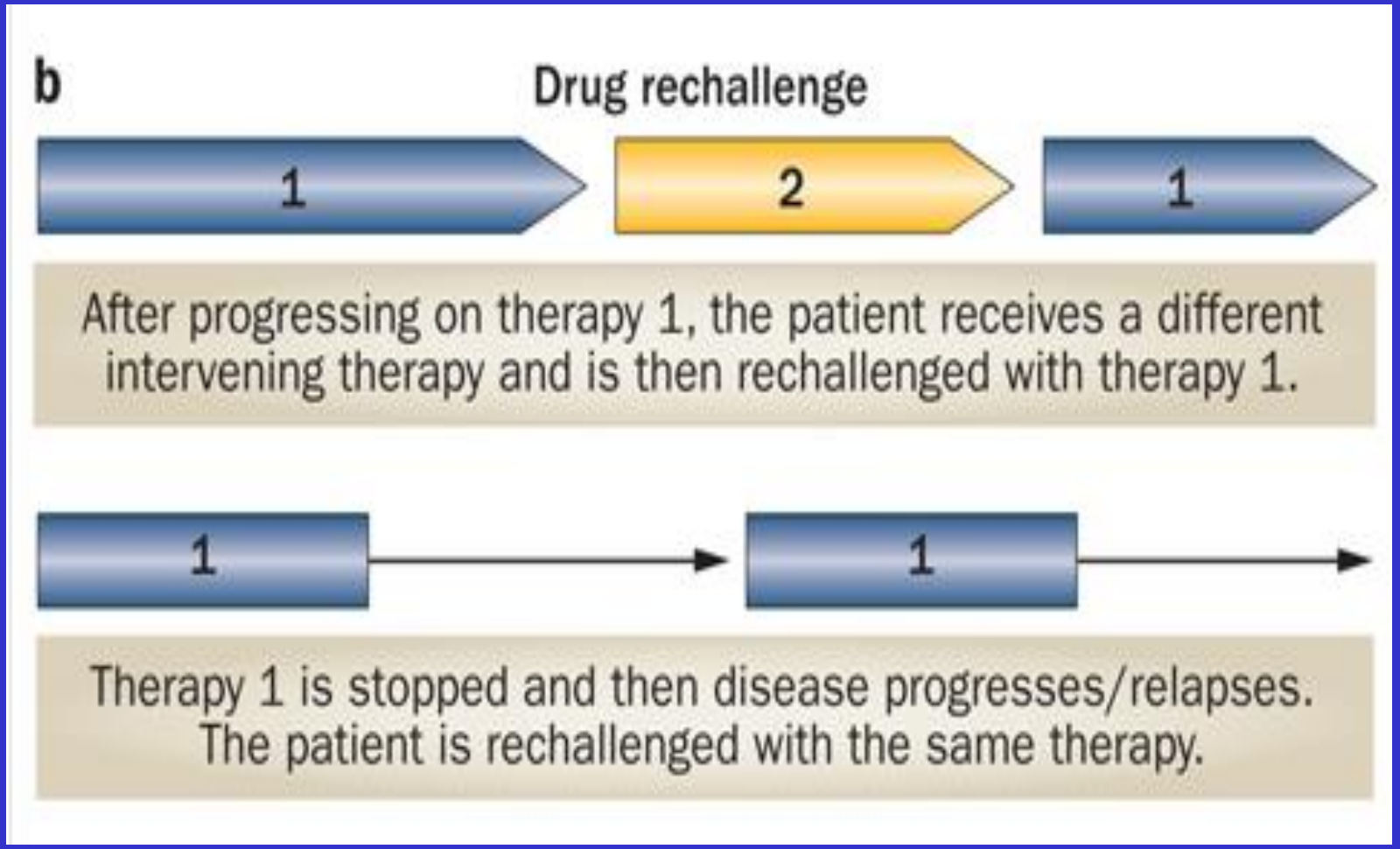
Oxaliplatin reintroduction at progression after FOLFOX 1st line



- 29 patients initially treated with Folfox (2, 3, 5, 6, 7)
  - 1st-line ORR: 24/29, SD 4/29, PD 1/29
  - 16 patients receive intervening therapy before Folfox reintroduction
    - 5FU-LV2, Irinotecan
    - Median Oxali-free interval 48 w
  - Median PFS after reintroduction: 11 weeks
  - Median OS after reintroduction: 36 weeks

Maindrault-Goebel et al Ann Oncol 2004; 15: 1210

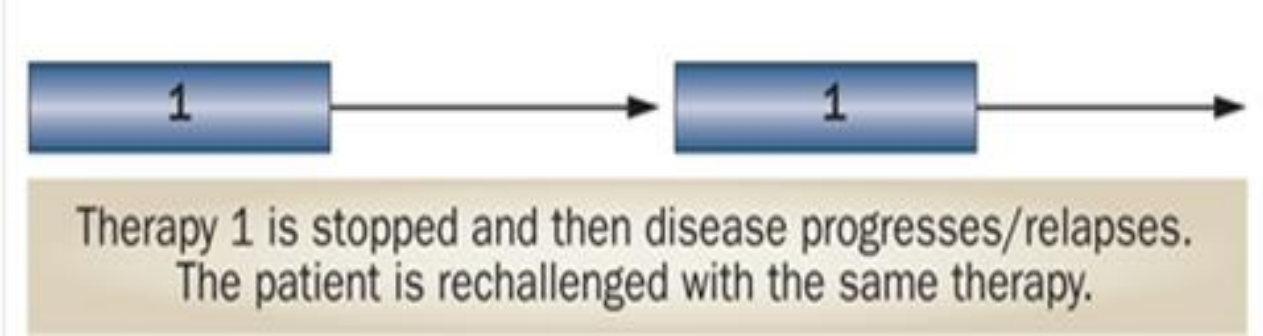
Conventional and nonconventional (drug rechallenge and treatment beyond progression) therapy regimens in medical oncology



Kuczynski, E. A. *et al.* (2013) Drug rechallenge and treatment beyond progression—implications for drug resistance
Nat. Rev. Clin. Oncol. Oct 2013;10: 571-87

nature REVIEWS CLINICAL ONCOLOGY

Reintroduction of the same regimen after progression following a break



- Relapses may be termed « sensitive » rather than « resistant » after initial control

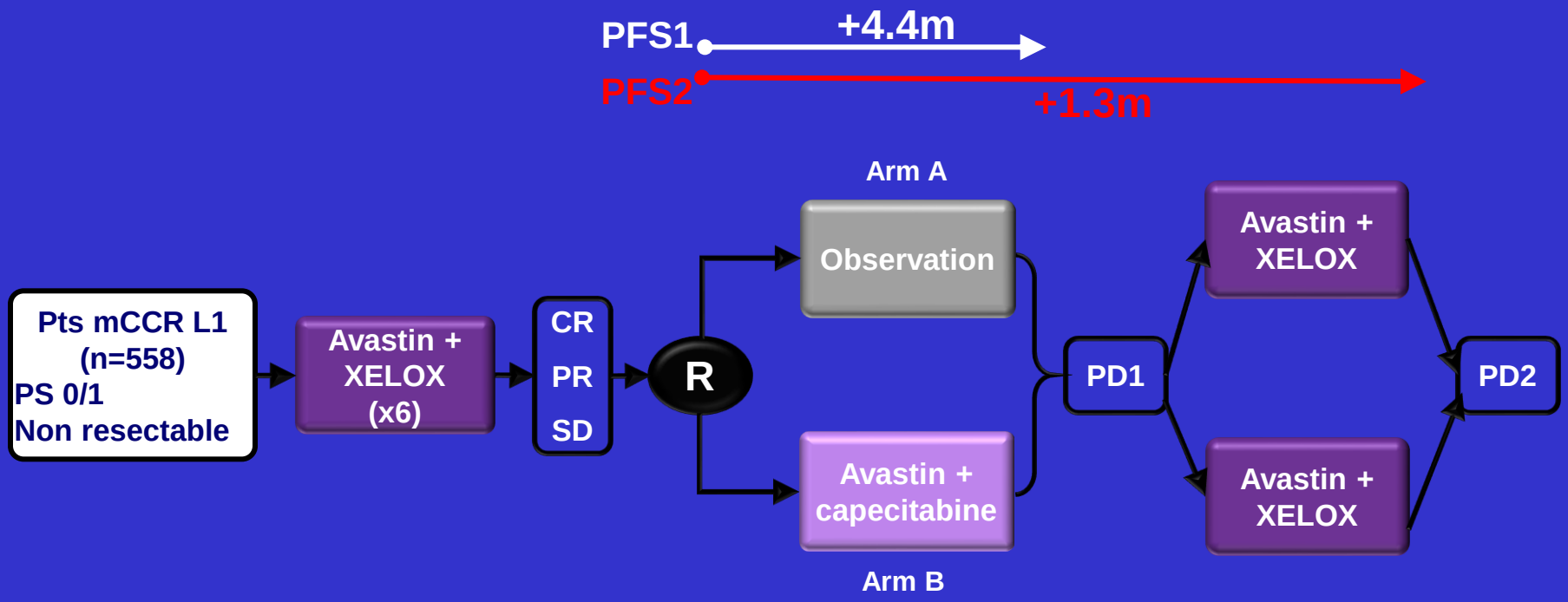
- Treatment-free interval should be considered
  - The longer the time to progression, the greater the chance of a response to re-treatment with the same regimen

Oxaliplatin reintroduction at progression after FOLFOX in 1st line

- 29 patients initially treated with Folfox (2, 3, 5, 6, 7)
  - 1st-line ORR: 24/29, SD 4/29, PD 1/29
  - 13 patients did not receive therapy until PD
    - Median treatment-free interval: 12 weeks (3-99w)
    - 12/13 had a disease control after reintroduction
  - Median PFS after reintroduction: 27 weeks
  - Median OS after reintroduction: 58 weeks

Maindrault-Goebel et al Ann Oncol 2004; 15: 1210

CAIRO-3 (phIII) Design

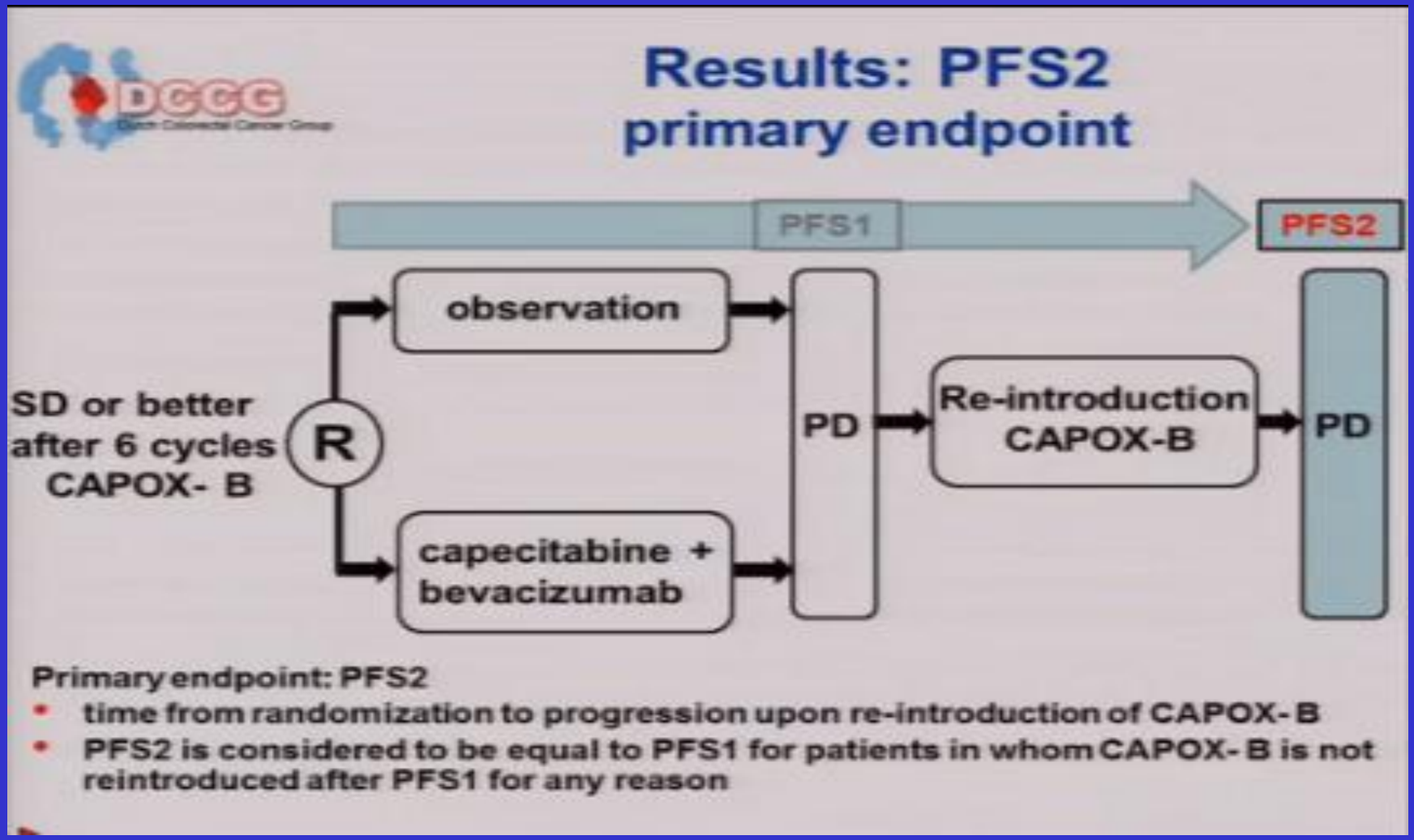


- **Primary Endpoint** : PFS after reintroduction of induction CT (PFS2)
- **Secondary Endpoints** : PFS1, OS, TTP2, ORR, tolerance
- **Sponsor** : Dutch Colorectal Cancer Group (DCCG)

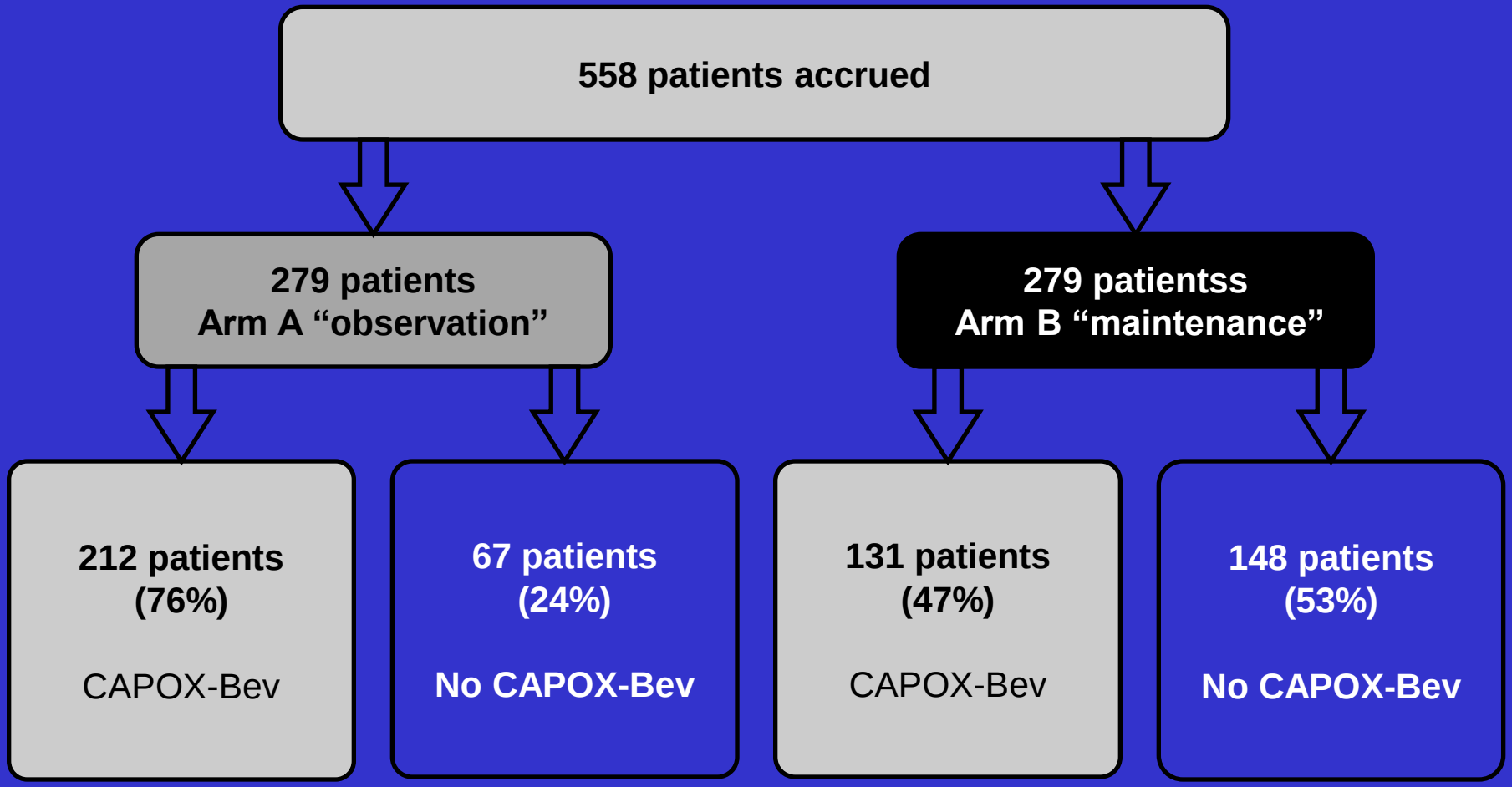
- **Treatments :** bevacizumab : 2,5 mg/kg/week (eq.) / Capecitabine : 625mg/m² x2/d

Koopman M et al. ASCO 2013 (abst. 3502)

Re-introduction of 1st-line regimen: CAIRO 3

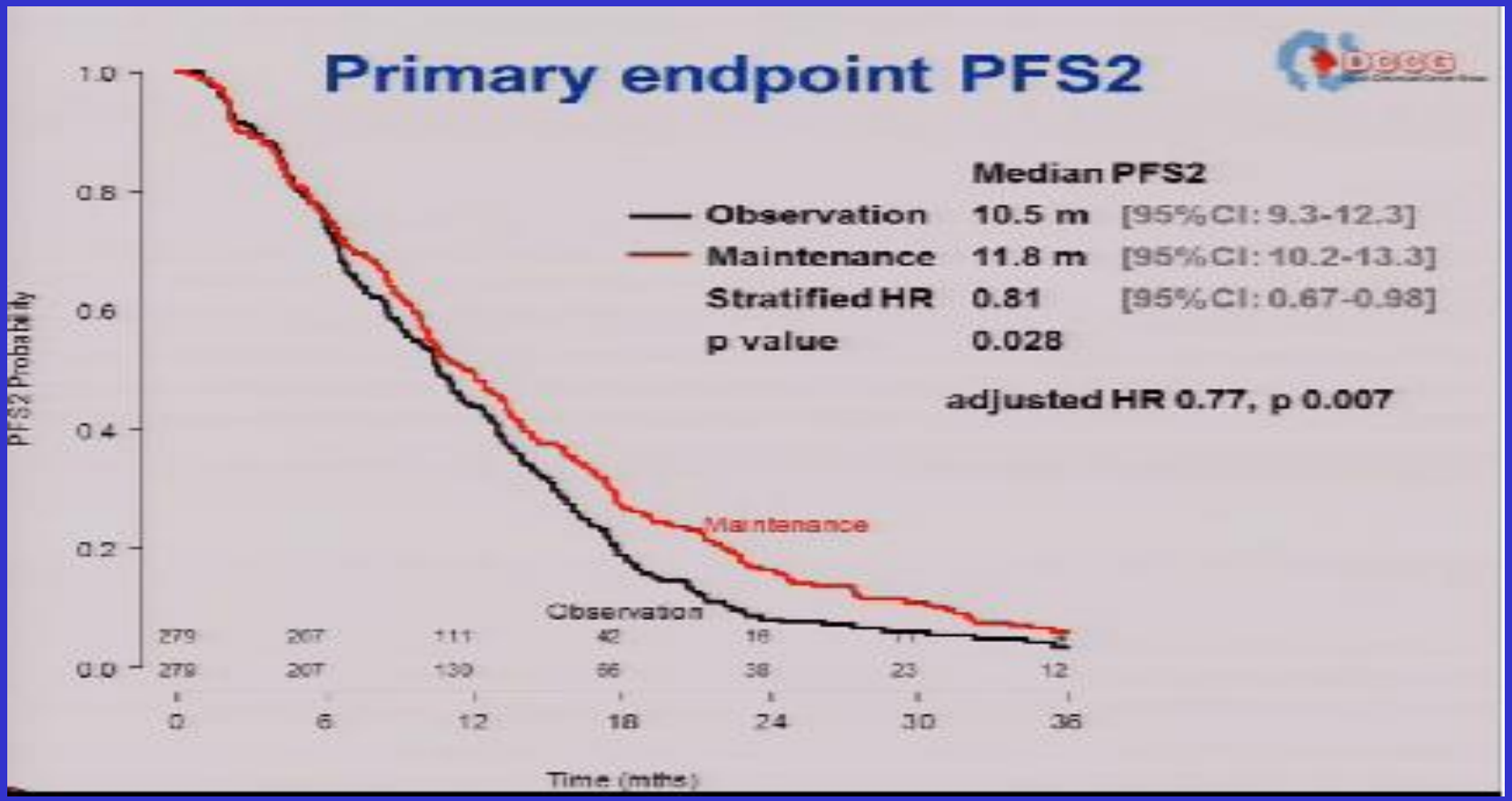


CAIRO-3 (phIII)
Patients Disposition

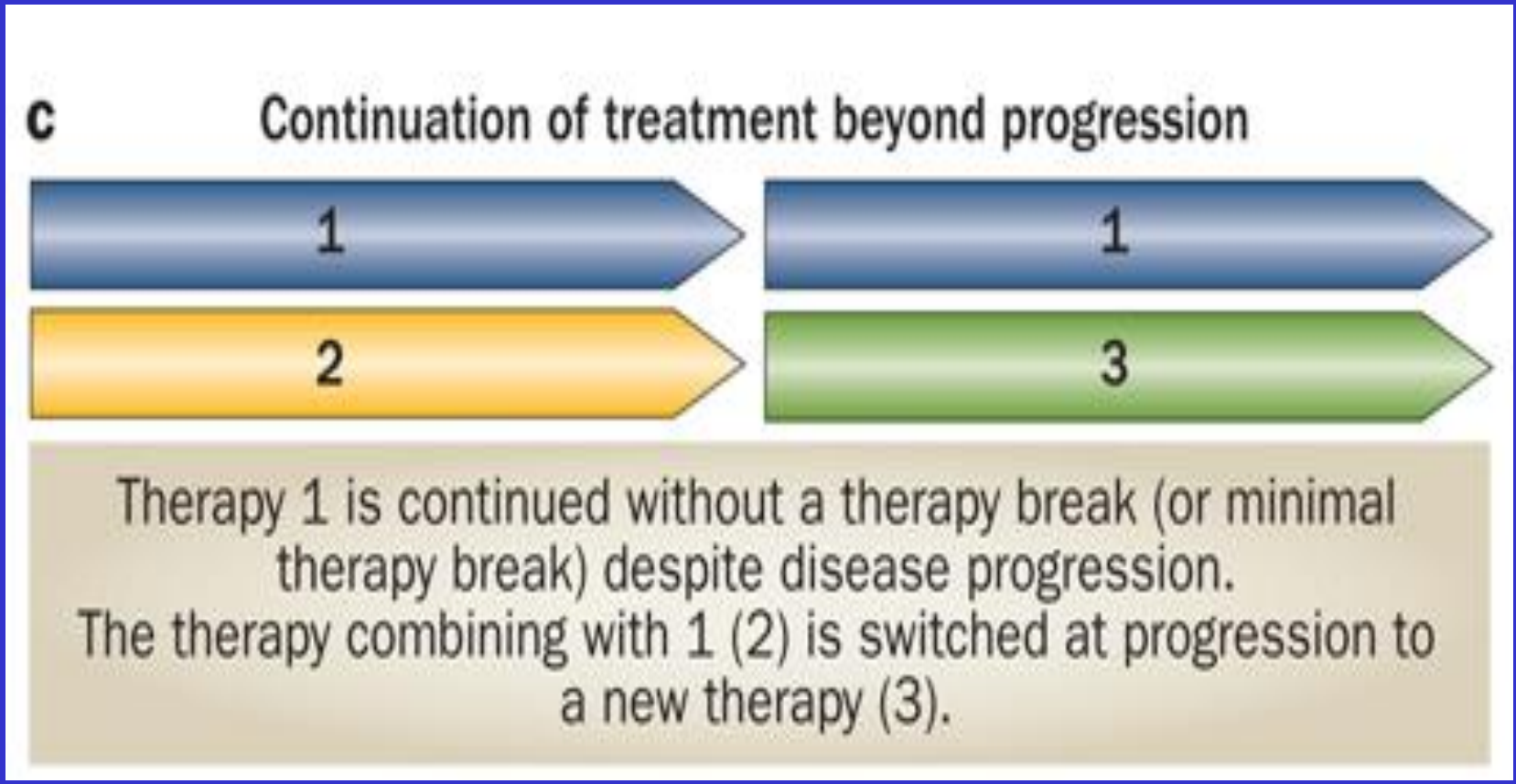


Koopman M et al. ASCO 2013 (abst. 3502)

Re-introduction of 1st-line regimen: CAIRO 3



Conventional and nonconventional (drug rechallenge and treatment beyond progression) therapy regimens in medical oncology



Kuczynski, E. A. *et al.* (2013) Drug rechallenge and treatment beyond progression—implications for drug resistance
Nat. Rev. Clin. Oncol. Oct 2013;10: 571-87

nature REVIEWS CLINICAL ONCOLOGY

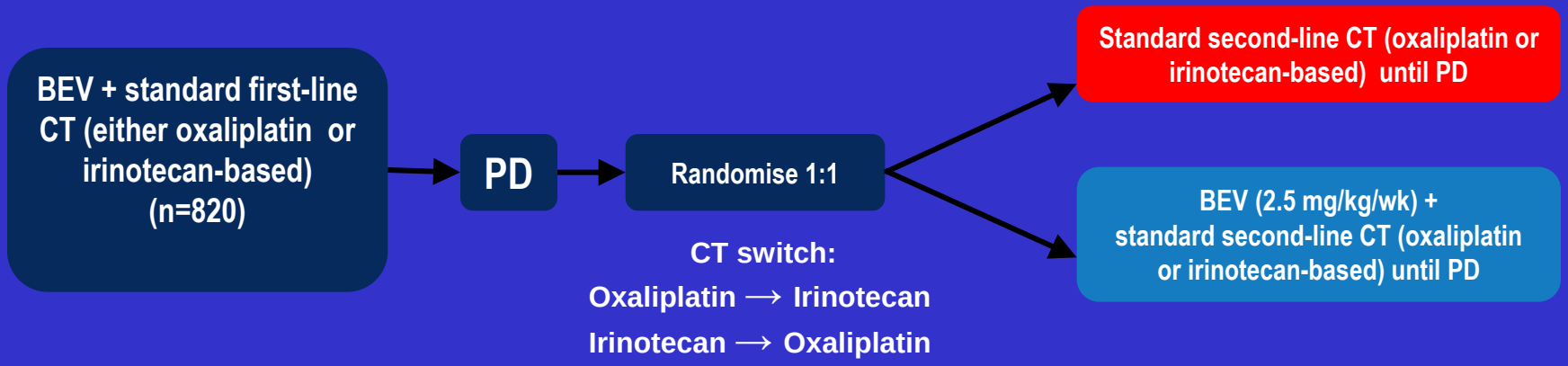
Continuous Blockade of Angiogenesis

Bevacizumab Beyond Progression (BBP)

- 2 randomized studies:
  - TML[1]
  - BEBYP[2]

1.Bennouna J et al. *The Lancet Oncology.* Jan 2013;14:29-37;
2.Masi G, ESMO Vienna 2012 LBA 17.

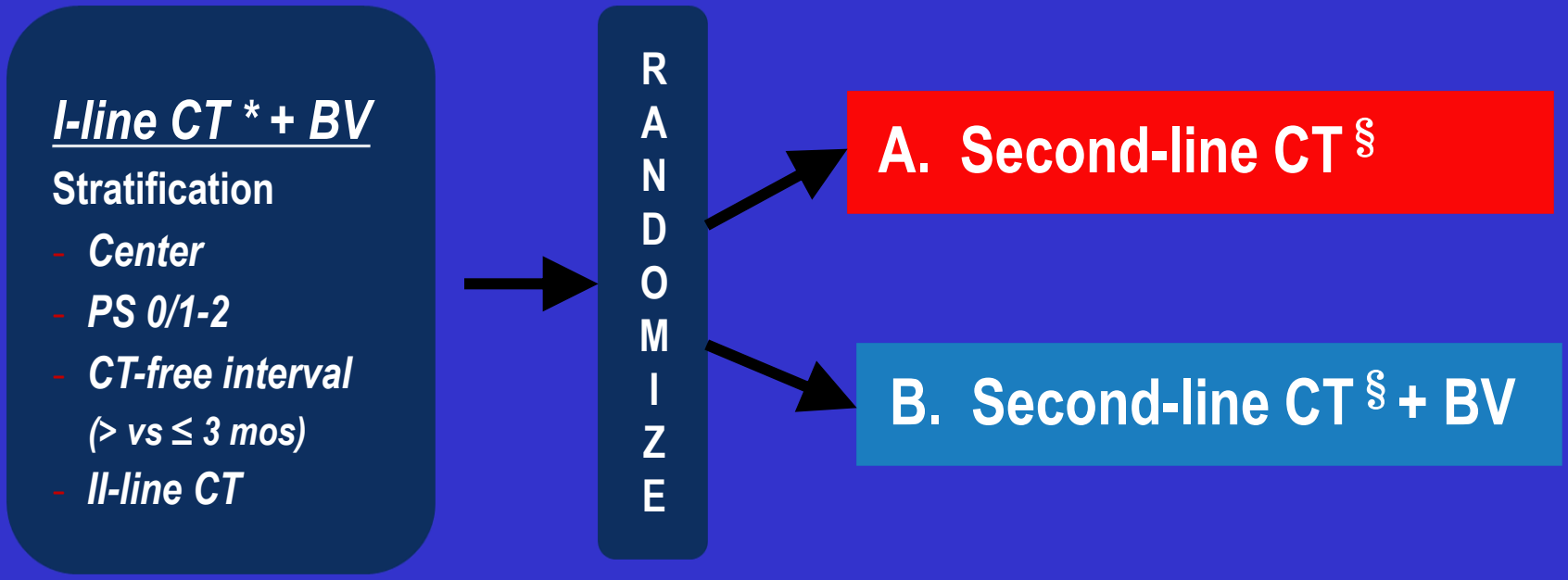
ML18147 Study Design (phase III)



Primary endpoint	• Overall survival (OS) from randomisation
Secondary endpoints included	• Progression-free survival (PFS) • Best overall response rate • Safety
Stratification factors	• First-line CT (oxaliplatin-based, irinotecan-based) • First-line PFS (≤9 months, >9 months) • Time from last BEV dose (≤42 days, >42 days) • ECOG PS at baseline (0/1, 2)

Bennouna J et al. *The Lancet Oncology*.Jan 2013;14:29-37.

BEBYP: Study Design



*
- FOLFIRI
- FOLFOX
- FOLFOXIRI
- Fluoropyrimidine mono-tx

§
- FOLFIRI
- mFOLFOX-6

- Study conducted in 19 Italian centers

Supported by AIFA

Masi G, ESMO Vienna 2012 LBA 17.

How Does BEBYP Compare with TML?

TML

- Randomized phase III
- N= 820
- Complete accrual
- All Bev. Pre-treated 1st line
- 2nd line w/wo Bev

- 1st EP: OS since rando
- 2nd EP:
  - PFS
  - ORR
  - Safety

BEBYP

- Randomized phase II
- N=262 planned
- Terminated early at 184 pt
- All Bev. Pre-treated 1st line
- 2nd line w/wo Be

- 1st EP: PFS since rando
- 2nd EP:
  - OS (immature)
  - ORR
  - Safety

Both studies evaluated the use of Bevacizumab beyond progression

How Does BEBYP Compare with TML? Patient Populations

TML

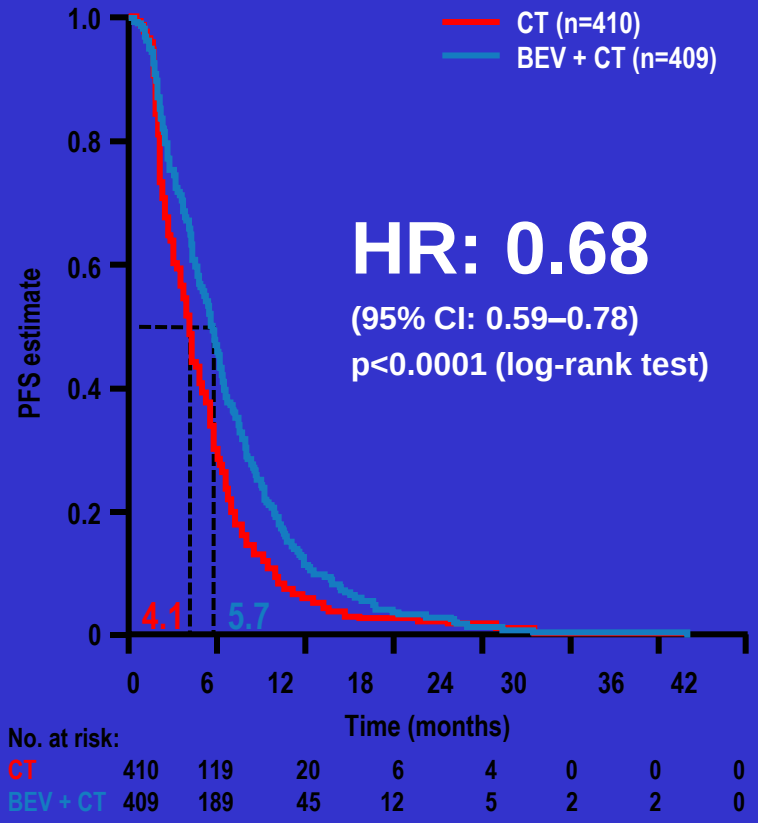
- **Exclusion criteria**
  - PD>3m after last Bev
  - 1st line PFS < 3 m
  - 1st line Bev< 3 consecutive m
- **1st line PFS**
  - ≤ 9m: 55%
  - > 9m: 45%
- **Post-study treatment (C/CB)**
  - Bev: 12%/11%
  - Anti EGFR: 39%/41%

BEBYP

- **Inclusion criteria**
  - PD after 3m or during 1st line CT+Bev
  - Or 3m after Folfoxiri Bev
- **1st line PFS**
  - 10.3 m
- **Post-study treatment (C/CB)**
  - Bev: 1%/3%
  - Anti EGFR: 46%/32%

How Does BEBYP Compare with TML? PFS Analysis

TML (2nd EP)

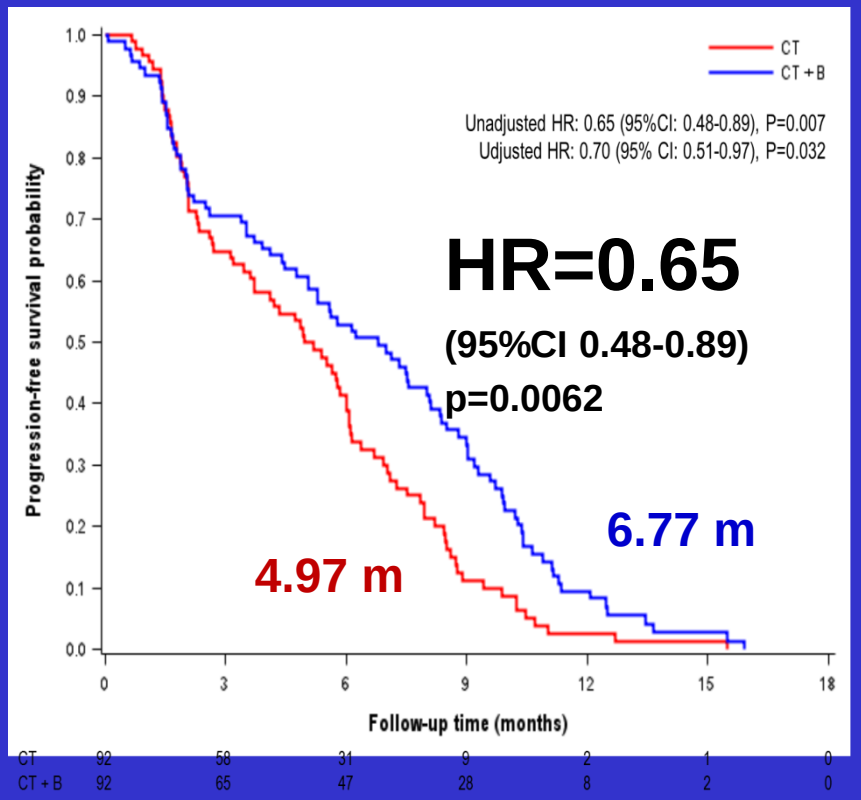


HR: 0.68

(95% CI: 0.59–0.78)

p<0.0001 (log-rank test)

BEBYP (1st EP)



HR=0.65

(95%CI 0.48-0.89)

p=0.0062

4.97 m

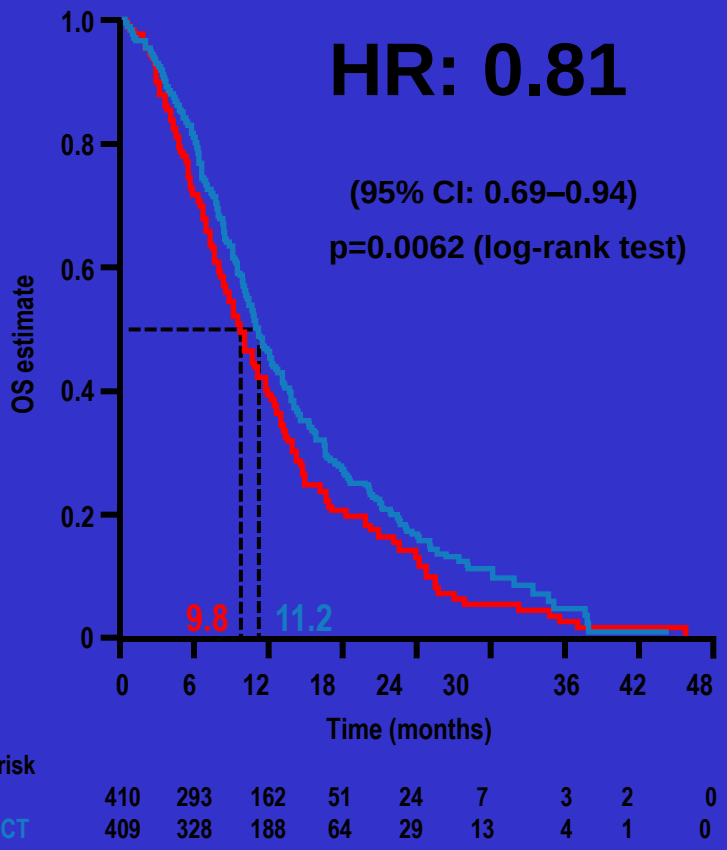
6.77 m

How Does BEBYP Compare with TML? ORR Analysis

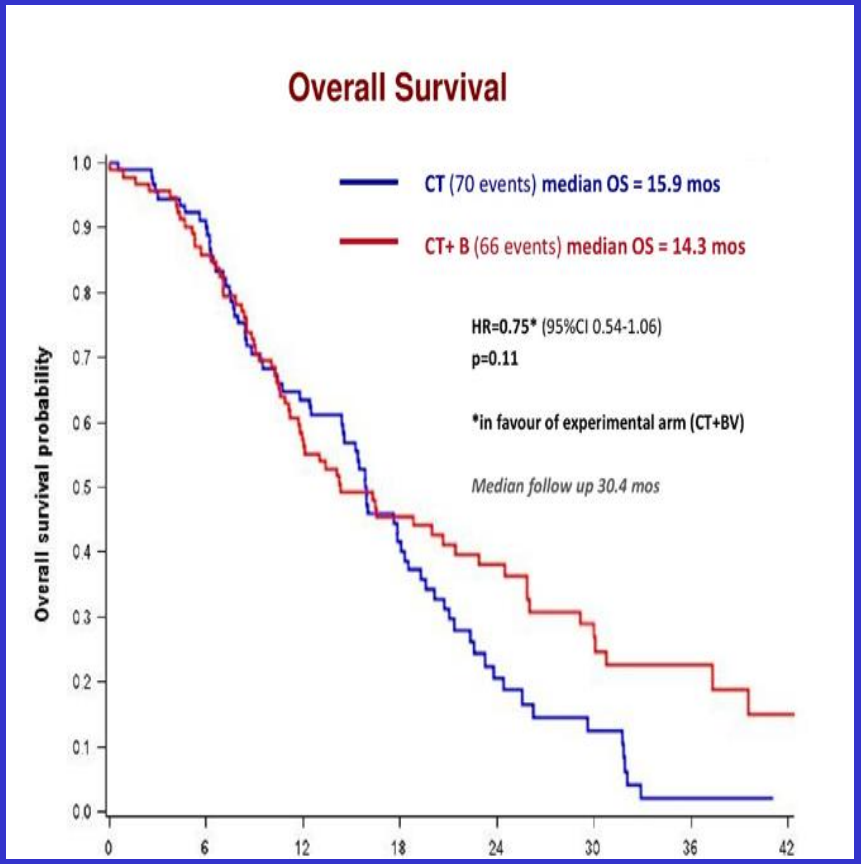
	TML			BEBYP		
	CT	p	CT+BEV	CT	p	CT+BEV
ORR %	4	0.31	5	18	ns	21
DCR	54	0.0001	68	62	ns	71

How does BEBYP compare with TML? OS analysis

TML



BEBYP

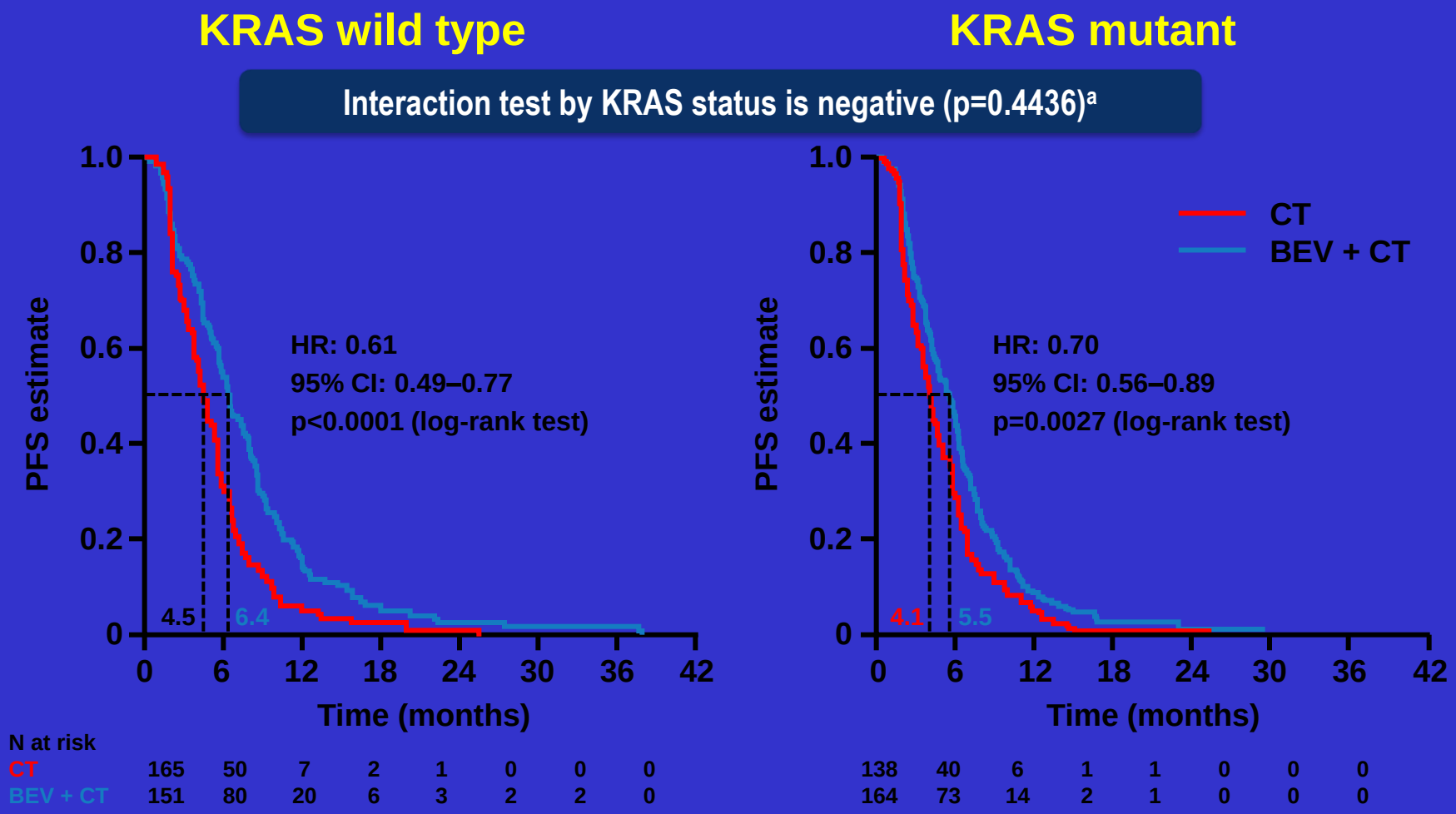


How Does BEBYP Compare with TML? Sub-group Analysis

- All sub groups studied in both TML and BEBYP benefited from Bevacizumab continuation on PFS
- No data on OS for BEBYP

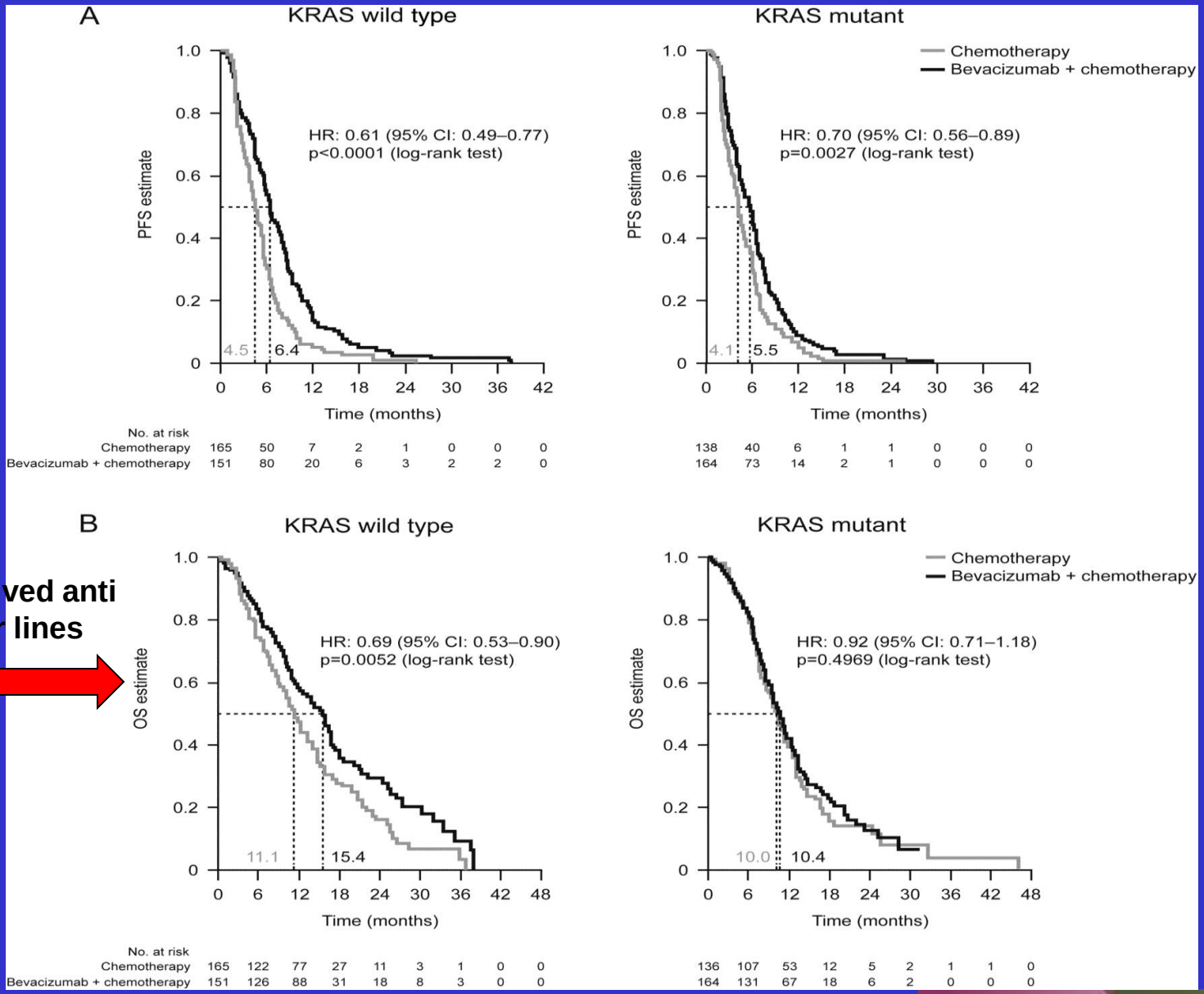
- Partial population analysis for Kras:
  - In both TML and BEBYP the benefit of Bev was independant of Kras for PFS
  - but not on OS for Kras mutant as opposed to wild-type (TML only)

TML: PFS in the KRAS Population



Courtesy from E Van Cutsem WCGIC Barcelona June 2012.

Survival according to the treatment group and tumor KRAS mutation status: (A) PFS and (B) OS.

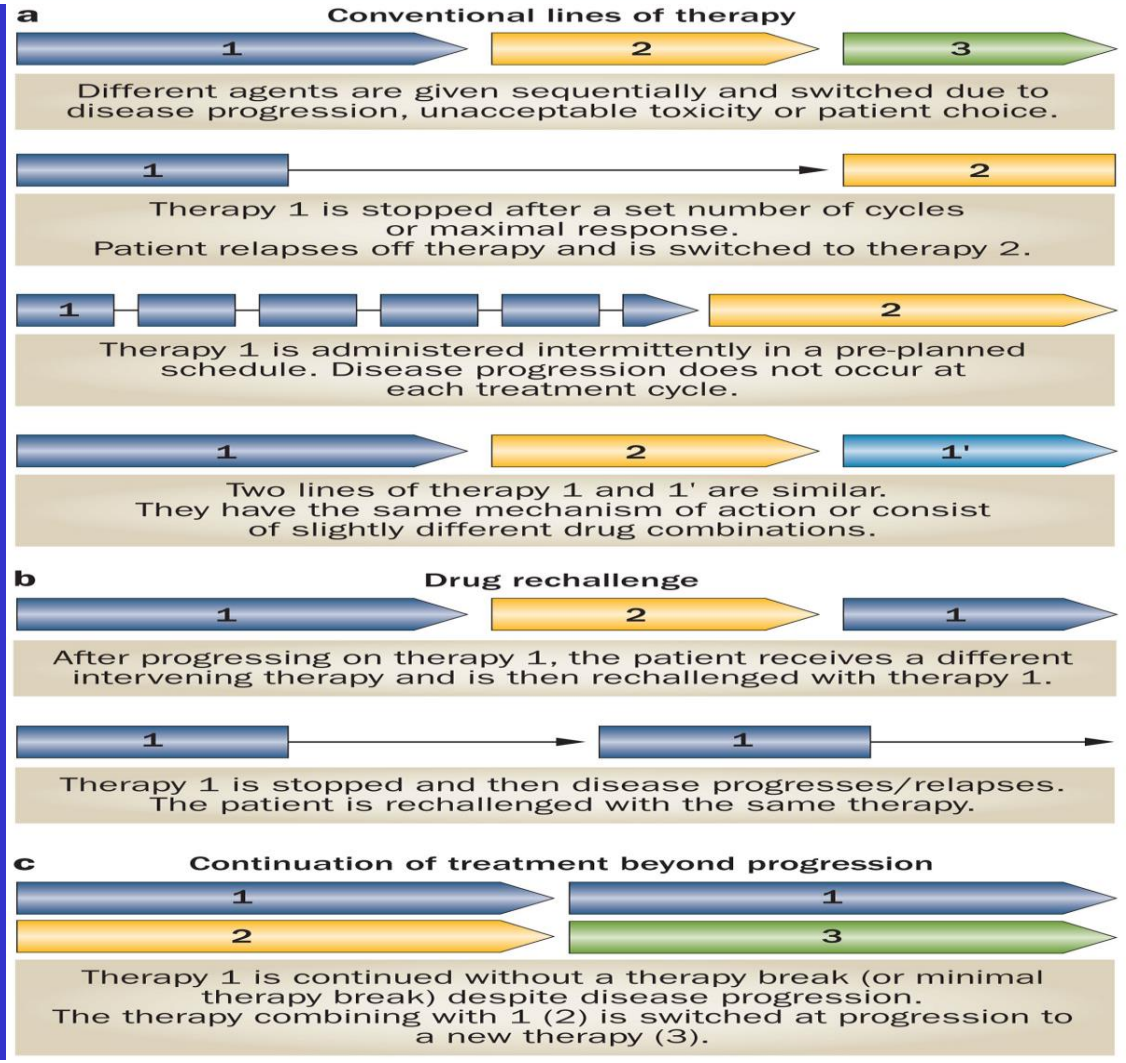


241/316 received anti EGFR in later lines

Kubicka S et al. Ann Oncol 2013;24:2342-2349

Annals of Oncology

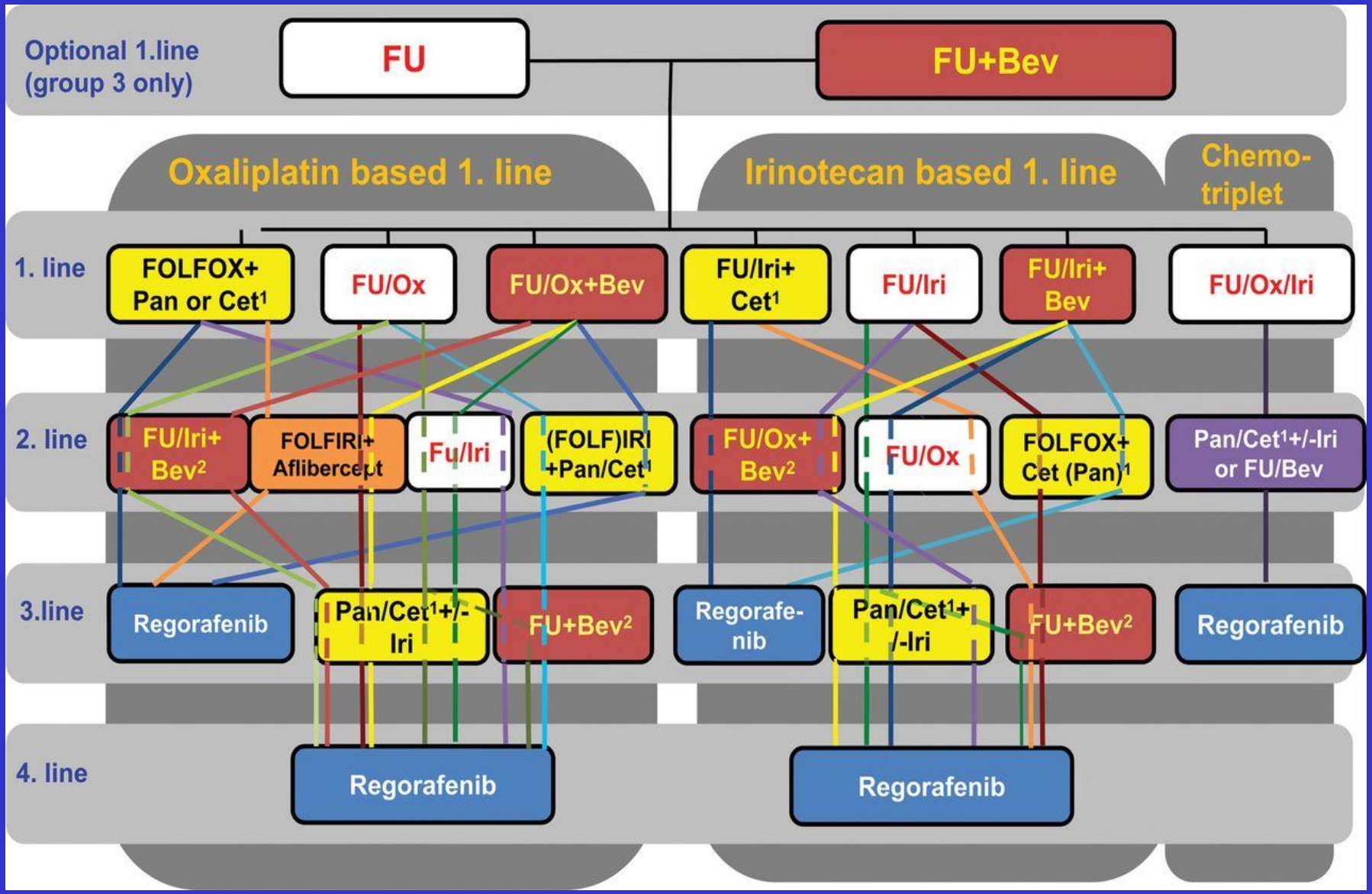
Figure 1 Conventional and nonconventional (drug rechallenge and treatment beyond progression) therapy regimens in medical oncology



Kuczynski, E. A. *et al.* (2013) Drug rechallenge and treatment beyond progression—implications for drug resistance
***Nat. Rev. Clin. Oncol.* Oct 2013;10: 571-87**

nature REVIEWS CLINICAL ONCOLOGY

Proposal for sequence of salvage-chemotherapy.



Schmoll H J et al. Ann Oncol 2012;23:2479-2516

Annals of Oncology

What to do after progression?

- Most of the patients with mCRC are not curable
- Quality of life should be considered as well as quatity

- Continuous exposure during all the surviving time is not feasible due to toxicity and compliance and is not demonstrated to be beneficial on OS

- Numerous alternative strategies are available, most often offering treatment breaks that will benefit to quality of life

- Patient opinion and desires must be considered for decision making