ESMO 18th World Congress on Gastrointestinal Cancer, Barcelona, Spain

Session XIX: Colorectal Cancer

Controversy debate 4

Treatment algorithms in metastatic CRC Asian guidelines

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July 2nd, 2016

Disclosure

I have no conflict of interest associated with this presentation.

Agenda

- **Current JSCCR* Guidelines for the Treatment of Colorectal Cancer**
- Newly published Phase III trials in Japan
  - SOFT and WJOG4407G study
- Recent Japanese contribution to international phase III trials
  - RAISE, CORRECT and RECOURSE study
- New JSCCR* Guideline *Draft* 2016 for the Treatment of Colorectal Cancer
- Current JSMO** Guideline for *RAS (KRAS/NRAS)* Mutation Testing
- Relevant Issue for Asian patients living in Western countries
  - Clinical impact on UGT1A1 *6
- Circumstance in other Asian Countries
- Future perspective

JSMO Japanese Society of Medical Oncology

大腸癌研究会 Japanese Society for Cancer of the Colon and Rectum

*JSCCR = Japanese Society for Cancer of the Colon and Rectum: **JSMO = Japanese Society of Medical Oncology

大腸癌研究会
Japanese Society for Cancer of the Colon and Rectum

History of JSCCR* Guidelines for the Treatment of Colorectal Cancer

http://www.jsccr.jp/index.html

Year	Japanese original version	English version
2005	2005 Edition	
2009	2009 Edition	
2010	2010 Edition	
2012		2010 Edition
2014	2014 Edition	
2015		2014 Edition
2016	2016 Edition *Draft*	

*JSCCR = Japanese Society for Cancer of the Colon and Rectum

Japan Guideline, 2014

Basic Principals of JSCCR Guidelines 2014 for mCRC

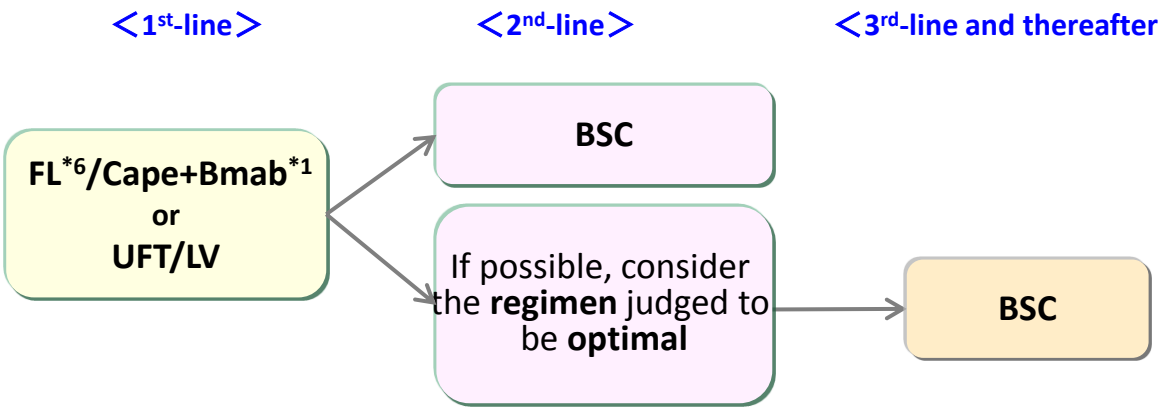
- **Only approved agents in Japan**
- **Patients divided into two groups;**
  - Patient appropriate for intensive therapy
  - Patient not appropriate for intensive therapy
- **Determinants of 'Patient not appropriate for intensive therapy' are follows;**
  - Patient factors
  - Tumor-related characteristics
- **Patient factors to be considered**
  - Patient preference
  - unable to administer oxaliplatin, irinotecan, or targeting agents (i.e. comorbidity)
- **Tumor-related characteristics to be considered**
  - Multiple (or multi-organ) metastases unlikely to conduct R0 resection in the future
  - asymptomatic slow progression (limited risk of rapid progression)
- **Combination with a targeting agent is recommended, but for patients who are not candidates, chemotherapy alone is recommended.**

Watanebe T, Yoshino T, et al. *Int J Clin Oncol*. 2015

Chemotherapy Algorithm for unresctable, metastatic colorectal cancer

Japan Guideline, 2014

Patient not appropriate for intensive therapy



*1 : Combination with molecular target drugs, such as Bmab or anti-EGFR antibodies, etc., is recommended, but for patients who are not candidates, chemotherapy alone is carried out.

*2 : KRAS wild-type only is indicated.

*3 : Refer to note 4.

*4 : It is stated in the regorafenib package insert that efficacy and safety of this drug have not been established for use in first-line and second-line chemotherapy.

*5 : PS2 and above are indicated.

*6 : Infusional 5-FU+LV

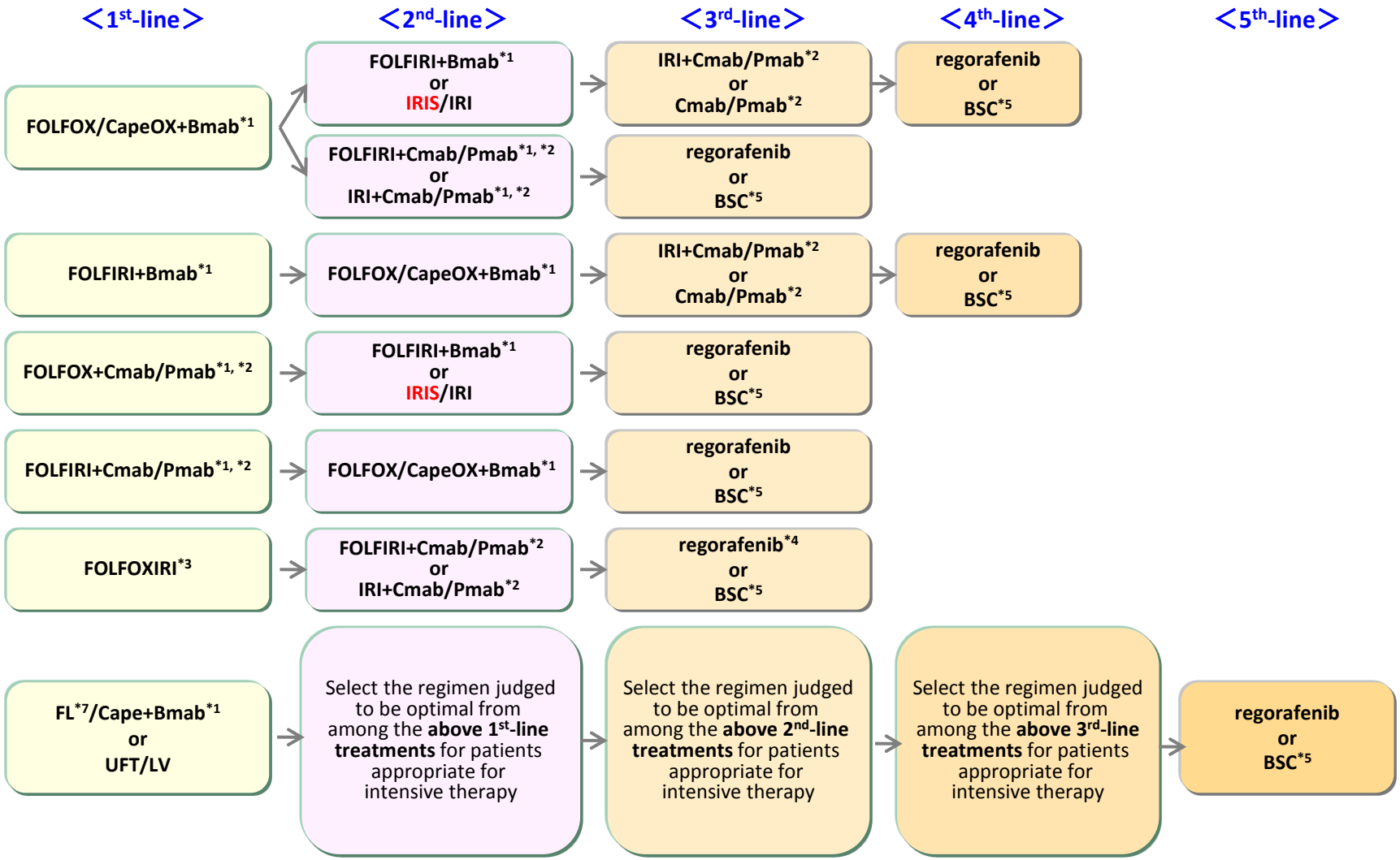
Note: "/", (slash) means select one of the listed regimens.

Note: BSC means best supportive care.

Chemotherapy Algorithm for unresectable, metastatic colorectal cancer

Japan Guideline, 2014

Patient appropriate for intensive therapy



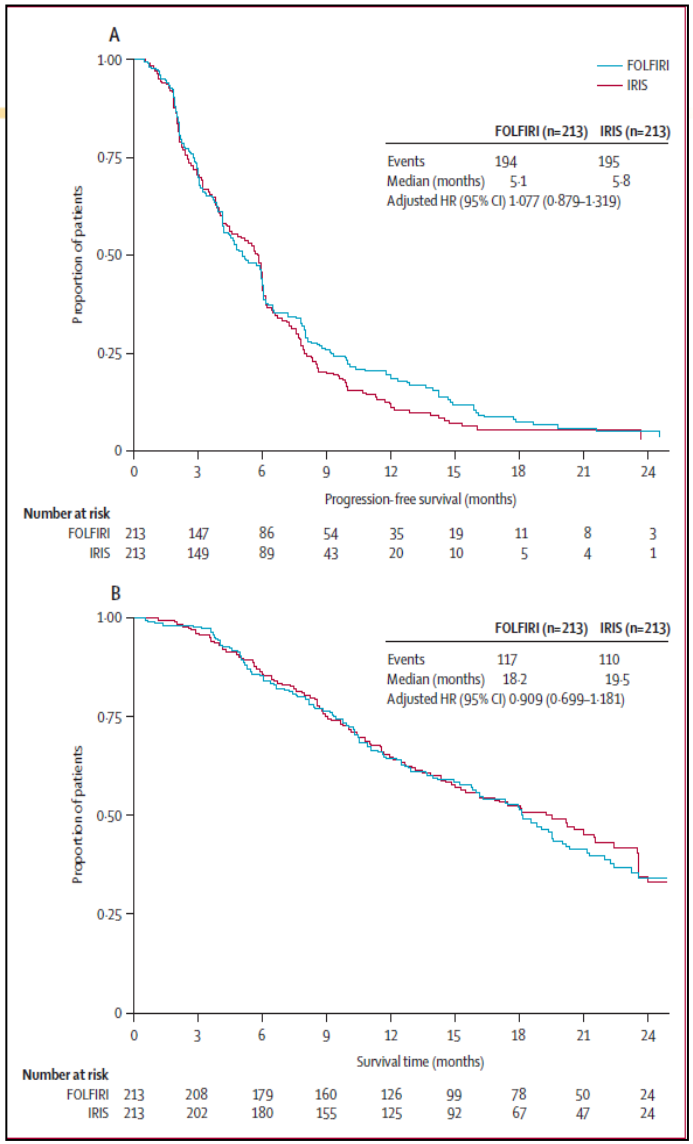
IRIS Regimen in the 2nd-line setting

Irinotecan plus S-1 (IRIS) versus fluorouracil and folinic acid plus irinotecan (FOLFIRI) as second-line chemotherapy for metastatic colorectal cancer: a randomised phase 2/3 non-inferiority study (FIRIS study)

Kei Muro, Narikazu Boku, Yasuhiro Shimada, Akihito Tsuji, Shinichi Sameshima, Hideo Baba, Taroh Satoh, Tadamichi Denda, Kenji Ina, Tomohiro Nishina, Kensei Yamaguchi, Hiroya Takiuchi, Taito Esaki, Shinya Tokunaga, Hiroyuki Kuwano, Yoshito Komatsu, Masahiko Watanabe, Ichinosuke Hyodo, Satoshi Morita, Kenichi Sugihara

Summary

Background Fluorouracil and folinic acid with either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) are widely used as first-line or second-line chemotherapy for metastatic colorectal cancer. However, infusional fluorouracil-based regimens, requiring continuous infusion and implantation of an intravenous port system, are inconvenient. We therefore planned an open-label randomised controlled trial to verify the non-inferiority of irinotecan plus oral S-1 (a combination of tegafur, 5-chloro-2,4-dihydroxypyridine, and potassium oxonate; IRIS) to FOLFIRI as second-line chemotherapy for metastatic colorectal cancer.



Muro K, et al. *Lancet Oncol*. 2010

mCRC 2nd line
Age20-80, PS 0-1
(N=426)

R

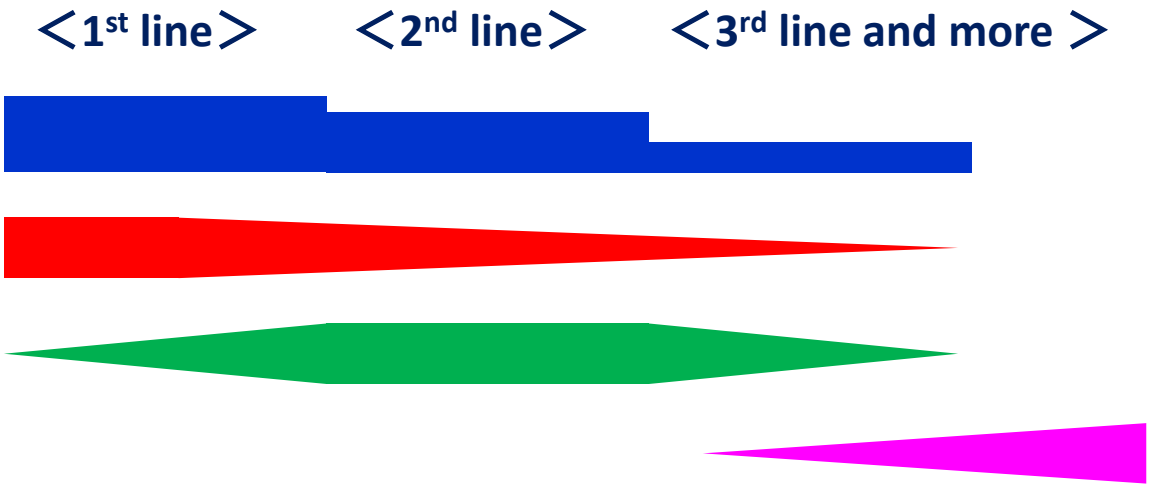
FOLFIRI q2w
IRI：150mg/㎡
（N=213）

IRIS q4w
S-1： 80-120mg/day
Day1-14
IRI：125mg/㎡
Day1,15
（N=213）

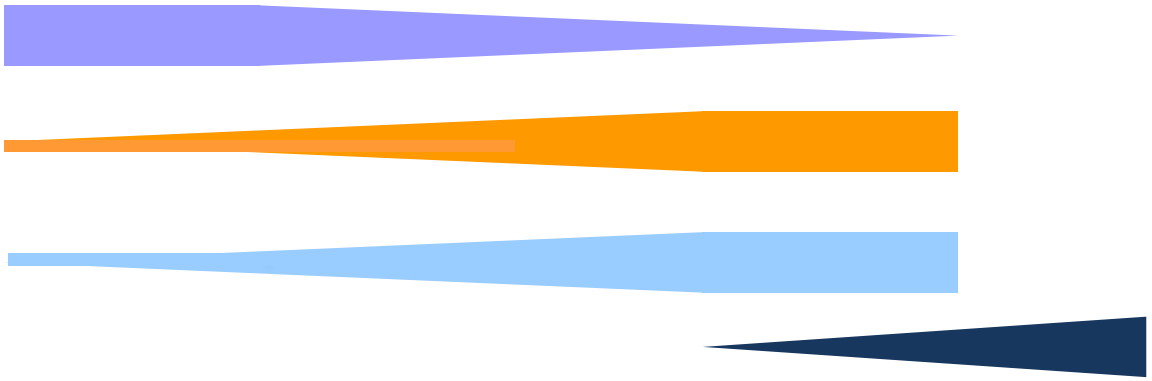
Primary endpoint:
PFS

Current medical practice for mCRC in Japan

Cytotoxic Backbone



Biologics



*: including IV 5-FU, capecitabine and S-1; **: RAS Wild Type (WT) only

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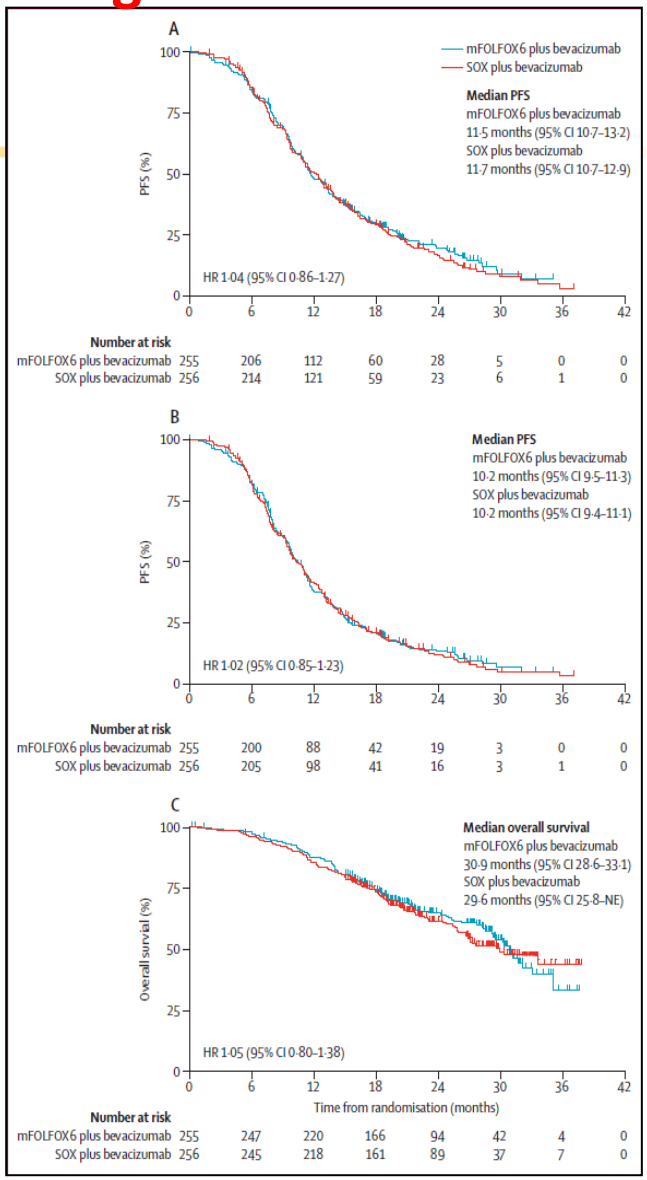
SOX + Bev Regimen in the 1st-line setting

Leucovorin, fluorouracil, and oxaliplatin plus bevacizumab versus S-1 and oxaliplatin plus bevacizumab in patients with metastatic colorectal cancer (SOFT): an open-label, non-inferiority, randomised phase 3 trial

Yasuhide Yamada, Daisuke Takahari, Hiroshi Matsumoto, Hideo Baba, Masato Nakamura, Kazuhiro Yoshida, Motoki Yoshida, Shigeyoshi Iwamoto, Ken Shimada, Yoshito Komatsu, Yasutsuna Sasaki, Taroh Satoh, Keiichi Takahashi, Hideyuki Mishima, Kei Muro, Masahiko Watanabe, Yuh Sakata, Satoshi Morita, Yasuhiro Shimada, Kenichi Sugihara

Summary

Background Studies done in Asia have shown that a regimen of S-1 plus oxaliplatin (SOX) has promising efficacy and safety in patients with metastatic colorectal cancer. We aimed to establish whether SOX plus bevacizumab is non-inferior to mFOLFOX6 (modified regimen of leucovorin, fluorouracil, and oxaliplatin) plus bevacizumab as first-line chemotherapy for metastatic colorectal cancer.



mCRC
Age 20-80, PS 0-1
（N=512）

R

mFOLFOX6+BEV q2w
Oxa：85mg/㎡
BEV：5mg/kg
（N=256）

SOX+BEV q3w
S-1： 80-120mg/day
Oxa：130mg/㎡
BEV：7.5mg/kg
（N=256）

Primary endpoint:
PFS

Yamada Y, et al. *Lancet Oncol*. 2013

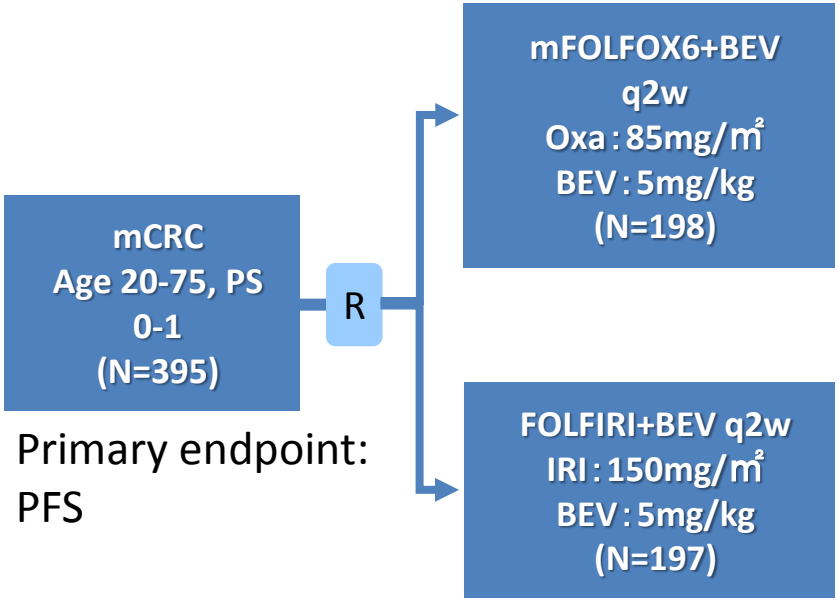
FOLFIRI+bev vs. FOLFOX+bev in the 1st-line setting

original article

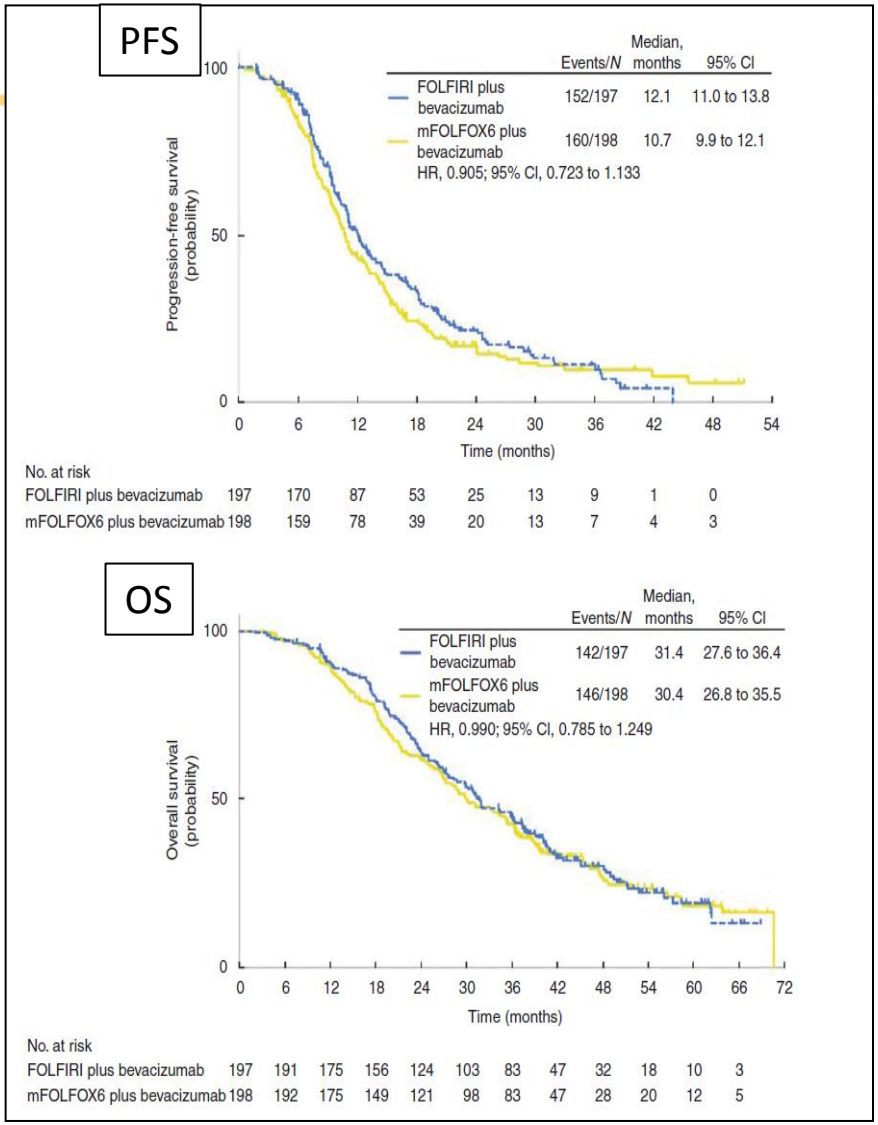
Annals of Oncology 00: 1–8, 2016
doi:10.1093/annonc/mdw206

Randomized phase III study of bevacizumab plus FOLFIRI and bevacizumab plus mFOLFOX6 as first-line treatment for patients with metastatic colorectal cancer (WJOG4407G)

K. Yamazaki[1*], M. Nagase[2], H. Tamagawa[3], S. Ueda[4], T. Tamura[5], K. Murata[6], T. Eguchi Nakajima[7], E. Baba[8], M. Tsuda[9], T. Moriwaki[10], T. Esaki[11], Y. Tsuji[12], K. Muro[13], K. Taira[14], T. Denda[15], S. Funai[16], K. Shinozaki[17], H. Yamashita[18], N. Sugimoto[19], T. Okuno[20], T. Nishina[21], M. Umeki[22], T. Kurimoto[23], T. Takayama[24], A. Tsuji[25], M. Yoshida[26], A. Hosokawa[27], Y. Shibata[28], K. Suyama[29],



Primary endpoint: PFS



Yamazaki K, et al. *Ann Oncol.* 2016

Overall Survival > 29 months establishes a new benchmark for mCRC treatment both in the West and in Japan

	Trial Name	Regimen	Primary Endpoint		MST（months）
	WJOG 4407G [1]	FOLFIRI + Bev	PFS (months)	12.0	31.8
		FOLFOX + Bev		10.7	28.9
	SOFT [2]	SOX + Bev	Baseline PFS (months)	11.7	29.6
		FOLFOX + Bev		11.5	29.7
	FIRE-3 [3] (*KRAS* wt)	FOLFIRI + Cmab	RR (%)	62.0	28.7
		FOLFIRI + Bev		58.0	25.0
	CALGB/SWOG 80405 [4] (*KRAS* wt)	Chemo + Cmab	OS (months)	29.9	29.9
		Chemo + Bev		29.0	29.0

1 Yamazaki K, et al. *Ann Oncol.* 2016, 2 Yamada Y, et al. *Lancet Oncol.* 2013,
3 Heinemann V, et al. *Lancet Oncol.* 2014, 4 Venook A, et al. *ASCO* 2014

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RAISE Trial, FOLFIRI+Ram vs. FOLFOX+PLB in the 2nd-line setting

Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study

Josep Tabernero, Takayuki Yoshino, Allen Lee Cohn, Radka Obermannova, Gyorgy Bodoky, Rocio Garcia-Carbonero, Tudor-Eliade Ciuleanu, David C Portnoy, Eric Van Cutsem, Axel Grothey, Jana Prausová, Pilar Garcia-Alfonso, Kentaro Yamazaki, Philip R Clingan, Sara Lonardi, Tae Won Kim, Lorinda Simms, Shao-Chun Chang, Federico Nasroulah, and the RAISE Study Investigators

Summary

Background Angiogenesis is an important therapeutic target in colorectal carcinoma. Ramucirumab is a human IgG-1 monoclonal antibody that targets the extracellular domain of VEGF receptor 2. We assessed the efficacy and safety of ramucirumab versus placebo in combination with second-line FOLFIRI (leucovorin, fluorouracil, and irinotecan) for metastatic colorectal cancer in patients with disease progression during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.

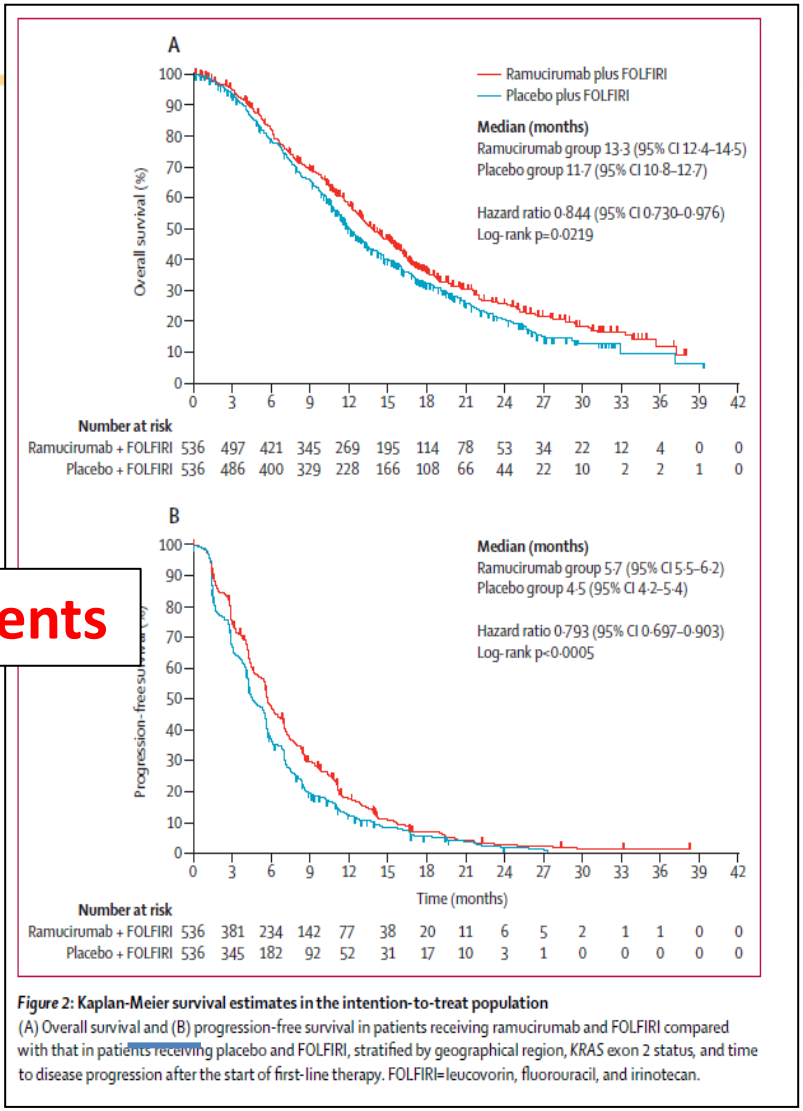


Figure 2: **Kaplan-Meier survival estimates in the intention-to-treat population**
(A) Overall survival and (B) progression-free survival in patients receiving ramucirumab and FOLFIRI compared with that in patients receiving placebo and FOLFIRI, stratified by geographical region, *KRAS* exon 2 status, and time to disease progression after the start of first-line therapy. FOLFIRI=leucovorin, fluorouracil, and irinotecan.

136 patients from JPN/1,072 patients

Progression during or after bevacizumab, oxaliplatin, and a fluoropyrimidine

R

- **Ram and FOLFIRI every 2 weeks per cycle N=536**
- **Placebo and FOLFIRI every 2 weeks per cycle N=536**

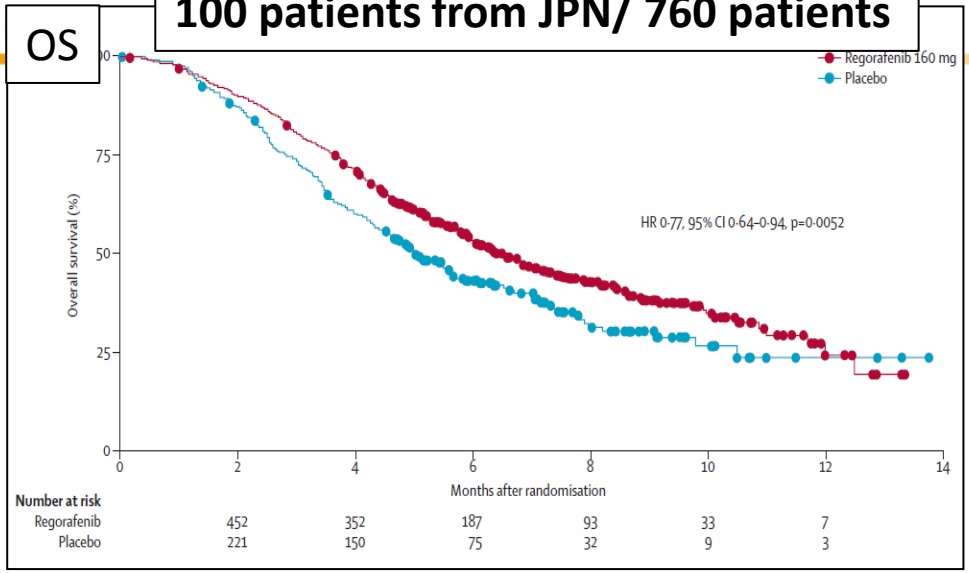
Primary endpoint: OS

Tabernero J, Yoshino T, et al. *Lancet Oncol.* 2015

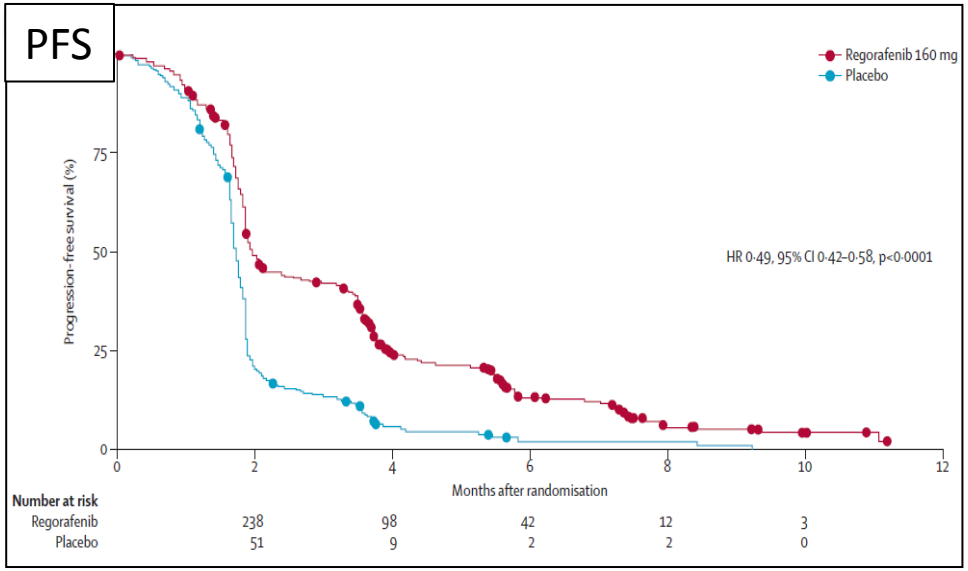
Regorafenib and TAS-102 in the Salvage-line setting

CORRECT Trial [1], Regorafenib, 100 patients from JPN/ 760 patients

OS

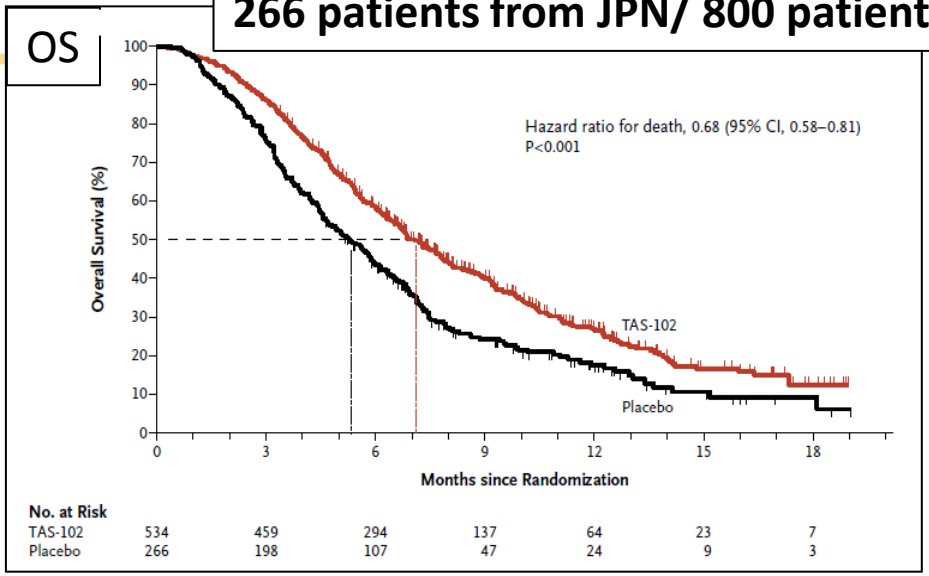


PFS

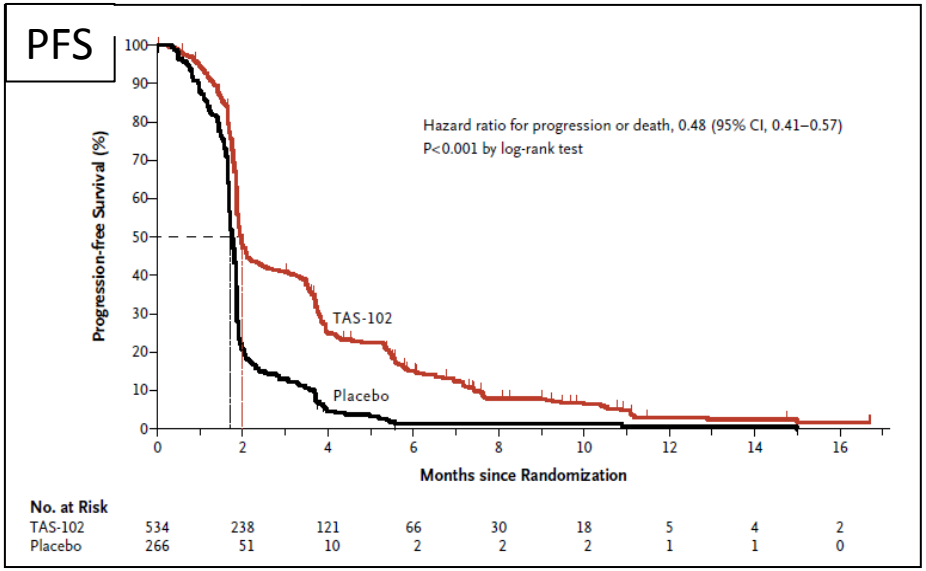


RECOURSE Trial [2], TAS-102, 266 patients from JPN/ 800 patients

OS



PFS



1 Grothey A, Van Cutsem E,….., Yoshino T, et al. *Lancet* 2013, 2 Mayer RJ, Van Cutsem E, Yoshino T, et al. *New Engl J Med* 2015

Drug approval for CRC as of July, 2016

Active drugs	US	Japan	Remarks
5-FU/Leucovorin	1957	1967	1999～l-LV
Irinotecan	1996	2001	150mg/m^2, q2w
Capecitabine	2001	2007	
Oxaliplatin	2002	2005	
Bevacizumab (Bmab)	2004	2007	All lines
ziv-aflibercept (AF)	2012	Under PMDA* review	2nd-line
Ramucirumab (Rmab)	2015	2016	2nd-line
Cetuximab (Cmab)	2004	2008	All lines
Panitumumab (Pmab)	2006	2010	All lines
Regorafenib	2012	2013	
TAS-102	2015	2014	

*: Pharmaceuticals and Medical Devices Agency

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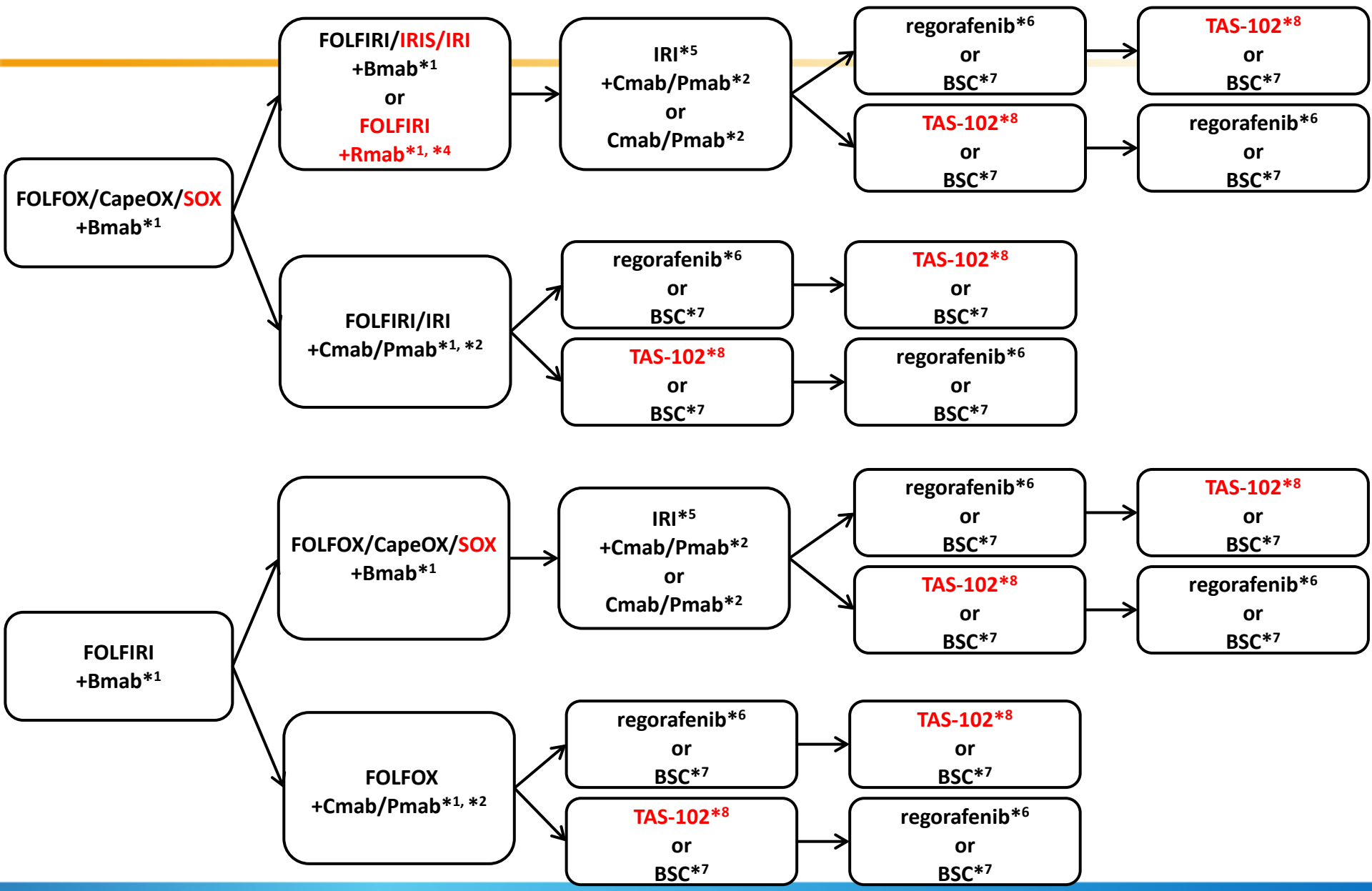
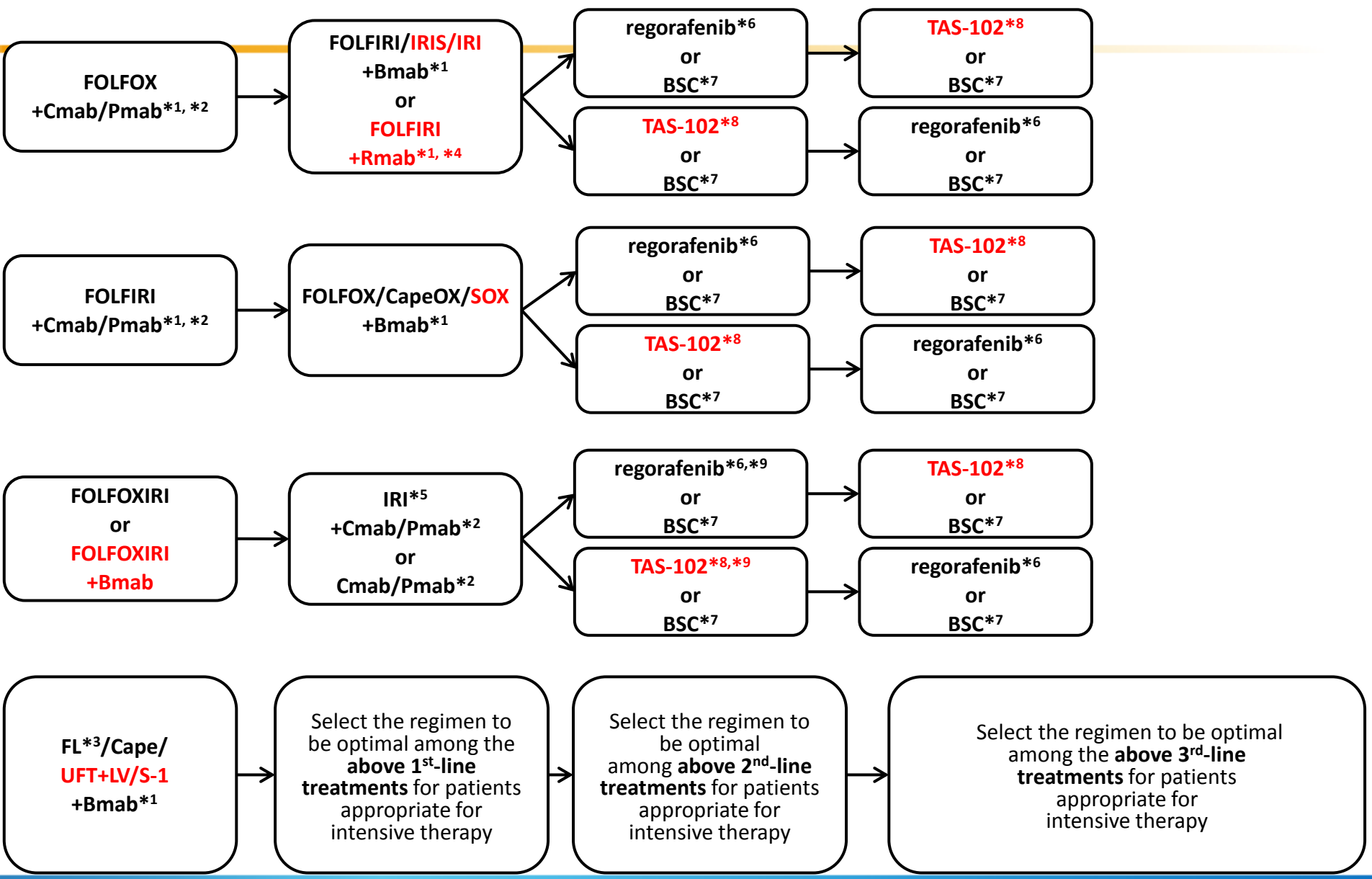
Patient appropriate for intensive therapy

Japan Guideline Draft, 2016



Patient appropriate for intensive therapy (cont.)

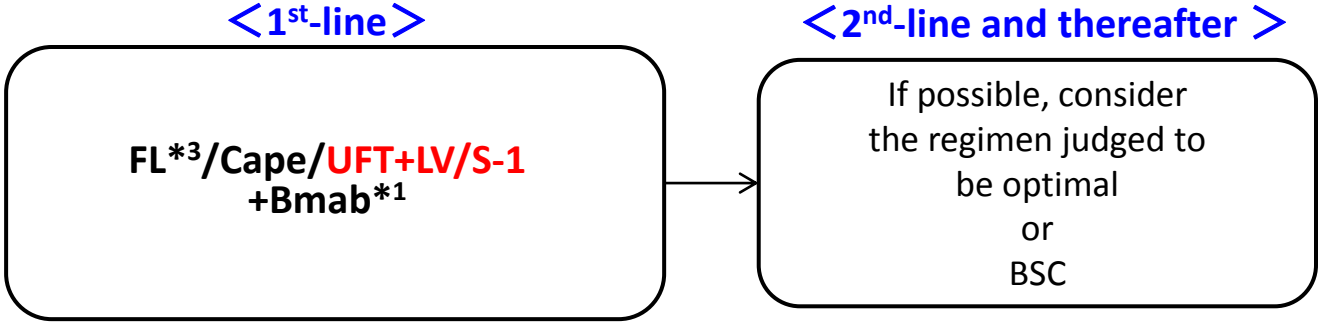
Japan Guideline Draft, 2016



Chemotherapy Algorithm for unresctable, metastatic colorectal cancer

Japan Guideline Draft, 2016

Patient not appropriate for intensive therapy



***1：Combination with molecular target drugs, such as Bmab or anti-EGFR antibodies, etc., is recommended, but for patients who are not candidates, chemotherapy alone is carried out.**

***2：*RAS* (*KRAS/NRAS*) wild-type only is indicated.**

***3：Infusional 5-FU＋l-LV**

***4：It is stated in the ramucirumab package insert that efficacy and safety of this drug have been established for use in second-line chemotherapy.**

***5：An anti-EGFR antibody in combination with irinotecan is recommended unless a patient was intolerant to the previous use of irinotecan.**

***6：Infusional 5-FU+LV**

***7: PS2 and above are indicated.**

***8: Refer to note 10.**

Note: "/", (slash) means select one of the listed regimens.

Note: BSC means best supportive care.

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Application of Predictive Biomarkers onto daily practice

EBioMedicine xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Original Article

Clinical Validation of a Multiplex Kit for *RAS* Mutations in Colorectal Cancer: Results of the RASKET (RAS KEy Testing) Prospective, Multicenter Study

Takayuki Yoshino [a,*], Kei Muro [b], Kensei Yamaguchi [c], Tomohiro Nishina [d], Tadamichi Denda [e], Toshihiro Kudo [f], Wataru Okamoto [g], Hiroya Taniguchi [b], Kiwamu Akagi [h], Takeshi Kajiwara [d], Shuichi Hironaka [i], Taroh Satoh [f]

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[b] Department of Clinical Oncology, Aichi Cancer Center Hospital, Aichi, Japan
[c] Division of Gastroenterology, Saitama Cancer Center, Saitama, Japan
[d] Department of Gastrointestinal Medical Oncology, National Hospital Organization Shikoku Cancer Center, Ehime, Japan
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[f] Department of Frontier Science for Cancer and Chemotherapy, Osaka University Graduate School of Medicine, Osaka, Japan
[g] Division of Translational Research, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center, Chiba, Japan
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CE

ARTICLE INFO

Article history:
Received 9 December 2014
Received in revised form 11 February 2015
Accepted 12 February 2015
Available online xxxx

Keywords:
Colorectal cancer
RAS mutation
Anti-EGFR antibody treatment
Biomarker
In vitro diagnostics
RASKET study

ABSTRACT

Background: *RAS* (*KRAS* and *NRAS*) testing is required to predict anti-epidermal growth factor receptor (EGFR) treatment efficacy in metastatic colorectal cancer (CRC). Although direct sequencing (DS) with manual microdissection (MMD) is widely used, a diagnostic kit providing rapid detections of *RAS* mutations would be clinically beneficial. We evaluated the MEBGEN™ RASKET KIT (RASKET KIT), a multiplex assay using PCR-reverse sequence specific oligonucleotide and xMAP® technology to concurrently detect exon 2, 3, and 4 *RAS* mutations in a short turnaround time (4.5 h/96-specimens).

Methods: Formalin-fixed paraffin-embedded (FFPE) tissues were obtained from 308 consenting patients with histologically-confirmed CRC at six hospitals in Japan. For the RASKET KIT, we used only 50–100 ng DNA from each FFPE specimen not processed by MMD. The primary endpoint was the concordance rate between *RAS* mutations identified with the RASKET KIT and two reference assays (DS with MMD and TheraScreen® K-RAS Mutation Kit). As the secondary endpoints, we evaluated the concordance rate between DS and the RASKET KIT for *RAS* mutations in the wild-type *KRAS* exon 2 population and the genotyping performance of the RASKET KIT compared with DS.

Findings: Among 307 analyzable specimens, the reference assays detected 140 (45.6%, 140/307) *RAS* mutations: 111 *KRAS* exon 2 and 29 other (minor) *RAS* mutations. The RASKET KIT detected 143 (46.6%, 143/307) mutations: 114 *KRAS* exon 2 and 29 minor *RAS* mutations. The between-method concordance rate was 96.7% (297/307) (95% CI: 94.1–98.4%). Minor *RAS* mutations were detected in 15.7% (30/191) of the wild-type *KRAS* exon 2 population ($n = 191$); the concordance rate was 98.4% (188/191) (95% CI: 95.5–99.7%). The concordance rate of *RAS* genotyping was 100% (139/139) (95% CI: 97–100%).

Interpretation: The RASKET KIT provides rapid and precise detections of *RAS* mutations and consequently, quicker and more effective anti-EGFR therapy for CRC (Study ID: UMIN000011784).

Funding: Medical & Biological Laboratories Co., Ltd. (MBL). MBL had roles in study design, data collection, data analysis, and writing of the report for the study.

EBioMedicine 2015

Japanese Society of Medical Oncology

Report

Japanese Society of Medical Oncology Clinical Guidelines: *RAS* (*KRAS/NRAS*) mutation testing in colorectal cancer patients[11]

Hiroya Taniguchi,[1] Kentaro Yamazaki,[2] Takayuki Yoshino,[3] Kei Muro,[1] Yasushi Yatabe,[4] Toshiaki Watanabe,[5] Hiromichi Ebi,[6] Atsushi Ochiai,[7] Eishi Baba[8] and Katsuya Tsuchihara[9]

[1]Department of Clinical Oncology, Aichi Cancer Center Hospital, Aichi; [2]Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka; [3]Department of Gastrointestinal Oncology, National Cancer Center Hospital East, Chiba; [4]Department of Pathology and Molecular Diagnostics, Aichi Cancer Center Hospital, Aichi; [5]Department of Surgical Oncology, Graduate School of Medicine and Faculty of Medicine, The University of Tokyo, Tokyo; [6]Division of Medical Oncology, Cancer Research Institute, Kanazawa University, Ishikawa; [7]Department of Pathology and Clinical Laboratories, National Cancer Center Hospital, Tokyo; [8]Department of Comprehensive Clinical Oncology, Faculty of Medical Sciences, Kyushu University, Fukuoka; [9]Division of Translational Research, Exploratory Oncology Research and Clinical Trial Center, National Cancer Center, Chiba, Japan

Key words
Anti-EGFR antibodies, colorectal cancer, guideline, K-ras genes, N-ras genes

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[11]This report is an English translation of "Japanese Society of Medical Oncology Clinical Guidelines: *RAS* (*KRAS/NRAS*) mutation testing in colorectal cancer patients". The original version written in Japanese is available at the Japanese Society of Medical Oncology website.[(1)]

Funding Information
KY receiving honoraria for lectures from Takeda Pharmaceutical and received research funding from Merck Serono. TY received honoraria for lectures from Takeda Pharmaceutical and Merck Serono, and received research funding from Merck Serono. KM received honoraria for lectures from Takeda Pharmaceutical and Merck Serono, and received research funding from Merck Serono. TW received honoraria for lectures from Takeda Pharmaceutical, Merck Serono and Bristol-Myers K.K., and received research funding from Bristol-Myers K.K.

Received December 2, 2014; Revised December 13, 2014; Accepted December 15, 2014

Cancer Sci (2015)

doi: 10.1111/cas.12595

The Japanese guidelines for the testing of *KRAS* mutations in colorectal cancer have been used for the past 5 years. However, new findings of *RAS* (*KRAS/NRAS*) mutations that can further predict the therapeutic effects of anti-epidermal growth factor receptor (EGFR) antibody therapy necessitated a revision of the guidelines. The revised guidelines included the following five basic requirements for *RAS* mutation testing to highlight a patient group in which anti-EGFR antibody therapy may be ineffective: First, anti-EGFR antibody therapy may not offer survival benefit and/or tumor shrinkage to patients with expanded *RAS* mutations. Thus, current methods to detect *KRAS* exon 2 (codons 12 and 13) mutations are insufficient for selecting appropriate candidates for this therapy. Additional testing of extended *KRAS/NRAS* mutations is recommended. Second, repeated tests are not required for the detection; tissue materials of either primary or metastatic lesions are applicable for *RAS* mutation testing. Evaluating *RAS* mutations prior to anti-EGFR antibody therapy is recommended. Third, direct sequencing with manual dissection or allele-specific PCR-based methods is currently applicable for *RAS* mutation testing. Fourth, thinly sliced sections of formalin-fixed, paraffin-embedded tissue blocks are applicable for *RAS* mutation testing. One section stained with H&E should be provided to histologically determine whether the tissue contains sufficient amount of tumor cells for testing. Finally, *RAS* mutation testing must be performed in laboratories with appropriate testing procedures and specimen management practices.

Cancer Science 2015

Prevalence of *RAS* mutations: Cross-trial comparison

	KRAS exon 2	KRAS exon 3	KRAS exon 4	NRAS exon 2	NRAS exon 3	NRAS exon 4	Total	Method
RASKET, JPN*	**38%**	**3.2%**	**5.3%**	**3.2%**	**4.2%**	**0%**	**16%**	Luminex
PRIME (1st line)	40%	4%	6%	3%	4%	0%	17%	Sanger SURVEYOR
20050181 (2nd line)	45%	4.4%	7.7%	2.2%	5.6%	0%	20%	Sanger SURVEYOR
20020408 (3rd line)	43%	4.8%	5.0%	4.2%	3.0%	1.1%	18%	Sanger SURVEYOR
OPUS (1st line)	43%	6.8%	9.3%	7.6%	5.1%	3.4%	31%	BEAMing
PEAK (1st line)	N/A	4%	7%	5%	6%	0%	22%	Sanger SURVEYOR
FIRE-3 (1st line)	N/A	4.3%	4.9%	3.8%	2%	0%	16%	Pyrosequencing
CRYSTAL (1st line)	37%	3.3%	5.6%	3.5%	2.8%	0.9%	15%	BEAMing
CALGB (1st line)	N/A	1.8%	5.9%	2.3%	4.2%	0%	14%	BEAMing

*Yoshino T. *EBioMedicine* 2015

Agenda

- Current JSCCR* Guidelines for the Treatment of Colorectal Cancer
- Newly published Phase III trials in Japan
  - SOFT and WJOG4407G study
- Recent Japanese contribution to international phase III trials
  - RAISE, CORRECT and RECOURSE study
- New JSCCR* Guideline *Draft* 2016 for the Treatment of Colorectal Cancer
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- **Relevant Issue for Asian patients living in Western countries**
  - **Clinical impact on UGT1A1 *6**
- Circumstance in other Asian Countries
- Future perspective

Japanese Society of Medical Oncology

大腸癌研究会
Japanese Society for Cancer of the Colon and Rectum

*JSCCR = Japanese Society for Cancer of the Colon and Rectum: **JSMO = Japanese Society of Medical Oncology

Incidence of UDP glucuronosyltransferase 1 family, polypeptide A1 (UGT1A1) polymorphisms - UGT1A1*28 -

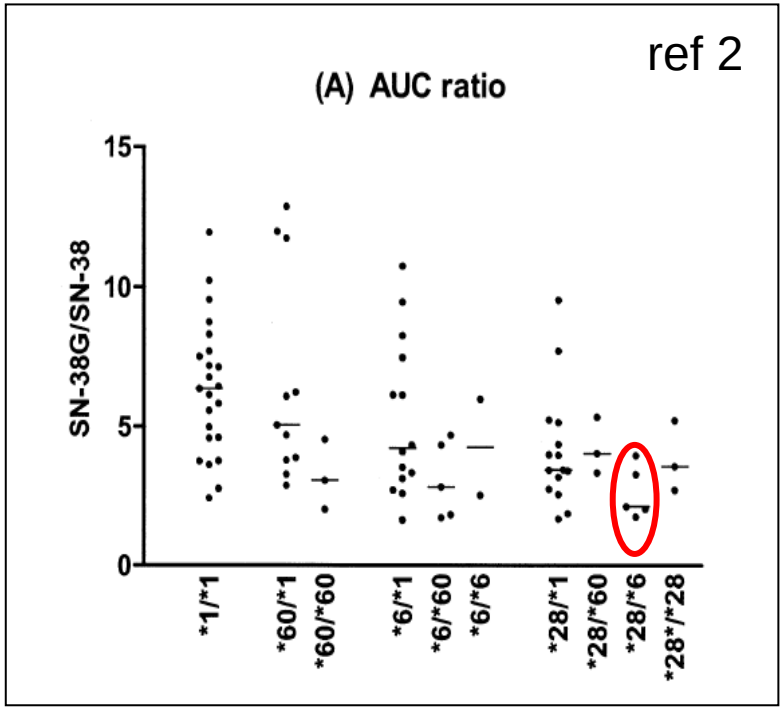
	n	6/6 Wild	6/7 Hetero	7/7 Homo	ref
African	101	26%	37%	19%	1
Caucasian (European)	71	34%	55%	11%	1
Caucasian (Scottish)	77	40%	48%	12%	2
Canadian	88	34%	49%	17%	3
Asian	47	70%	28%	2%	1
Japanese	58	76%	21%	3%	4

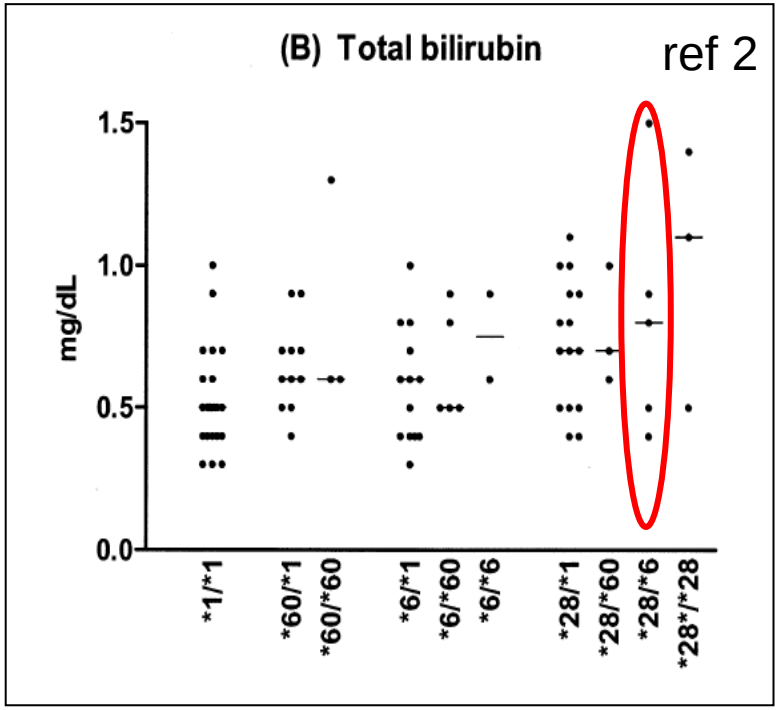
1 Beutler E et al ; Proc Natl Acad Sci USA, 1998, 2 Iyer L et al ; Clin Pharmacol Ther, 1999, 3 Iyer L et al ; Pharmacogenetics J, 2002, 4 Ando Y et al ; Pharmacogenetics, 1998

Incidence of UGT1A1*6 polymorphisms

	n	-/- Wild	+/- Hetero	+/+ Homo	ref
Caucasian	150	99%	1%	0%	1
Japanese	150	73%	23%	4%	1

Reduction in AUC ratio in *28/*6 group receiving Irinotecan





1 Kaniwa N et al. Drug Metabo 2005, 2 Sai K, et al. Clin Pharmacol Ther 2004

Classification of *UGT1A1* Polymorphism subtypes in Asian patients

UGT1A1 Genotype		*28		
		TA6/TA6	TA6/TA7	TA7/TA7
*6	- /-	Wild	Hetero	Homo
	-/+	Hetero	Homo	
	+/+	Homo		

Patients in the gray color parts did not exist, as presumed by the evidence of no existence of *28 and *6 on the same chromosome.

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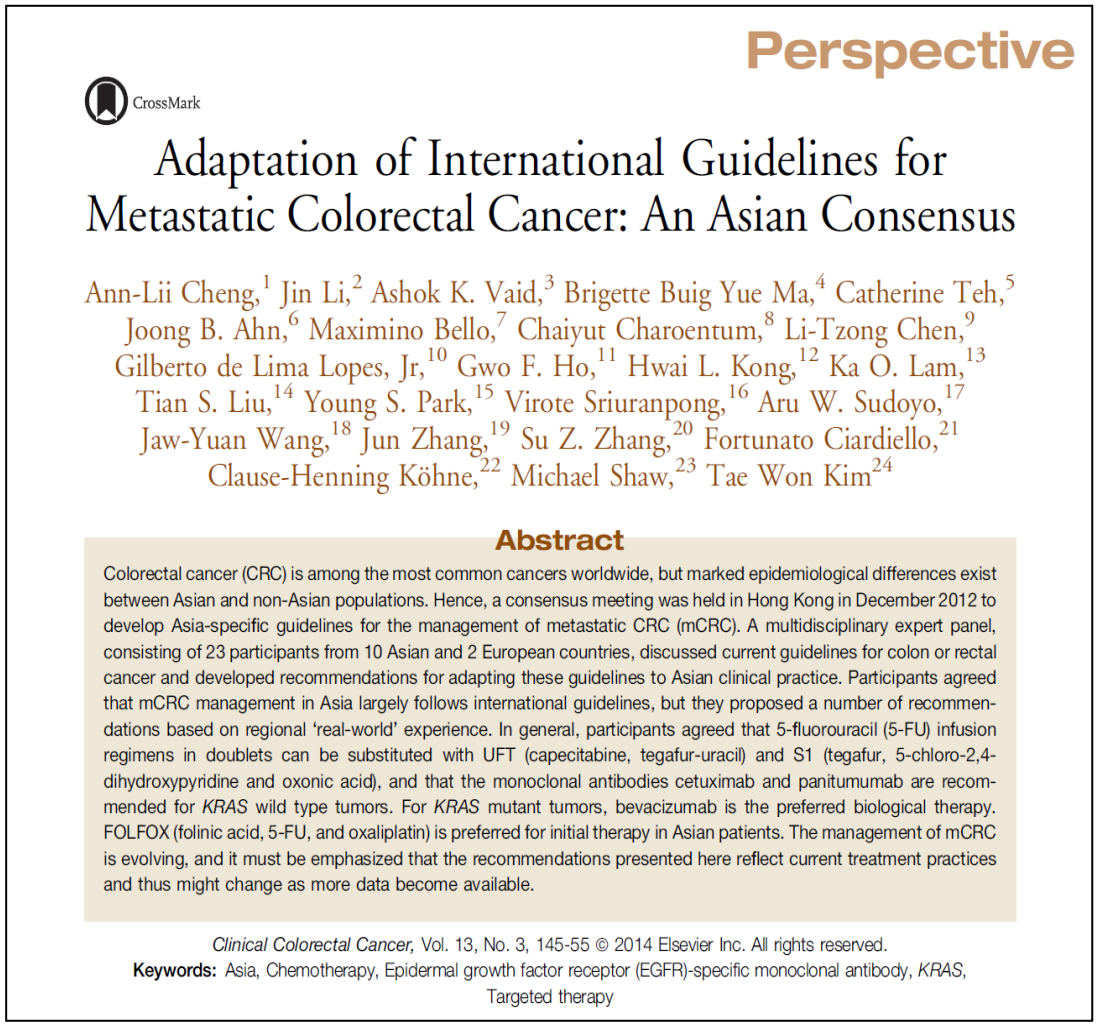
Recent Asian Consensus 2012



Perspective

CrossMark

Adaptation of International Guidelines for Metastatic Colorectal Cancer: An Asian Consensus

Ann-Lii Cheng,[1] Jin Li,[2] Ashok K. Vaid,[3] Brigette Buig Yue Ma,[4] Catherine Teh,[5] Joong B. Ahn,[6] Maximino Bello,[7] Chaiyut Charoentum,[8] Li-Tzong Chen,[9] Gilberto de Lima Lopes, Jr,[10] Gwo F. Ho,[11] Hwai L. Kong,[12] Ka O. Lam,[13] Tian S. Liu,[14] Young S. Park,[15] Virote Sriuranpong,[16] Aru W. Sudoyo,[17] Jaw-Yuan Wang,[18] Jun Zhang,[19] Su Z. Zhang,[20] Fortunato Ciardiello,[21] Clause-Henning Köhne,[22] Michael Shaw,[23] Tae Won Kim[24]

Abstract

Colorectal cancer (CRC) is among the most common cancers worldwide, but marked epidemiological differences exist between Asian and non-Asian populations. Hence, a consensus meeting was held in Hong Kong in December 2012 to develop Asia-specific guidelines for the management of metastatic CRC (mCRC). A multidisciplinary expert panel, consisting of 23 participants from 10 Asian and 2 European countries, discussed current guidelines for colon or rectal cancer and developed recommendations for adapting these guidelines to Asian clinical practice. Participants agreed that mCRC management in Asia largely follows international guidelines, but they proposed a number of recommendations based on regional 'real-world' experience. In general, participants agreed that 5-fluorouracil (5-FU) infusion regimens in doublets can be substituted with UFT (capecitabine, tegafur-uracil) and S1 (tegafur, 5-chloro-2,4-dihydroxypyridine and oxonic acid), and that the monoclonal antibodies cetuximab and panitumumab are recommended for *KRAS* wild type tumors. For *KRAS* mutant tumors, bevacizumab is the preferred biological therapy. FOLFOX (folinic acid, 5-FU, and oxaliplatin) is preferred for initial therapy in Asian patients. The management of mCRC is evolving, and it must be emphasized that the recommendations presented here reflect current treatment practices and thus might change as more data become available.

Clinical Colorectal Cancer, Vol. 13, No. 3, 145-55

Keywords: Asia, Chemotherapy, Epidermal growth factor receptor (EGFR)-specific monoclonal antibody, *KRAS*, Targeted therapy

A consensus meeting was held in Hong Kong in December 2012 from 10 Asian countries (China, Hong Kong, India, Indonesia, Malaysia, the Philippines, Singapore, South Korea, Taiwan, and Thailand) and 2 EU (Germany and Italy)

The objective was to develop Asia-specific guidelines for the management of mCRC.

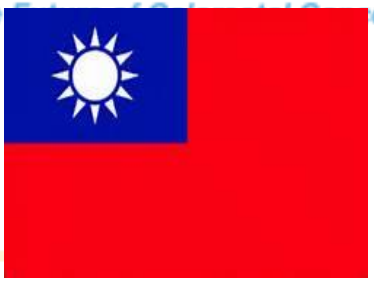
There are few major differences between the approach to the treatment of CRC in Asian and Western countries. In particular, all guidelines emphasize the importance of a multidisciplinary approach to CRC management, and Asian practice is consistent with this.

Present Circumstance in South Korea

- ***Indication and Reimbursement in management of mCRC***
  - Indication does not mean reimbursement.
  - Bevacizumab is reimbursed in 1st and 2nd line setting in combination with FOLFOX or FOLFIRI
  - Cetuximab is reimbursed in 1st line setting in combination with FOLFIRI.
  - The use of 2nd and 3rd line setting of cetuximab is indicated, but not reimbursed yet.
  - Regorafenib is indicated, but not reimbursed.

- ***Role of RAS in management of mCRC***
  - Use of EGFR inhibitors should be confined to *RAS (KRAS & NRAS)* wild-type patients.
  - Direct Sanger sequencing is approved for extended *RAS* test.
  - Cost and/or reimbursement issues are more important determinants.

Courtesy of Prof Tae Won Kim



Present Circumstance in Taiwan

- ***Indication and Reimbursement in management of mCRC***
  - Indication does not mean reimbursement.
  - In the 1st-line setting, for patients with wild-type *RAS*, FOLFIRI + bevacizumab, FOLFIRI + cetuximab, or FOLFOX + panitumumab are reimbursed by National Health Insurance (NHI).
  - For patients with *RAS* mutant, FOLFIRI + bevacizumab is the only reimbursed regimen in 1st-line.
  - 2nd-line bevacizumab, cetuximab or panitumumab are not reimbursed yet.
  - Cetuximab and panitumumab are reimbursed in the 3rd-line and thereafter when not used in 1st- and 2nd-line setting.
  - Regorafenib is reimbursed in the 3rd-line and thereafter.
- ***Role of RAS in management of mCRC***
  - Use of EGFR inhibitors should be confined to *RAS (KRAS & NRAS)* wild-type patients.
  - Direct Sanger sequencing is NOT approved for extended *RAS* test.
  - Cost and/or reimbursement issues are more important determinants.

Courtesy of Prof Kun-Huei Yeh

Agenda

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Prevalence of *BRAF* V600E mutated mCRC : Cross-trial comparison

Trial Name	N	Prevalence
Pooled dataset [1]	3,063	8.2%
GI-SCREEN-JAPAN [2]	**853**	**4.6%**
NCCE [3]	**277**	**5.4%**

Pooled dataset included CAIRO, CAIRO 2, COIN and FOCUS.

The survival outcome in patients harboring *BRAF* V600E mutation is similarly worse in both Asian and Western population. In addition, clinicopathological features and treatment effects for *BRAF* V600E mutation tumor in Asian population were consistent with those in Western population [3].

Note: GI-SCREEN-JAPAN is the Nationwide Cancer Genome Screening Project for Gastrointestinal Cancer in Japan:

1 Venderbosch S, et al. *Clin Cancer Res* 2014, 2 Denda T, Yoshino T. *ESMO* 2015, 3 Kawazoe A, Yoshino T. *BMC Cancer* 2015

Prevalence of microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) mCRC: Cross-trial comparison

Trial Name	N	Prevalence of MSI-H/dMMR	Overlapping BRAF V600E mutation
Pooled dataset [1]	3,063	5.0%	34.6%
AIO Colorectal Study Group [2]	104	4 %	Not reported
Australia and United States [3]	NA	Not reported	30%
Review Article [4]	NA	3 - 5%	Not reported
GI-SCREEN-JAPAN [5]	**853**	**1.9%**	**40%**
NCCE [6]	**277**	**1.9%**	**40%**

Note: GI-SCREEN-JAPAN is the Nationwide Cancer Genome Screening Project for Gastrointestinal Cancer in Japan: NA, not applicable

1 Venderbosch S, et al. *Clin Cancer Res* 2014, 2 Muller CI, et al. *Int J Colorectal Dis* 2008, 3 Goldstein J, et al. *Ann Oncol.* 2014, 4 Cohen R, et al. *Curr Ocol Rep* 2016, 5 Kajiwara T, Yoshino T. *ASCO* 2016, 6 Kawazoe A, Yoshino T. *ASCO-GI* 2016

JSMO initiative *New* guideline regarding biomarkers and emerging technologies in mCRC will be available.

- **Biomarkers**
  - *RAS (KRAS/NRAS)* testing update
  - *BRAF* V600E testing
  - Microsatellite instability testing

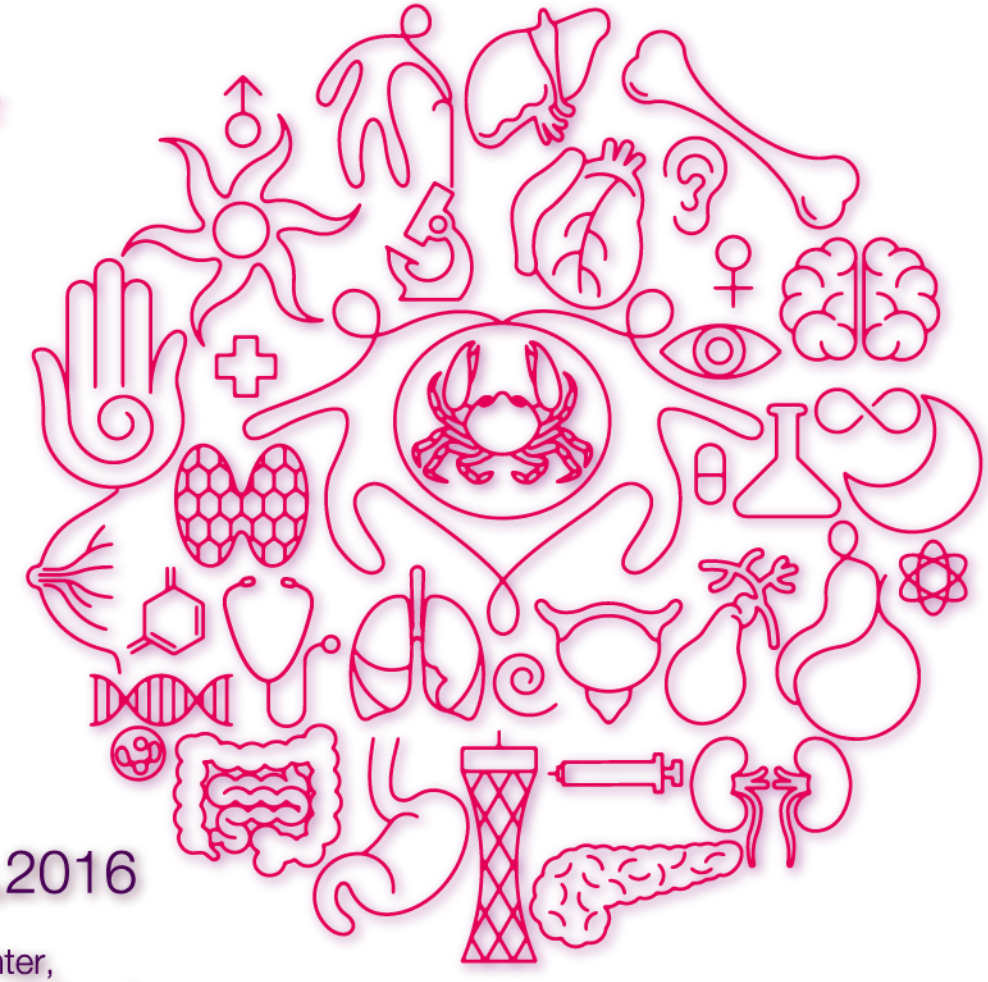
- **Emerging technologies**
  - Comprehensive cancer genome alteration testing by next-generation sequencing
  - Blood-based molecular testing

My Conclusion

- Asian Guideline for the Treatment of Colorectal Cancer does not exist since 2013.
- International phase III trials including Asia play an important role in clinical development of new agents and should be incorporated into Asian Guideline.
- Asian phase III trials should be incorporated into Asian Guideline.
- Both evidence-based vs. approved/reimbursed-based approach are key to developed new Asian guideline.
- Asian Guideline is for Asian patients, as well as for Asian patients living in Western countries.
- International harmonization of NCCN, ESMO and Asian Guidelines may become the best way in the near future.

The Japanese Society of Medical Oncology
2016 Annual Meeting

Breaking Through the Barriers:
Optimizing Outcomes by
Integration and Interaction



Date	July 28(Thu) – 30(Sat),2016
Venue	Kobe International Conference Center, Kobe International Exhibition Hall in Kobe, Japan
Congress President	Hironobu Minami, M.D., D.Med.Sci Professor, Oncology / Hematology, Department of Medicine Kobe University Hospital Kobe University Graduate School of Medicine

JSMO JSMO2016 KOBE

http://www2.convention.co.jp/jsmo2016

Thank you for your kind attention

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