2021 ESMO congress

NCC NATIONAL CANCER CENTER JAPAN
EPOC
Exploratory Oncology Research & Clinical Trial Center

Stage II, lacking evidence: What to do in daily practice?

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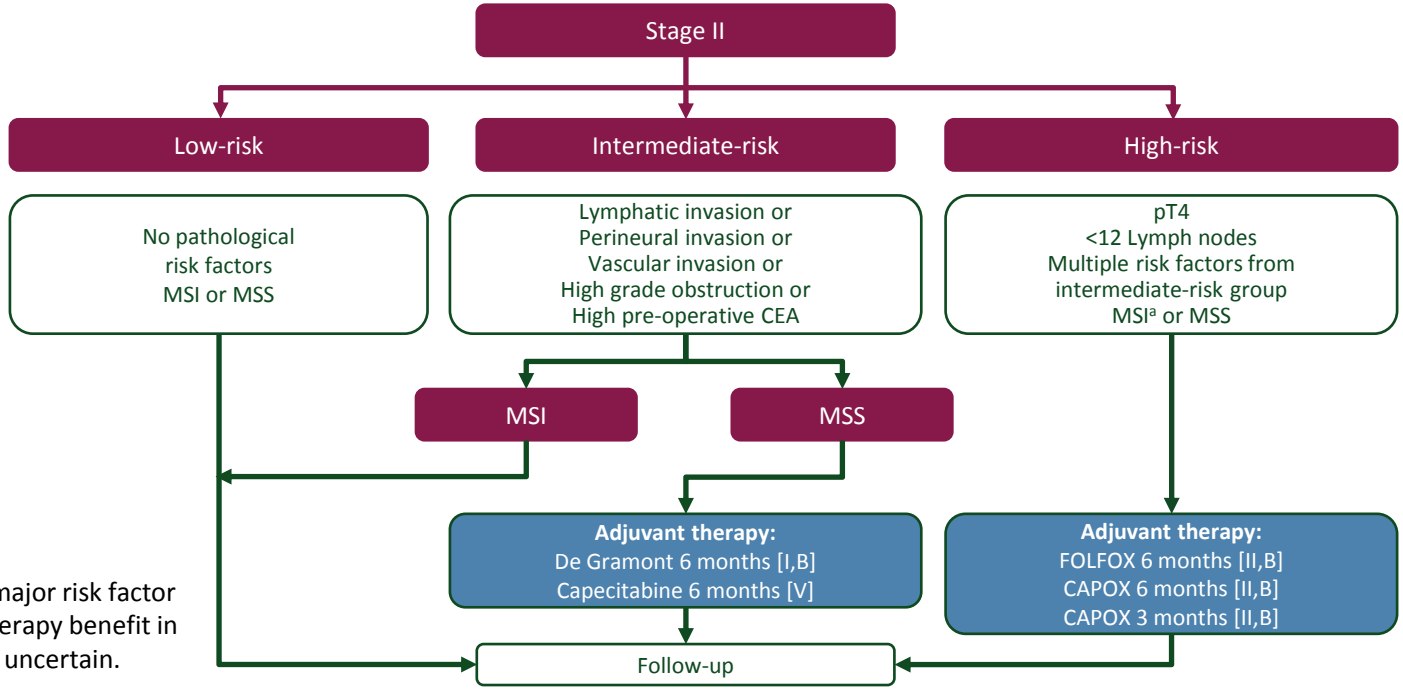
Conflict of Interest

Lecture Fee;
Bayer, Chugai, Eli Lilly, Merk Biopharma, Ono, and Taiho

Research grant;
Amgen, Chugai, Daiichi Sankyo, MSD, Ono, Parexel, Sanofi, Sumitomo Dainippon, and Taiho

What to do in daily practice?

ESMO Clinical Practice GLs for localized CC 2020



a For pT4 MSI: pT4 is a major risk factor but adjuvant chemotherapy benefit in the presence of MSI is uncertain.

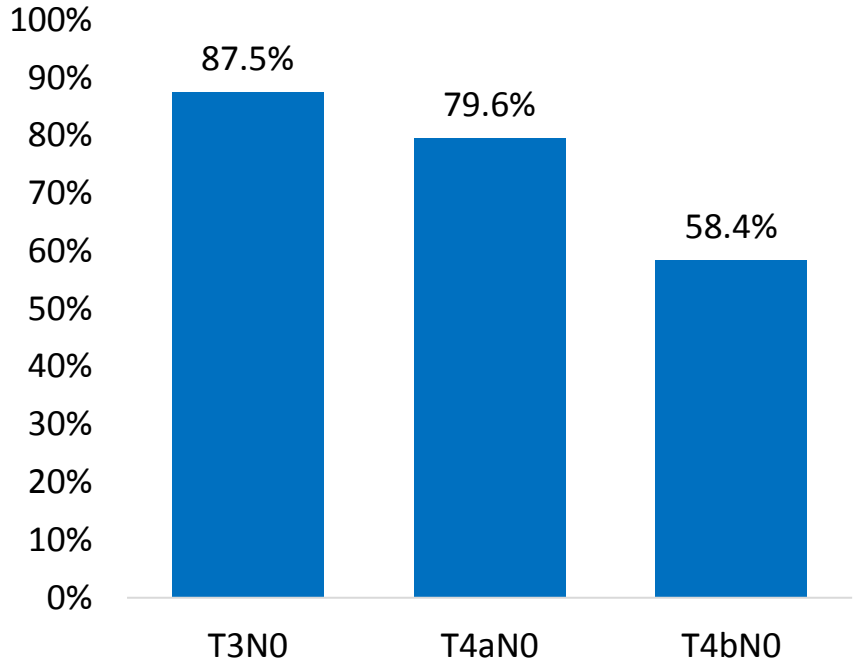
Argiles G, Yoshino T, et al. Ann Oncol 2020.

Prognosis of Stage II colon cancer; “Stage II colon cancer is a heterogeneous disease”

TNM Classification of Malignant Tumors, 8th edition

TNM8	N0	N1	N2a	N2b
Tis	0			
T1	I	IIIA	IIIA	IIIB
T2	I	IIIA	IIIB	IIIB
T3	IIA	IIIB	IIIB	IIIC
T4a	IIB	IIIB	IIIC	IIIC
T4b	IIC	IIIC	IIIC	IIIC

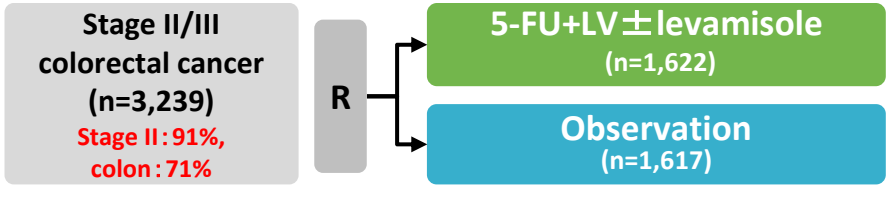
SEER 5-Year Relative Survival Rate (%)

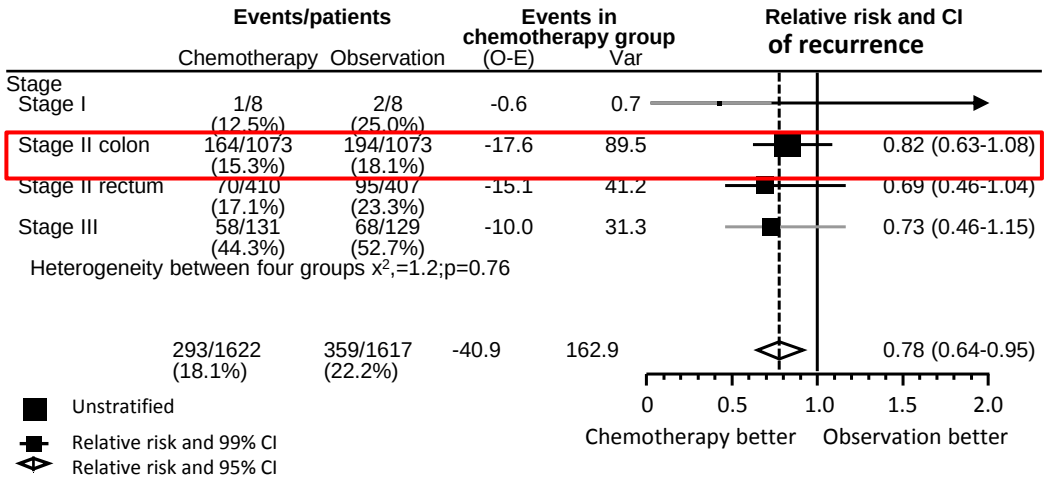


Brierley JD, eds.TNM Classification of Malignant Tumours. 8th edition. Oxford: John Wiley & Sons, Inc.; 2016.: Gunderson LL, et al. J Clin Oncol. 2010.

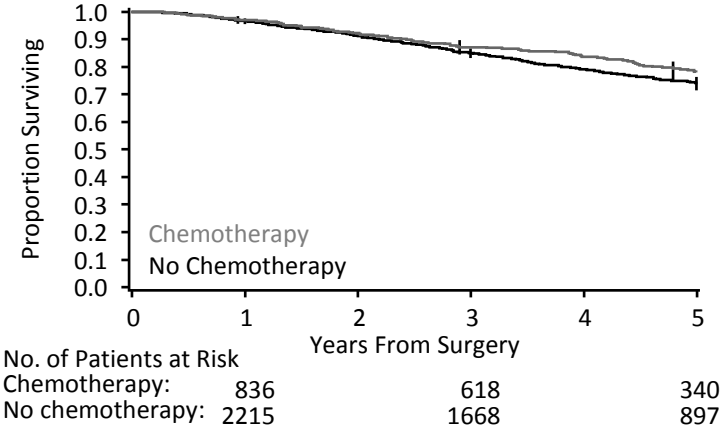
Is adjuvant chemotherapy needed for “ALL” Stage II colon cancer?

QUASAR trial (64%, < 12 LN examined)





SEER database review (Stage II)



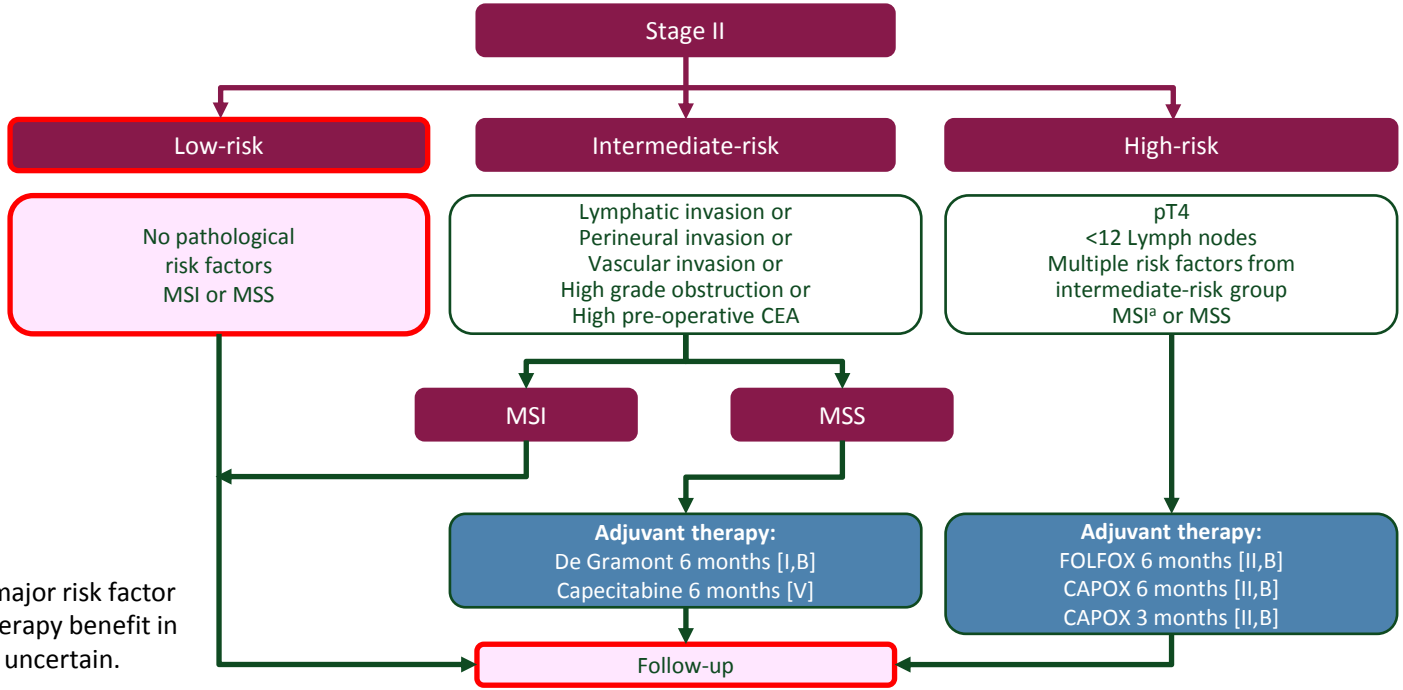
	5yOS	HR(95% CI)
No Chemotherapy (n=2291)	75%	unadjusted :0.80 (0.68 to 0.95) **Adjusted: 0.91 (0.77 to 1.09).**
Chemotherapy (n=860)	78%	

FP adjuvant chemotherapy is not required for all Stage II colon cancer

QUASAR Collaborative Group , Lancet 2007. Hutchins G, et al. J Clin Oncol. 2011. Schrag D, et al. J Clin Oncol 2002.

What to do in daily practice?

ESMO Clinical Practice GLs for localized CC 2020



a For pT4 MSI: pT4 is a major risk factor but adjuvant chemotherapy benefit in the presence of MSI is uncertain.

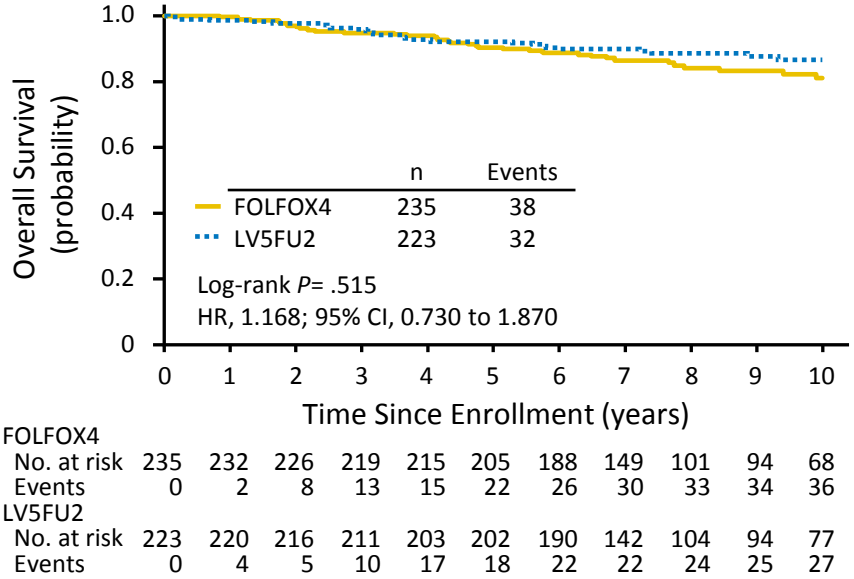
Follow-up for Stage II without risk factors

Argiles G, Yoshino T, et al. Ann Oncol 2020.

Good prognosis for Low-risk stage II colon cancer

MOSAIC Study

Low-risk stage II



DFS and OS Estimates according to Disease Stage for Patients in the LV5FU2 and FOLFOX4 Treatment Arms

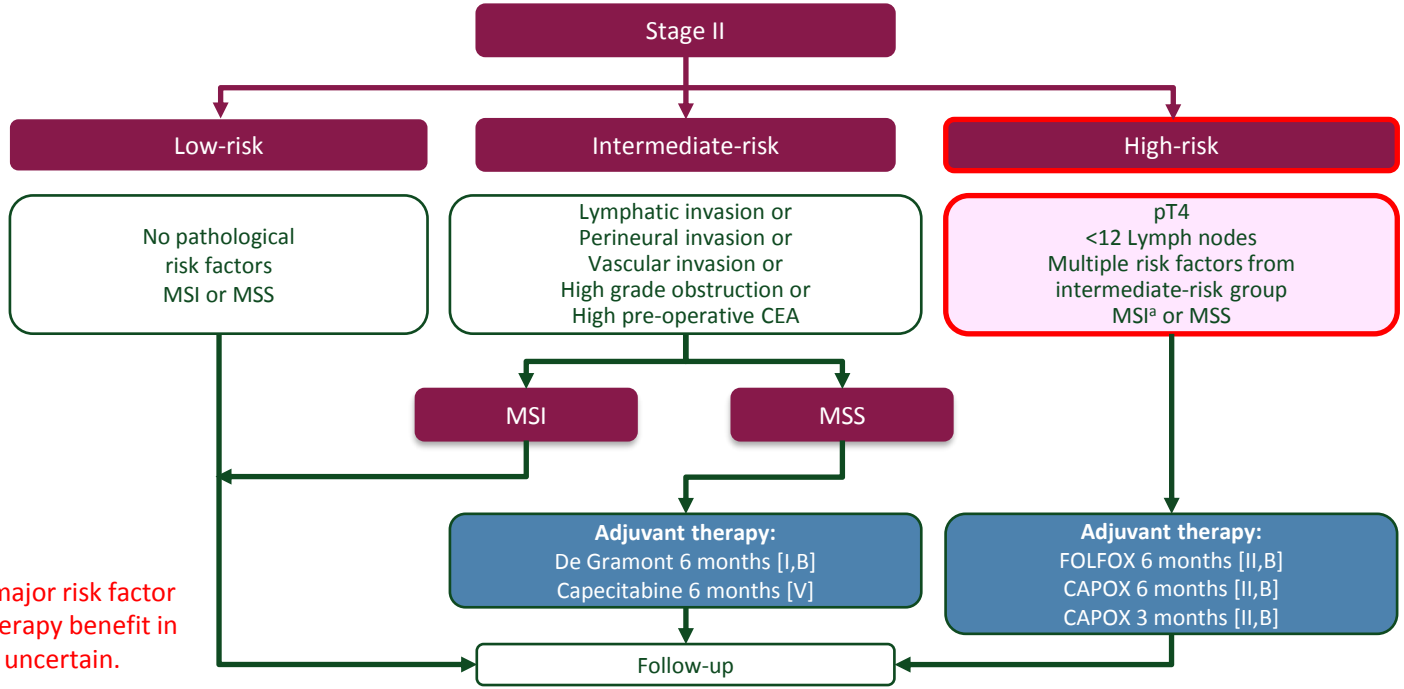
Low-risk stage II No. of patients	LV5FU2 223	FOLFOX4 235
DFS		
No. of events	46	49
3 year, % (SE)	87.9 (2.2)	88.0 (2.1)
5 year, % (SE)	86.1 (2.3)	84.9 (2.4)
10 year, % (SE)	79.7 (3.0)	77.4 (3.2)
OS		
No. of events	32	38
3 year, % (SE)	95.9 (1.3)	94.9 (1.5)
5 year, % (SE)	92.3 (1.8)	90.5 (1.9)
10 year, % (SE)	86.7 (2.5)	81.2 (3.0)

FP ± OX adjuvant chemotherapy is not required for low-risk Stage II colon cancer

Andre T, et al. J Clin Oncol 2015.

What to do in daily practice?

ESMO Clinical Practice GLs for localized CC 2020



a For pT4 MSI: pT4 is a major risk factor but adjuvant chemotherapy benefit in the presence of MSI is uncertain.

What is the definition of risk factors? What is the treatment?

Argiles G, Yoshino T, et al. Ann Oncol 2020.

What is major prognostic parameters for stage II risk assessment

Risk analysis of Stage II colon cancer patients in the California Cancer Registry database

OS-adjusted hazard ratio for each recurrence risk factor

High-risk feature	HR	95% CI
T4	**2.56**	**2.03–3.21**
< 12 LN examined	**1.65**	**1.34–2.02**
Positive margin	1.31	0.90–1.91
perineural invasion	1.04	0.66–1.63
lymphovascular invasion	0.83	0.57–1.21
High grade	0.84	0.65–1.08

B.D. Babcock et al. Ann Surg Oncol 2018.

Impact of High-Risk Features on DFS in Patients with High-Risk Stage II Colon Cancer in ACHIEVE-2 Trial as part of the IDEA Collaboration

Multivariate Analysis of High-Risk Features for DFS

High-risk features	HR	95% CI	P
T4	**3.77**	**2.18 – 6.53**	**< 0.0001**
< 12 LN examined	**2.98**	**1.59 – 5.59**	**0.0006**
Obstruction	0.75	0.38 – 1.51	0.4263
Perforation	1.93	0.94 – 3.98	0.0754
Poorly Differentiated	0.92	0.41 – 2.06	0.8446
Vascular Invasion	0.68	0.36 – 1.28	0.2307

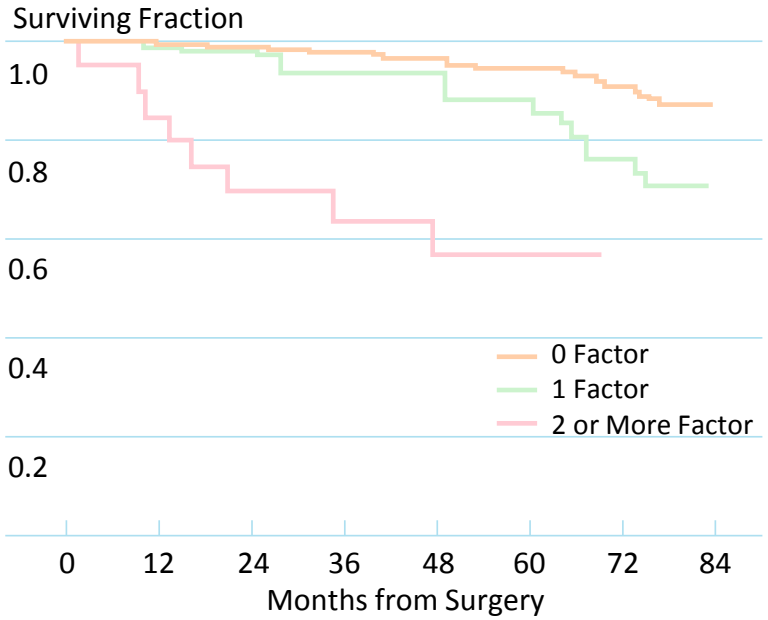
Manaka D, Yoshino T, et al.: ASCO 2020 #4011.

The magnitude of the risk to the OS/DFS depends on the factors.

Effect of multiple risk factors

Prospective analysis conducted on 448 patients with stage II CC

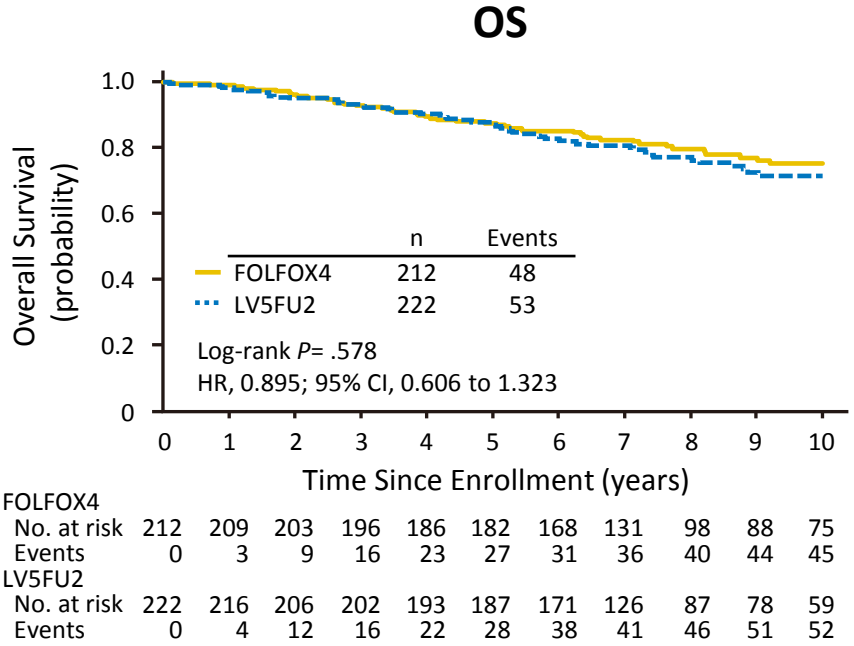
Factor Category		Univariate analysis 5y DSS (95% CI) *p*		Multivariate analysis HR(95% CI) *p*	
T stage	T3	92% (89–95)	0.04	2.7 (1.1–6.2)	0.02
	T4	69% (51–88)			
Preoperative CEA	≤5	93% (89–97)	0.04	**2.1** (1.1–4.1)	0.02
(ng/ml)	**>5**	**87%** (78–95)			
Lymphovascular	Absent	92% (89–95)	0.02	**2.1** (1–4.4)	0.04
or perineural invasion	**Present**	**80%** (68–92)			



The presence of multiple adverse prognostic factors identifies a high-risk subgroup

Quah HM, et al. Dis Colon Rectum. 2008.

Subgroup analysis from MOSAIC trial (High-risk Stage II)



Variable	LV5FU2	FOLFOX4	Absolute Change*	Relative Change†	HR	95% CI	*P*
High-risk stage II							
No. of patients	222	212	–	–	–	–	–
DFS							
No. of events	68	56	–	–	**0.79**	**0.55 to 1.13**	**.194**
3 year, % (SE)	81.3 (2.6)	86.3 (2.4)	+5	+6.2	–	–	–
5 year, % (SE)	73.8 (3.0)	81.5 (2.7)	+7.7	+10.4	–	–	–
10 year, % (SE)	67.0 (3.5)	72.7 (3.3)	+5.7	+8.5	–	–	–
OS							
No. of events	53	48	–	–	**0.89**	**0.60 to 1.32**	**.579**
3 year, % (SE)	93.1 (1.7)	92.9 (1.8)	-0.2	-0.21	–	–	–
5 year, % (SE)	87.5 (2.2)	87.6 (2.3)	+0.1	+0.1	–	–	–
10 year, % (SE)	71.7 (3.5)	75.4 (3.3)	+3.7	+5.2	–	–	–

*Absolute difference reflects a comparison of survival between the FOLFOX and LV5FU2 arms.
†Relative difference reflects a ratio of the observed survival in the FOLFOX arm and the LV5FU2 arm [(X year OS rate in the FOLFOX group - X year OS rate in the LV5FU2 group)/(X year OS rate in the LV5FU2 group) × 100].

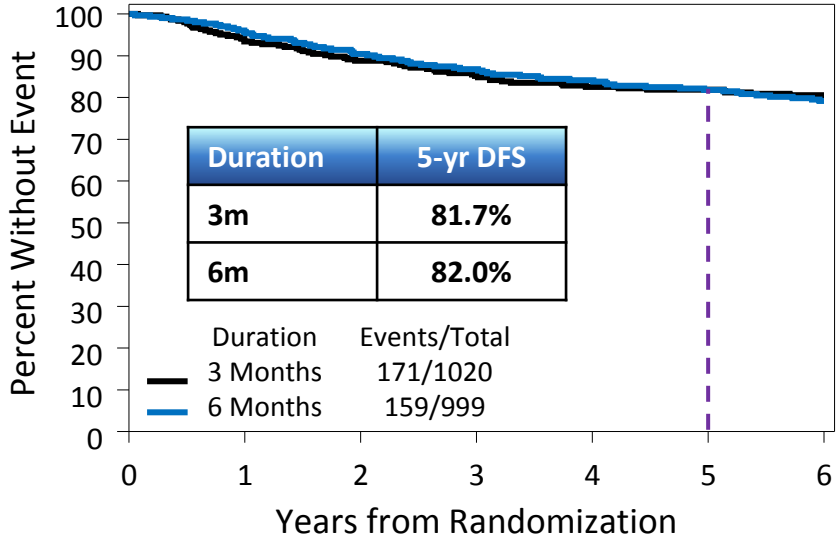
High-risk:
T4, tumor perforation,
or fewer than 10 lymph nodes examined

6 months of FOLFOX is an option for high-risk stage II

Andre T, et al. J Clin Oncol 2015.

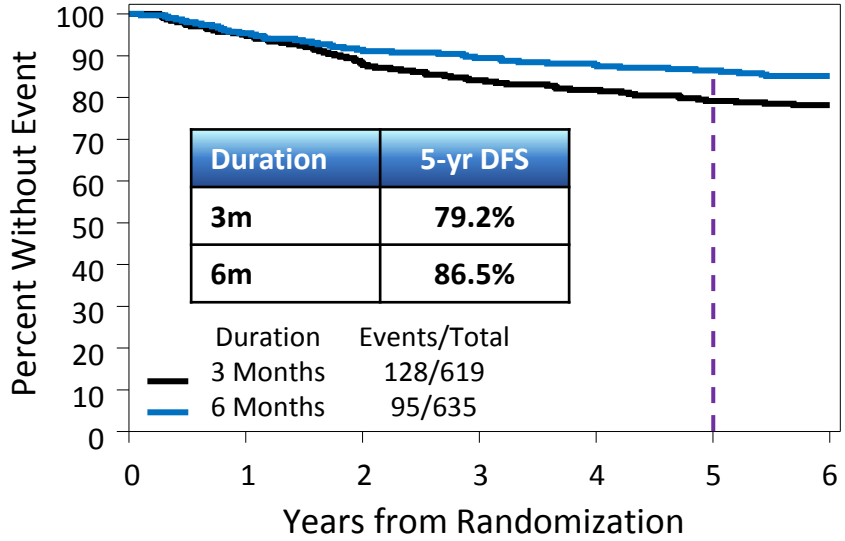
Subgroup analysis from IDEA High-risk stage II colorectal cancer (colon: 96.0%, rectal: 4.0%)

CAPOX



N Pts	1020	924	810	675	534	357	201
At risk	999	906	786	653	504	361	185

FOLFOX



N Pts	619	569	508	462	404	311	214
At risk	635	586	545	503	442	332	220

Both 6 and 3 months of CAPOX are options as well

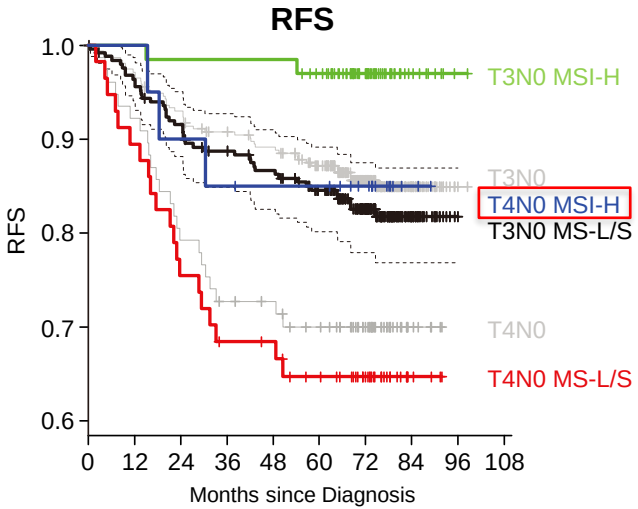
Iveson TJ, Yoshino T, et al. J Clin Oncol 2021.

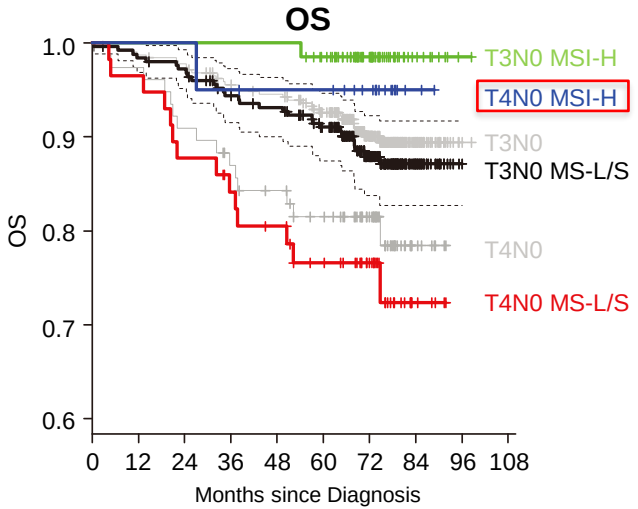
What is the prognosis for pT4 MSI-H ?

Tumors from patients in the PETACC3 adjuvant chemotherapy trial were examined for MSI

		Stage II (n=420)
Sex	Female	175
	Male	245
Grade	G-1/2	394
	G-3/4	24
	NA	2
T stage	T12	0
	T3	341
	T4	79
Site	Left	237
	Right	183
Treatment group	5-FU/LV	213
	FOLFIRI	207
MSI status	**MS-L/S**	**309**
	MSI-H	**86**
	NA	25

MSI-H = microsatellite instability high
MS-L/S = microsatellite instability low and microsatellite stable





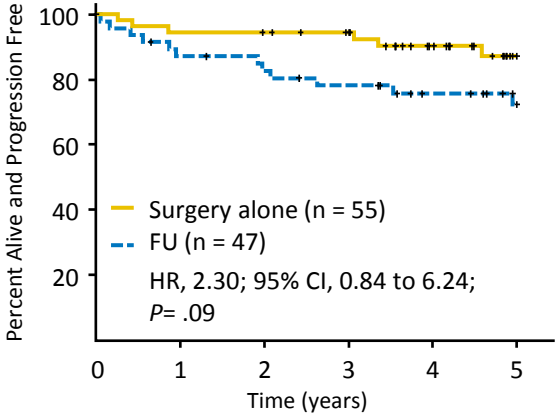
The presence of MSI/MMR in localised disease confers better prognosis

Roth AD, et al. J Natl Cancer Inst 2012.

What is the treatment for Stage II MSI-H ?

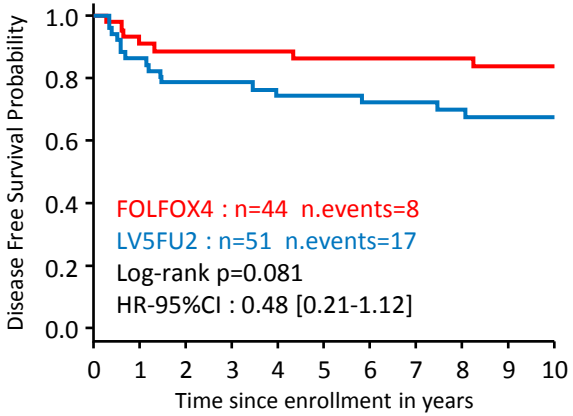
A meta-analysis of a phase III trial comparing postoperative 5-FU therapy with surgery alone in stage II / III colon cancer

DFS: stage II, dMMR



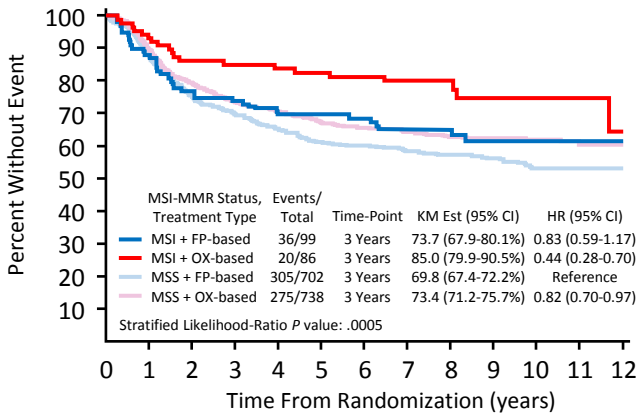
Updated 10-Year Survival and Outcomes of the MOSAIC Study

DFS: stage II/III, dMMR



An ACCENT Pooled Analysis of 12 Adjuvant Trials

DFS: stage III, dMMR



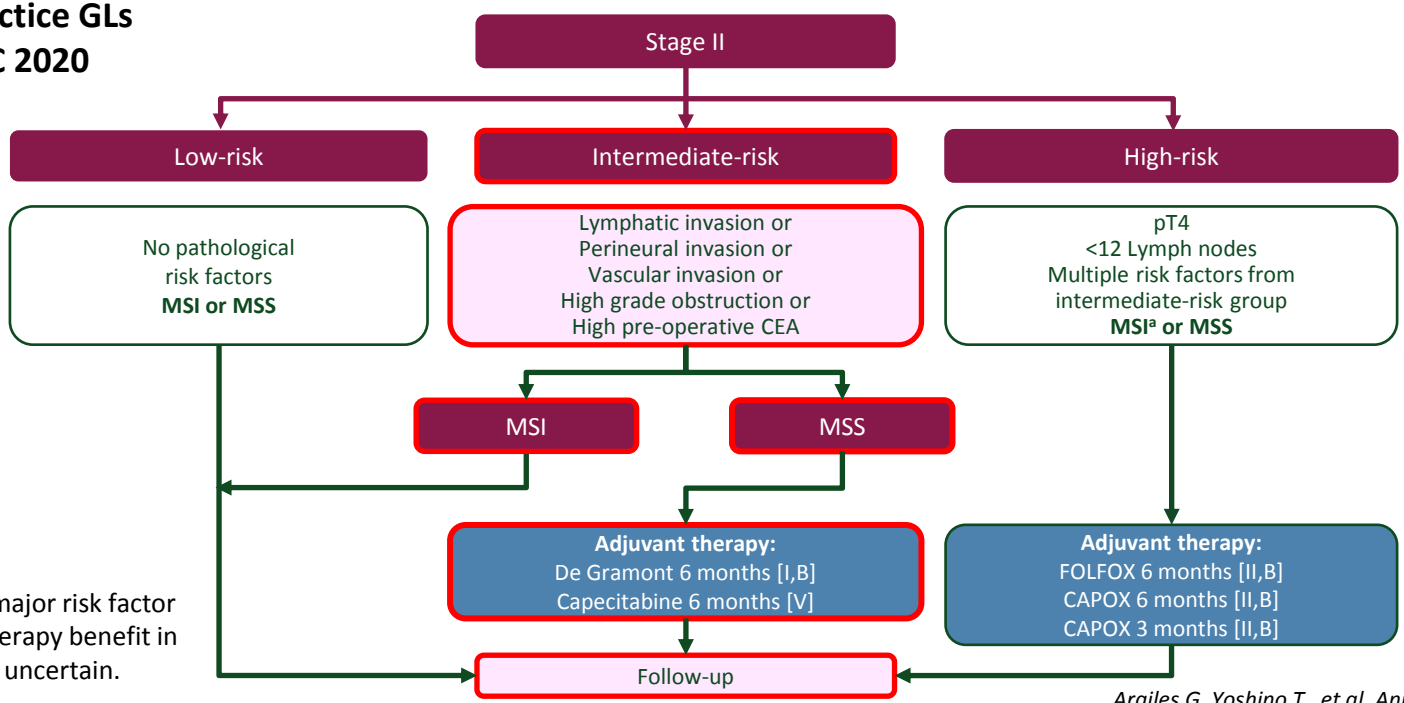
FP mono for Stage II dMMR is ineffective, OX for Stage II/III dMMR and Stage III dMMR population is useful. The effectiveness of OX for Stage II dMMR is unclear. Here is "a lacking evidence"

Takayuki Yoshino, MD., Ph.D.

Sargent DJ, et al. J Clin Oncol 2010. Andre T, et al. J Clin Oncol 2015. Cohen R, Yoshino T, et al. J Clin Oncol. 2021.

What to do in daily practice?

ESMO Clinical Practice GLs for localized CC 2020



a For pT4 MSI: pT4 is a major risk factor but adjuvant chemotherapy benefit in the presence of MSI is uncertain.

Argiles G, Yoshino T, et al. Ann Oncol 2020.

Adjuvant chemotherapy for Intermediate-risk with MSI-H?

Adjuvant chemotherapy should be considered for intermediate risk and MSS?

What is the prognosis for pT3 MSI-H ?

Tumors from patients in the PETACC3 adjuvant chemotherapy trial were examined for MSI

		Stage II (n=420)
Sex	Female	175
	Male	245
Grade	G-1/2	394
	G-3/4	24
	NA	2
T stage	T12	0
	T3	341
	T4	79
Site	Left	237
	Right	183
Treatment group	5-FU/LV	213
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MSI-H = microsatellite instability high
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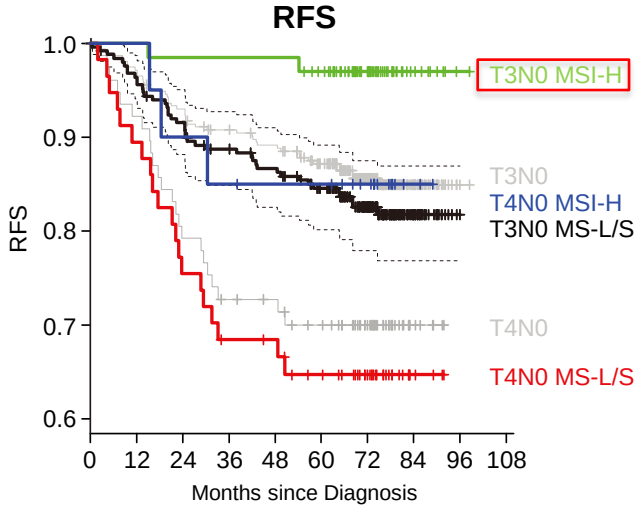
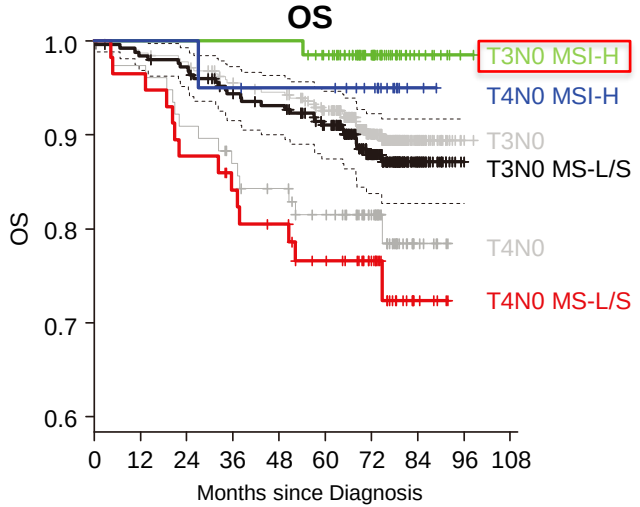




No need for adjuvant chemotherapy for T3N0 and MSI-H colon cancer

Roth AD, et al. J Natl Cancer Inst 2012.

Lymphovascular or perineural invasion are associated with High risk of recurrence

Prospective analysis conducted on 448 patients with stage II CC

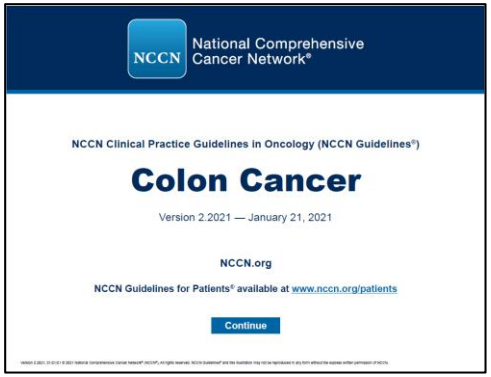
Factor	Category	Univariate analysis 5-yr DSS (95% CI)	Log-rank P value	Multivariate analysis Hazard ratio(95% CI)	P value
T stage	T3	92% (89–95)	0.04	2.7 (1.1–6.2)	0.02
	T4	69% (51–88)			
Preoperative CEA (ng/ml)	≤5	93% (89–97)	0.04	**2.1** (1.1–4.1)	0.02
	>5	**87%** (78–95)			
Lymphovascular or perineural invasion	Absent	92% (89–95)	0.02	**2.1** (1–4.4)	0.04
	Present	**80%** (68–92)			

Quah HM, et al. Dis Colon Rectum. 2008.

These factors can be used to identify intermediate risk Stage II patients who should be considered for adjuvant therapy.

NCCN Guidelines Colon Cancer Version 2.2021

PATHOLOGIC STAGE[m]	ADJUVANT TREATMENT[b,u]
Tis; T1, N0, M0; T2, N0, M0; T3–4, N0, M0[n] (MSI-H/dMMR)	Observation
T3, N0, M0[n,o] (MSS/pMMR and no high-risk features)	Observation or Consider capecitabine (6 mo)[q] or 5-FU/leucovorin (6 mo)[q]
T3, N0, M0 at high risk for systemic recurrence[o,p] or T4, N0, M0 (MSS/pMMR)	Capecitabine (6 mo)[q,r] or 5-FU/leucovorin (6 mo)[q,r] or FOLFOX (6 mo)[q,r,s,t] or CAPOX (3 mo)[q,r,s,t] or Observation

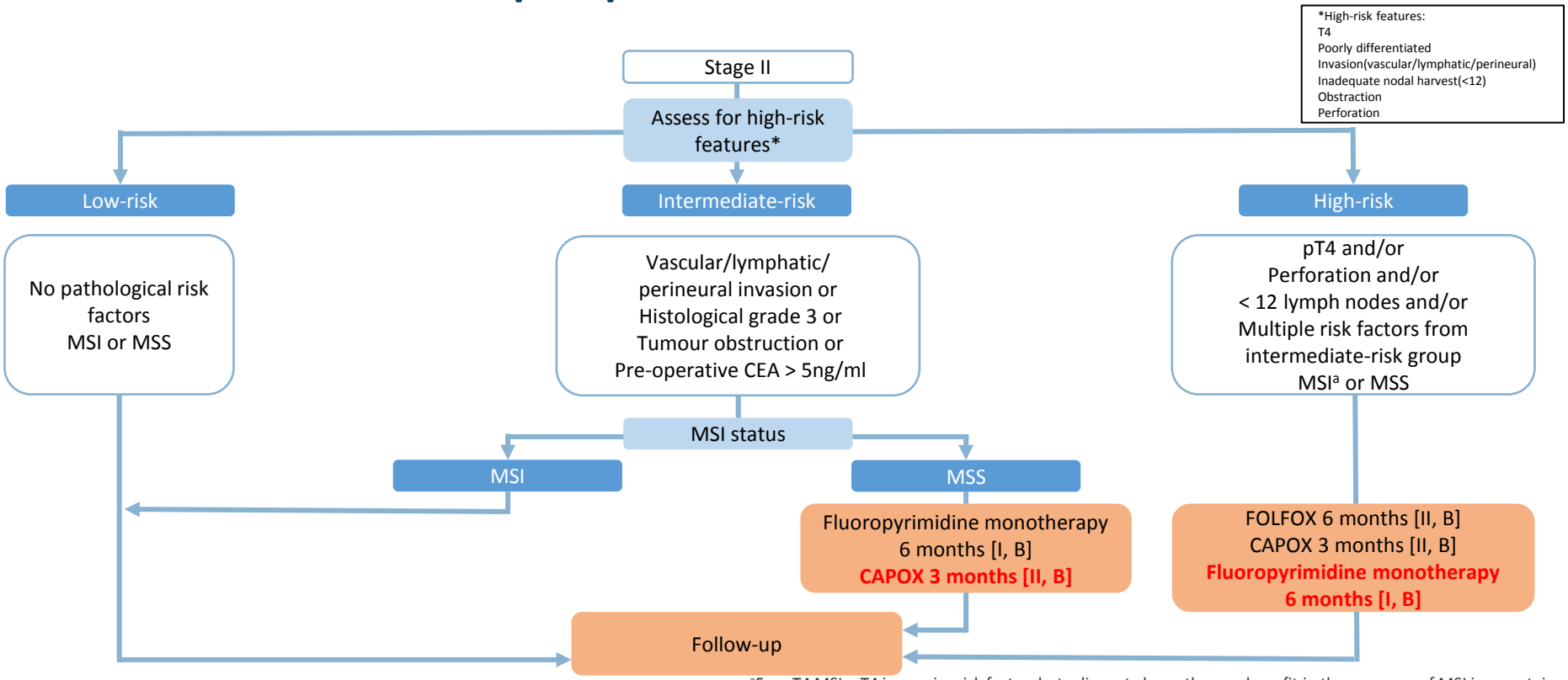


PRINCIPLES OF RISK ASSESSMENT FOR STAGE II DISEASE

- Patient/physician discussion regarding the potential risks of therapy compared to potential benefits, including prognosis. This should include discussion of evidence supporting treatment, assumptions of benefit from indirect evidence, morbidity associated with treatment, high-risk characteristics, and patient preferences.
- When determining if adjuvant therapy should be administered, the following should be taken into consideration:
  - ✓ **Number of lymph nodes analyzed after surgery (<12)**
  - ✓ **Poor prognostic features (eg, poorly differentiated histology [exclusive of those that are MSI-H]; lymphatic/vascular invasion; bowel obstruction; PNI; localized perforation; close, indeterminate, or positive margins)**
  - ✓ **Assessment of other comorbidities and anticipated life expectancy.**
- The benefit of adjuvant chemotherapy does not improve survival by more than 5%.
- MSI or MMR testing

NCCN Guidelines Colon Cancer Version 2.2021

Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis treatment and follow-up of patients with localised colon cancer

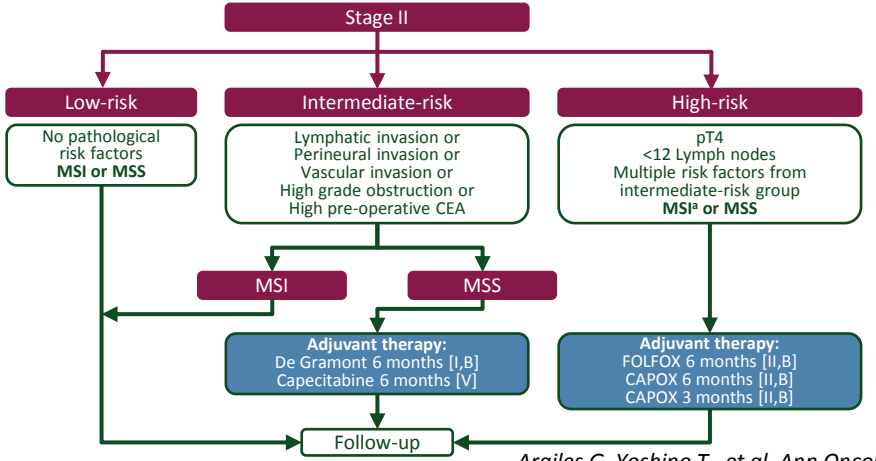


[a]For pT4 MSI: pT4 is a major risk factor, but adjuvant chemotherapy benefit in the presence of MSI is uncertain

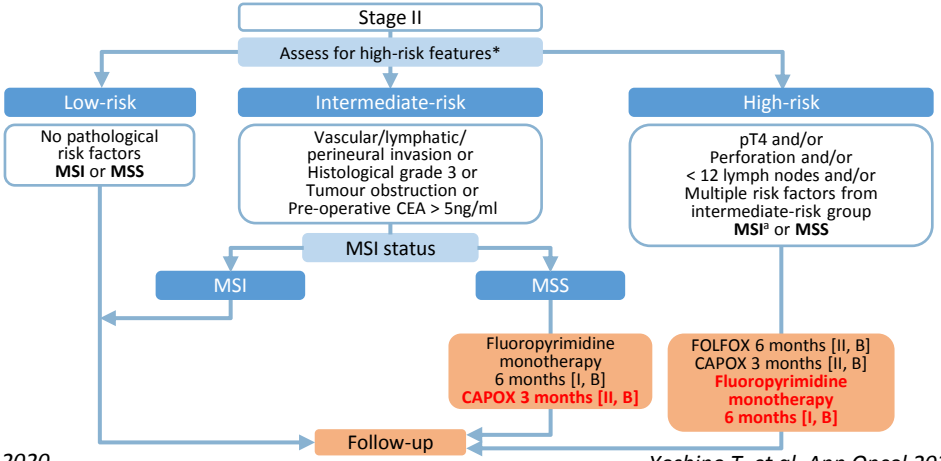
Yoshino T, et al. Ann Oncol 2021.

Takayuki Yoshino, MD., Ph.D.

Differences between ESMO GLs and Pan-Asian GLs



Argiles G, Yoshino T, et al. Ann Oncol 2020.

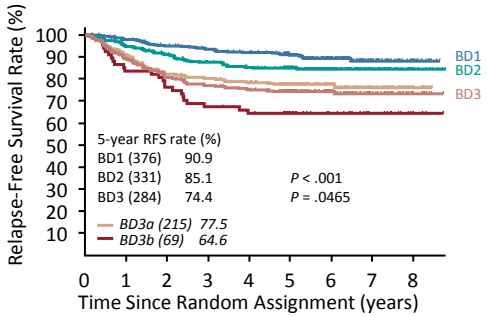


Yoshino T, et al. Ann Oncol 2021.

	ESMO Clinical Practice Guidelines (2020)	Pan-Asian adapted ESMO Clinical Practice Guidelines (2021)
intermediate-risk	For patients with intermediate risk (non-MMR/MSI + any risk factor except pT4 or <12 lymph nodes assessed), 6 months of fluoropyrimidines should be recommended [I, B].	For patients with intermediate-risk stage II (non-MMR/MSI + any risk factor except pT4/**perforation** or < 12 lymph nodes assessed) 6 months of fluoropyrimidine therapy is recommended [**II, B**]. **Three months of CAPOX is an acceptable alternative in fit patients, after being informed of the risk/benefit profile [V; consensus = 100%]**
high-risk	Patients with high-risk stage II (pT4 or <12 lymph nodes or multiple intermediate risk factors, regardless of MSI) may be considered for the addition of oxaliplatin [I, C].	For patients with high-risk stage II disease (pT4/**perforation** or < 12 lymph nodes assessed or multiple intermediate risk factors, regardless of MSI status) the addition of oxaliplatin **should be considered, in view of a higher risk of relapse and anticipated benefit [II, C; consensus = 100%]**

The Prognostic and Predictive Impact of Tumor Budding in Stage II Colon Cancer: Results From the SACURA Trial

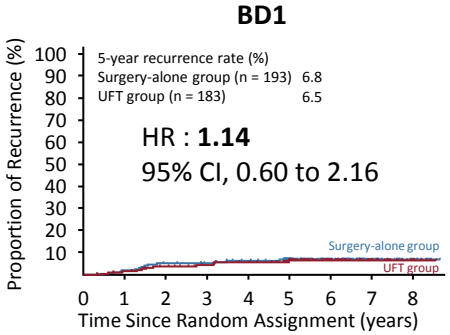
RFS rate in patients with colon cancer according to grade of tumor budding



No. at Risk

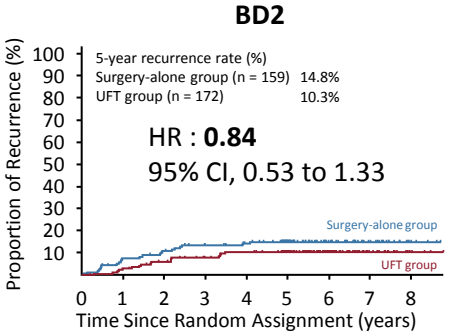
BD1	376	367	352	341	331	224	121	50	17
BD2	331	309	295	274	263	183	99	42	8
BD3	284	252	228	217	209	142	77	40	9
BD3a	215	195	176	171	166	109	55	28	6
BD3b	69	57	52	46	43	33	22	12	3

Impact of Adjuvant Chemotherapy on Recurrence Rate According to Tumor Budding Grade



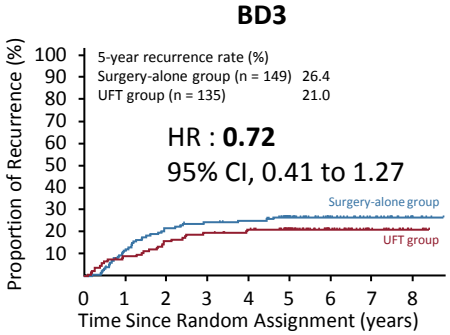
No. at Risk

Surgery alone	193	189	182	178	172	114	63	26	10
UFT	183	178	170	163	159	110	58	24	7



No. at Risk

Surgery alone	159	144	138	128	123	81	42	22	4
UFT	172	165	157	146	140	102	57	20	4



No. at Risk

Surgery alone	149	131	116	110	107	67	38	23	5
UFT	135	121	112	107	102	75	39	17	4

BD1: less than five budding foci,
BD2: five to nine budding foci
BD3: 10 or more budding foci
(BD3a: 10 to 19 budding foci , BD3b: 20 or more budding foci)

Tumour budding is one of the risk factors, FP mono was seen to improve relapse-free survival in stage II patients with high tumour budding.

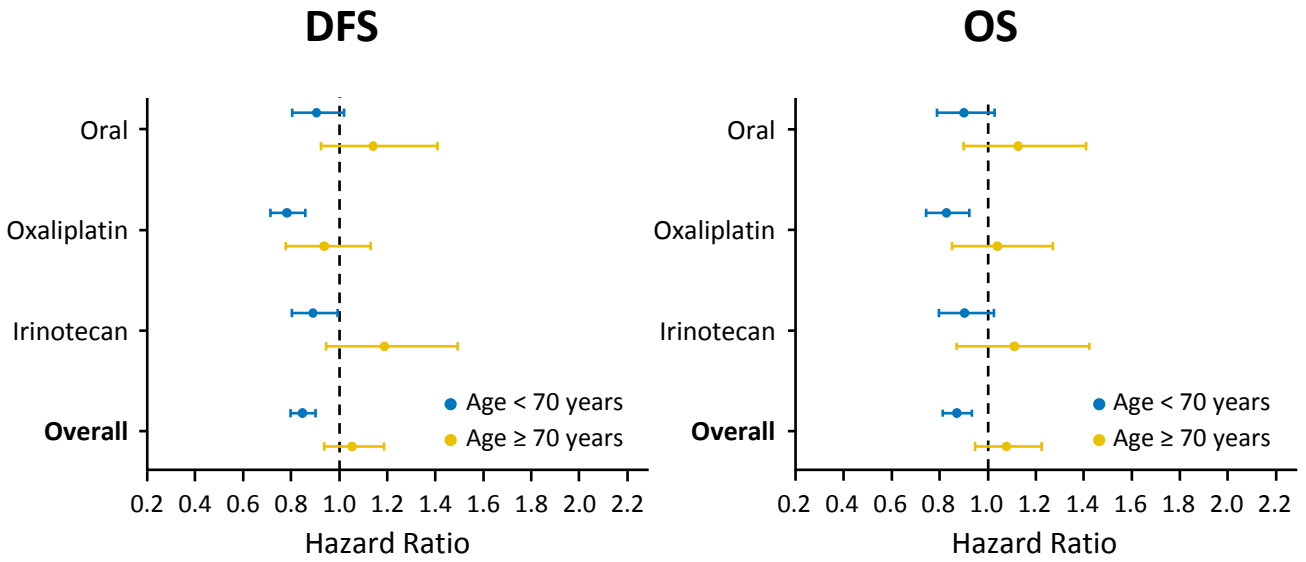
Ueno H, et al. J Clin Oncol 2019.

Age should be considered when decision making

Impact of Age on the Efficacy of Newer Adjuvant Therapies in Patients With Stage II/III Colon Cancer: Findings From the ACCENT Database

Overall Baseline Patient Characteristics

Characteristic	Age < 70 Years (%; n = 11,953)	Age ≥ 70 Years (%; n = 2,575)
Sex		
Female	45	45
Male	55	55
Stage		
II	23	19
III	77	81
Treatment arm		
Control	49	52
Experimental	51	48



Treatment decisions need to be carefully considered

McCleary NJ, et al. J Clin Oncol 2013.

Testing for DPD insufficiency should be conducted before initiating FP based chemotherapy in Europe

Prospective, multicentre, safety analysis in 17 hospitals in the Netherlands (n=1103)

	DPYD variant allele carriers	Wild-type patients	p value
No of patients(%)	85 (8%)	1018 (92%)	
FP-related severe toxicity(%)	33 (39%)	231 (23%)	0.0013

Prospective genotyping for **DPYD*2A**, **c.2846A>T**, **c.1679T>G**, **c.1236G>A**. Heterozygous DPYD variant allele carriers received an initial FP dose reduction of 25% (c.2846A>T and c.1236G>A) or 50% (DPYD*2A and c.1679T>G),

Prevalence of impaired DPD genotype and its association with FP-related toxicities in East Asian (n=1365)

HGVS*	MAF	Diarrhea (%)		Stomatitis (%)		Neutropenia (%)	
		Gr1-4	Gr 0	Gr1-4	Gr 0	Gr1-4	Gr 0
c.C2303A	0.0022	4.0	4.7	4.5	4.5	4.4	4.5
c.G2194A	0.019	4.0	3.9	4.1	3.8	3.8	4.1
c.T1896C	0.13	22.0	24.2	20.9	24.4	20.4	24.3
c.A1627G	0.28	43.9	41.9	44.9	41.8	43.2	40.9
c.G1294A	0.00036	0.0	0.1	0.0	0.1	0.0	0.0
c.G1003T	0.00073	0.3	0.1	0.3	0.1	0.3	0.0
c.A496G	0.02	5.7	3.3	3.4	4.0	4.4	3.9
c.A451G	0.0029	0.0	0.8	0.0	0.8	0.9	0.2

*None of the 4 major DPD variants (DPYD*2A, c.2846A>T, c.1679T>G, c.1236G>A)

None of DPD variants showed a clinically significant association with FP related toxicities

Differences between ESMO GLs and Pan-Asian GLs

	ESMO Clinical Practice Guidelines (2020)	Pan-Asian adapted ESMO Clinical Practice Guidelines (2021)
DPD phenotype	Based on the recommendation of the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) dated 13 March 2020, testing for DPD insufficiency should be conducted before initiating fluoropyrimidine based chemotherapy [III, A].	**Depending on the anticipated genetic profile of a specific Asian patient population**, DPD genotyping or phenotyping **may be considered** before initiating fluoropyrimidine-based adjuvant therapy [III, A]. **DPD genotyping or phenotyping should be implemented in patients who experience severe fluoropyrimidine toxicity [V; consensus = 100%]**

Henricks LM, et al, Lancet Oncol 2018. Kanai M, Yoshino T, et al, ESMO-ASIA 2020 #300MO. Argiles G, Yoshino T, et al. Ann Oncol 2020. Yoshino T, et al. Ann Oncol 2021.

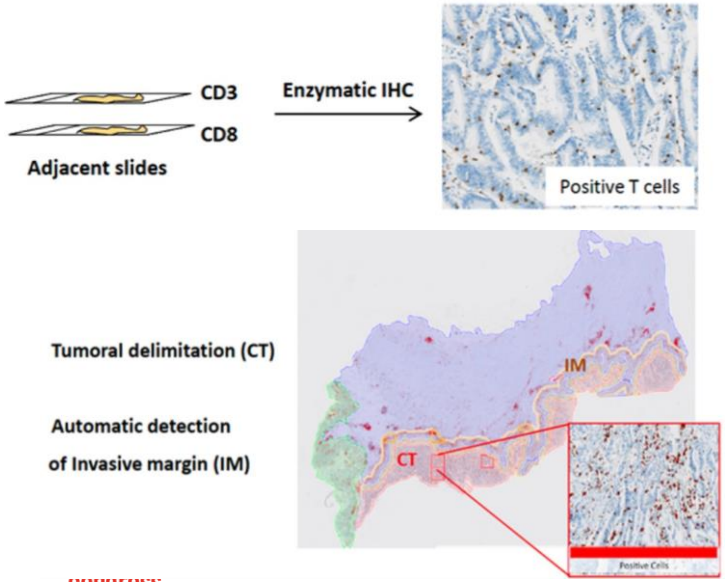
Use of personalized medicine in localized colon cancer/ biomarkers for risk assessment

Biomarker/tool	Clinical significance	Potential use and relevance
dMMR	**Prognostic** & **predictive**	Associated with favorable prognosis in stage II and possibly low-risk (IDEA defined) stage III patients. Predicts lack of benefit and possibly harm with 5-FU based adjuvant chemotherapy in both stage II and III patients.
***KRAS* and *BRAF*^{V600E} mutation**	**Prognostic**	KRAS and BRAFV600E mutations have been reported to be associated with a worse prognosis in several large retrospective studies, in both stage II and III patients. dMMR status attenuates adverse prognostic impact of BRAFV600E mutation, possibly except in IDEA defined high-risk stage III CC.
***PIK3CA* mutations**	**Predictive**	Retrospective analysis suggests an association between the use of aspirin and improved survival among the patients with mutated-PIK3CA colorectal cancer including stage I-III patients.
CDX2 expression	**Prognostic** & **predictive**	Retrospective analysis suggested lack of CDX2 expression was associated with worse outcome in stage II and III CC. Lack of CDX2 expression appears to be predictive of benefit from adjuvant chemotherapy in stage II patients.
Genomic profiling (Oncotype Dx Colon Cancer®)	**Prognostic**	Prognostic discrimination capacity is insufficient to guide therapy in routine clinical practice.
CMS	**Prognostic**	CMS1 tumors have a good prognosis, the CMS4 tumors have a poor prognosis, and the CMS2 and CMS3 types have an intermediate prognosis. Not validated to guide therapy in routine clinical practice.
Immunoscore (IS)	**Prognostic**	High immunoscore is associated with favorable prognosis in both stage II and III patients independent of patient T stage, N stage and microsatellite instability. High-risk stage II patients with high Immunoscore had similar time to recurrence compared with average risk stage II patients in a recent report.
ctDNA	**Prognostic**	ctDNA detection in the bloodstream after surgical resection and adjuvant chemotherapy provides direct evidence of residual micro-metastatic disease and correlates with a very high risk of cancer recurrence in resected stage II and III patients. Sensitivity, specificity, positive and negative predictive values are 48%, 100%, 100% and 91%, respectively. Reported studies suggest that ctDNA can potentially serve as a real time marker of adjuvant therapy efficacy in stage II and III patients.

Chakrabarti S et al., World J Gastrointest Oncol 12: 808-832, 2020.

Immunoscore® Colon kit

Material: FFPE block or FFPE slides from tumor resection
Target: CD3+ & CD8+ T cells
Location: Center (CT) and invasive margin (IM) of the tumor
Technology: Image Analysis



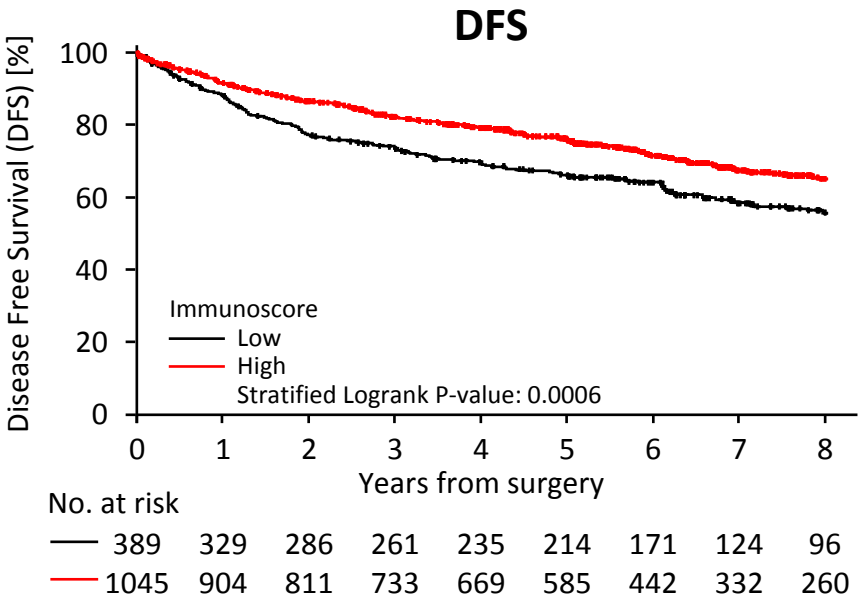
Immnoscore Classification

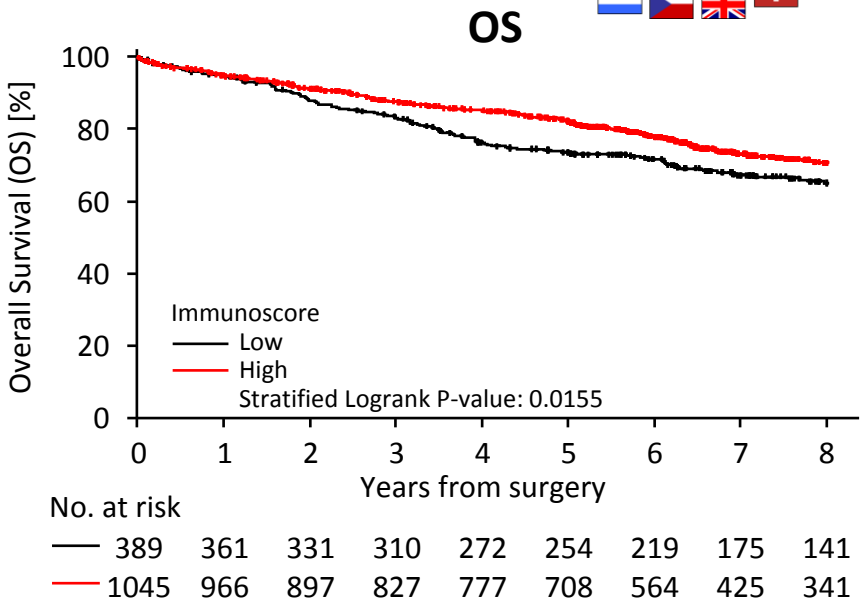
Percentiles	Immunoscore Classes	Patients IS groups
>95-100%	I4	High
>70-95%	I3	
>25-70%	I2	Intermediate
>10-25%	I1	Low
0-10%	I0	

Marliot, F, et al. Methods Enzymol 2020.

KM curves in patients with stage II colon cancers (n=1,434)

The Immunoscore based on 2 categories for DFS, OS

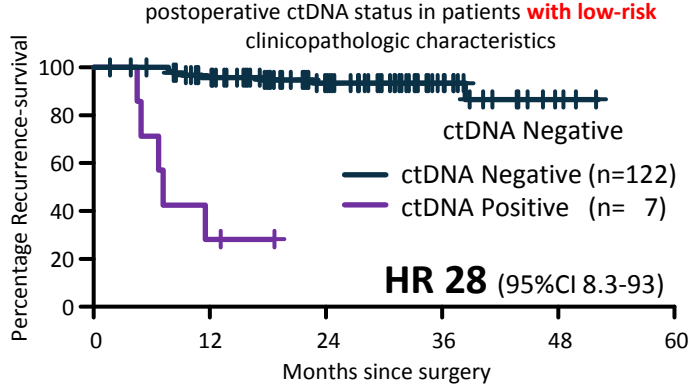


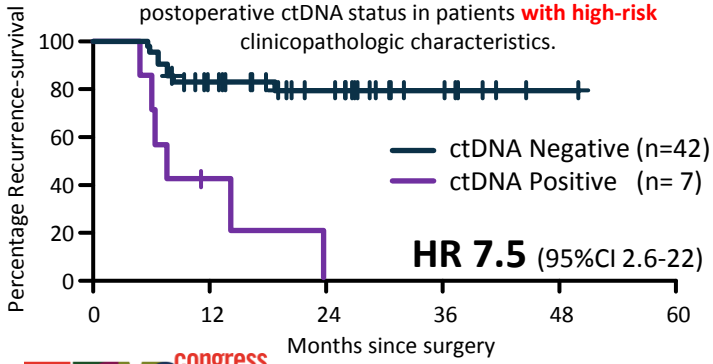


Pages F, et al. Lancet 2018.

The Immunoscore significantly predicted survival in patients with stage II colon cancer

DFS, pStageII (Patients not treated with chemotherapy, n=178)



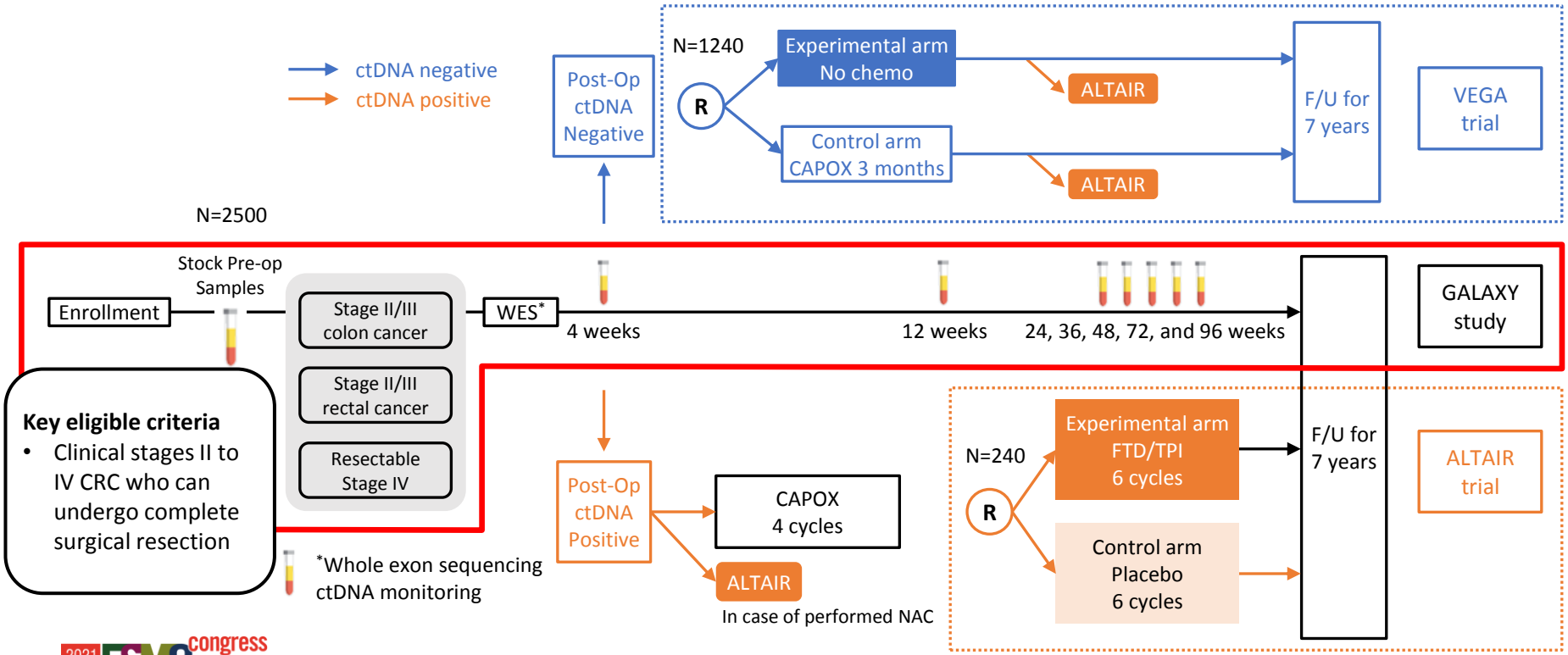


Variable	Univariate analysis HR	95% CI	P	Multivariate analysis HR	95% CI	P
All patients (n = 230)						
Age, <70 versus ≥70	1	0.50–2.0	1			
Sex, male versus female	1.1	0.57–2.2	0.7			
Tumor site, right versus left	1.1	0.55–2.1	0.8			
Tumor differentiation, well/moderate versus poor	0.32	0.08–1.3	0.1			
T stage, T3 versus T4	**2.4**	**1.2–5.1**	**0.02**	**2.6**	**1.2–5.5**	**0.01**
Lymph node yield, ≥12 versus <12	**2.2**	**0.97–4.8**	**0.06**			
Lymphovascular invasion, no versus yes	**1.9**	**0.92–4.1**	**0.08**			
MMR status, deficient versus proficient	**3.5**	**0.83–14.5**	**0.09**			
Clinicopathologic risk group, low versus high	2.1	1.06–4.2	0.03			
Adjuvant chemotherapy, no versus yes	0.79	0.34–1.8	0.6			
Postoperative CEA, normal versus elevated	**2.8**	**0.98–7.9**	**0.06**			
Postoperative ctDNA status, negative versus positive	**13**	**6.6–27**	**<0.001**	**14**	**6.8–28**	**<0.001**

Tie J, et al. Sci Transl Med 2016.

ctDNA is the greatest prognostic factor in Stage II colon cancer

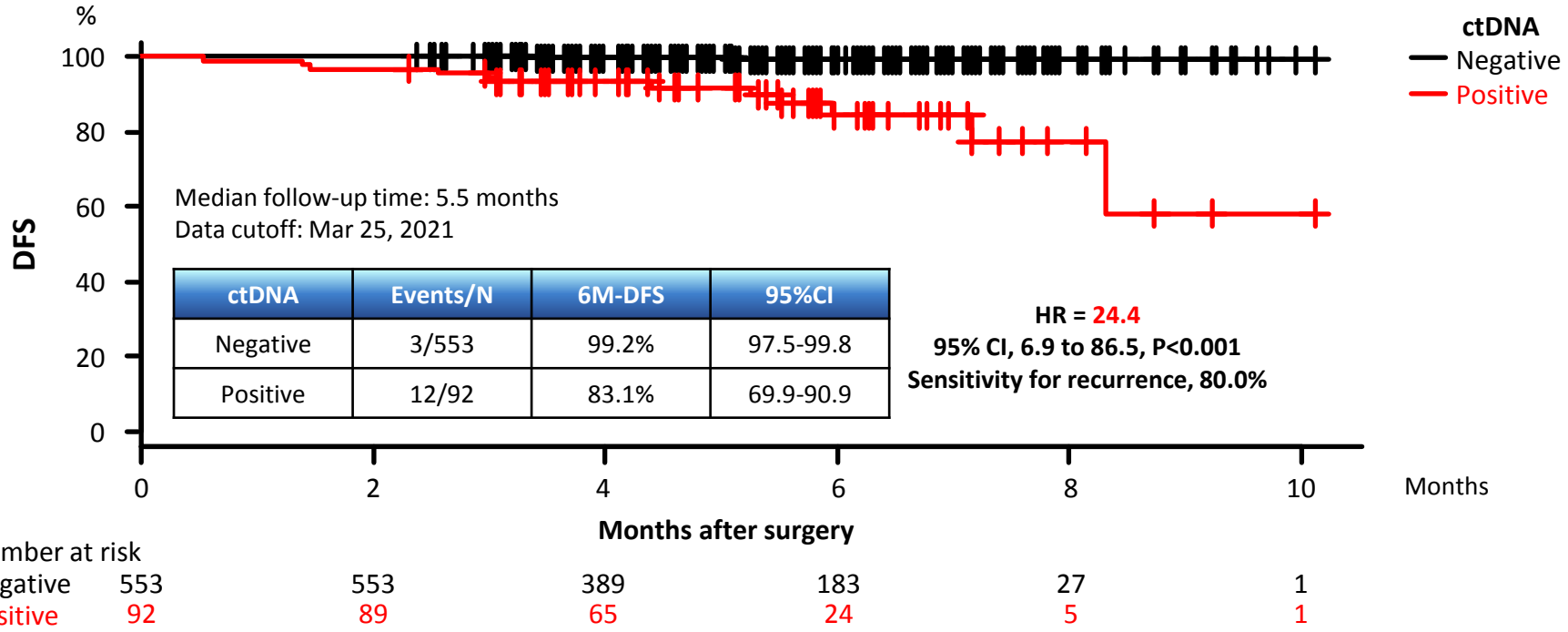
Schema of CIRCULATE-Japan project



Takayuki Yoshino, MD., Ph.D.

Taniguchi H, Yoshino T, et al. Cancer Sci 2021.

DFS by post-op-4w ctDNA status in pStage I-III



ctDNA	Events/N	6M-DFS	95%CI
Negative	3/553	99.2%	97.5-99.8
Positive	12/92	83.1%	69.9-90.9

ctDNA positive rate is 14 % in pStage I-III

Shirasu H, Yoshino T, et al.: WCGC2021 #O-11.

Multivariate analysis for recurrence in pStage I-III

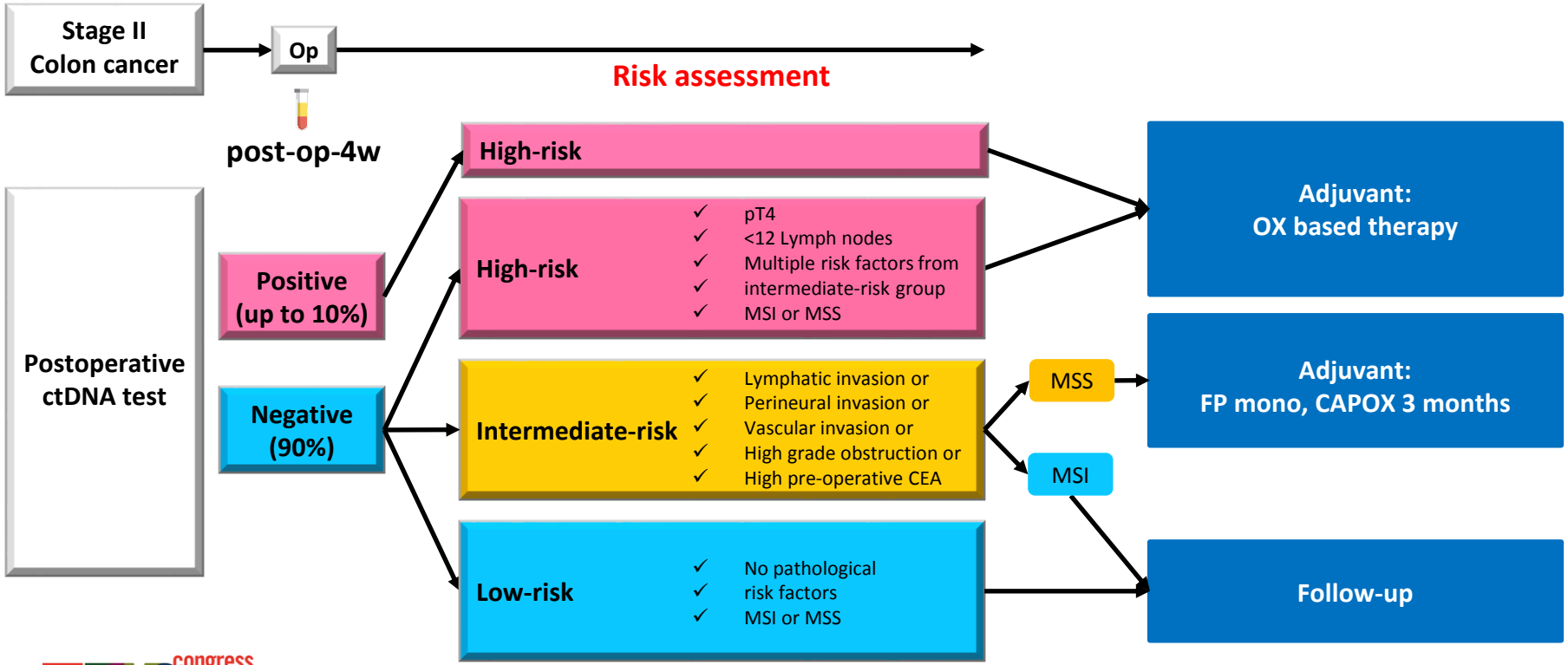
Covariates	HR	95% CI	P
Post-op-4w ctDNA positive vs. negative	**17.1**	**4.6-63.1**	**<0.001**
N1-2 vs. N0	**7.1**	**0.9-57.7**	**0.06**
RAS mt vs. wt	1.1	0.3-3.3	0.91
BRAF mt vs. wt	3.5	0.7-17.6	0.13
Gender Female vs. Male	1.5	0.5-4.2	0.46
PS 1 vs 0	1.4	0.3-6.5	0.65

No recurrence cases in T1-T2, and MSI-High patients so far. Hence T stage and MSI not included in the analysis.

Multivariate analysis was performed by Cox proportional hazard model.

Shirasu H, Yoshino T, et al.: WCGC2021 #O-11.

What to do in the future?



Takayuki Yoshino, MD., Ph.D.

Conclusion

- ✓ Adjuvant is not required for low-risk Stage II and Intermediate-risk Stage II with MSI-H.
- ✓ FP mono or FP+OX is required for Intermediate-risk Stage II with MSS.
- ✓ FP ± OX is recommended for high-risk Stage II with MSS, while a lacking evidence for high-risk Stage II with MSI-H exists.
- ✓ Benefit of adjuvant therapy have not been observed in the elderly, treatment decisions should be carefully considered.
- ✓ DPD testing should be conducted before initiating FP based chemotherapy, while DPD testing is not needed because it is rare in Asia.
- ✓ Optimization of ctDNA-guided treatment selection W or W/O the immunoscore is desired.

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