Clinical Trials in older patients with colorectal cancer:

The French Initiative

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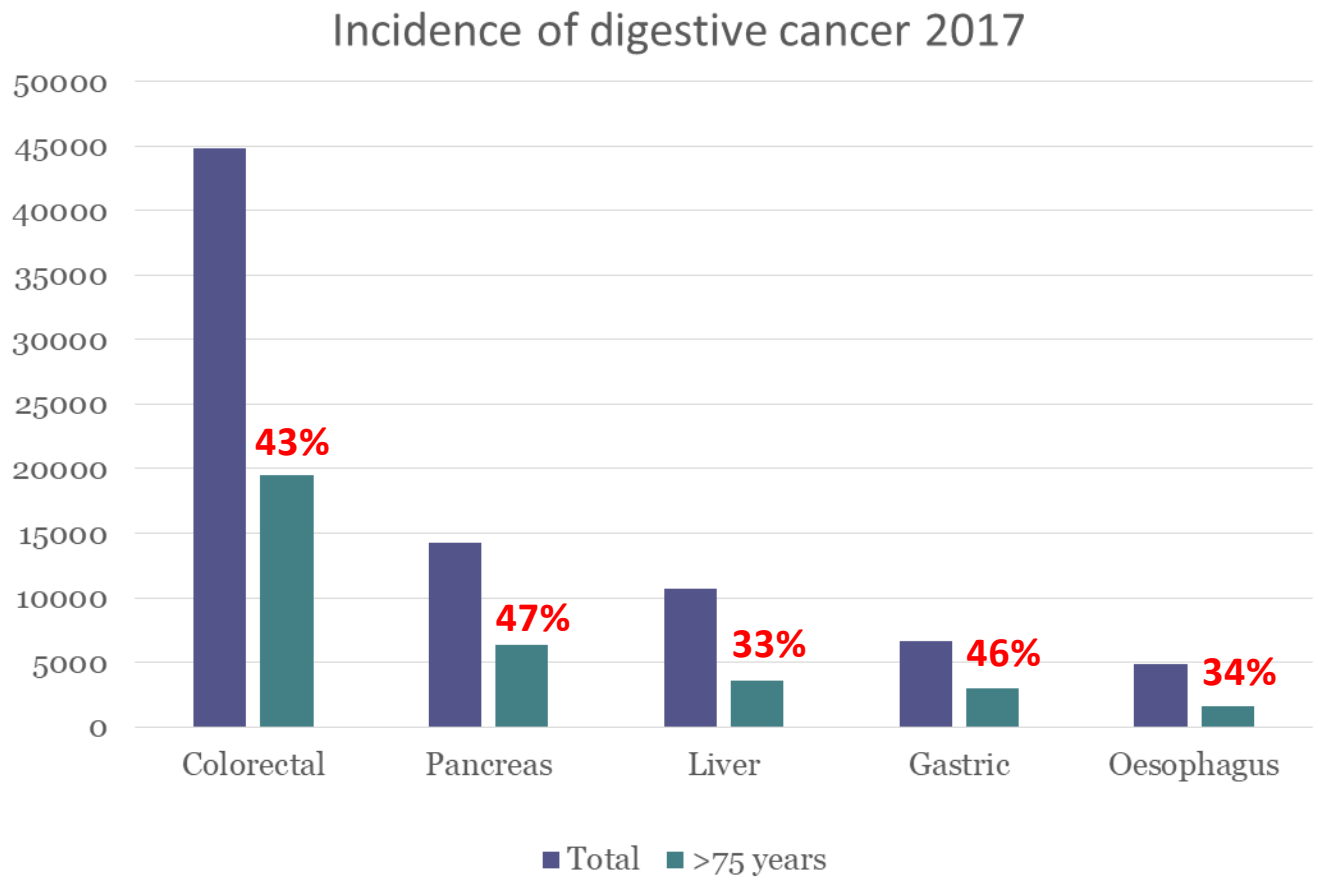
Journée DIALOG

05/05/2025

Incidence of GI cancers by age group

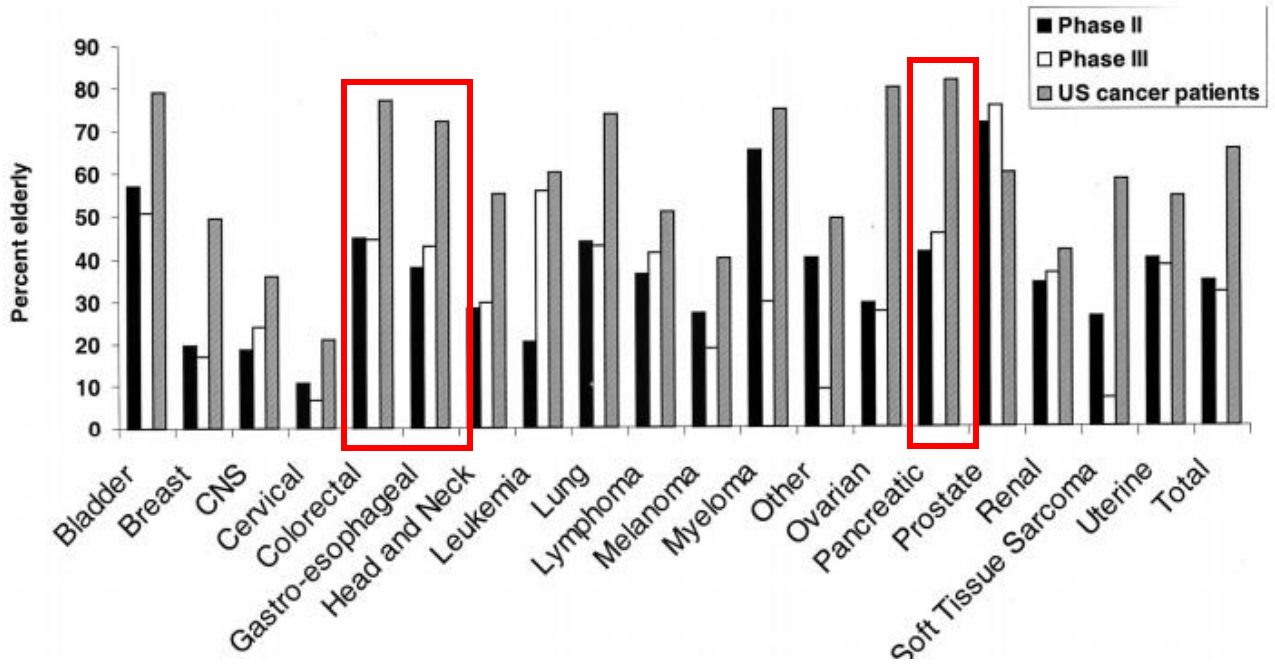
34 to 47% of GI cancers are diagnosed in patients aged >75 yrs



https://www.e-cancer.fr/Expertises-et-publications/Les-donnees-sur-les-cancers

Under-representation of older patients in clinical trials

Pts > 65 yrs in clinical trials

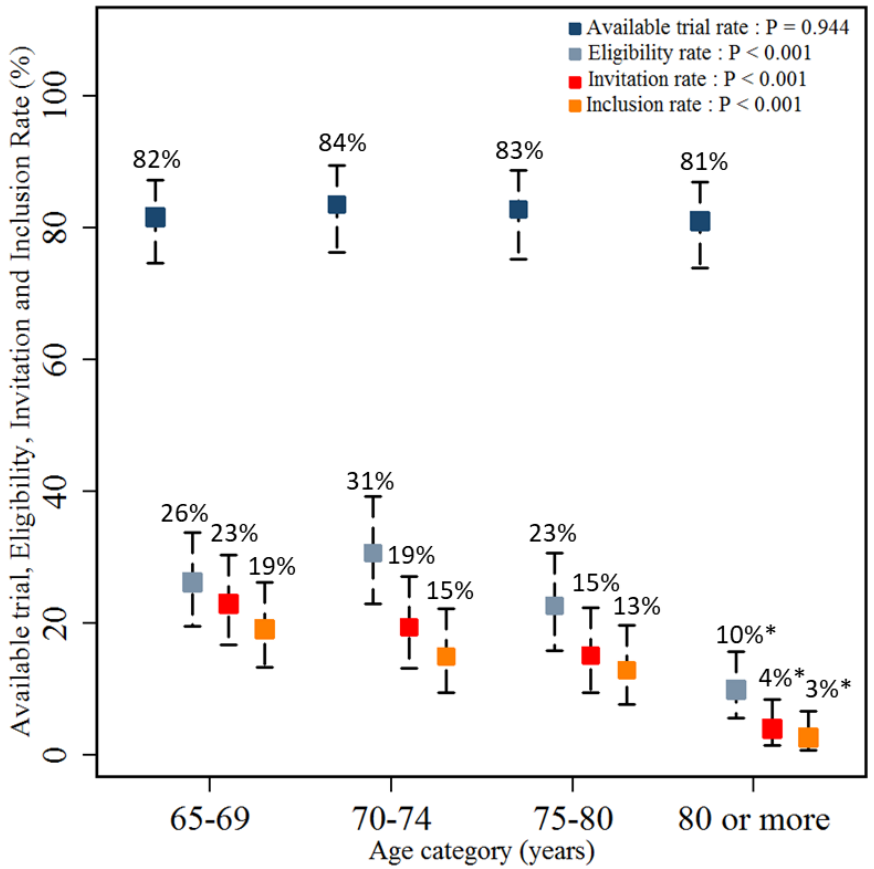


Exclusion criteria on age, second cancer, health status, organ dysfunction

Lewis J H et al. JCO 2003;21:1383-1389

SAGE prospective study

Inclusions of pts > 65 yrs in colorectal cancer trials in France (2012-2016)



Canouis-Poitrine F et al, The Oncologist 2019

Treatment differences by age

All colorectal cancers diagnosed in France in 2009 (n=41,342; median age 72 yrs)

Doat S et al. Eur J Cancer 2014; 50: 1276-83	<75 years	≥75 years	p
Localized stage, %	**80.5**	**79.5**	
Resection, %	83	82.5	0.52
Median time to surgery, days	23	8	<0.0001
Adjuvant chemotherapy, %	29	15	<0.0001
Type of chemotherapy, %			
Fluoropyrimidines	20.5	58	<0.0001
FOLFOX	79.5	41	<0.0001
Metastatic stage, %	**19.5**	**20.5**	
First line chemotherapy, %	85	48	<0.0001
Type of treatment (%)			
Fluoropyrimidine	10	30	<0.0001
Oxali-FU	34	31	0.1
Irinotecan.-FU	6	11	<0.0001
Cetuximab-Chemotherapy	9	4	<0.0001
Bevacizumab-Chemotherapy	35	20	<0.0001

Which treatment?

SURVIVAL
&
QUALITY OF LIFE

TOXICITIES
Side Effects

QUESTIONS :

- Will the patient die of his cancer or with his cancer?
- Is the patient at risk of complications due to cancer?
- Is the patient able to tolerate cancer treatments?
- Need for geriatric evaluation & specific management?

INCa recommendations

Oncogeriatry = priority of cancer plan 2009-2013

- Improve training of health care professionals to manage elderly patients >75 years
- Make sure there is a sufficient number of trained medical and paramedical health care professionals
- **Obtain that all cancer patients aged >75 years have a geriatric evaluation prior to any treatment decision**
- Inform population and health care professionals of factors favouring cancer in elderly patients
- Favor cooperation between oncologists and geriatricians → **UCOG**

www.e-cancer.fr

UCOG: Units of Coordination in OncoGeriatry

There is a need for specific trials in geriatric population

Metastatic colorectal cancer

- **Doublet or single drug regimen?**
- **Targeted therapy?**

Localized colon cancer

- **Adjuvant doublet or single drug regimen?**
- **Observation?**

FFCD 2001-02 phase III study design

2001

Stratification criteria

- Center
- Charlson index (0 vs 1-2 vs 3+)
- Karnofsky index (100 vs 90-80 vs 70-60)
- Previous adjuvant CT
- Sex
- Age (< 80 vs. ≥ 80 yrs)
- Alkaline phosphatases (≤ 2N vs. > 2N)

Irinotecan

- **150 mg/m²** for C1 and C2
- **180 mg/m²** ≥ C3 if toxicity ≤ grade 2 (except. alopecia)

Still some eligibility limitations

- Karnofsky index ≥60
- Adequate organ and bone marrow function
- Creatinin clearance ≥ 45 ml/min (Cockroft)

Limited geriatric assessment

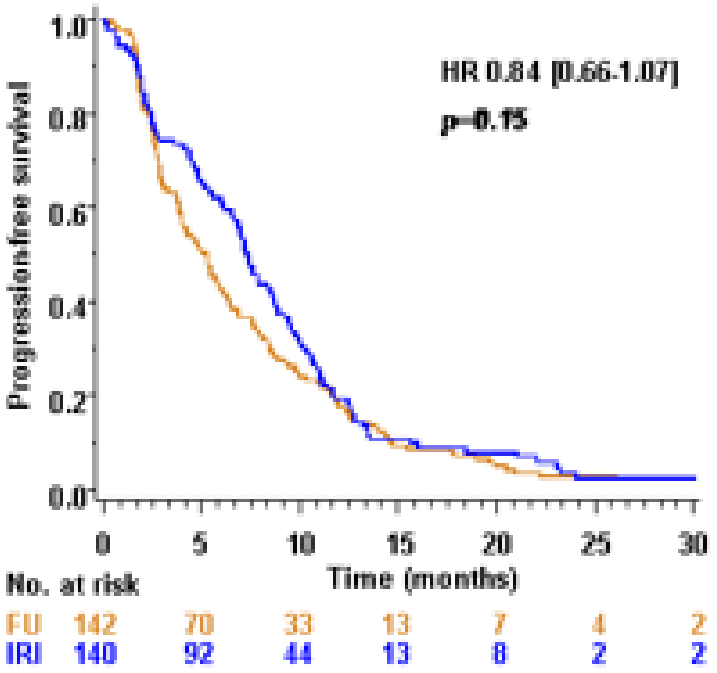
- Visual analogic QoL scale
- MMSE, IADL, GDS
- **But no nutritional assessment**

Funding: PFIZER

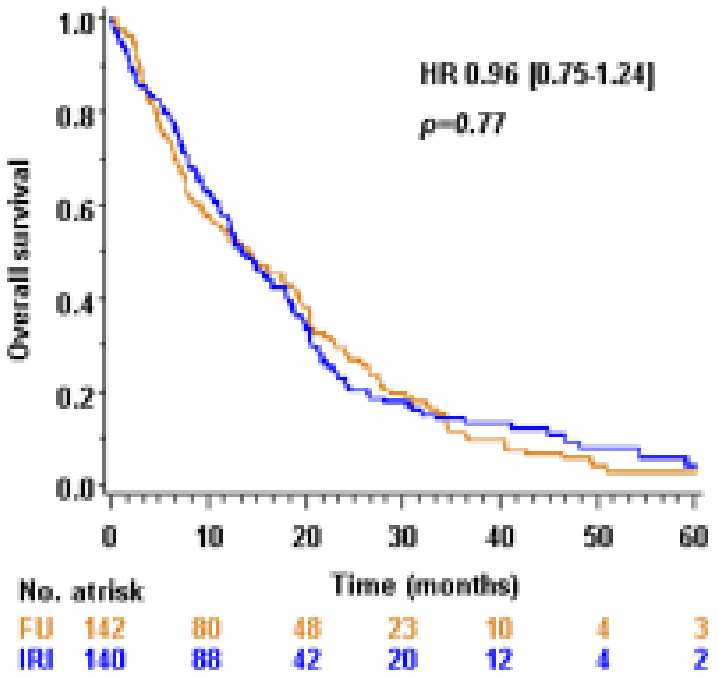
FFCD 2001-02: findings

282 patients randomized from 2003 to 2010: **7 years of recruitment**

Progression free survival



Overal survival

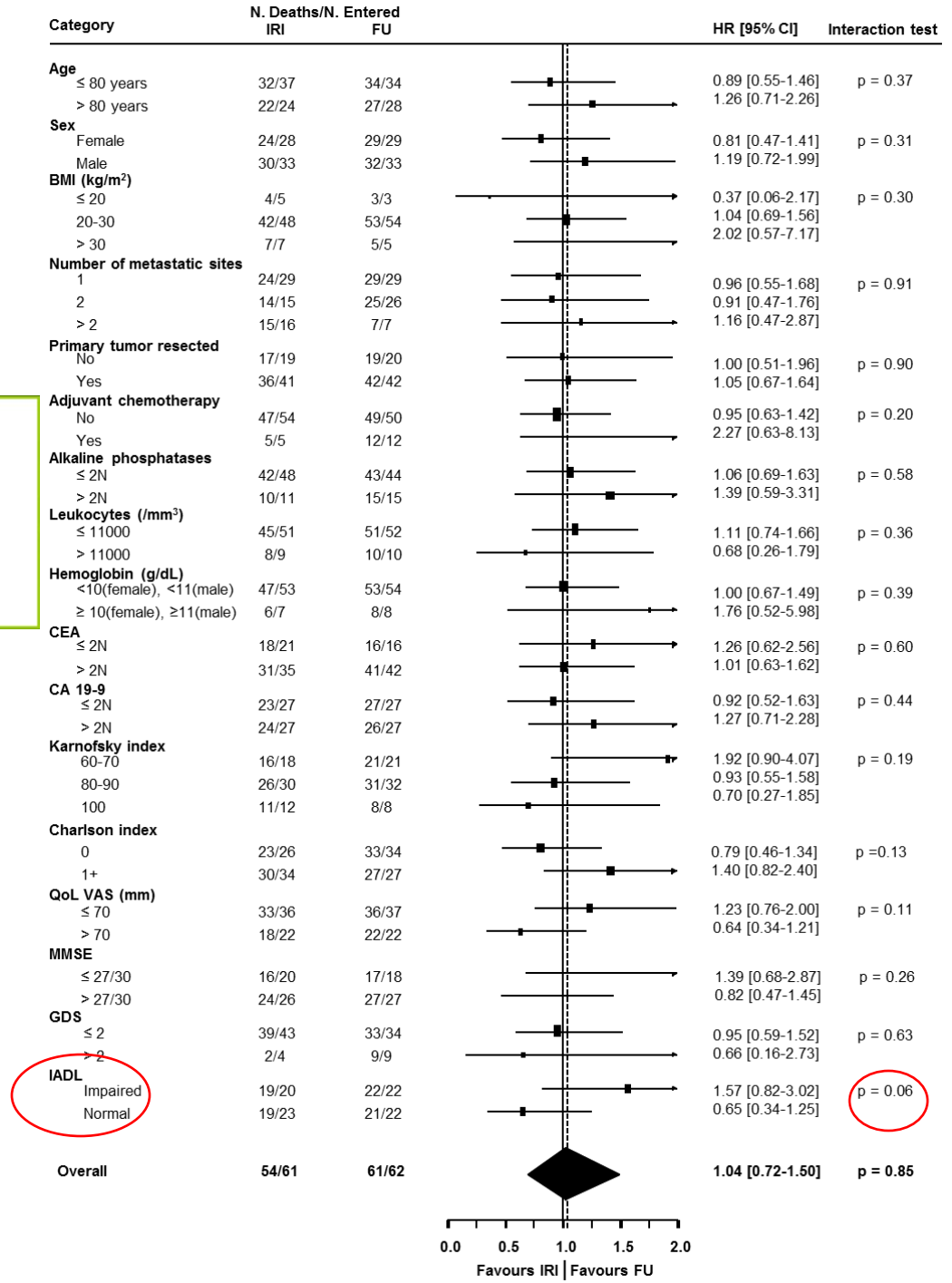


Intensification of chemotherapy in first line does’nt improve overall survival

Aparicio T et al Ann Oncol 2015

FFCD 2001-02 trial

Others findings



Overall survival subgroup analysis

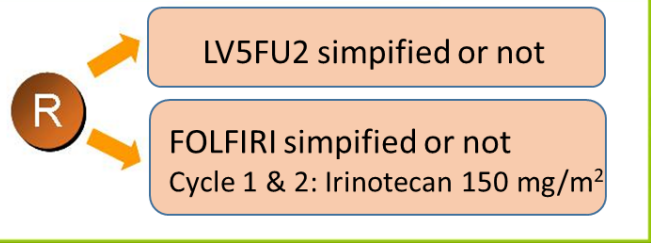
Patients with normal IADL have a greater benefit of irinotecan-based chemotherapy

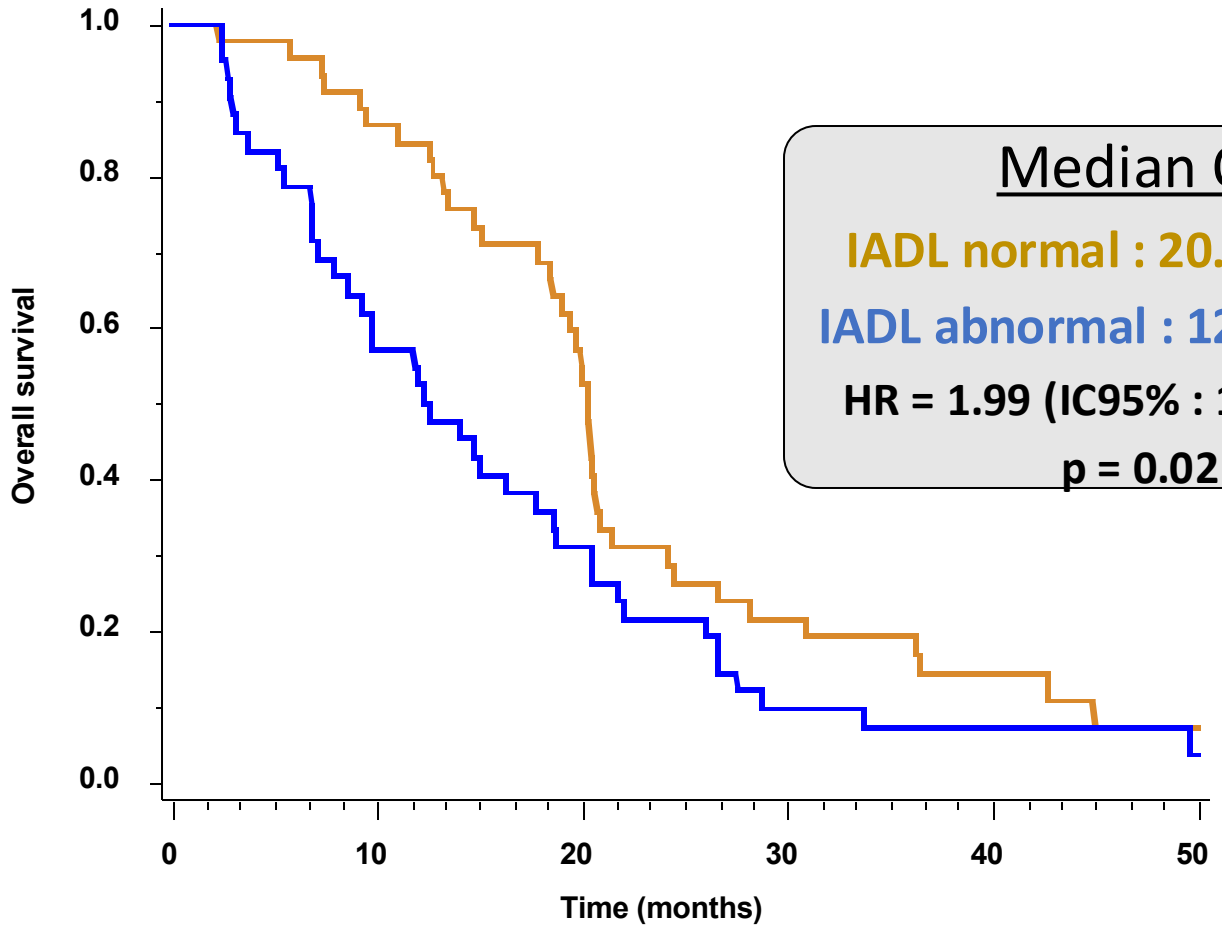
Aparicio T, Eur J Cancer 2017

IADL score at inclusion predicts overall survival

FFCD 2001-02 trial

Others findings





Median OS

IADL normal : 20.3 months

IADL abnormal : 12.5 months

HR = 1.99 (IC95% : 1.12 ; 3.55)

p = 0.02

N. at risk						
Normal IADL	45	39	23	9	5	1
Impaired IADL	42	24	13	4	3	1

Aparicio T, Eur J Cancer 2017

Geriatric factors predict toxicity

FFCD 2001-02 trial Others findings

Factors predicting toxicity grade 3-4	OR	p
Chemotherapy with irinotecan	**5,03**	**0.006**
Impaired cognitive functions (MMSE ≤27/30)	**3,84**	**0.019**
Impaired autonomy (IADL<8/8)	**4,67**	**0.011**

Aparicio T et al, J Clin Oncol 2013

Concordant findings of FFCD 2001-02 with others trials

Publication	Chemotherapy	Objective response	PFS (months)	OS (months)
Seymour M, Lancet 2011	5FU ou capécitabine	13%	**HR : 0,84** (0,69-1,01)	**HR : 0,99** (0,81-1,18)
	FOLFOX ou CAPOX	35% p<0,0001		
Hong YS, Am J Clin Oncol 2013	Capécitabine	22%	4,4	14,2
	Capécitabine + oxaliplatine	35% p=0,217 OR : 0,54 (0,20-1,45)	6,6 p=0,335 **HR : 1,33** (0,74-2,37)	11 p=0,106 **HR : 0,67** (0,41-1,10)
Aparicio T, Ann Oncol 2016	5FU	21%	5,2	14,2
	5FU + irinotecan	41% p=0,0003	7,3 p=0,15 **HR : 0,84** (0,66-1,07)	13,3 p=0,77 **HR : 0,96** (0,75-1,24)

Median age

74 years

Worst tolerance of capecitabine

80 years

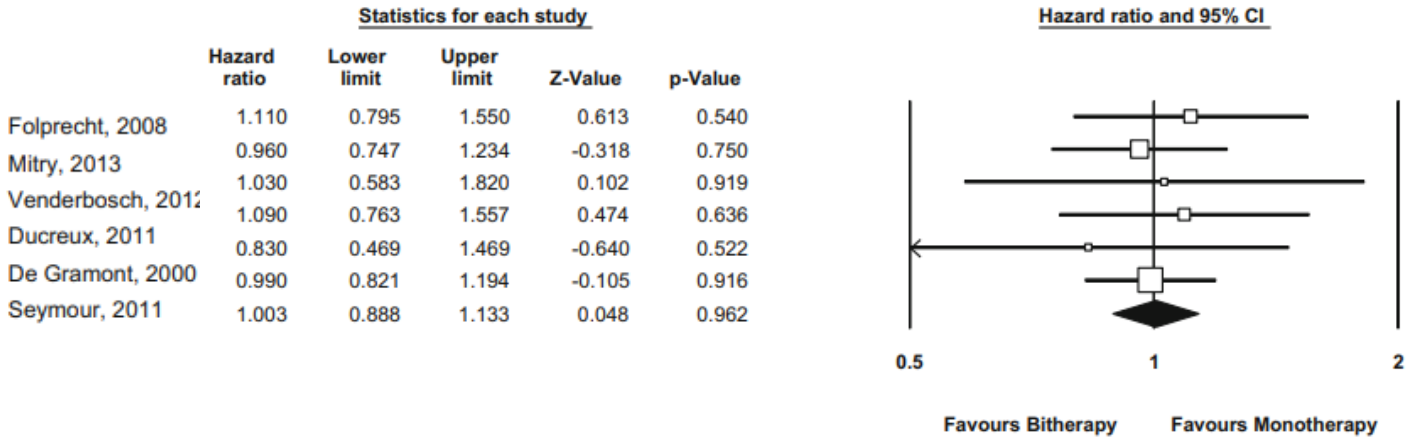
Meta-analysis

PFS : doublet CT > FU

HR = 0.82 (0,72–0,93)

No difference in OS

HR = 1,00 (0,89–1,13)



Landré T et al, Int J Colorectal Dis 2015

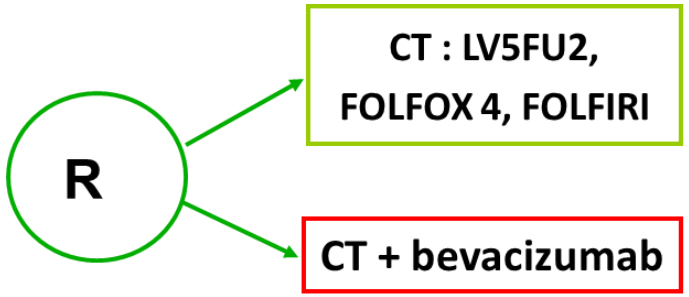
Conclusions of trials evaluating doublet vs monochemotherapy

- Doublet chemotherapy doesn't improve overall survival in front line
- Some geriatric parameters may predict efficacy and toxicity

- These findings could not have been established without specific trial on older and frail patients
- Concern: patient enrolled in specific trials are fit enough to received a doublet chemotherapy (mandatory to be enrolled) but have probably some frailty → super fit and super frail are under-represented
- Findings from specific cohorts with geriatric evaluation may add findings in unselected patients

Specific trials to evaluate targeted therapy

Randomized phase II: PRODIGE 20



102 patients enrolled from 2011 to 2013

2010

Composite end-point at 4 months: efficacy co-criterion: tumor control (stable disease or objective response) and no decrease ≥2 points of the Spitzer QoL index ; and safety co-criterion: absence of severe cardiovascular toxicities defined by arterial hypertension grade 4 or thromboembolic event grade 3-4 or cardiac insufficiency grade 3-4 or an unexpected hospitalization

Eligibility limitations

- ECOG <2,
- Adequate organ and bone marrow function
- No uncontrolled hypertension, myocardial infarction, cardiac insufficiency, stroke, arterial ischemia grade>2, pulmonary embolism

Geriatric parameters mandatory

- G8, Spitzer QoL scale, MMSE, IADL, ADL, mini-GDS, mini-Cog, MNA-SF, RFQ, social support
- **Geriatrician consultation not mandatory**

Funding: PHRC

PRODIGE 20: findings

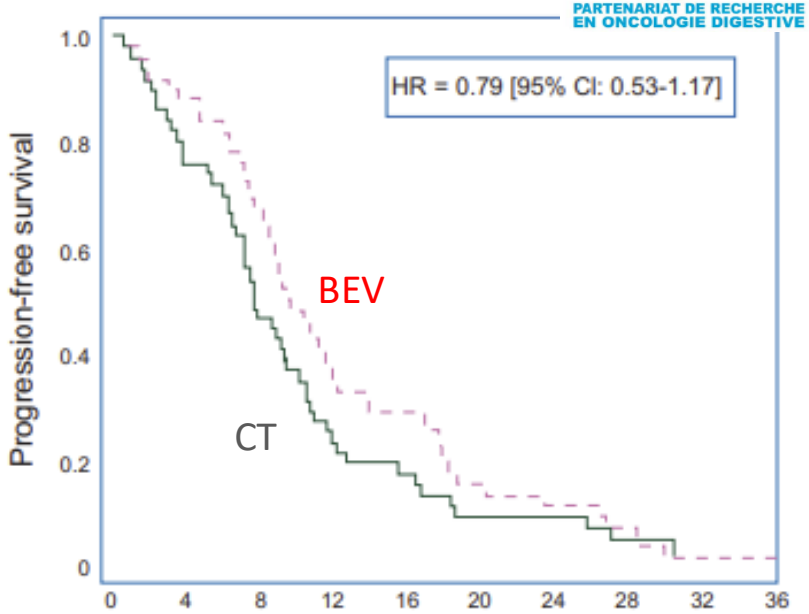
Hypothesis: efficacy co-criterion >20% of the patients
and a safety co-criterion >40%

Table 2. Primary end point assessed 4 months after randomization

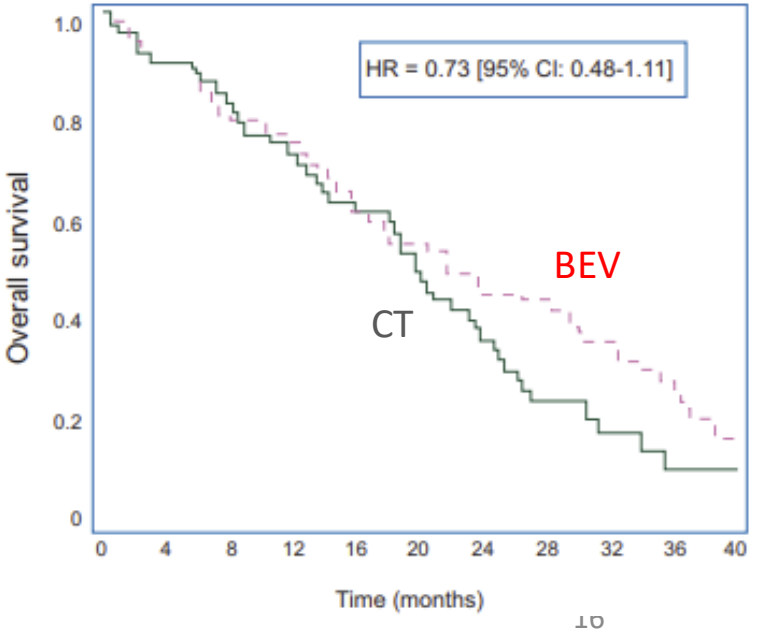
Primary end point	CT *N* = 45	BEV *N* = 46
Tumor controlled	33 (73.3%)	36 (78.3%)
No QoL degradation >2	29 (64.4%)	27 (58.7%)
Efficacy co-criterion reached	**26 (57.8%)**	**23 (50.0%)**
No unexpected hospitalization	32 (71.1%)	30 (65.2%)
No grade 3–4 cardiovascular toxicity	41 (91.1%)	40 (87.0%)
Safety co-criterion reached	**32 (71.1%)**	**28 (60.9%)**
Both efficacy and safety end point reached	**21 (46.7%)**	**16 (34.8%)**

Aparicio T et al. Ann Oncol 2018

PFS

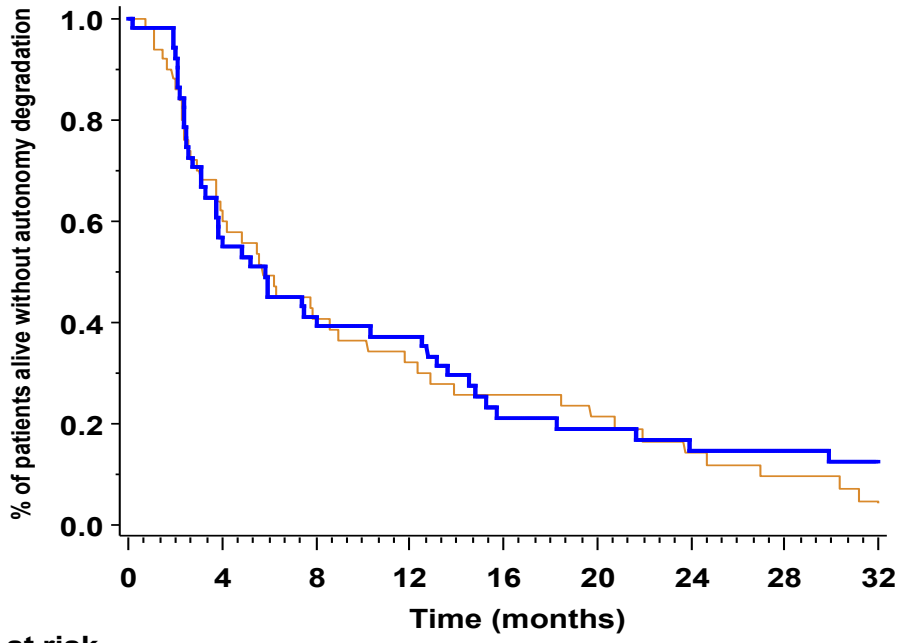


OS



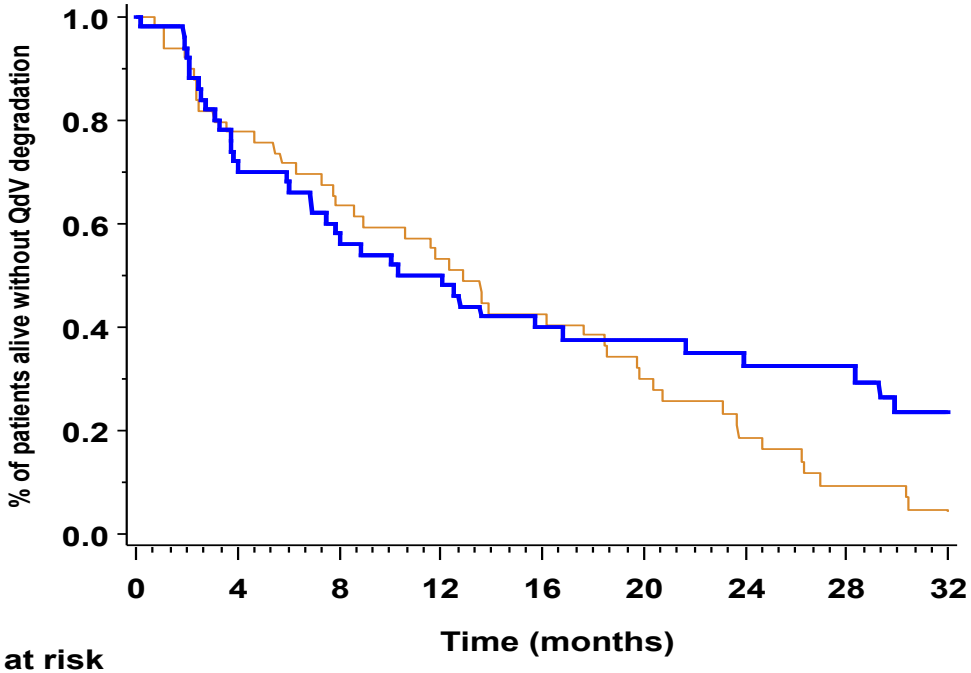
PRODIGE 20: other findings

Survival without autonomy degradation



N. at risk									
CT	51	30	19	15	12	9	6	4	2
BEV	51	29	21	19	10	9	7	7	6

Survival without QoL degradation



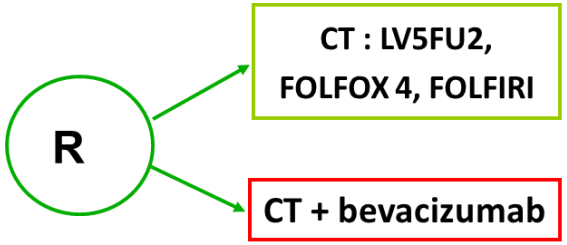
N. at risk									
CT	51	38	31	26	20	14	8	4	2
BEV	51	36	29	25	18	15	12	11	8

Questionary are poorly fulfilled during long follow-up

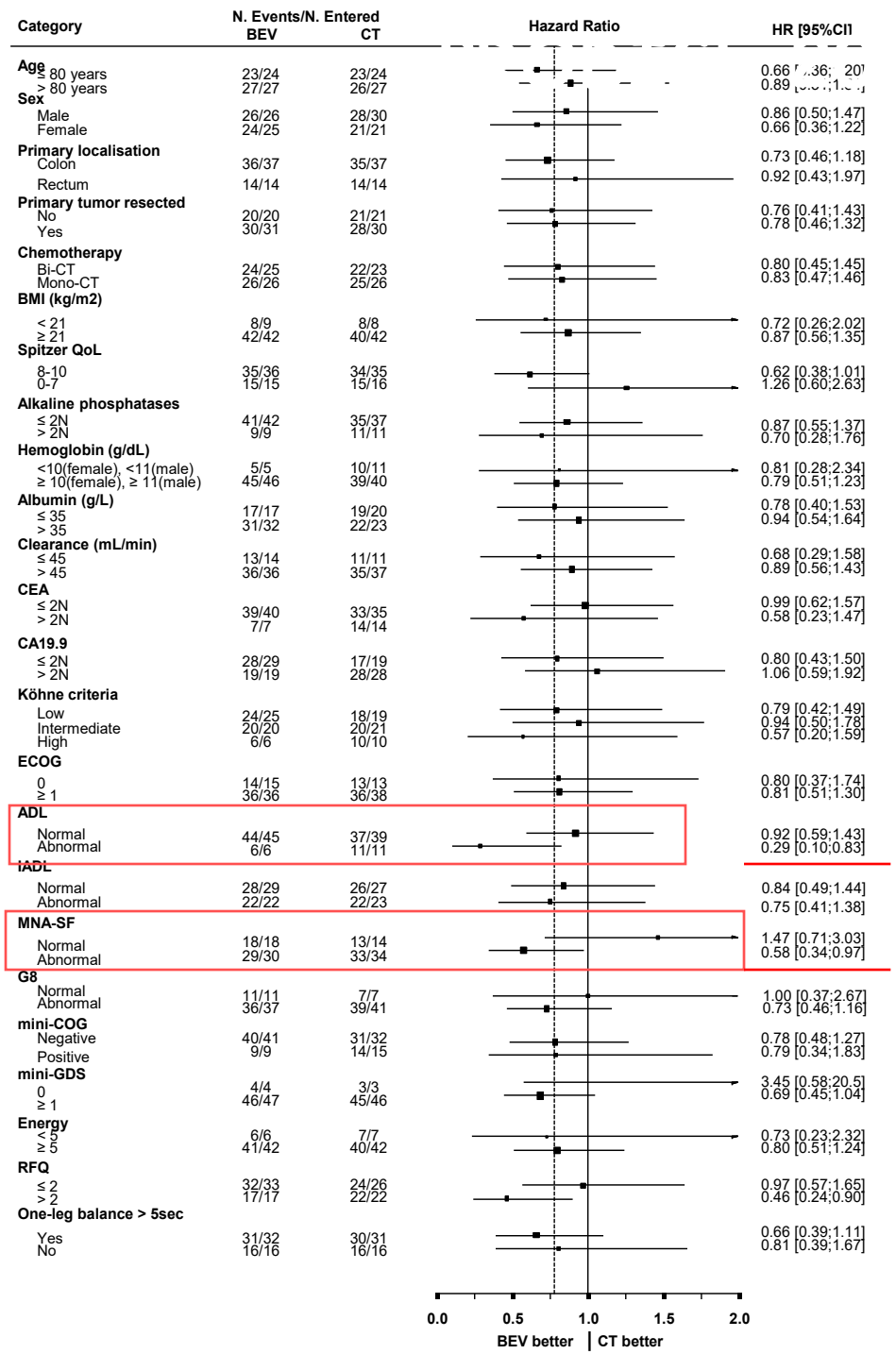
Bevacizumab is efficient and well tolerated in older patients and did not produce autonomy or QoL degradation

Aparicio T et al. Eur J Cancer 2018

PRODIGE 20 trial



Aparicio T et al, Eur J Cancer 2018



PFS subgroup analysis

bevacizumab is significantly associated with prolonged PFS in patients with impaired nutritional status and ADL

Multivariate analysis:

- **for primary endpoint**: normal IADL and no previous cardiovascular disease.
- **For PFS**: Köhne score
- **For OS**: Kohne score, QoL, low albumin, CA 19-9>2N,

Randomized trials in 1st line with bevacizumab in older patients

Publication	Chemotherapy	Objective response	PFS , months	OS , months
Cunningham D, Lancet Oncol 2013	Capécitabine	10%	5,1	16,8
	Capécitabine + bévacizumab	19% p=0,042	9,1 p<0,001 HR : 0,53 (0,41-0,69)	20,7 p=0,182 HR : 0,79 (0,57-1,09)
Price T, Ann Oncol 2012	Capécitabine	28%	5,6	13,4
	Capécitabine + bévacizumab	23%	8,8 p<0,001 HR : 0,53 (0,32-0,86)	15,7 p=0,41 HR : 0,80 (0,47-1,36)
Aparicio T, Ann Oncol 2018	5FU +/- oxali. ou irino.	32,6%	7,8	19,8
	Idem + bévacizumab	37,2%	9,7 HR : 0,78 (0,53-1,17)	21,7 HR : 0,73 (0,48-1,11)

Meta-analysis

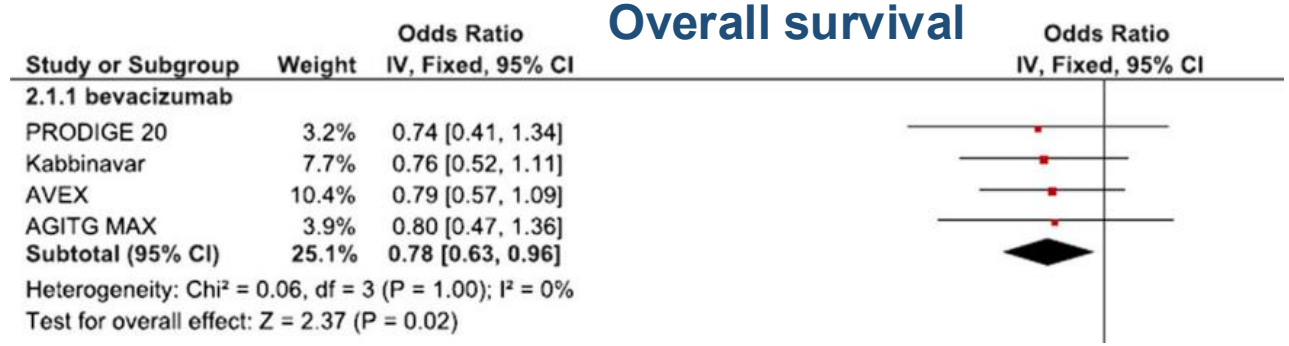
PFS: CT + Bev > CT

HR = 0.55 (0.44–0.67)

OS: CT + Bev > CT

HR = 0.78 (0.63–0.96)

Overall survival

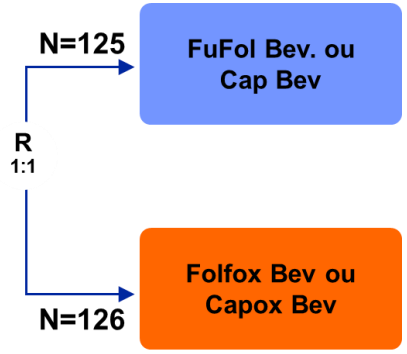


Landré T, Int J Colorectal Dis 2018

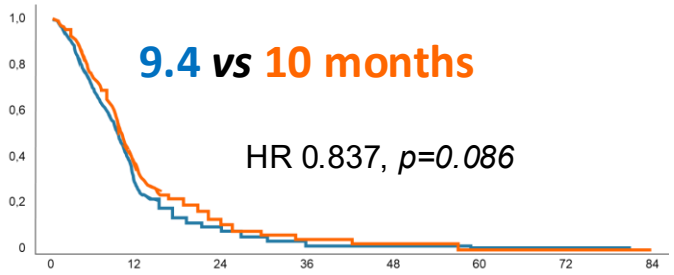
Fluoropyrimidine monotherapie + targeted therapy for older patients

bi-CT + bevacizumab vs mono-CT + bevacizumab

Hamaguchi T, ASCO GI® 2022, Abs #10



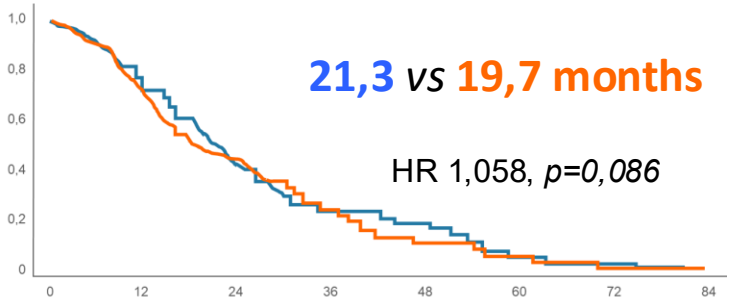
Progression free survival



9.4 *vs* 10 months

HR 0.837, *p=0.086*

Overall survival

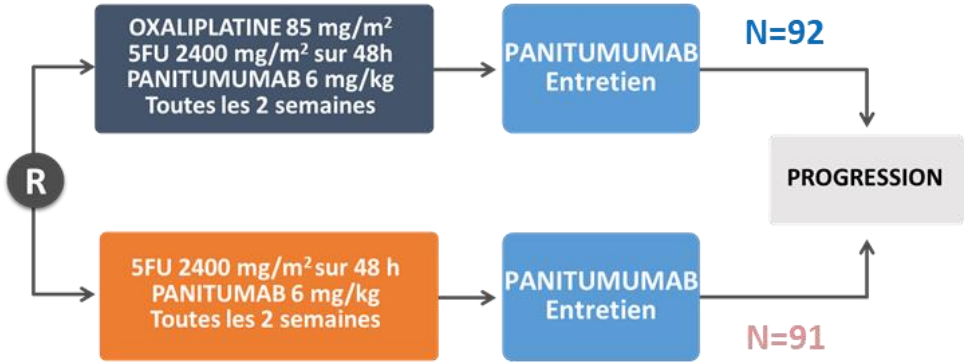


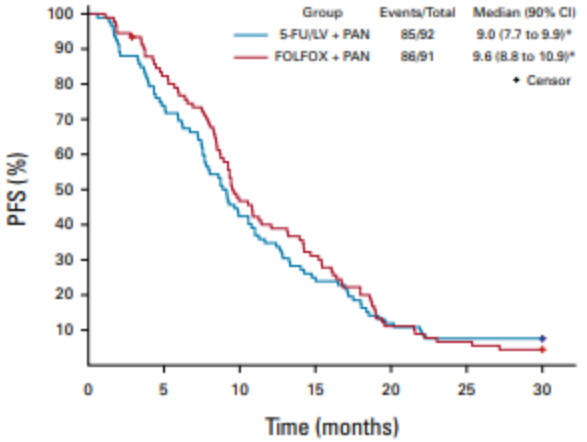
21,3 *vs* 19,7 months

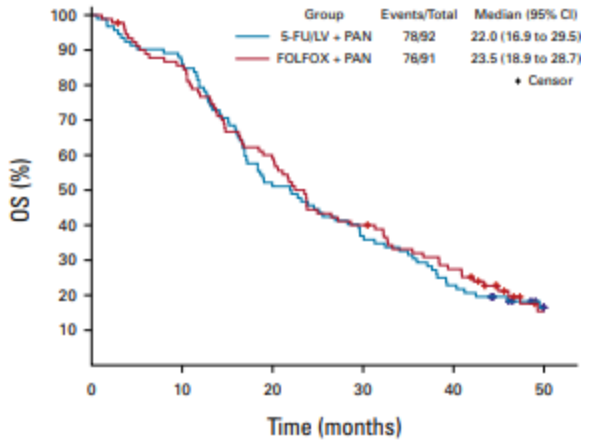
HR 1,058, *p=0,086*

bi-CT + anti-EGFR vs mono-CT + anti-EGFR

Lonardi S, J Clin Oncol 2023







Conclusion of trials evaluating bevacizumab

- Bevacizumab is efficient in older patients in first line
- The efficacy remains in more frail patients

- Number of patients with cardiovascular disease are excluded
- Underpowered study could not assess heterogeneity of older population
- Concordance of a mini geriatric evaluation by an oncologist and a full geriatric assessment is not fully demonstrated

Regorafenib after 70 years?

FFCD 1404 - REGOLD

N=42

Median age: 77 years

37% >80 years

Tumor control rate at 2 months: 31,4%

Median PFS: 2.2 months

1.9 months in CORRECT study

Median OS: 7.5 months

6.4 months in CORRECT study

Patients ≥ 80 years vs < 80 years

No tumor control at 2 months OR: 3.21 [IC95%: 0.57 ; 18.20], p=0,187

Progression free survival HR: 0.60 [IC95%: 0.30 ; 1.17], p=0.134

Overall survival HR: 0,47 [IC95%: 0,23 ; 0, 97], p=0,042

Aparicio T, J Ger Oncol 2020

Treatment stop for toxicity: 28% patients among them 83% **ECOG 1,** 50% **>80 years,** 50% **impaired ADL**

Optimisation of regorafenib schedule

- **Start at reduce dose**
- **Schedule: 2/3 weeks**

Petrioli R, Clin Colorectal Cancer 2018
Bekaii-Saab T, Lancet Oncol 2019

Conclusions

- Regorafenib sems feasible in fit patient <80 years, ECOG=0
- Few results from geriatric assessment due to small number of patient

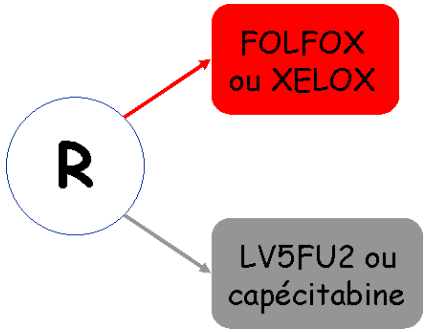
Trial in adjuvant setting: PRODIGE 34 – ADAGE trial

2015

Adjuvant in patients ≥70 ans, stage III, R0

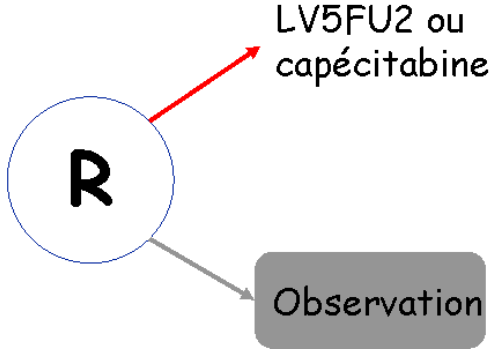
Fit patient

N=756



Vulnerable patient

N=226



Stratification: center, sex, stage (IIIA *vs* IIIB *vs* IIIC), occlusion and/or perforation (yes *vs* no) and IADL (normal *vs* anormal)

Eligibility limitations

- ECOG <2,
- Adequate organ and bone marrow function
- No other cancer uncontrolled for less than 2 years

Geriatric parameters mandatory

- G8, Spitzer QoL scale, MMSE, IADL, ADL, mini-GDS, mini-Cog, MNA-SF, RFQ, social support, Lee score
- **Geriatrician consultation not mandatory**
- **Attribution of group by the investigator**

Funding: FFCD

PRODIGE 34 – ADAGE: first findings

Preliminary analysis at 50% of inclusion in 491 patients (378 in Group 1 and 113 in Group 2)

Preliminary results for toxicity n=434	Groupe 1 : Fluoropyrimidine, n=189	Groupe 1 : FOLFOX/XELOX, n=189	Groupe 2 : Fluoropyrimidine, n=56
Chemotherapy regimen	LV5FU2 : 83% Capecitabine : 17%	FOLFOX : 89% XELOX : 11%	LV5FU2 : 36% Capecitabine : 64%
Early stop of treatment	17%	21%	38%
Total grade 3-5 toxicities	**26%**	**58%**	**40%**
Neurologic grade 1-2 / 3-4	20% / 1%	87% / 21%	19% / 4%
Neutropenia grade 1-2 / 3-4	18% / 3%	36% / 22%	17% / 6%
Asthenia grade 1-2 / 3-4	59% / 4%	64% / 8%	49% / 11%

- Patients in Group 2 were older and showed more frailty criteria than those in Group 1.
- Cumulative grade 3-5 toxicities were more frequent in patients treated with oxaliplatin in Group 1 or with fluoropyrimidine in Group 2 than in patients treated with fluoropyrimidine in Group 1.
- At least one course was deferred in more than half of the patients in all groups. Early treatment cessation was more frequent in Group 2.

Aparicio T et al, Dig Liver Dis 2022

PRODIGE 34 – ADAGE: analysis of toxicity in group 1

10 years accrual

Inclusion of 982 patients, 756 in group 1

Multivariate analysis for grade 3-5 toxicity in all patients

	OR [95% CI]	p
Treatment Ox vs F	3.86 [2.80-5.32]	<0.0001
Age: <75 **[75-80]** **>80**	Ref 1.64 [1.13-2.39] 1.43 [0.94-2.17]	0.031
Male vs women	0.72 [0.52-0.99]	0.042

- Adjuvant chemotherapy with oxaliplatin is feasible in fit older patients
- Oxaliplatin cause an increase of severe toxicity and a decrease of dose intensity.
- Patients >75 and women are more at risk for toxicity.

Multivariate analysis for grade 3-5 toxicity in Arm F

	OR [95% CI]	p
5FU vs capecitabine	0.67 [0.37-1.22]	0.187
Male vs women	**0.60 [0.38-0.96]**	**0.034**
Creatinin clearance >45 vs ≤45 ml/min	0.39 [0.14-1.06]	0.064

Multivariate analysis for grade 3-5 toxicity in Arm Ox

	OR [95% CI]	p
FOLFOX vs XELOX	1.66 [0.83-3.31]	0.151
Age: <75 **[75-80]** **>80**	Ref 2.05 [1.21-3.47] 1.29 [0.70-2.35]	0.025
Cognition Impaired vs normal	1.52 [0.86-2.68]	0.151

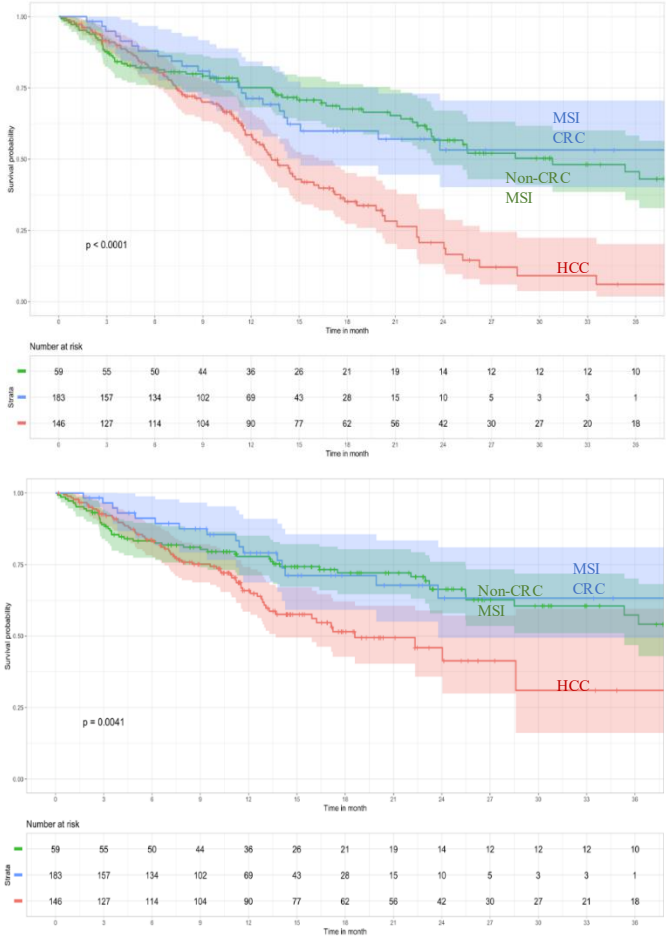
Aparicio T et al, ESMO 2024

New player: immunotherapy in dMMR/MSI

Some concerns for older patients (immunotoxicity and efficacy) but preliminary data from retrospectives study are reassuring

Data from AGEO retrospective study: immunotherapy for digestive cancer in patients over 70

- For MSI MCRC, median OS not reach [IQR 35,3-NR], median PFS: 30.8 months [23.3-49.4].
- For MSI non-CRC, median OS: 75.3 months [23.8-NR] and median PFS: 46.4 months [15.1-NR].
- For HCC, median OS: 18.6 months [13.7-NR] and median PFS: 13.3 moths [12.1-16.2].



Univariate analysis for mortality

	Alive	Death	p
	n = 100	n = 47	
Female sex – n (%)	55 (55.0)	32 (68.1)	0.185
Age category – n (%)			0.356
70-75	29 (31.5)	18 (41.9)	
75-80	29 (31.5)	9 (20.9)	
80+	34 (37.0)	16 (37.2)	
EI ≥ grade 3 – n (%)	18 (18.0)	8 (17.0)	1.000
BMI - median [IQR]	24.4 [22.3 ; 27.5]	22.6 [19.0 ; 25.3]	**0.017**
BMI <22 – n (%)	22 (22.7)	21 (44.7)	**0.012**
Albumin <30 g/L – n (%)	13 (16.0)	13 (35.1)	**0.037**

Denutrition is a major prognostic factor

Dupuis C et al ,JFHOD 2024

Prospective cohort with geriatric assessment is needed

Conclusions for colorectal cancer in older patients

- Specific trials for older patients are needed
- Poor information from small sample size trial
- Standardized geriatric parameters should be collected to allow meta-analysis
- New endpoint assessing QoL and autonomy could be elaborate but with caution
- Translational study are also needed to assess potential biologic specificity