Discussion on proffered paper session: Gastrointestinal tumors 1; 1420 & 1430

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Disclosure slide

- I have nothing to declare

Papers for discussion

1420: Xu R, He M, et al: Single-agent capecitabine maintenance therapy after induction of XELOX (or FOLFOX) in first-line treatment of mCRC

1430: Cheng JC, et al: High Anus Preservation and Low Toxicity Rates in a Phase I Trial of Neoadjuvant Bowel-Sparing IMRT/Bevacizumab/FOLFOX and TME for Locally Advanced Rectal Cancer

1420: Single-agent capecitabine maintenance therapy after induction of XELOX (or FOLFOX) in first-line treatment of mCRC

- **Corresponding author:** *Ruihua Xu*
- **Authors:** *R. Xu, Y. Li, H. Luo, W. Wang, Z. Wang, X. Yuan, D. Ma, F.H. Wang, D. Zhang, D.R.Lin, J. Jia, X.H. Hu, J.W. Peng, Y.C. Lin, and M.He*
- **Presented by:** *Mingming He*
- **Affiliation:** *Sun yat-sen university cancer center, China*

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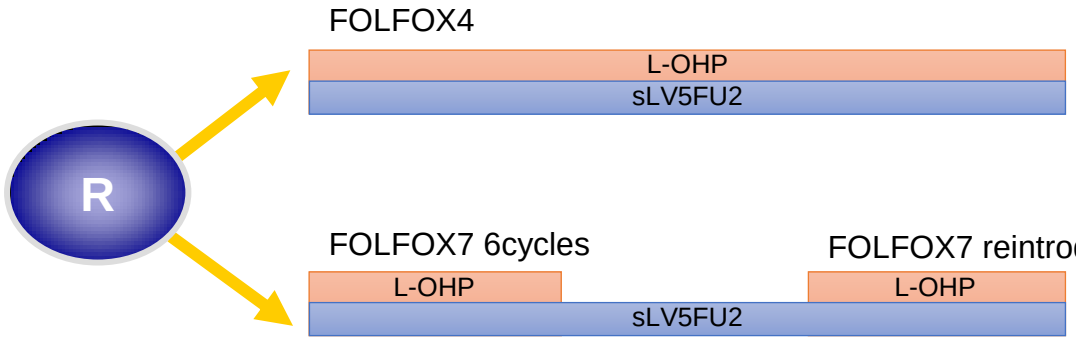
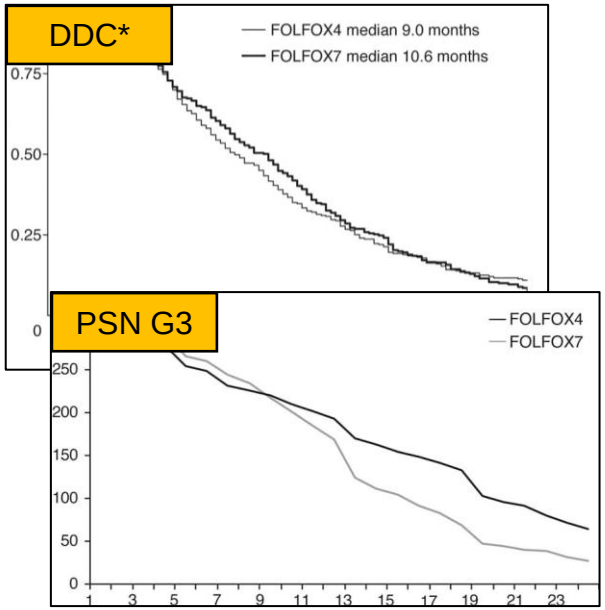
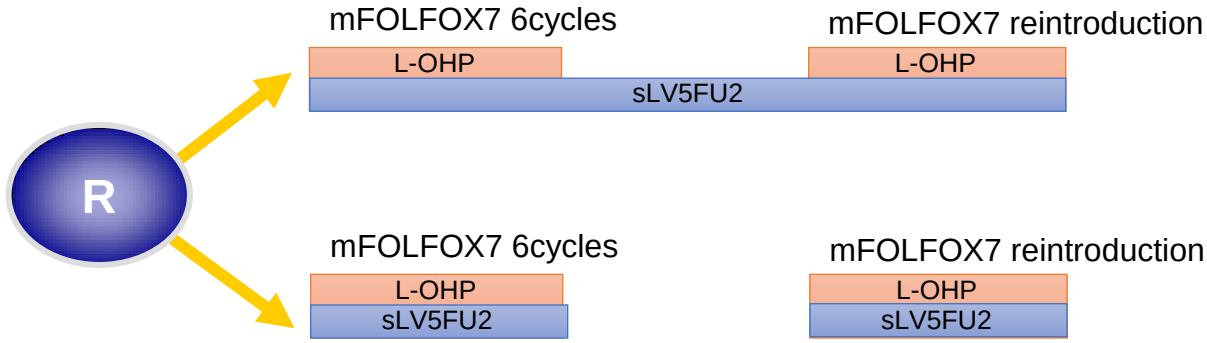
Maintenance therapy in FOLFOX

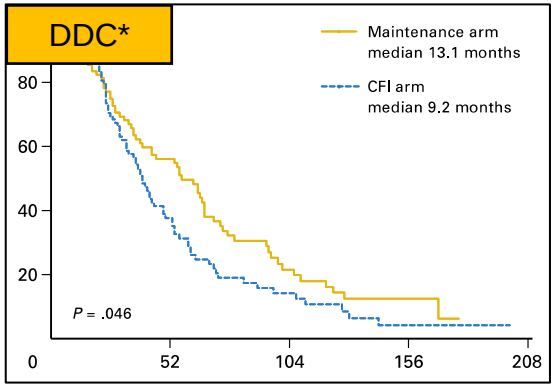
➢ OPTIMOX1





➢ OPTIMOX2





* duration of disease control

C Tournigand, et al. J Clin Oncol. 2006. B Chibaudel, et al. J Clin Oncol. 2006. 2009.

RCTs evaluating maintenance therapy

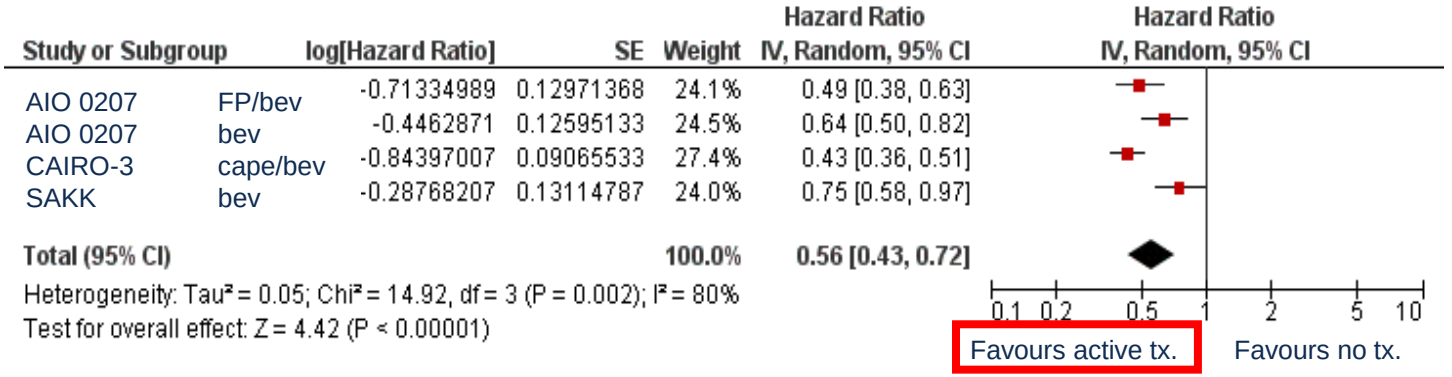
Trial name	design	Induction chemo (M)	Maintenance	Primary EP HR, p	Primary EP(M)	OS
Spanish TTD MACRO	2 arm Non-inferiority N=480	4.5	CapeOX+BEV*	PFS 1.098 0.3811	10.4	23.2
			BEV		9.7	20.0
Swiss SAKK	2 arm Non-inferiority N=262	4-6	BEV*	TTP 0.74 0.47	4.1	25.1
			observation		2.9	22.8
Dutch CAIRO3	2 arm superiority N=558	4.5	Cape+BEV	PFS2 0.67 <0.0001	11.7	21.6
			observation*		8.5	18.1
Germany AIO0207	3 arm Non-inferiority N=473	6	FP+BEV*	TFS	6.8	23.8
			BEV		6.5	26.2
			observation		6.1	23.1

*Control arm

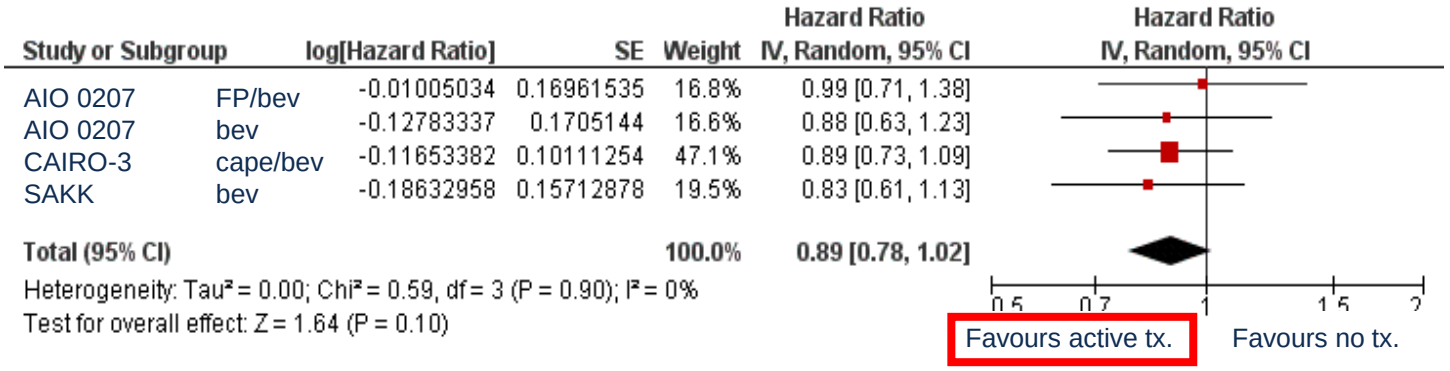
E Diaz-Rubio, et al. Oncologist. 2012. K Dieter, et al. ASCO. 2013.
Simkens H, et al. Lancet 2015. Hegewisch-Becker S, et al. Lancet Oncol. 2015.

Maintenance trials: Combined analysis, vs. no tx.

PFS



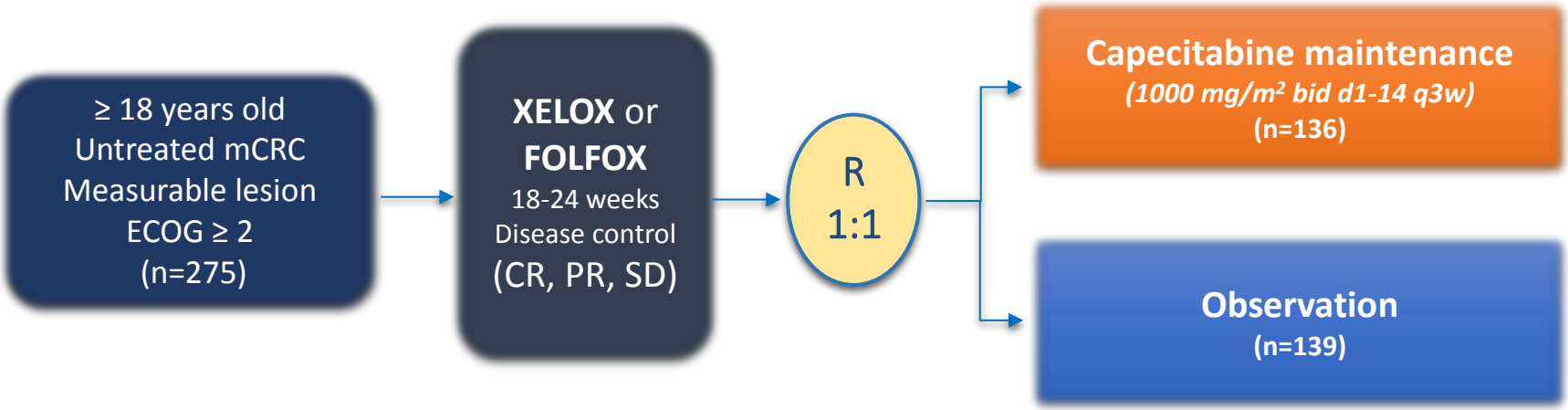
OS



Koopman et al., GI Cancer Symposium 2014; abstract LBA388;
Köberle et al., ASCO 2013 J Clin Oncol 31, 2013 (suppl.); abstr. 3503)

D Arnold, et al: ASCO 2014

Study design (#1420)



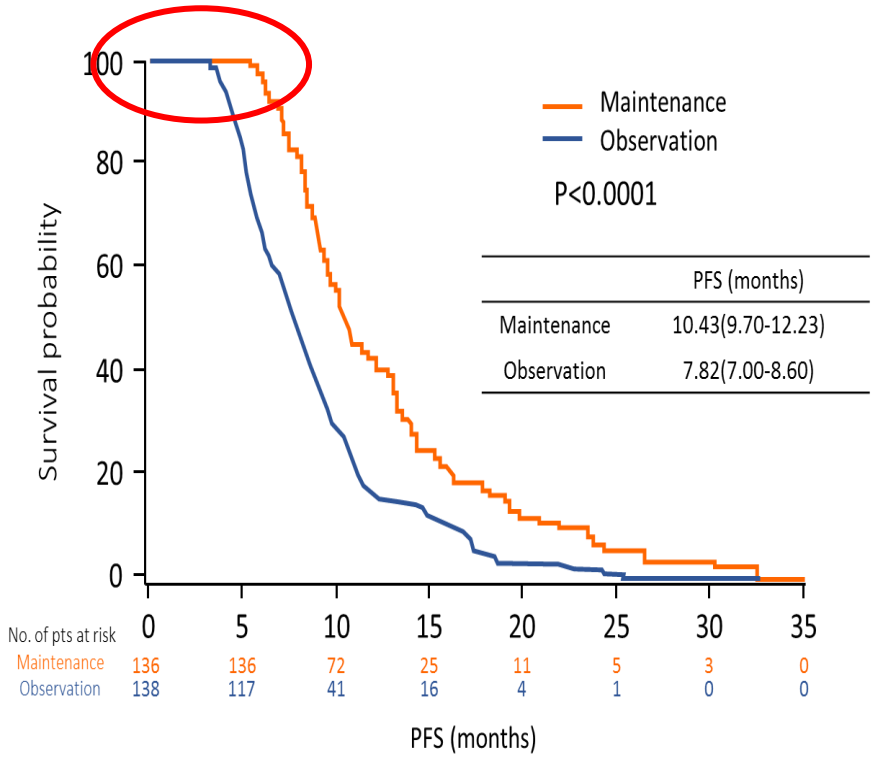
- Primary endpoint: **Progression-free disease (PFS)**
- Secondary endpoints: **Overall survival (OS), Overall response rate (ORR), Safety.**

Under unavailability of bevacizumab

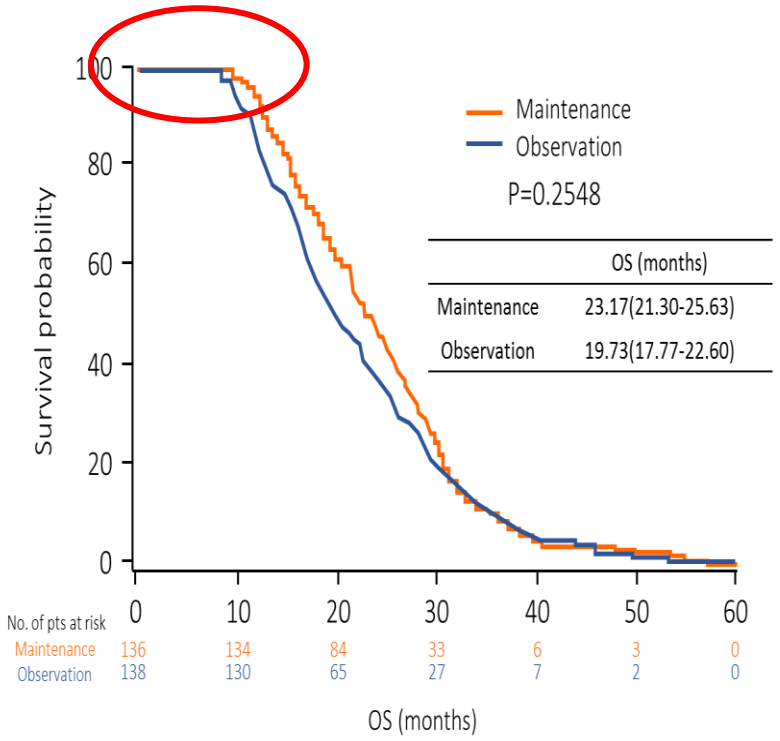
Xu R and He M, et al: ESMO Asia 2015 (#1420)

This study met primary endpoint

Primary endpoint： PFS (total population)

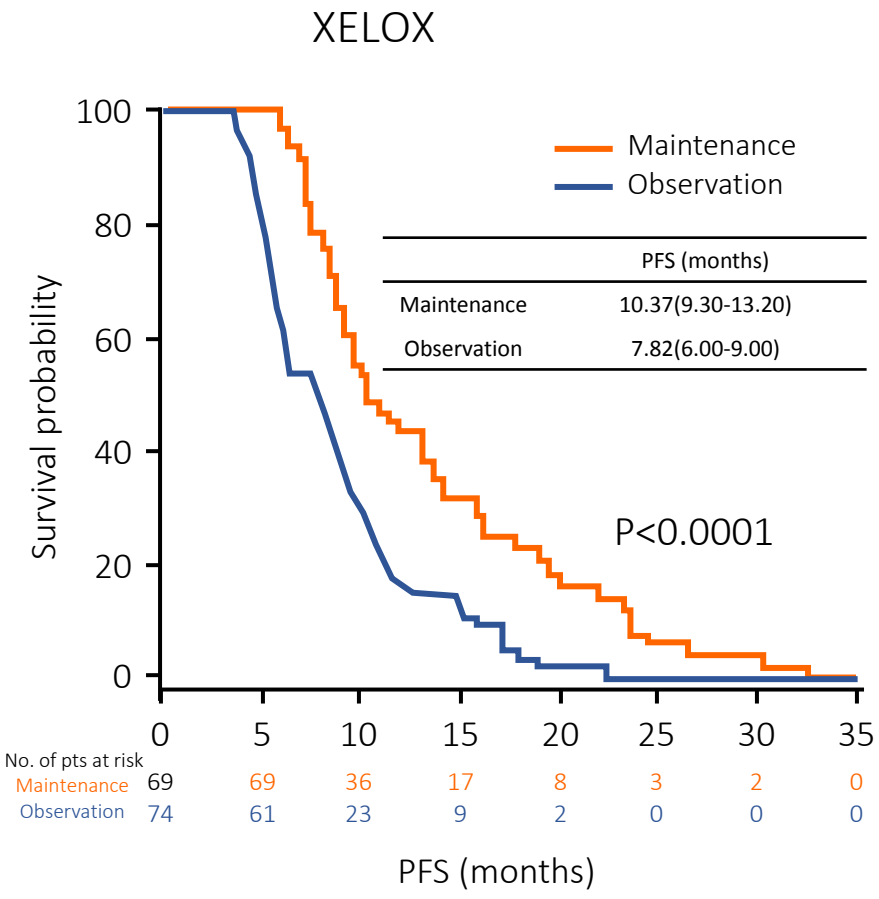


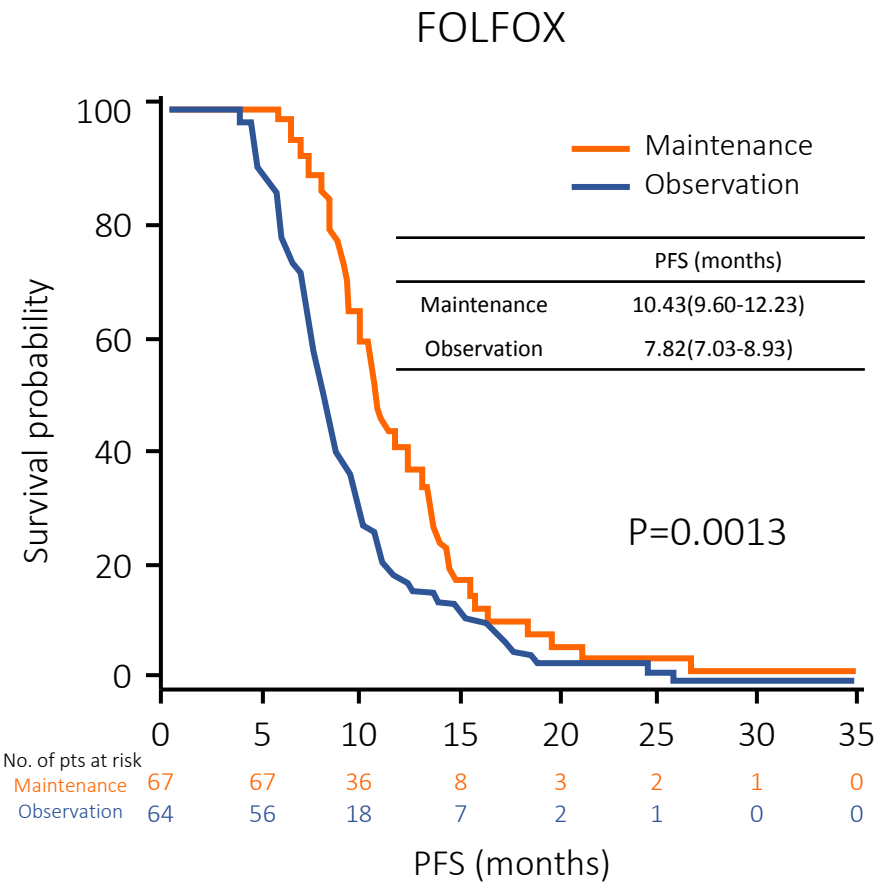
Secondary endpoint： OS (total population)



Xu R and He M, et al: ESMO Asia 2015 (#1420)

Subgroup analysis: PFS (XELOX / FOLFOX)





Xu R and He M, et al: ESMO Asia 2015 (#1420)

RCTs evaluating maintenance therapy: vs observation

Trial name	design	Induction chemo (M)	Maintenance	Primary EP(M)	Primary EP HR, p	OS
Dutch CAIRO3	2 arm Superiority N=558	4.5	Cape+BEV	11.7	PFS2 0.67 <0.0001	21.6**
			observation*	8.5		18.1**
German AIO0207	3 arm Non-inferiority N=473	6	FP+BEV*	6.8	TFS	23.8**
			BEV	6.5		26.2**
			observation	6.1		23.1**
This study	2 arm Superiority N=275	4.5-6	Cape	10.4	PFS2 0.67 <0.0001	23.2
			observation*	7.8		19.7

*Control arm

** OS from the start of maintenance

Simkens H, et al. Lancet 2015. Hegewisch-Becker S, et al. Lancet Oncol. 2015.

Xu R and He M, et al: ESMO Asia 2015 (#1420)

Re-introduction rate of oxaliplatin

	observation	maintenance
CAIRO 3	60%	47% (cape+BV)
AIO	45%	21% (FL/cape+BV)
This study	27%	19% (cape)

Simkens H, et al. Lancet 2015. Hegewisch-Becker S, et al. Lancet Oncol. 2015.

Xu R and He M, et al: ESMO Asia 2015 (#1420)

Summary & comments (#1420)

- This study firstly showed a significant prolongation of PFS by capecitabine single agent maintenance therapy compared with observation in the 1st line randomized trials

- Capecitabine monotherapy can be a standard as a maintenance therapy under situation of unavailable for bevacizumab

- OS benefit is still limited

High Anus Preservation and Low Toxicity Rates in a Phase I Trial of Neoadjuvant Bowel-Sparing IMRT/Bevacizumab/FOLFOX and TME for Locally Advanced Rectal Cancer

- Jason Chia-Hsien Cheng, Jin-Tung Liang, Chiao-Ling Tsai, Ji-Shiang Hung, John Huang, Yu-Lin Lin, Chia-Chun Wang
- Departments of Oncology and Surgery
- National Taiwan University Hospital
- Taipei, Taiwan

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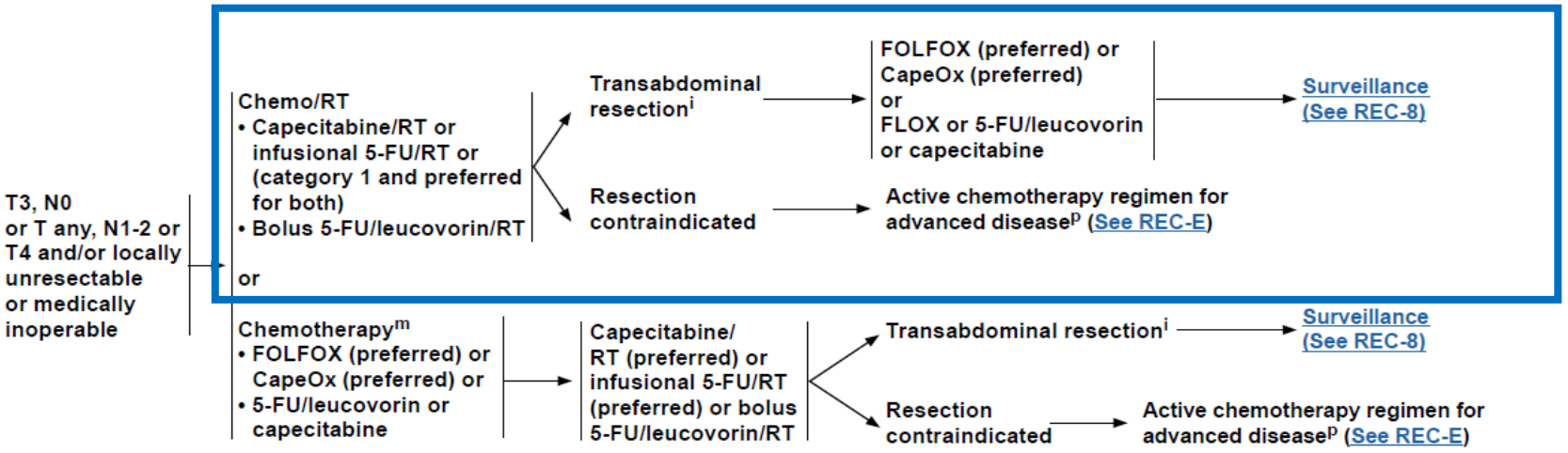


[i] See Principles of Surgery (REC-B).
[k] See Principles of Adjuvant Therapy (REC-C).
[l] See Principles of Radiation Therapy (REC-D).
[m] Fernandez-Martos C, Pericay C, Aparicio J, et al: Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: Grupo cancer de recto 3 study. J Clin Oncol 2010;28:859-865.
Cercek A, Goodman KA, Hajj C, et al. Neoadjuvant chemotherapy first, followed by chemoradiation and then surgery, in the management of locally advanced rectal cancer. J Natl Compr Canc Netw 2014;12:513-519.

[n] Postoperative therapy is indicated in all patients who receive preoperative therapy, regardless of the surgical pathology results.
[o] Total duration of perioperative chemotherapy, inclusive of chemotherapy and radiation therapy, should not exceed 6 months.
[p] FOLFOXIRI is not recommended in this setting.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Methods

- Eligibility
  - Age < 70 MRI and PET staged T3-4 or N+M0 rectal adenocarcinoma within 12 cm from anal verge
- Treatment
  - **Bevacizumab 5 mg/kg on day 1, 15, 29**
  - **Oxaliplatin 40 mg/m^2**; leucovorin 400; 5-fluorouracil (5-FU) bolus 400 mg /m^2 followed by 2400 mg/m^2 IV continuous infusion over 46 hours at week 1, 3, 5
  - **IMRT** : 1.8 → 2.0 → 2.2 Gy per fraction for 25 fractions
    - Rectal tumor dose level 1: 45 Gy (**5 patients**) → level 2: 50 Gy (**5 patients**) → level 3: 55 Gy (**5 patients**) (45 Gy to pelvic lymphatics)
  - **Surgery (TME)** at 6-10 weeks after completion of CCRT

Cheng JC, et al: ESMO Asia 2015 (#1430)

CAO/ARO/AIO-04 trial

Best arm of CAO/ARO/AIO-94

RT 50.4 Gy + 5-FU (n=623)
1000 mg/m² days 1-5 + 29-33

5-FU
500 mg/m² d 1-5, q29
4 cycles (4 months)

T

M

E

Based on phase I/II trials:

RT 50.4 Gy + 5-FU/OX (n=613)
Ox: 50 mg/m² d 1, 8, 22, 29
5-FU: 250 mg/m² d 1-14 + 22-35

Note: Chemo gap 3rd week of RT !

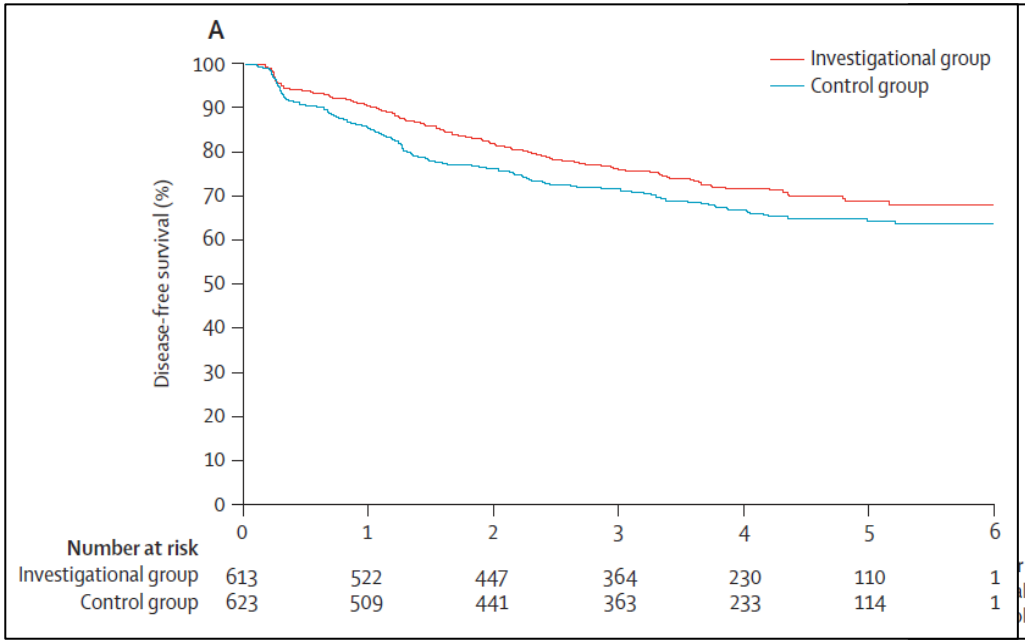
mFOLFOX6
Oxaliplatin: 100 mg/m² d1,q15
Folinic Acid: 400 mg/m² d1
5-FU: 2400 mg/m² d1-2
8 cycles (4 months)

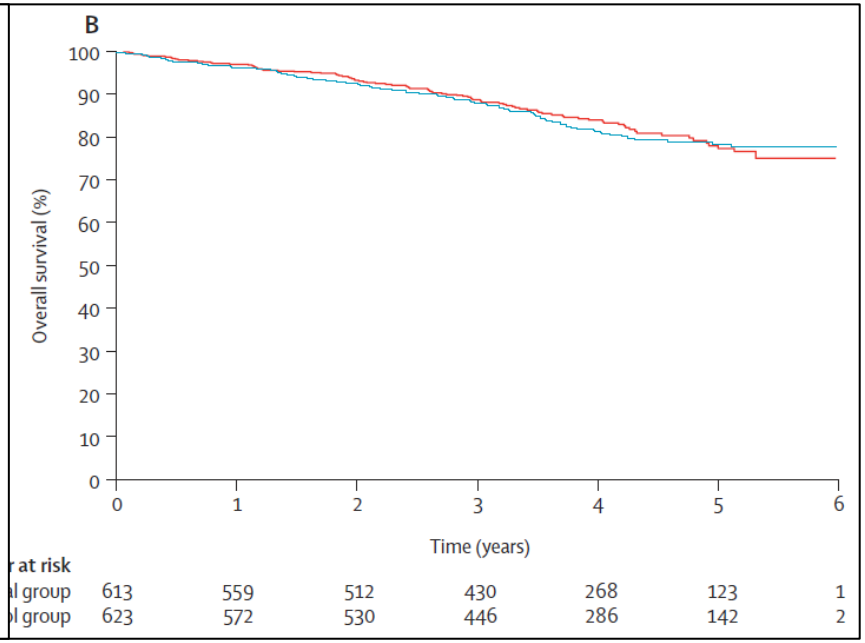
Rodel C, et al. Lancet Oncol. 2015.

DFS and OS

DFS

OS





3-year DFS: 71.2% vs. 75.9%
HR: 0.79 P=0.03

3-year OS: 88.7% vs. 88.0%
HR: 0.96

Rodel C, et al. Lancet Oncol. 2015.

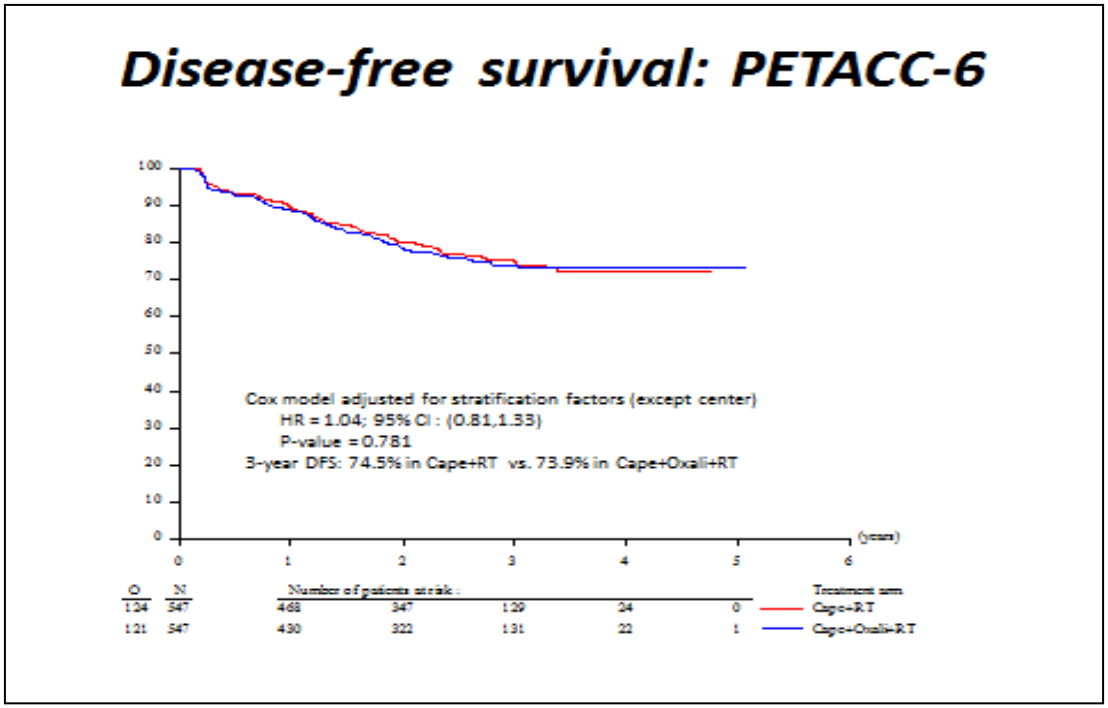
PETACC-6

Rectal adenocarcinoma
cT3/4 and/or cN+, cM0
PS 0-2

R

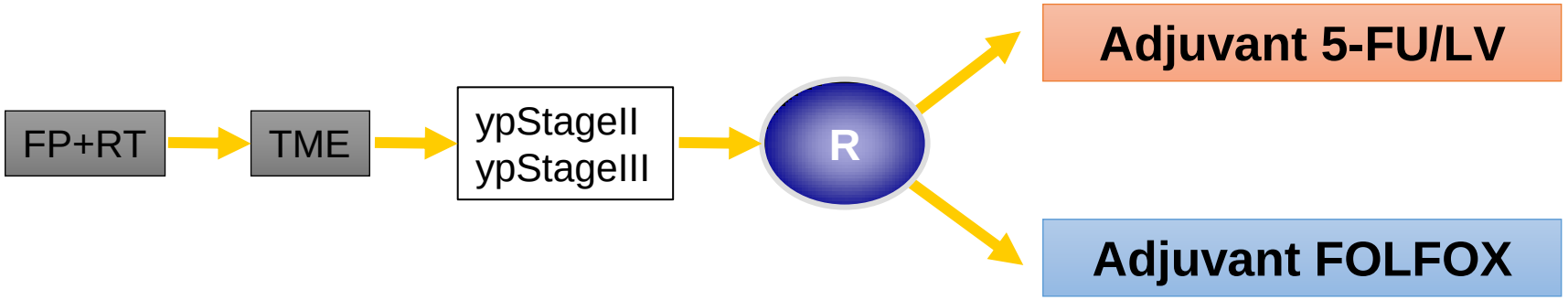
Cape+RT → TME → Adj Cape

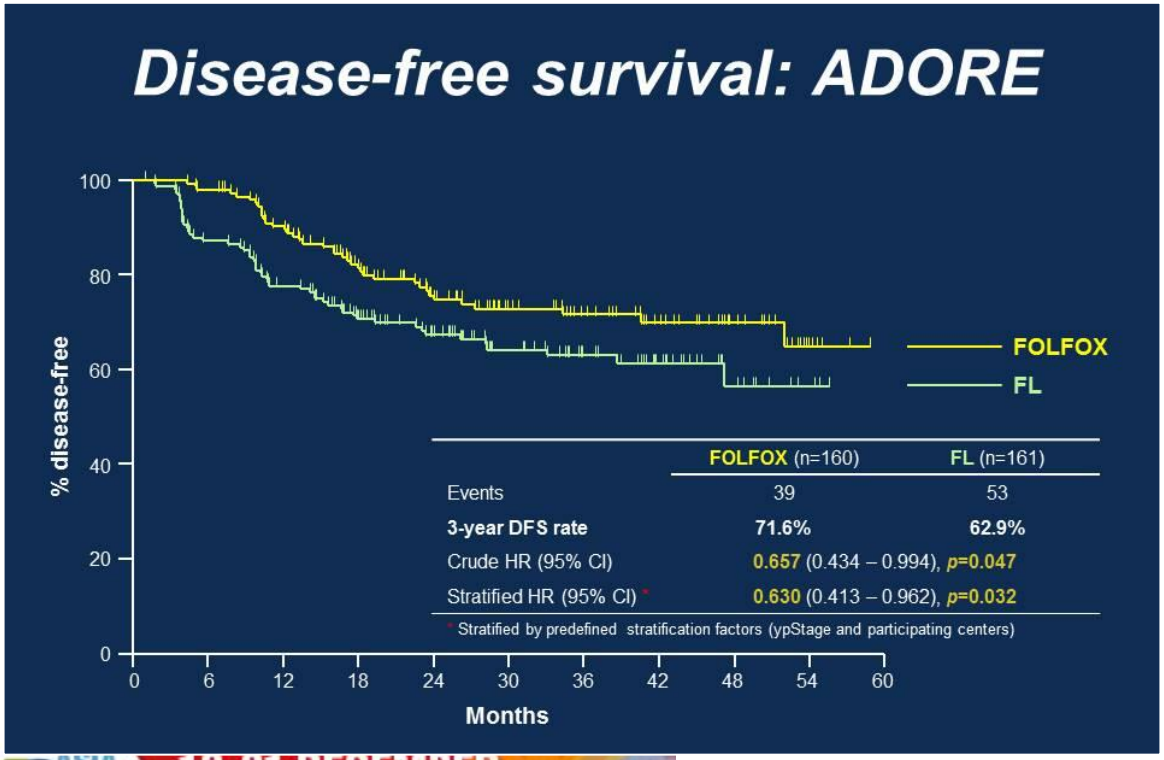
Cape+LOHP+RT → TME → Adj Cape+LOHP (CapeOX)



HJ Schmoll, et al. ASCO. 2014.

ADORE trial





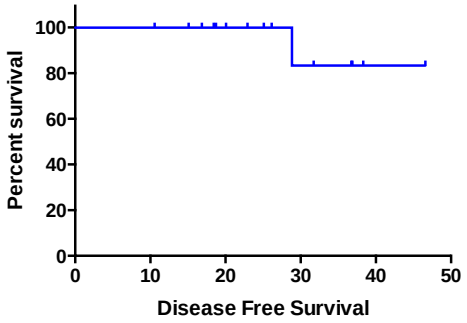
TW Kim, et al. ASCO. 2014.

Controversies in pre-ope CRT for rectal cancer

- Adding oxaliplatin in pre-ope CRT is controversial
- Post-ope FOLFOX might yeild survival advantage compared with fluoropyrimidine alone
- No confirmatory evidences of bevacizumab radio-sensitizing effect
- No. of clinical trials with IMRT is still limited

Results (Survival Outcomes)

- pCR rate: **5/15 (33%) (3 with 55Gy; 2 with 45Gy)**
- 14/15 (93%) with T or N downstaging effect
  - 11/15 (73%) with T and 12/15 (80%) with N downstaging
- **14 / 15 patients with anal preservation (13 functional)**
- 1 anal incontinence in the 45 Gy group
- 1 gangrene of scrotum (tumor invasion to seminal vesicle) in the 55 Gy group, s/p debridement
- No death or local recurrence yet, one liver metastasis s/p RFA with disease free again in the 50-Gy group
- 3-year disease free survival : 83%



Cheng JC, et al: ESMO Asia 2015 (#1430)

Addition of oxaliplatin in pre-ope CRT: pCR rate

Study	# Pts	ChemoRT Regimen	yCR Rate (%)
ACCORD 12 (JCO 2010)	291	Cape +RT	**14**
	293	Cape +Oxali (50mg/m^2 wkly) +RT	**19 (p=0.09)**
STAR-01 (JCO 2011)	379	5FU CI +RT	**16**
	368	5FU CI +Oxali (60mg/m^2 wkly) +RT	**16 (p=NS)**
CAO/ARO/AIO-04 (Lancet Oncol 2012 Lancet Oncol 2015)	623	5FU CI +RT	**13**
	613	5FU CI +Oxali (50mg/m^2 wkly) +RT	**17 (p=0.04)**
PETACC-06 (ASCO 2013)	547	Cape +RT	**12**
	547	Cape +Oxali (50mg/m^2 wkly) +RT	**14 (p=0.27)**
NSABP R-04 (JCO 2014)	636	5FU/Cape +RT	**18**
	640	5FU/Cape +Oxali (50mg/m^2 wkly) +RT	**20 (p=0.42)**

Issues raised in the study (#1430)

- Adding oxaliplatin in pre-ope CRT is necessary?
- How to evaluate the benefit of IMRT and radio-sensitizing effect of Bev?
- What is the next study design?

Waiting for the next step of the big challenge