Metastatic Colorectal Cancer session

Review of the ESMO Consensus Conference on metastatic colo-rectal cancer General strategy Group 0-3

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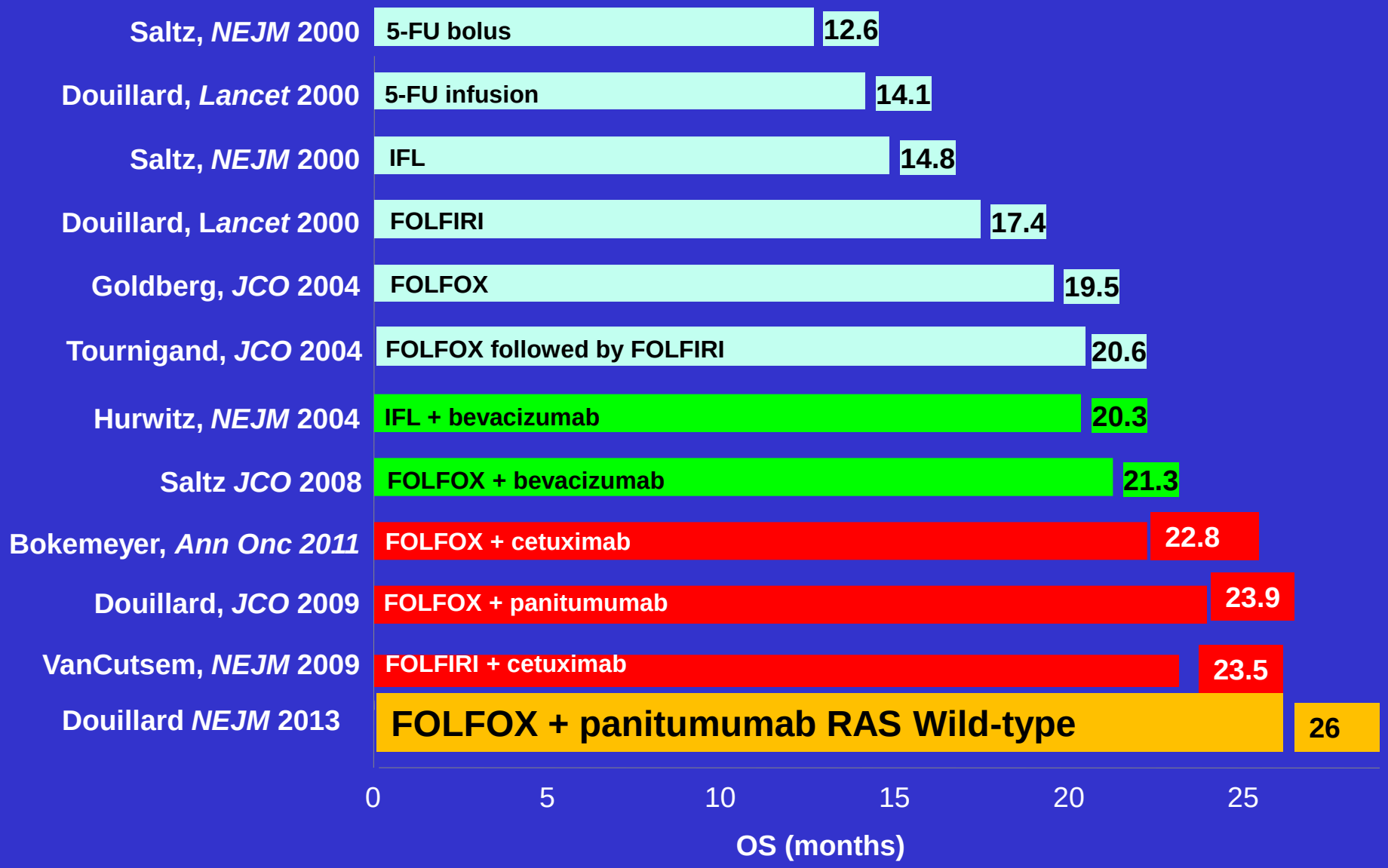
Disclosure JY Douillard

- Compensated participations in:
  - Advisory Boards and Symposia:
    - Amgen
    - Bayer
    - Boehringer Ingelheim
    - Merckserono
    - Roche/Genentech
    - Sanofi
  - Research Funding
    - Merckserono

Incremental Improvements in Overall Survival in the Last Decade



Unresectable mCRC treatment in 2013

- Median expected OS: 20-30 months
- Most of the patients will receive several lines of treatment
  - From 100 in 1st line
    - 60-70 will receive a 2nd line
    - 30-40 will receive a 3rd Line
    - 15-20% will receive 4+ lines

special article

Annals of Oncology 23: 2479–2516, 2012
doi:10.1093/annonc/mds236

ESMO Consensus Guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making

H. J. Schmoll[1*], E. Van Cutsem[2], A. Stein[3], V. Valentini[4], B. Glimelius[5,6], K. Haustermans[7], B. Nordlinger[8,9], C. J. van de Velde[10], J. Balmana[11], J. Regula[12], I. D. Nagtegaal[13], R. G. Beets-Tan[14], D. Arnold[3], F. Ciardiello[15], P. Hoff[16,17], D. Kerr[18], C.H. Köhne[19], R. Labianca[20], T. Price[21], W. Scheithauer[22], A. Sobrero[23], J. Tabernero[24], D. Aderka[25], S. Barroso[26], G. Bodoky[27], J. Y. Douillard[28], H. El Ghazaly[29], J. Gallardo[30], A. Garin[31], R. Glynne-Jones[32], K. Jordan[1], A. Meshcheryakov[31], D. Papamichail[33], P. Pfeiffer[34], I. Souglakos[35], S. Turhal[36] & A. Cervantes[37]

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

Groups according to clinical presentation

ESMO Consensus Conference 2011 Schmoll H J et al. Ann Oncol 2012;23:2479

Groups	Clinical Criteria
Group 0	Upfront resectable metastasis, Goal: cure, reduced relapse rate
Group 1	Potentially resectable metastasis Goal: Objective Response, tumor shrinkage.
Group 2	Multiple metastasis, rapid progression, associated symptoms even in patients without major co-morbidities Goal: Disease control, symptom improvement.
Group 3	Multiple metastasis or organ involved, definitely never resectable, Mild symptoms associated, co-morbidities Goal: Disease control, increased survival with preserved quality of life, regimen with mild toxicity profile prefered..

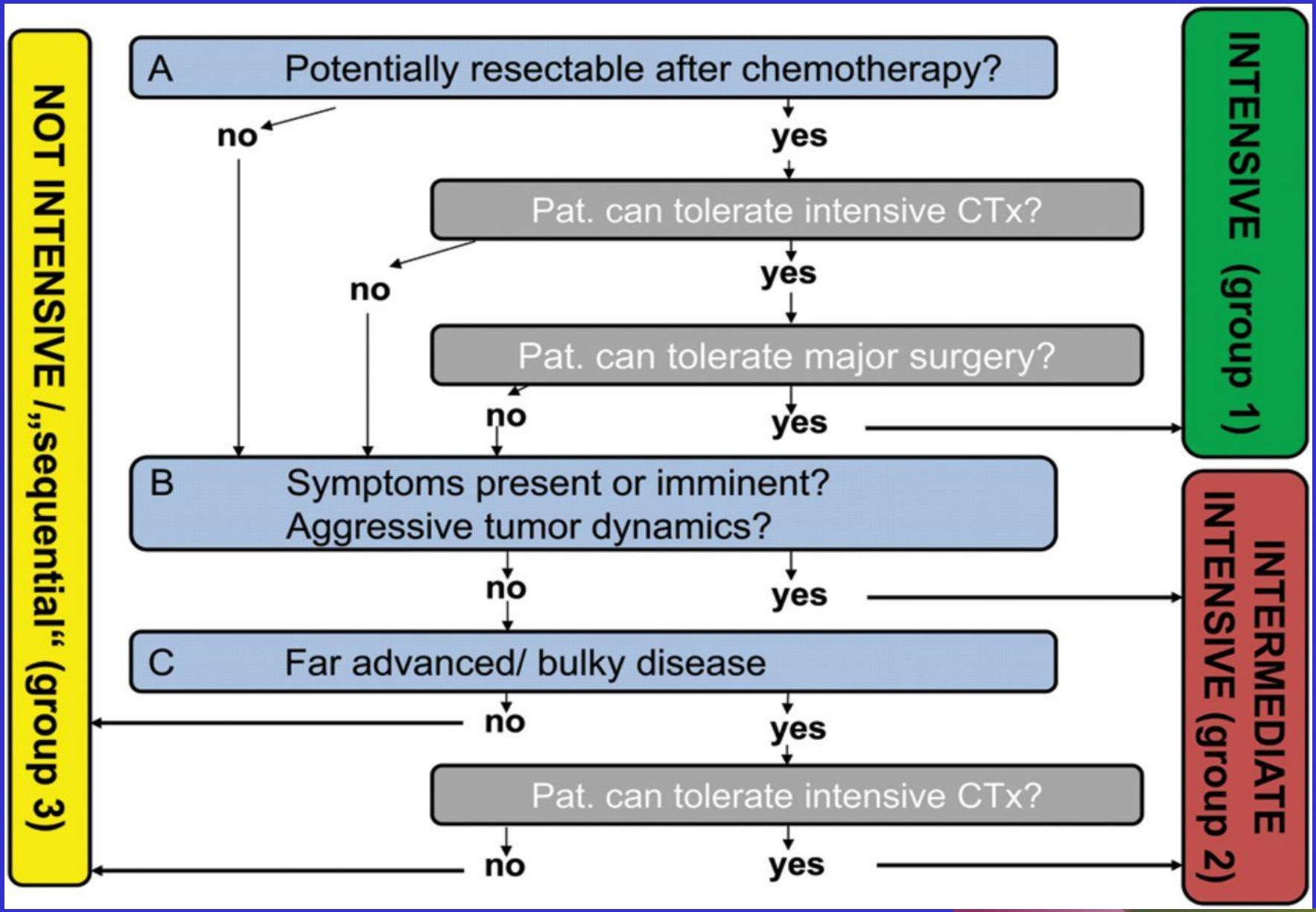
Clinical Groups 0 and 1

	Clinical presentation	Treatment aim	Treatment intensity
0	Clearly R0-resectable liver and/or lung metastases	• Cure, decrease risk of relapse	Nothing or moderate (FOLFOX)
1	Not R0-resectable liver and/or lung metastases only which • Might become resectable after response to induction chemotherapy • ±Limited/localized metastases to other sites, e.g. loco regional lymphnodes • Patient is physically able to undergo major surgery (biological age, heart/lung condition) and more intensive chemotherapy	• Maximum tumour shrinkage	Upfront most active combination regimen

Clinical Groups 2 and 3

	Clinical presentation	Treatment aim	Treatment intensity
2	Multiple metastases/sites, with Rapid progression and/or Tumour-related symptoms and/or risk of rapid deterioration Co-morbidity allows intensive treatment	Clinically relevant tumour shrinkage as soon as possible At least achieve control of progressive disease	Upfront active combination: at least doublet
3	Multiple metastases/sites, with Never option for resection and/or no major symptoms or risk of rapid deterioration and/or severe comorbidity (excluding from later surgery and/or intensive systemic treatment, as for groups 1 + 2)	Abrogation of further progression Tumour shrinkage less relevant Low toxicity most relevant	Treatment selection according to disease characteristics and patients preference re toxicity and efficacy: "Watchful waiting" (exceptional) Sequential approach: start with Single agent, or Doublet with low toxicity Exceptional triplets

Hierarchy of factors for definition of treatment aim/group.



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Factors influencing the choice of 1st-line treatment (1) in group 1, 2 and 3

Tumour biology-related factors

- Localization
  - Liver- or lung-only metastases versus
  - Multiple sites
  - Potentially R0-resectable lesions after induction chemotherapy and sufficient downsizing versus massive disease extension
- Growth dynamics
  - Aggressive versus indolent growth
- Asymptomatic versus symptomatic disease
- Imminent relevant tumour symptoms if low active or inactive treatment
- Second-line treatment after ineffective first-line single-agent treatment may not be possible anymore
- Chemosensitivity (not detectable before start of chemotherapy)
- Prognostic molecular or biochemical markers (e.g. BRAF mutation)

Factors influencing the choice of 1st-line treatment (2) in group 1, 2 and 3

Patient-related factors

- Biological age
- Co-morbidity
- Physical capacity to tolerate more intensive treatment
- Eligibility for potential secondary resection of liver/lung
- Psychological capacity/willingness to undergo more intensive treatment

Drug efficacy/toxicity profile of chemotherapy

- Potential to induce maximal regression of metastases size/number
- Potential to prolong PFS or OS
- Toxicity profile
- Drug sensitivity/predictive biomarkers

Drug availability and cost

- Availability (depending on region)
- Reimbursement
- Cost/economic reasons

1st-line options according to clinical groups

Group	RAS wild-type	Recommendation[a]	RAS mutant	Recommendation[a]
1	FOLFIRI + Cet	+++	FOLFOX/XELOX + Bev	+++
	FOLFOX + Pan/Cet	+++	FOLFOXIRI	++(+)[b]
	FOLFOX/XELOX + Bev	++(+)	FOLFIRI/XELIRI + Bev	++(+)[c]
	FOLFOXIRI	++(+)[b]	FOLFOX/XELOX	+
	FOLFIRI/XELIRI + Bev	++(+)[c]	FOLFIRI/XELIRI	+
	FOLFOX/XELOX	+	IRIS	+
	FOLFIRI/XELIRI	+		
	IRIS	+		
2	FOLFIRI + Cet	+++	FOLFOX/XELOX + Bev	+++
	FOLFOX + Pan/Cet	+++	FOLFIRI/XELIRI + Bev	++(+)[c]
	FOLFOX/XELOX + Bev	+++	FOLFOX/XELOX	++
	FOLFIRI/XELIRI + Bev	++(+)[c]	FOLFIRI/XELIRI	++
	FOLFOXIRI	+(+)[b]	FOLFOXIRI	++[b]
	FOLFOX + Cet	+(+)	IRIS	+
	FOLFOX/XELOX	+		
	FOLFIRI/XELIRI	+		
	IRIS	+		
3	FUFOL/Cape (mono)	+++	FUFOL/Cape (mono)	+++
	FUFOL/Cape + Bev	+++	FUFOL/Cape + Bev	+++
	XELOX/FOLFOX	++	XELOX/FOLFOX	++
	FOLFIRI/XELIRI	++	FOLFIRI/XELIRI	++
	IRIS	+	IRIS	+
	Cet/Pan (mono)	(+)	watchful waiting	+ selected pts.[d]
	Watchful waiting	+ selected pts.[d]	triplets (±Bev)	+ option for spec. situation
	Triplets (+/−Bev or Cet/Pan)	+ option for spec.		

ESMO consensus patients groups

- **Additional predictive biomarkers should be incorporated in treatment decision**
  - **Ras phenotype allows to select for anti-EGFR therapy**
  - **Braf phenotype for chemotherapy intensification?**

ESMO Group 2 mCRC

- **Need for an active regimen for an agressive tumor to stop tumor growth**
  - **Doublets or Triplets chemo-regimen are preferred**
    - **To be selected according to tolerance profile/pre-existing conditions**
  - **Targeted agents may be used in combination with chemotherapy for improved efficacy**
    - **Decision should be based on RAS phenotype and contra-indications**
- **In some cases, patient file should be reviewed in a MDT to discuss possible resection.**

Preceptorship program: colorectal cancer

Group 3 patients

Clinical Groups for 1st-line treatment stratification

	Clinical presentation	Treatment aim	Treatment intensity
3	Multiple metastases/sites, with Never option for resection and/or no major symptoms or risk of rapid deterioration and/or severe comorbidity (excluding from later surgery and/or intensive systemic treatment, as for groups 1 + 2)	Abrogation of further progression Tumour shrinkage less relevant Low toxicity most relevant	Treatment selection according to disease characteristics and patients preference re toxicity and efficacy: "Watchful waiting" (exceptional) Sequential approach: start with Single agent, or Doublet with low toxicity Exceptional triplets

1st-line options according to clinical groups

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3	FUFOL/Cape (mono)	+++	FUFOL/Cape (mono)	+++
	FUFOL/Cape + Bev	+++	FUFOL/Cape + Bev	+++
	XELOX/FOLFOX	++	XELOX/FOLFOX	++
	FOLFIRI/XELIRI	++	FOLFIRI/XELIRI	++
	IRIS	+	IRIS	+
	Cet/Pan (mono)	(+)	watchful waiting	+ selected pts.[d]
	Watchful waiting	+ selected pts.[d]	triplets (±Bev)	+ option for spec. situations
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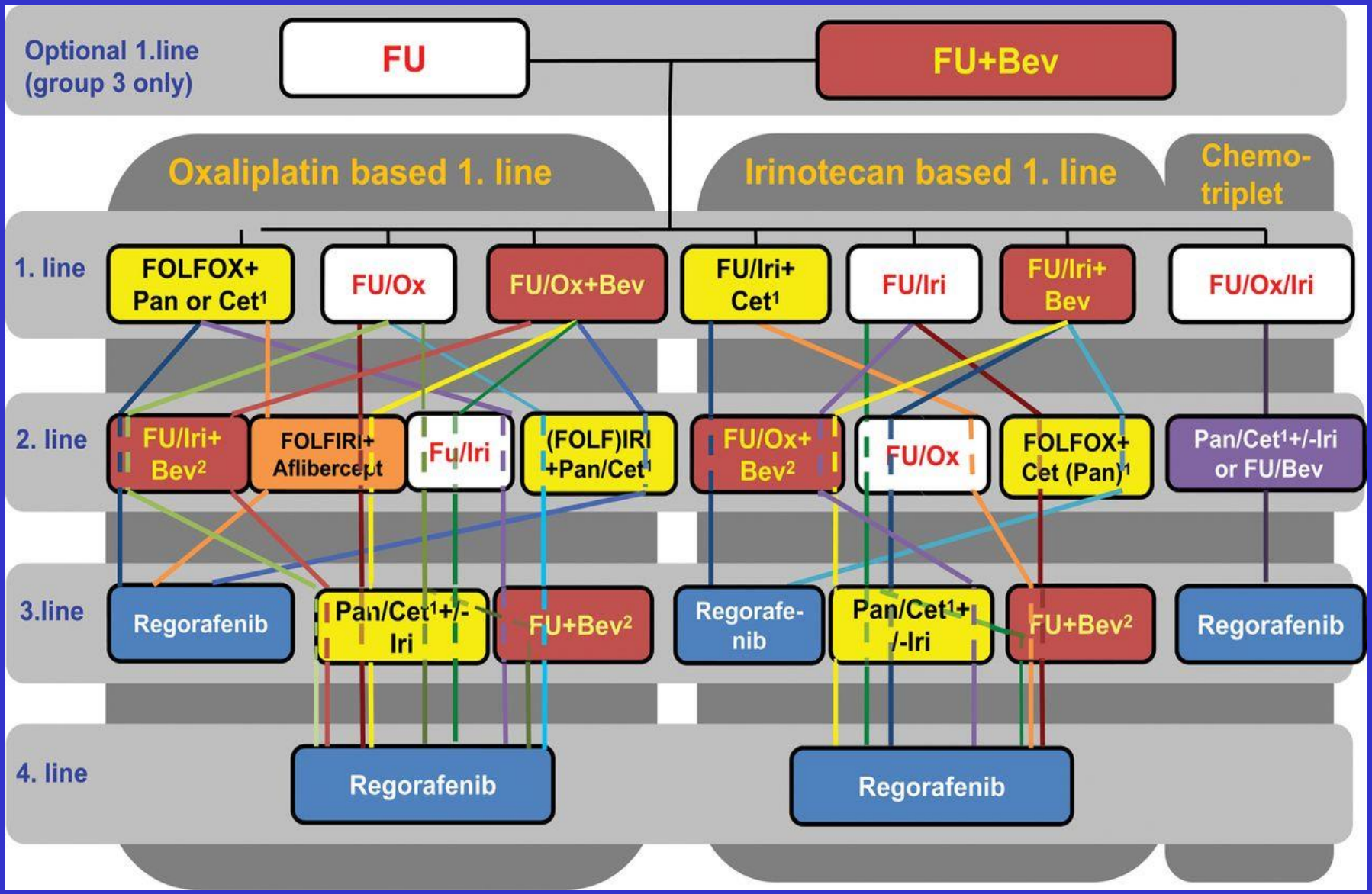
Proposal for sequence of salvage-chemotherapy.



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ESMO Group 3 mCRC

- Multiple strategies are possible
- Several lines will be used
- The important points are:
  - To try to use all available agents
  - Drug re-introduction may apply
  - To improve survival and preserve quality of life
- Stop and Go strategies are convenient and may allow longer treatment overall

ESMO Group 3 mCRC
Targeted agents + Chemotherapy

- **Bevacizumab is active in combination with chemotherapy**
  - **Survival benefit is not constantly seen but PFS is**
  - **Risk factors should be considered**
  - **If used, should be preferred in early lines**
  - **No activity as single agent**
  - **To be discussed if maintenance is used**

ESMO Group 3 mCRC

- **Anti-EGFR Monoclonal Antibodies are generally used at a later line of treatment in this patients population**
  - **Patients should be selected according to K and N RAS wt**
  - **No sequential trials in this group of patients are available**
  - **Upfront use of anti EGFR MoAb has been reported in small trial with high efficacy**
  - **Most frequently used in 3rd or 4th line**

State of Art for treatment strategy in mCRC

- ESMO consensus guidelines as a reference in clinical practice
- Each individual patient should be referred to 1 of the 4 groups
  - Treatment goal will be stated upfront
  - Treatment options will be identified for discussion