Treatment of patients with RAS wt mCRC in light of recent guidelines

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Outline

1. Survival Improvement over past 20 years
2. RWE: Liver resection rate in US & Taiwan
3. Guidelines and recommendations for cytoreduction
4. Efficacy of Erbitux vs Avastin in 1L mCRC
5. Efficacy of Erbitux vs Avastin in RS mCRC
6. Factors that influence conversion to respectability
7. When to perform surgery

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Survival Improvement over past 20 years

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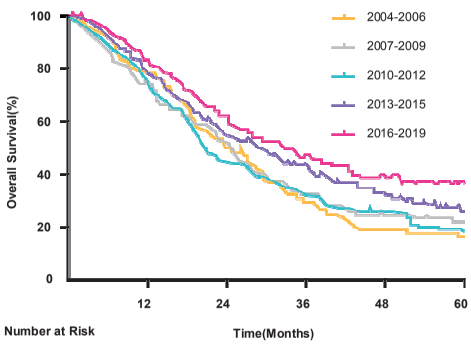
ARTICLE OPEN

Survival improvement for patients with metastatic colorectal cancer over twenty years



Significant variables from univariate and multivariate analyses.

		Univariate Analysis			Multivariate Analysis		
Variate	Reference	HR	P-value	95% CI	HR	P-value	95% CI
Liver Resection	No	0.26	200E-17	0.19-0.35	0.26	9.20E-16	0.19-0.37
Immunotherapy	No	0.39	5.8E-06	0.27-0.61	0.44	0.00013	0.29-0.67
Third Line Chemotherapy	No	0.69	0.0015	0.55-0.87	0.74	0.018	0.58-0.95
Race: Asian	White	0.72	0.026	0.53-0.96	0.8	0.15	0.59-1.1
Year of Diagnosis	NA	0.96	3.5E-06	0.95-0.98	0.99	0.44	0.98-1
Age at diagnosis	NA	1.012	0.000015	1.007-1.01	1.007	0.021	1.001-1.01
Chronic Kidney Disease	NO	1.4	0.0029	1.1-1.8	1.3	0.025	1.03-1.68
Race: Black or African American	White	1.4	0.00047	1.2-1.7	1.3	0.015	1.04-1.54
Right sided primary tumor	Left	1.7	8.10E-12	1.4-1.9	1.7	4.50E-12	1.5-2

Only variables significant in invariable analysis were included in the multivariable model. Regression Formula:
OS ~ Age at Diagnosis + Primary Tumor Side + Immunotherapy + Third Line Treatment + Race + Liver Resection + Chronic Kidney Disease + Year of diagnosis.

Fadl A. Zeineddine, Mohammad A. Zeineddine, Abdelrahman Yousef, Rue Gu, Saikat Chowdhury, Arvind Dasari, Ryan W. Huey, Benny Johnson, Bryan Kee, Michael S. Lee, Maria Pia Morelli, Van K. Morris, Michael J. Overman, Christine Parseghian, Kanwal Raghav, Jason Willis, Robert A. Wolff, Yoshikuni Kawaguchi, Jean-Nicolas Vauthey, Ryan Sun, Scott Kopetz and John Paul Shen

Precision Oncology (2023) 7:16 ; https://doi.org/10.1038/s41698-023-00353-4

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RWE: Liver resection rate in US & Taiwan

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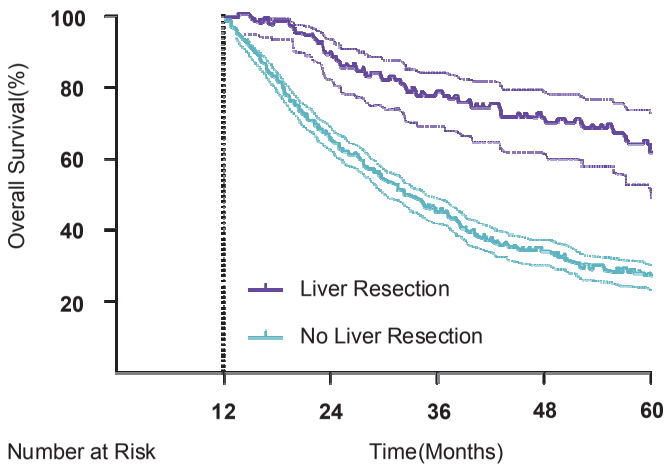
Primary Driver of Survival Improvement is Increased Utilization of CLM Resection

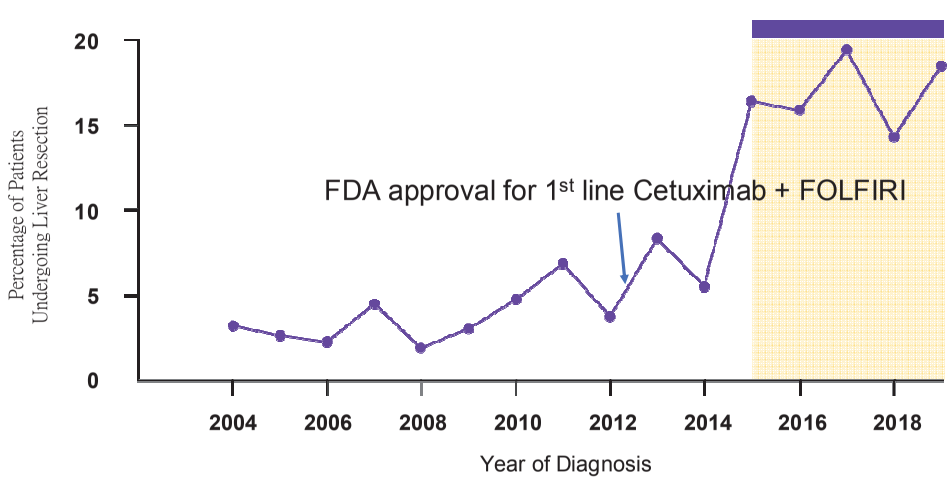


Survival benefit of liver resection

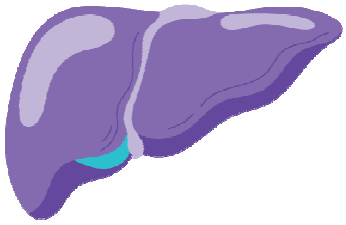
Liver resection: 74.3 mOS
No Liver resection: 32.6 mOS

Precision Oncology (2023) 7:16 ; https://doi.org/10.1038/s41698-023-00353-4

Liver resection rate has stabilized at 20% after 2014



Around 20%



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Taiwan RWE retrospective study

Inclusion Criteria

- Histologically confirmed RAS wild-type mCRC
- Cetuximab plus chemotherapy prescribed in first line treatment during **2016/11/01 to 2020/8/30**
- Patients received ≥3 cycles of 1st line Cetuximab treatment

ITT

- Cetuximab + FOLFIRI
- Cetuximab + FOLFOX
- Cetuximab + other chemotherapy

13 Institutions

16 investigators

698 cases

A total of 698 mCRC patients received the 1L cetuximab-based chemotherapy, with a median age of 61.8 years. 626 (90%) had a left-sided primary tumor. 423 (60%) had liver metastases.

Annals of Oncology (2022) 33 (suppl_7): S136-S196. 10.1016/annonc/annonc1048

Baseline Characteristics (N=698)

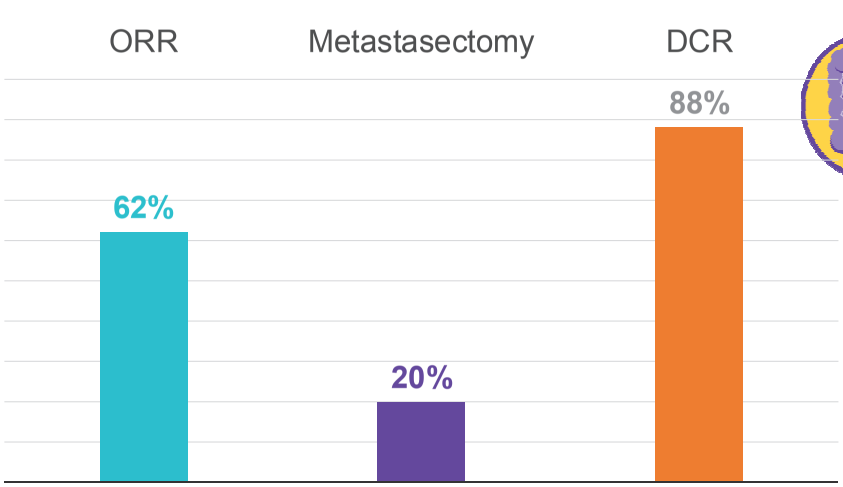
Characteristics	Number(%)	
Median age, years(range)	61.8	52.1-70.6
Sex		
Male	472	67.6%
Female	226	32.4%
EcOG performance status		
0	477	68.3%
1	196	28.1%
2	18	2.6%
≥3	6	0.9%
Location of primary tumor		
Left-sided	626	89.8%
Right-sided	68	9.8%
Both	3	0.4%
Primary tumor resection		
Yes	472	67.6%
No	216	30.9%
MMR and BRAF status		
BRAF Status		
Wild-Type	506	97.1%
V600E mut	15	2.9%
MMR Status		
dMMR	27	7.6%
pMMR	329	92.4%
Prior adjuvant therapy		
Yes	184	26.8%
No	503	73.3%

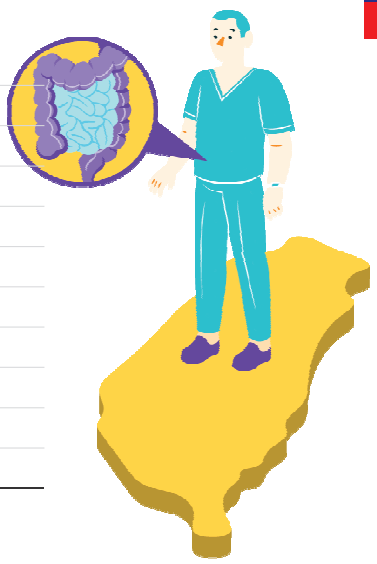
Characteristics	Number(%)	
Metachronous or synchronous Metastasis		
Synchronous	434	62.2%
Metachronous	260	37.2%
Metastatic site		
Liver	425	60.9%
Lung	178	25.5%
Peritoneum	146	20.9%
Distant lymph-node	100	14.3%
Number of metastatic sites		
1	380	54.4%
2	159	22.8%
≥3	142	20.3%
Metastasectomy		
Yes	190	27.2%
No	503	72.1%
Regimen in combination with cetuximab(N=691)		
FOLFIRI	576	83.4%
FOLFOX	87	12.6%
Others	28	4.1%

Percentages do not always add up to 100% because of missing data classified as unknown. †More than one could be present in the same patient. A total of 695 patients have records of distant metastasis location

Annals of Oncology (2022) 33 (suppl_7): S136-S196. 10.1016/annonc/annonc1048

Taiwan mCRC Registry





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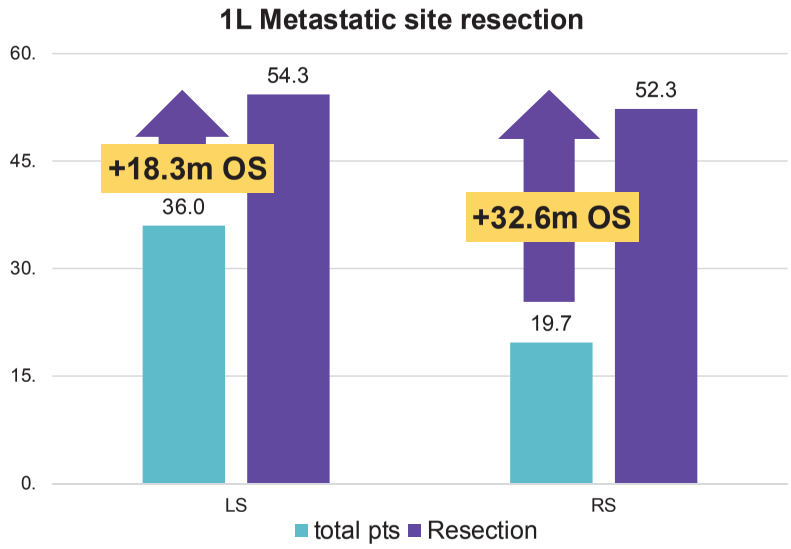
The mCRC patients who undergo metastasectomy have longer mOS than total patients, regardless tumor sidedness



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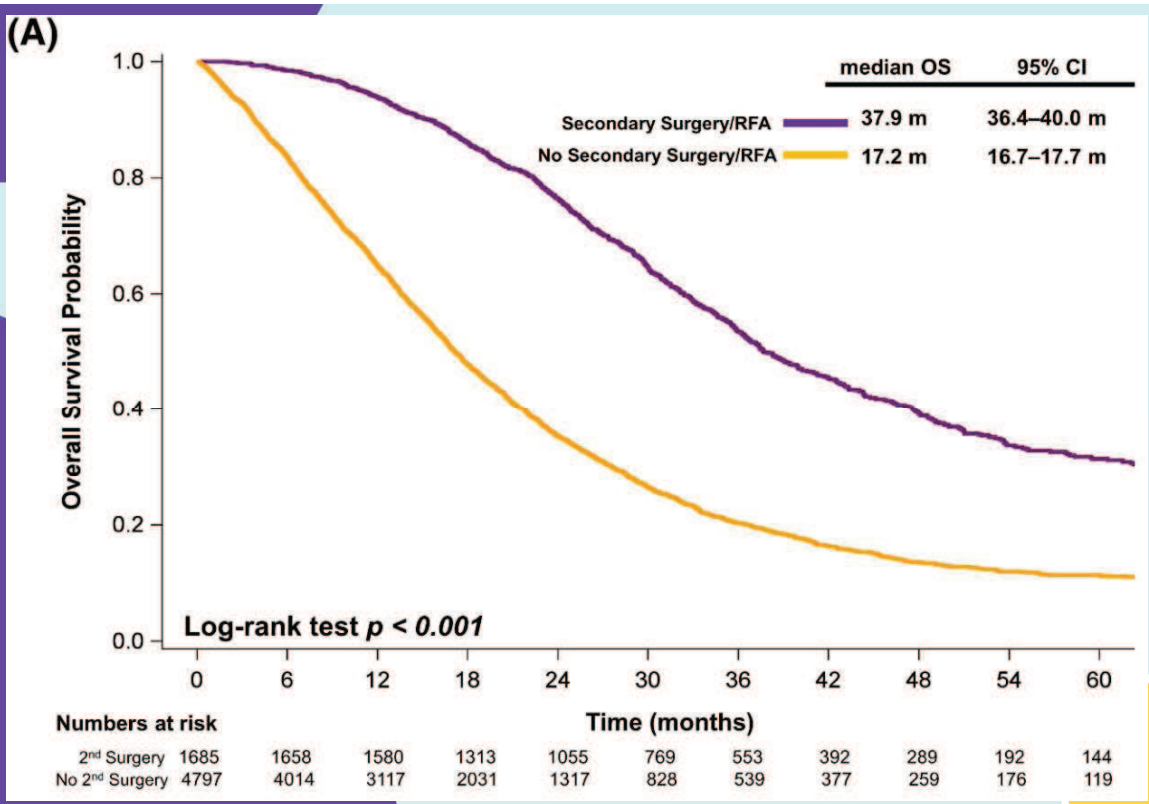
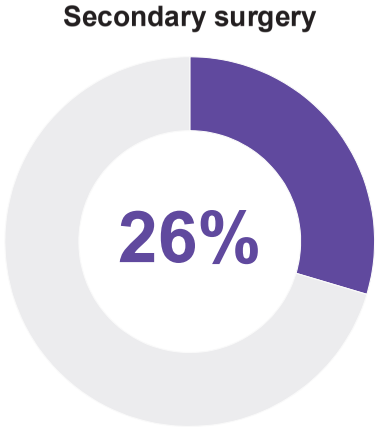
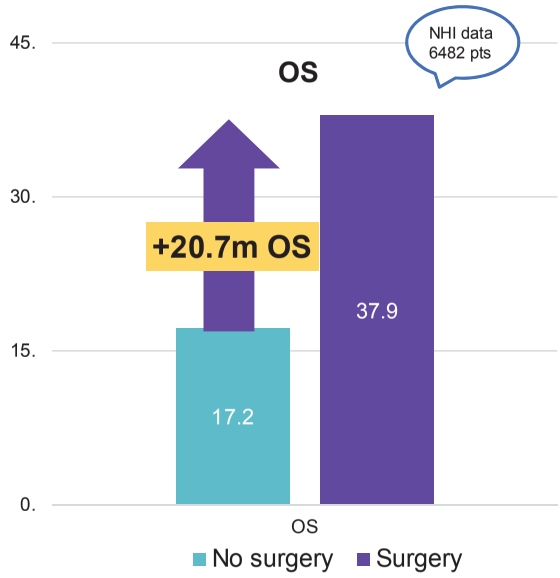


Cancer Med. 2023;12(14):15176-15186

Taiwan mCRC nationwide NHI data (6482 patients)





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Guidelines and recommendations for cytoreduction

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National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2025
pMMR/MSS Colon Cancer

NCCN Guidelines Index
Table of Contents
Discussion

TREATMENT
Unresectable[g] synchronous liver and/or lung metastases only
pMMR/MSS

ADJUVANT TREATMENT[b] (UP TO 6 MO PERIOPERATIVE TREATMENT)

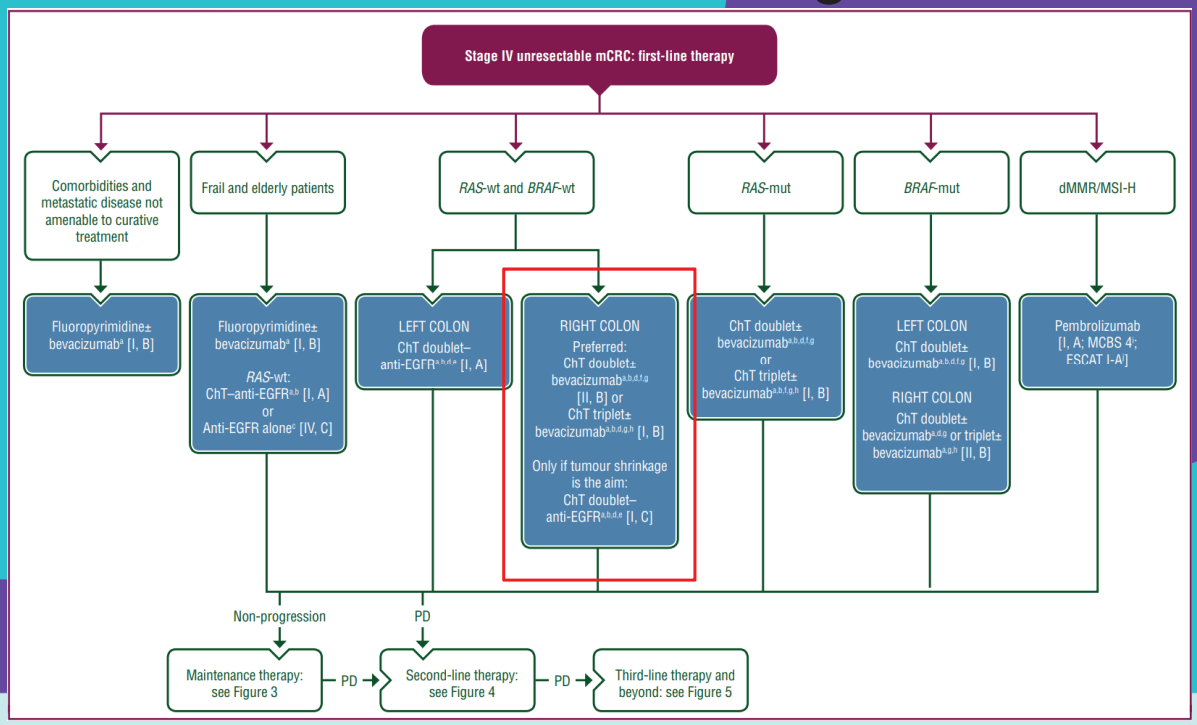
- **Systemic therapy[y]**
  - **FOLFIRI or FOLFOX or CAPEOX or FOLFIRINOX ± bevacizumab[z]**
  - **or**
  - **FOLFIRI or FOLFOX ± panitumumab or cetuximab[aa] (*KRAS/NRAS/BRAF* WT and left-sided tumors only)[e,bb,cc]**
- **Consider colon resection[g] only if imminent risk of obstruction, significant bleeding, perforation, or other significant tumor-related symptoms**

→ **Re-evaluate for conversion to resectable[b,g] every 2 mo if conversion to resectability is a reasonable goal**

→ **Converted to resectable** → **Synchronized or staged resection[g] (preferred) and/or local therapy[x] of colon and metastatic cancer** → **Systemic therapy ± biologic therapy[dd] (COL-D) (category 2B for biologic therapy) or Consider observation or shortened course of chemotherapy** → **Surveillance (COL-8)**

→ **Remains unresectable[w]** → **Systemic Therapy (COL-D) and consider local therapy[g,l] for select patients**

ESMO/Pan-Asian ESMO guidelines

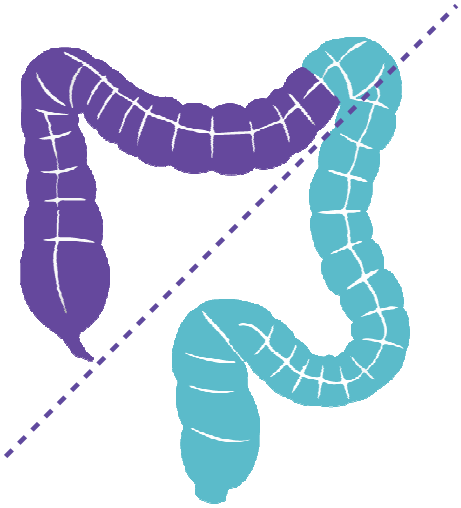


mCRC:
2024 ESMO guideline and Taiwan Society of Colon and Rectal Surgeons treatment consensus

1L therapies for RAS wt (BRAF wt) mCRC[1]

Right sided

Anti-EGFR+CT *is recommended for RAS WT* ***RS*** *mCRC patients* ***when a higher response for conversion therapy is the goal.***



Left sided

Anti-EGFR+CT *is recommended for RAS WT* ***LS*** *mCRC patients* ***(irrespective of tumor goal)***

Cervantes A, et al. ESMO Metastatic Colorectal Cancer Living Guidelines, v1.2 September 2024. Accessed on Sep 23, 2024. Available at: https://www.esmo.org/living-guidelines/esmo-metastatic-colorectal-cancer-living-guideline;

(2)Bevacizumab(除 Zirabev 及 Abevmy 以外)與含有5-fluorouracil/leucovorin/oxaliplatin 的化學療法合併使用，作為先前接受過以 fluoropyrimidine 為基礎的化學療法併用 cetuximab 或 panitumumab 無效且未曾接受過 bevacizumab 治療，RAS 基因沒有突變的轉移性大腸或直腸癌病人的第二線治療。(114/3/1)

Ⅱ. 使用總療程以24週為上限。

Ⅲ. 須經事前審查核准後使用，每次申請事前審查之療程以12週為限，再次申請必須提出客觀證據（如：RECIST criteria）證實無惡化，才可繼續使用。

Ⅳ. 使用劑量：限5mg/kg，每兩週一次。

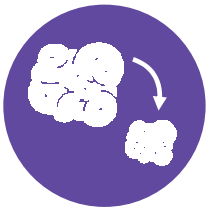
Addressing issue:

1. 1st line treatment: Bevacizumab vs Cetuximab
2. Right side colon: Cetuximab or not?

Tumor shrinkage (cytoreduction) can be a primary treatment goal for patients with mCRC[1,2]

Cytoreduction is a primary treatment goal for patients with:[2]

Potentially resectable disease in which **conversion** is a key treatment goal[2]



Aggressive disease **that requires rapid reduction in tumor burden** to limit impending clinical threat[2]

Severe disease-related **symptoms** or impending **organ dysfunction**[2]

ESMO/Pan-Asian ESMO guidelines recommend treatments for tumor shrinkage in RAS wt mCRC, regardless of tumor sidedness[1,3]

1. Yoshino T, et al. Ann Oncol 2018;29:44–70 2. Van Cutsem E, et al. Ann Oncol 2016;27:1386–1422 3. Annals of Oncology (2022), doi: https://doi.org/10.1016/j.annonc.2022.10.003.

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Efficacy of Erbitux vs Avastin in 1L mCRC

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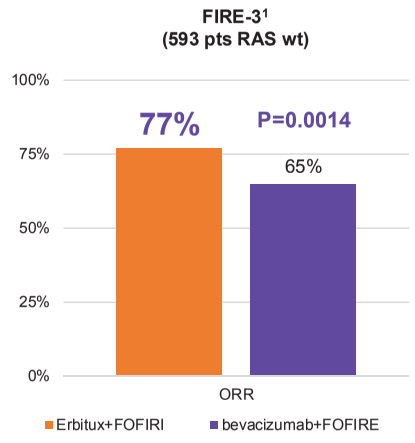
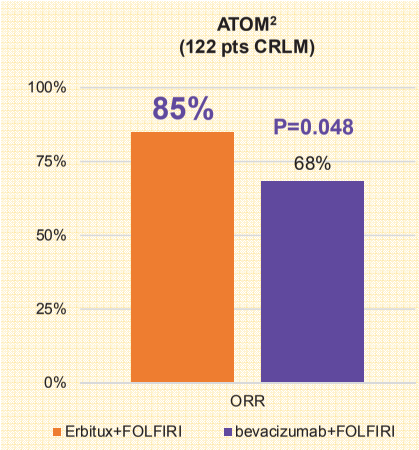
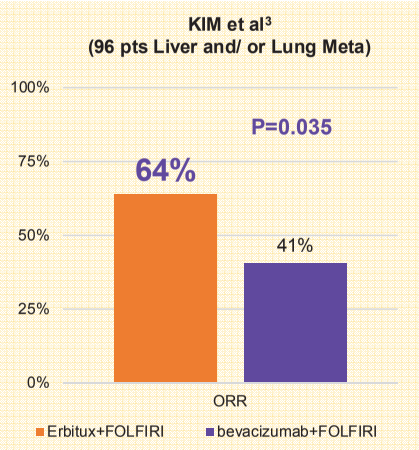
Erbitux is superior to Beva in Objective Response Rate in 1L patients





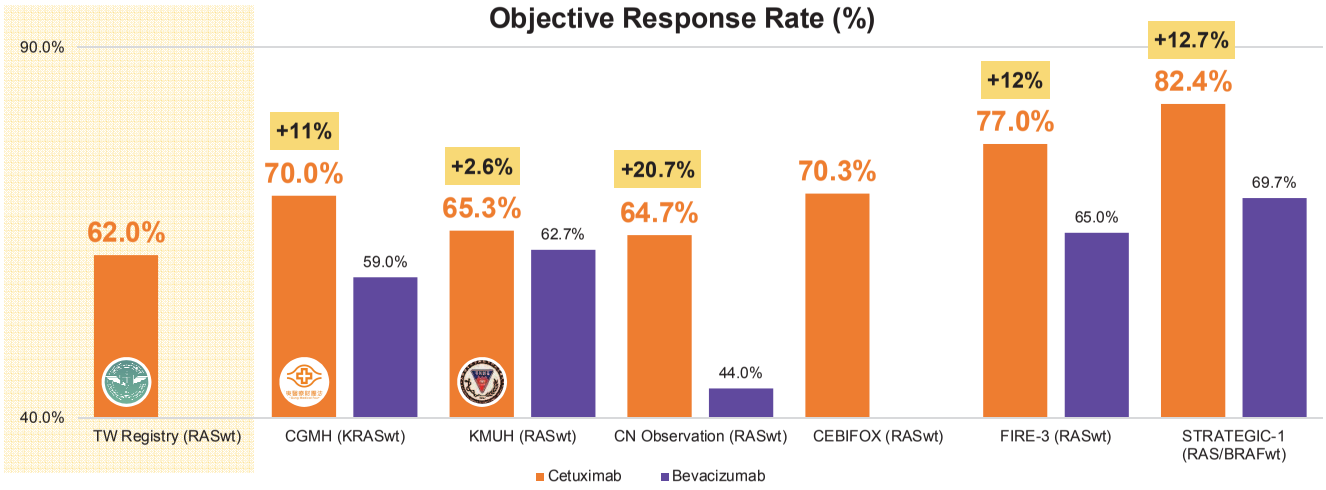


Around 80% ORR in FIRE-3 and ATOM
Add additional **+12% to 23%** response rate with Erbitux vs Beva

Note: This is not a cross-trial comparison, hence data from these trials are not comparable!

1. V Heinemann1 et al British Journal of Cancer (2021) 124:587–594;2. E Oki et al. British Journal of Cancer (2019) 121:222–229 3. Kim et al, Journal of Cancer Research and Clinical Oncology, 2020

Cetuximab consistently provides 60%+~80% ORR in 1L mCRC



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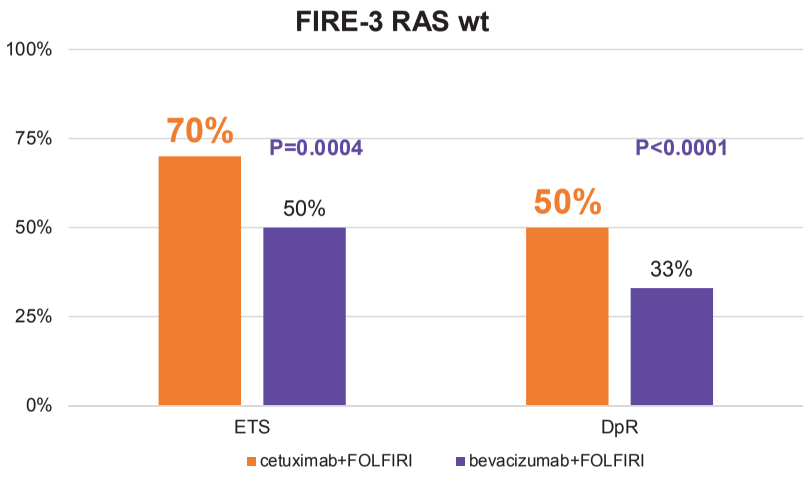
Erbitux is superior to Beva in ETS, DpR

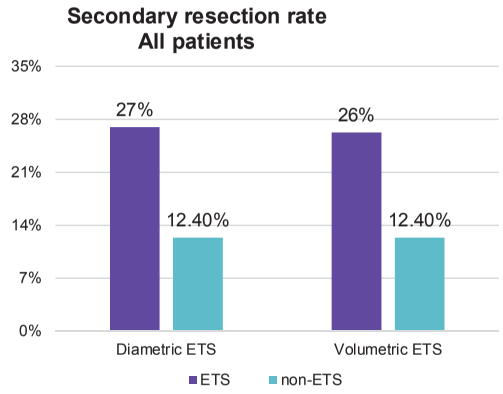


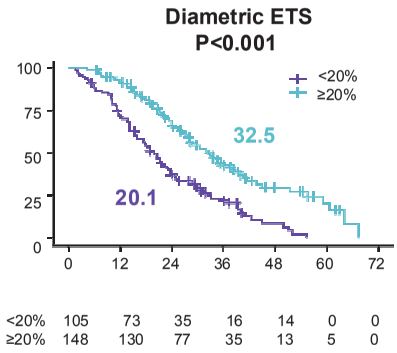
70% ETS, **50%** DpR in 1L patients with Erbitux

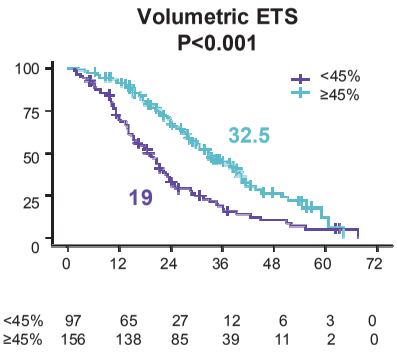
ETS：腫瘤在治療第六週縮小20%以上的比例

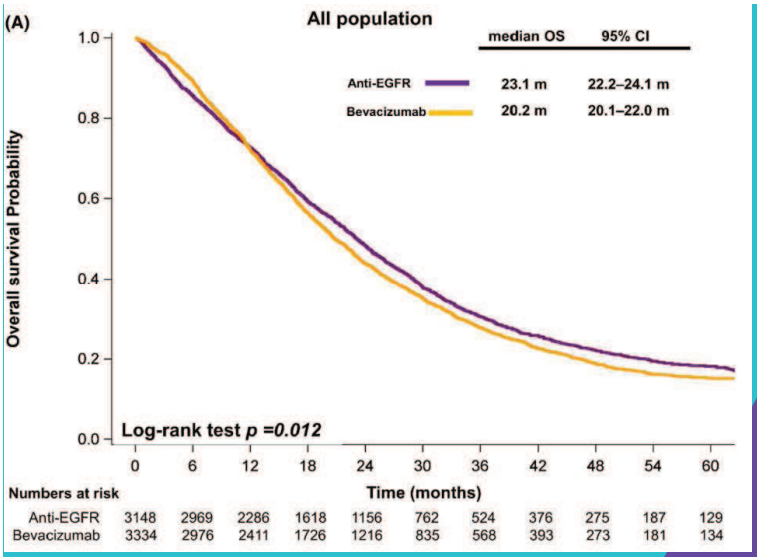
V Heinemann et al.FIRE-3 BJC2020

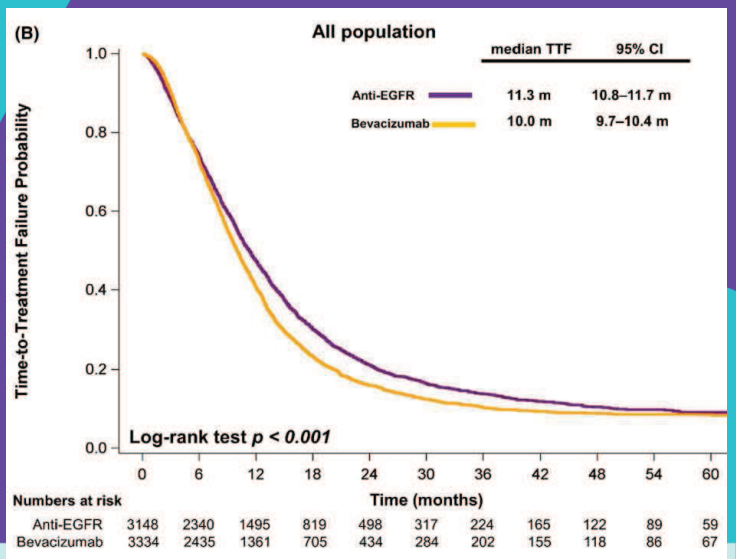
Patients achieving diametric/ volumetric ETS demonstrated significant better resection rate and OS benefits in FIRE-3



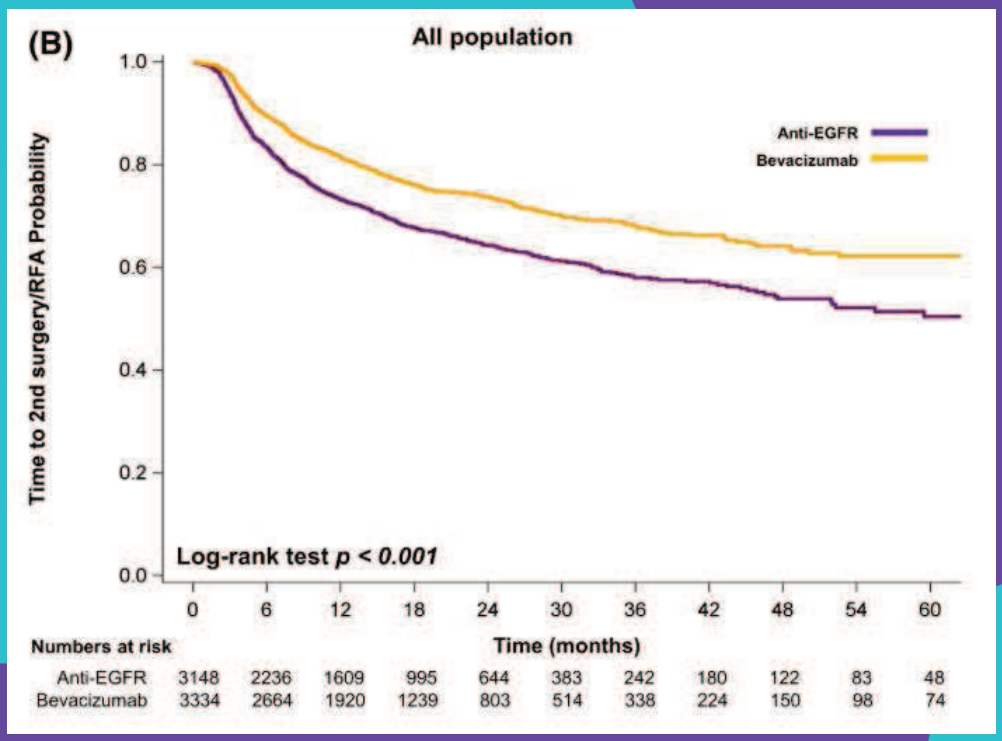






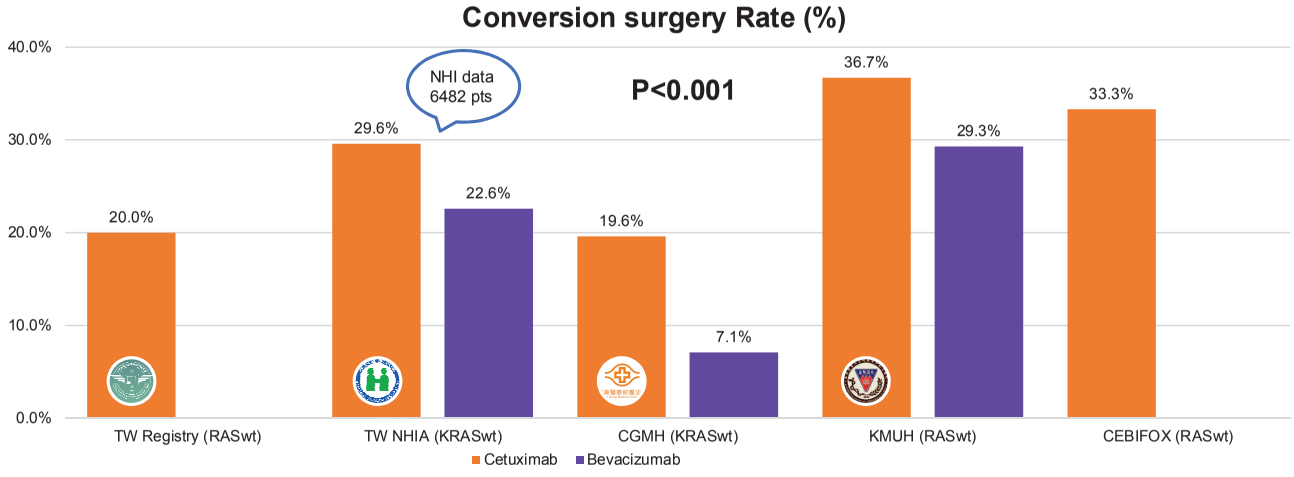


Cancer Med. 2023;12(14):15176-15186



Cancer Med. 2023;12(14):15176-15186

In terms of cytoreduction the Conversion surgery rate is 20%+



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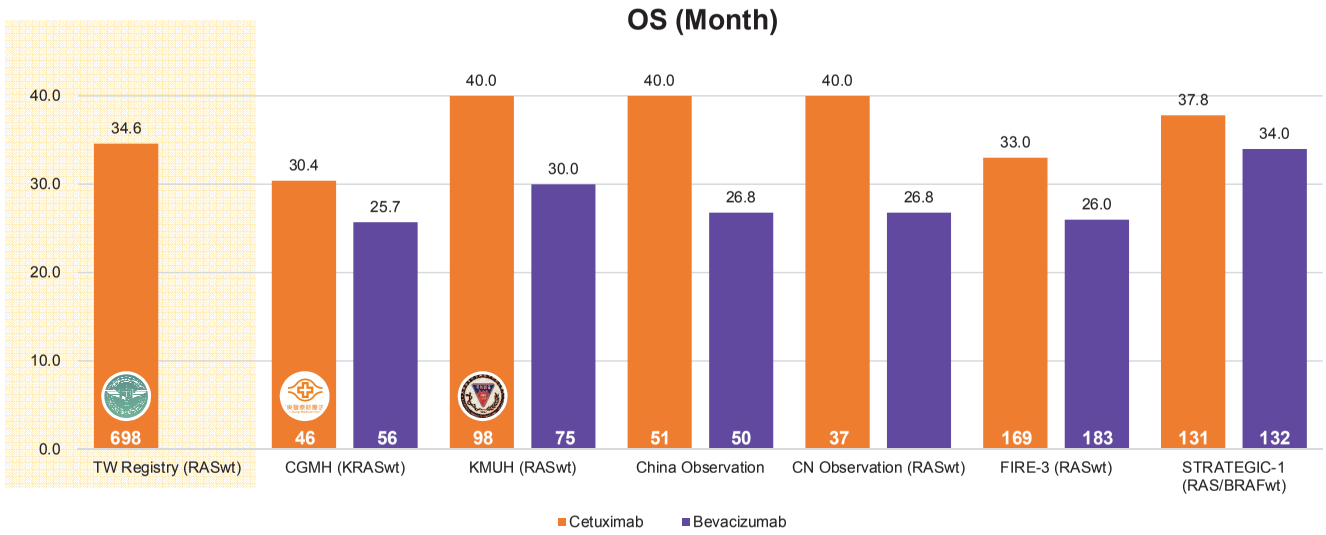
Overall, Cetuximab delivers reliable 30M+ OS performance in all 1L mCRC settings



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Efficacy of Erbitux vs Avastin in RS mCRC

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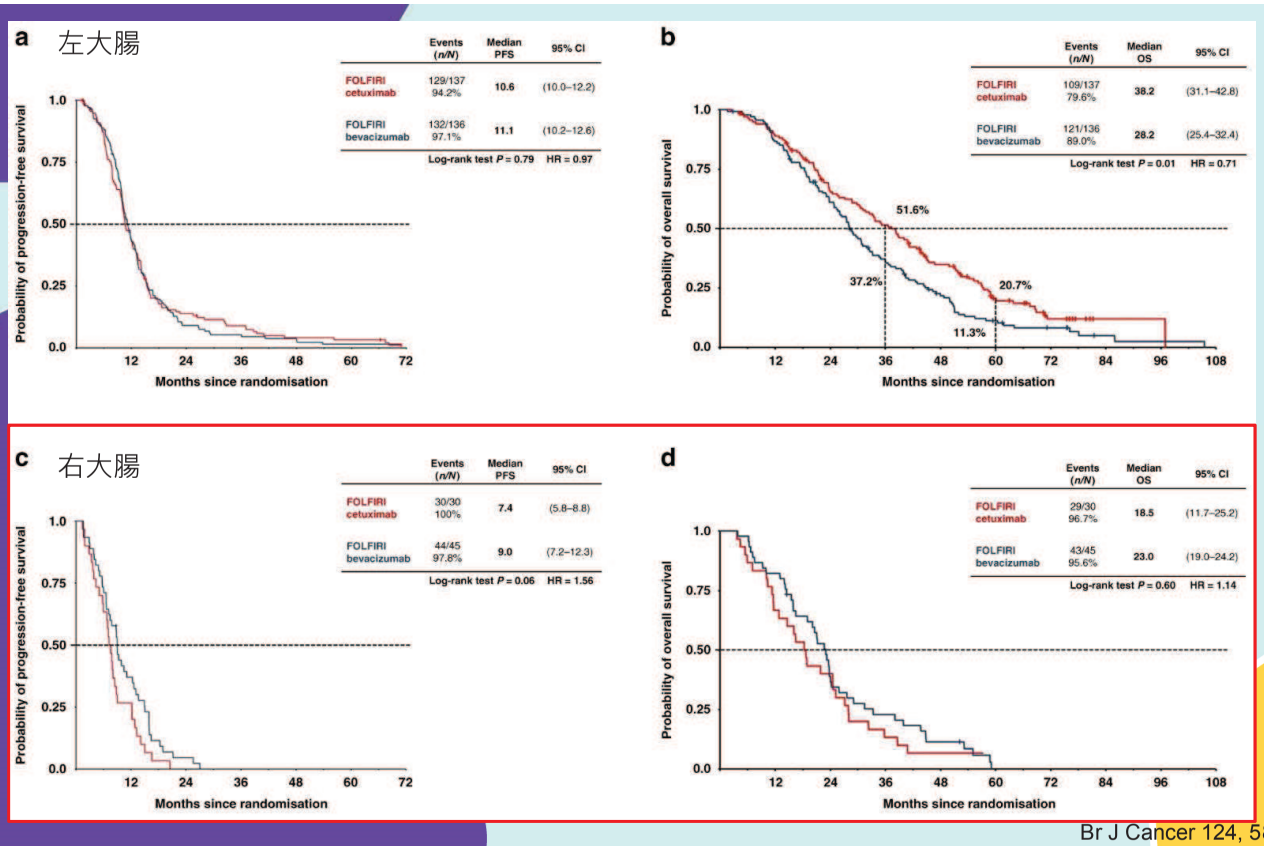
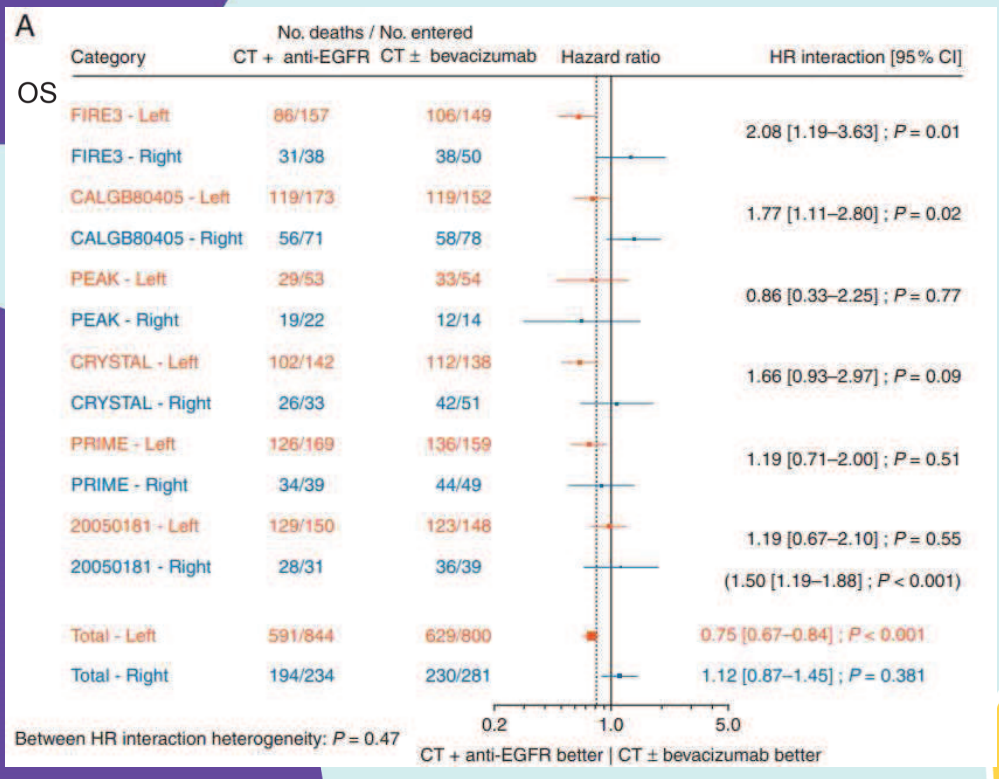
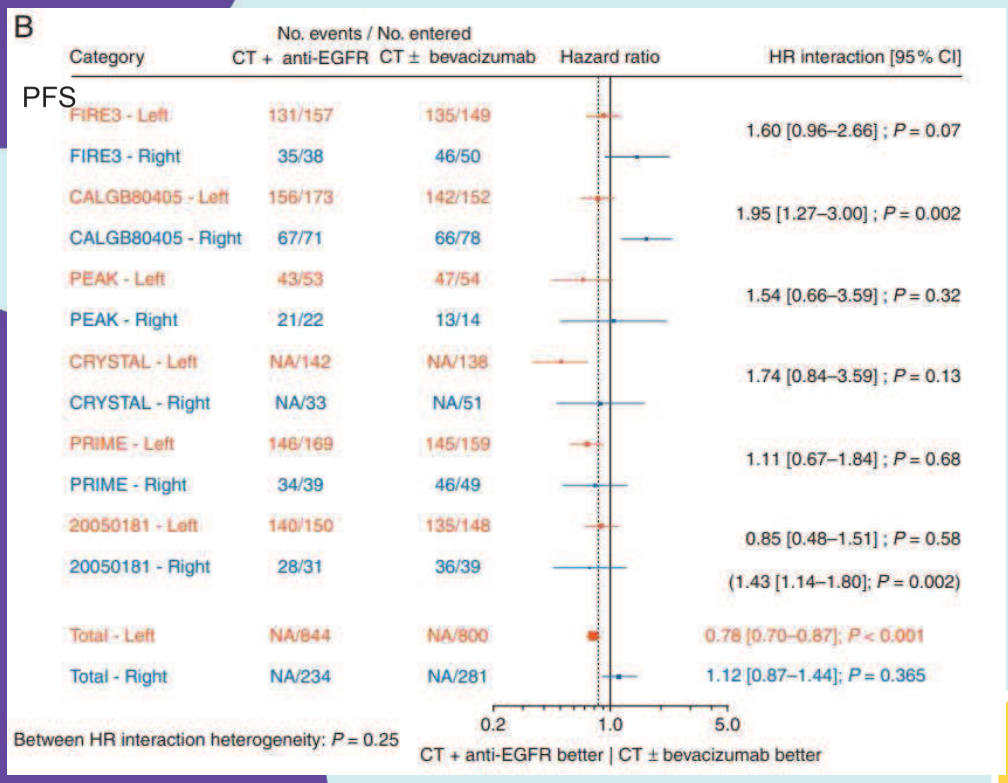


Br J Cancer 124, 587–594 (2021)



Annals of Oncology 28: 1713–1729, 2017



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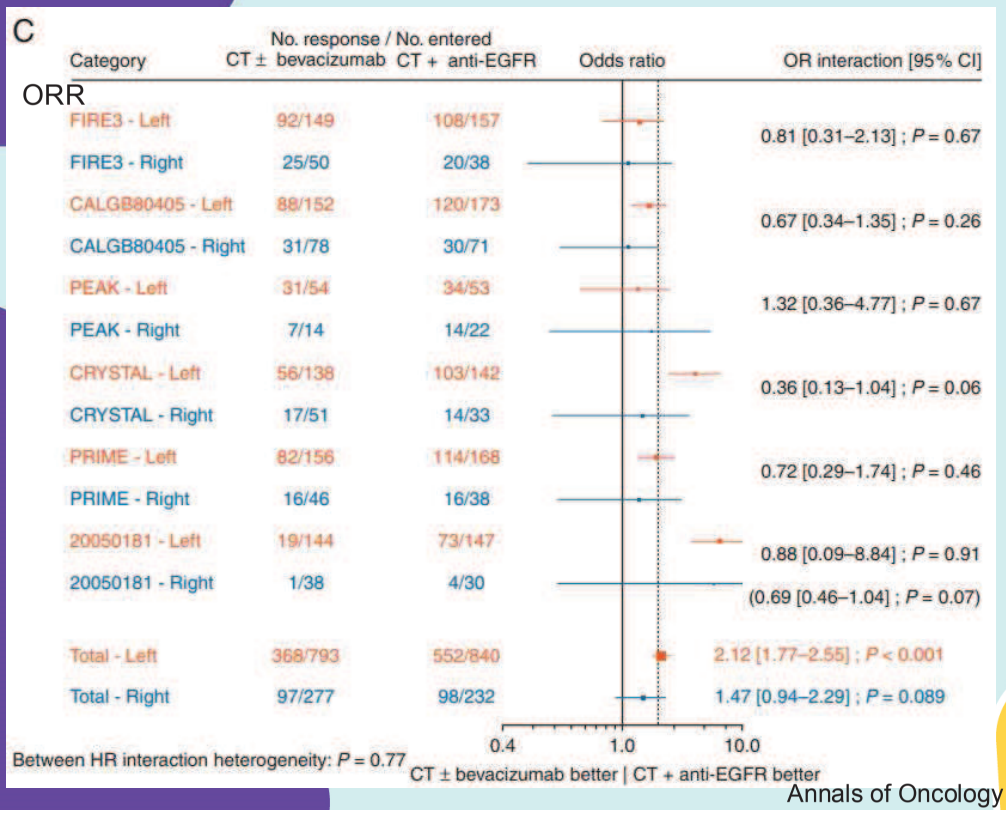

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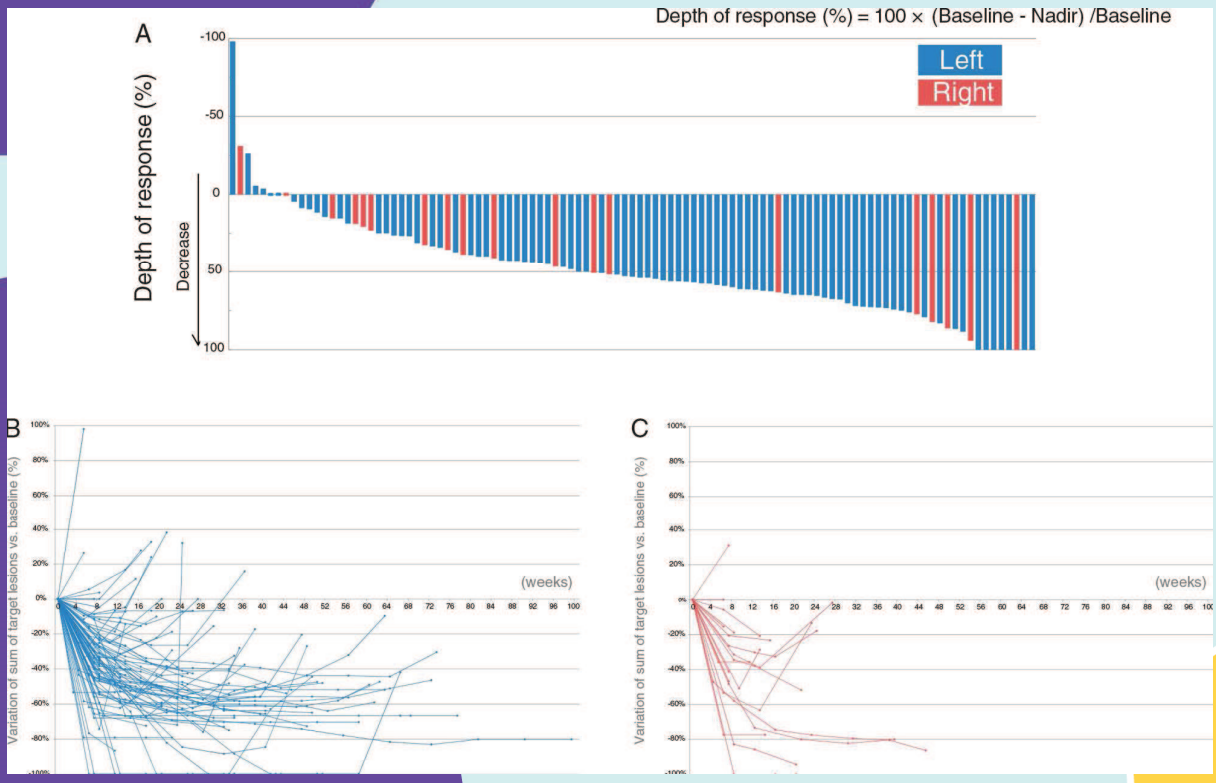
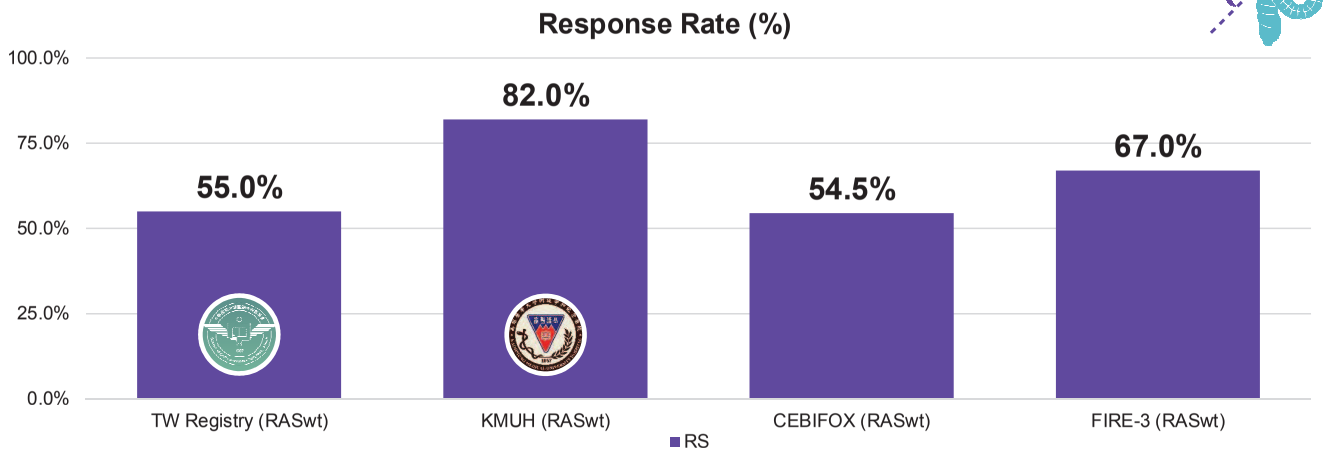


Annals of Oncology, Volume 28, Issue 8, 2030 - 2031

	mPFS (95%CI)			mOS (95%CI)		
	w/o anti-EGFR	w/ anti-EGFR	all	w/o anti-EGFR	w/ anti-EGFR	all
LS bulky (N = 148)	9.0 (8.4-10.5)	8.9 (6.5-10.2)	8.9 (8.1-9.8)	19.4 (15.9-22.5)	17.4 (15.6-24.6)	18.3 (16.6-21.2)*
RS bulky (N = 63)	8.0 (4.3-11.1)	6.1 (5.4-9.4)	7.4 (5.8-9.2)	13.5 (9.8-24.1)	13.0 (8.8-26.1)	13.4 (9.8-20.7)
LS non-bulky (N = 192)	9.2 (8.4-11.3)	8.7 (8.3-10.8)	8.9 (8.4-10.6)	23.0 (20.7-28.3)	22.1 (17.8-27.0)	22.4 (20.3-26.7)*
RS non-bulky (N = 73)	8.1 (6.6-10.3)	7.8 (7.0-10.5)	8.1 (7.1-9.0)	18.6 (13.2-31.4)	18.3 (10.1-25.1)	18.6 (13.8-24.8)

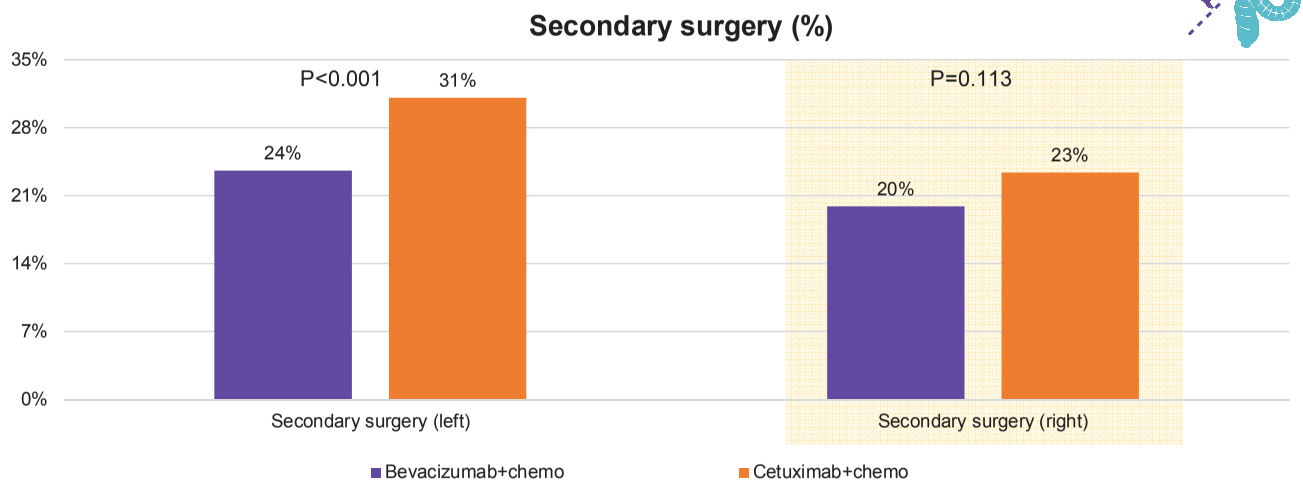
Meeting Abstract: 2021 Gastrointestinal Cancers Symposium

Cetuximab also demonstrates 55%~80% ORR in RS RAS wt mCRC



1. Taiwan CRC Registry (2022 ESMO abstract) 2. Tsai., Oncol Res. 2022 May 4;29(1):47-61 3. Kasper et al., Clin Colorectal Cancer. 2020 Dec;19(4):236-247.e6 4. Heinemann et al., Br J Cancer. 2021 Feb;124(3):587-594

When cytoreduction or conversion therapy is the goal, anti-EGFR + CT* is an option for patients with RS RAS wt mCRC

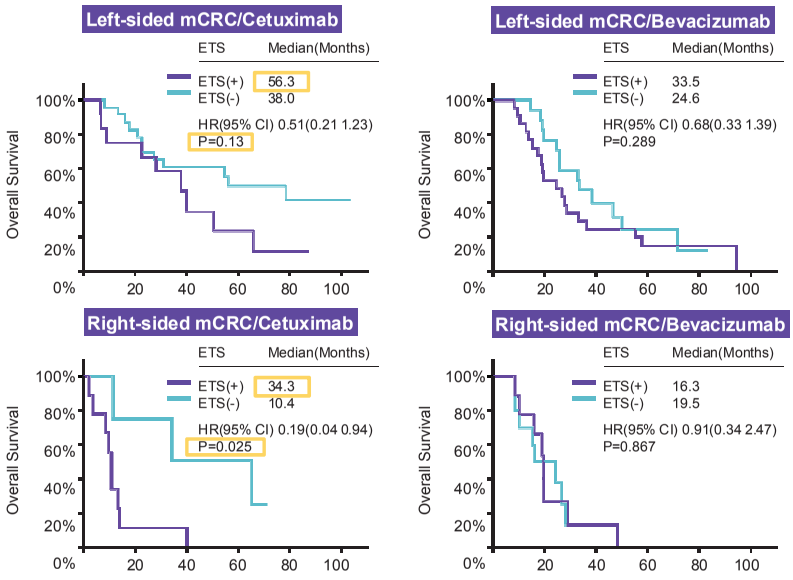


Liang et al., Cancer Medicine 2023 May;00:1-11

Facts in RASwt mCRC:

- 左側大腸: OS/PFS/ORR: Cetuximab都顯著優於Bevaiczumab
- 右側大腸: OS/PFS: Bevacizumab近似或略優於Cetuximab (不顯著)
- 右側大腸: OSS: Cetuximab近似或略優於Bevacizumab (不顯著)

Patients who achieved ETS with cetuximab +CT had a significantly longer OS than those without ETS, regardless tumor sidedness



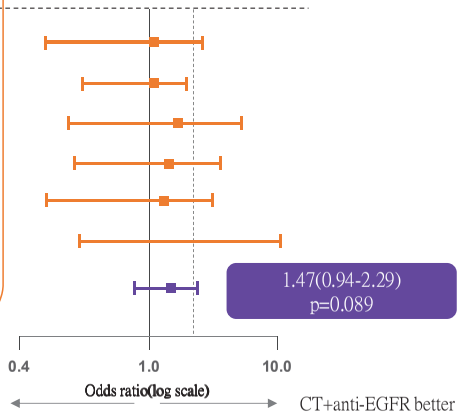
Retrospective analysis, 110 patients unresectable mCRC, Japan

*ETS (≥ 20% at week 8) Tamotsu Sagawa et al, Scientific Reports | (2020) 10:19815

Across multiple trails, Erbitux+CT provided numerically greater shrinkage over CT ± Beva in RS RAS wt mCRC*

83% of patients treated with anti-EGFR agents in these trials received Erbitux®+CT*

Category	CT±bevacizumab	CT+anti-EGFR
FIRE-3†	25/50	20/38
CALGB/SWOG 80405†	31/78	30/71
PEAK	7/14	14/22
CRYSTAL	56/138	14/33
PRIME	16/46	16/38
20050181	1/38	4/30
Total	**136/364**	**98/232**



*objective response rate 1. Arnold D, et al. Ann Oncol 2017;28:1713–1729 2. Yoshino T, et al. Ann Oncol 2018;29:44–70 3. Curigliano G, et al. ESMO pocket guidelines: Lower gastrointestinal cancer 2020 4. Erbitux SmPC, May 2019 5. Heinemann V, et al. Lancet Oncol 2014;15:1065–1075 6. Venook A, et al. JAMA 2017;317:2392–2401 7. Adam R, et al. Eur J Cancer 2017;78:7–17.

1L anti-EGFR agent + doublet CT are recommended in patients with RS RAS wt mCRC when cytoreduction or a higher response for Conversion therapy is the goal[1-4]

	2024 ESMO guidelines[1]	2022 ASCO guidelines[2]	2023 ESMO pocket guidelines[3]	2023 ESMO Pan-Asian guidelines[4]
1L	Higher response For conversion therapy: Anti-EGFR agent + doublet CT [II, C]		High response for conversion therapy: Anti-EGFR agent + doublet CT	Higher response for conversion therapy: Anti-EGFR agent + doublet CT [II, C]
	Anti-VEGF agent + CT [II, B ESMO 2024 and ESMO Pan-Asian guidelines[1,4]; 2023 ESMO pocket guideline[3]]			

The strength of evidence, presented as [level of evidence, grade of recommendation], have been provided where available.
1L, first line; ASCO, American Society of Medical Oncology; CT, chemotherapy; EGFR, epidermal growth factor receptor; ESMO, European Society for Medical Oncology; RS, right-sided; VEGF, vascular endothelial growth factor.
1. Cervantes A, et al. ESMO Metastatic Colorectal Cancer Living Guidelines, v1.2 September 2024. Accessed on Sep 23, 2024. Available at: https://www.esmo.org/living-guidelines/esmo-metastatic-colorectal-cancer-living-guideline; 2. Morris VK, et al. J Clin Oncol 2022;doi: 10.1200/JCO.22.01690; 3. Curigliano G, et al. ESMO pocket guidelines: Lower gastrointestinal cancer 2023; 4. Yoshino T, et al. ESMO Open. 2023;8(3):101558.

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Factors that influence conversion to respectability

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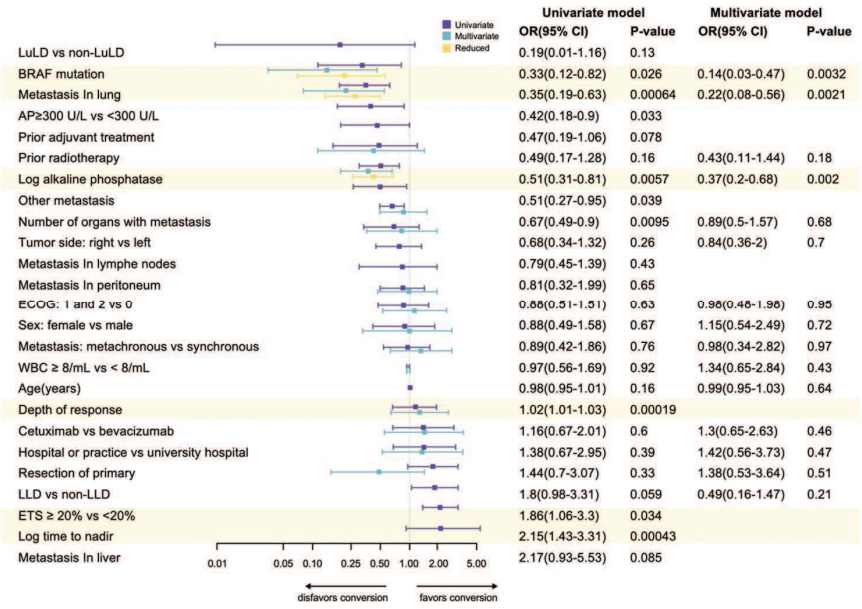
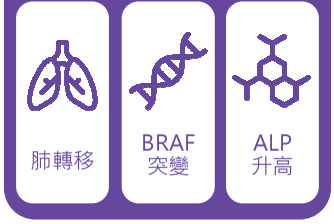
Factors That Influence Conversion to Resectability and Survival After Resection: Analysis of FIRE-3-AIOKRK 0306



	Univariate model		Multivariate model	
	OR(95% CI)	P-value	OR(95% CI)	P-value
LuLD vs non-LuLD	0.19(0.01-1.16)	0.13		
BRAF mutation	0.33(0.12-0.82)	0.026	0.14(0.03-0.47)	0.0032
Metastasis In lung	0.35(0.19-0.63)	0.00064	0.22(0.08-0.56)	0.0021
AP≥300 U/L vs <300 U/L	0.42(0.18-0.9)	0.033		
Prior adjuvant treatment	0.47(0.19-1.06)	0.078		
Prior radiotherapy	0.49(0.17-1.28)	0.16	0.43(0.11-1.44)	0.18
Log alkaline phosphatase	0.51(0.31-0.81)	0.0057	0.37(0.2-0.68)	0.002
Other metastasis	0.51(0.27-0.95)	0.039		
Number of organs with metastasis	0.67(0.49-0.9)	0.0095	0.89(0.5-1.57)	0.68
Tumor side: right vs left	0.68(0.34-1.32)	0.26	0.84(0.36-2)	0.7
Metastasis In lymphe nodes	0.79(0.45-1.39)	0.43		
Metastasis In peritoneum	0.81(0.32-1.99)	0.65		
ECOG: 1 and 2 vs 0	0.86(0.51-1.51)	0.63	0.96(0.48-1.96)	0.95
Sex: female vs male	0.88(0.49-1.58)	0.67	1.15(0.54-2.49)	0.72
Metastasis: metachronous vs synchronous	0.89(0.42-1.86)	0.76	0.98(0.34-2.82)	0.97
WBC ≥ 8/mL vs < 8/mL	0.97(0.56-1.69)	0.92	1.34(0.65-2.84)	0.43
Age(years)	0.98(0.95-1.01)	0.16	0.99(0.95-1.03)	0.64
Depth of response	1.02(1.01-1.03)	0.00019		
Cetuximab vs bevacizumab	1.16(0.67-2.01)	0.6	1.3(0.65-2.63)	0.46
Hospital or practice vs university hospital	1.38(0.67-2.95)	0.39	1.42(0.56-3.73)	0.47
Resection of primary	1.44(0.7-3.07)	0.33	1.38(0.53-3.64)	0.51
LLD vs non-LLD	1.8(0.98-3.31)	0.059	0.49(0.16-1.47)	0.21
ETS ≥ 20% vs <20%	1.86(1.06-3.3)	0.034		
Log time to nadir	2.15(1.43-3.31)	0.00043		
Metastasis In liver	2.17(0.93-5.53)	0.085		

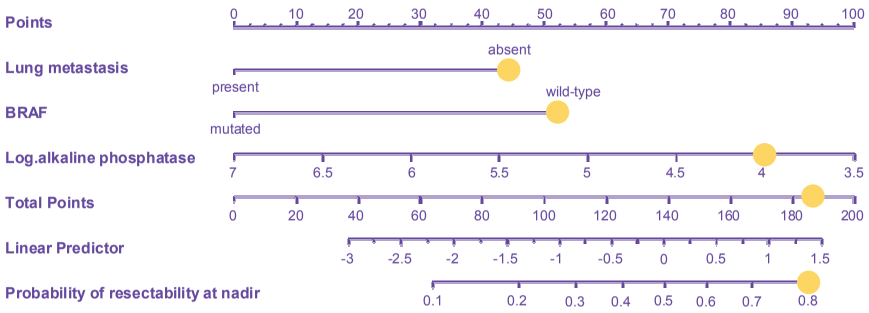
Positive predictors:
- ETS
- Short time to best response
- DpR

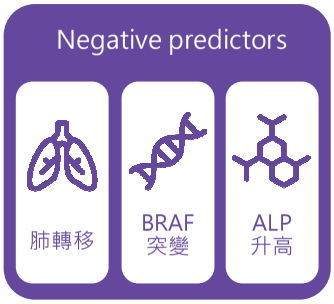
Negative predictors



Ann Surg Oncol (2020) 27:2389–2401

Nomogram for the prediction of conversion therapy



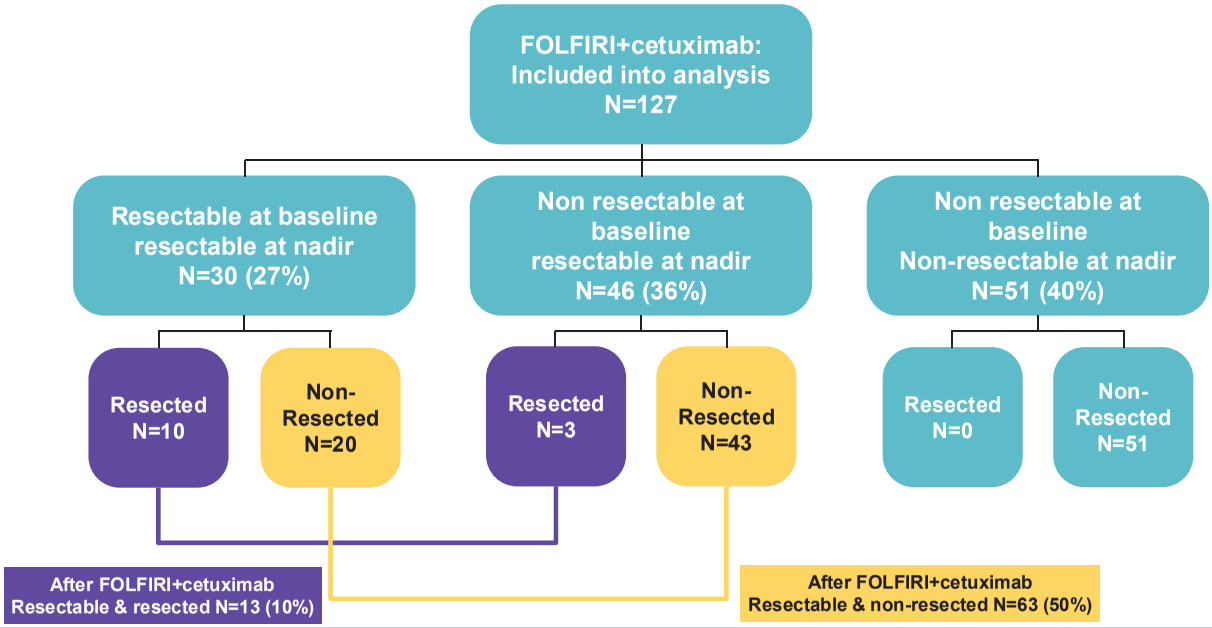


A patient without any lung metastasis, a wild-type BRAF tumor and log transformed baseline alkaline phosphatase of 4 would get a total number of points of 44 + 52 + 86 = 182.

The intersection of this vertical line with "Probability of resectability at nadir" scale gives the patient probability of resectability at nadir. 80% !

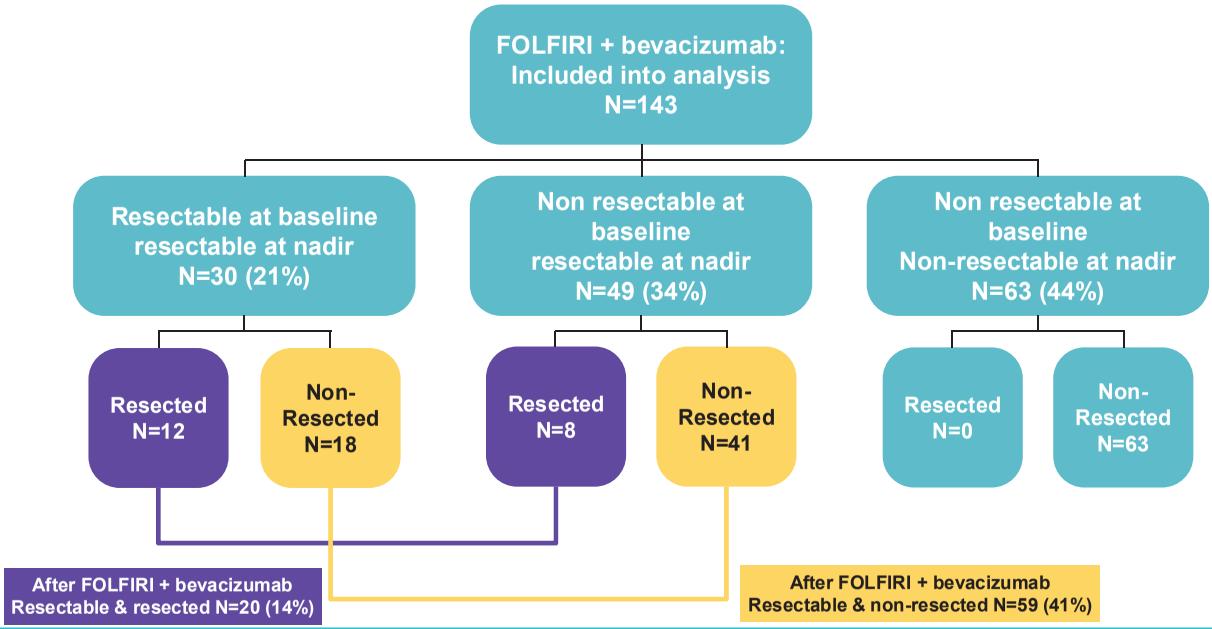
Ann Surg Oncol (2020) 27:2389–2401

Factors That Influence Conversion to Resectability and Survival After Resection: Analysis of FIRE-3-AIOKRK 0306



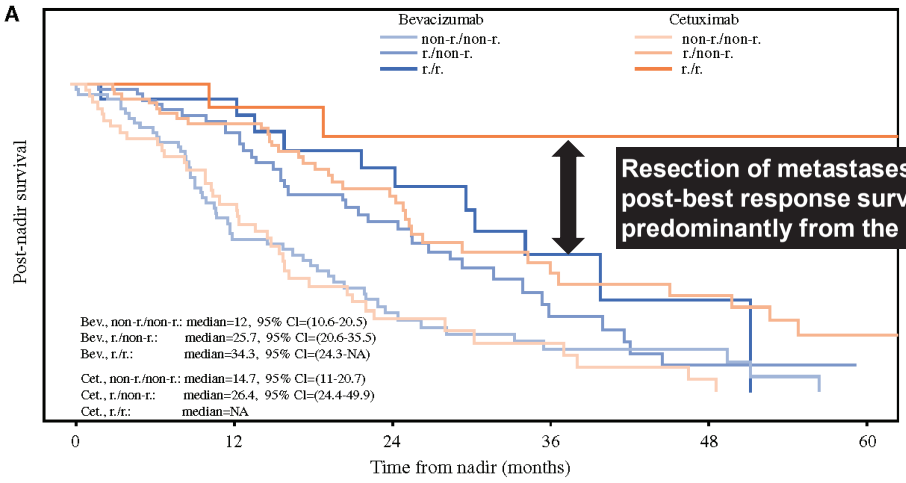
Ann Surg Oncol (2020) 27:2389–2401

Factors That Influence Conversion to Resectability and Survival After Resection: Analysis of FIRE-3-AIOKRK 0306



Ann Surg Oncol (2020) 27:2389–2401

Factors That Influence Conversion to Resectability and Survival After Resection of Metastases in RAS WT mCRC

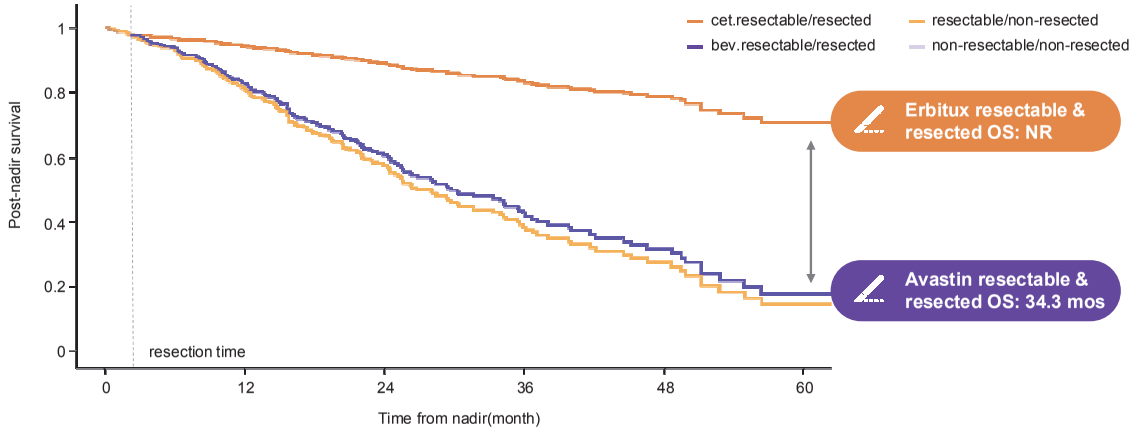


Resection of metastases was associated with improved post-best response survival, this effect originated predominantly from the cetuximab-based study arm

Erbi Resectable / resected: NA
Beva Resectable / resected: 34.3 mo
Erbi Resectable/nonresected: 26.4 mo
Beva Resectable/nonresected: 25.7 mo
Erbi Nonresectable/nonresected: 14.7 mo
Beva Nonresectable/nonresected: 12 mo

Ann Surg Oncol (2020) 27:2389–2401

Post-best Response Survival



In FIRE-3, resection of metastases was associated with improved post-best response survival. This effect originated predominantly from the cetuximab-based study arm, suggesting that EGFR-targeted therapy provides a favorable background for the resection of metastases in mCRC

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When to perform secondary surgery?

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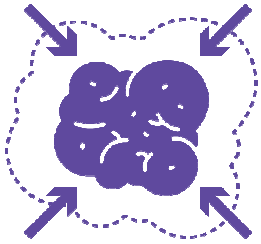
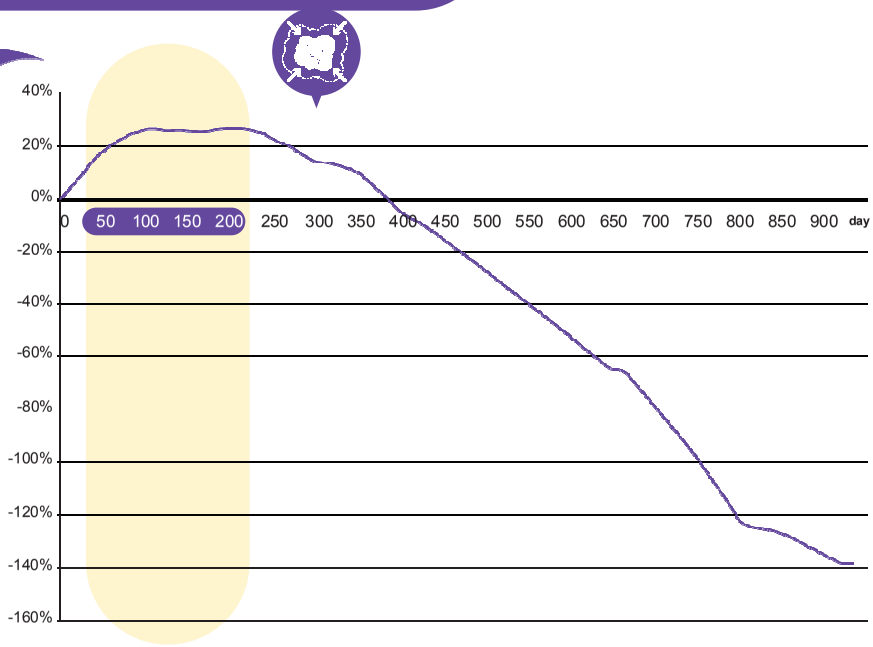
Evaluation of chemotherapeutic effect according to tumor shrinkage rate





The rate of tumor shrinkage of whole cases was highest during the **first 50 days from starting, and decreased gradually over 210 days** after a plateau of 105 days.

Int J Med Sci. 2013 Aug 1;10(9):1231-41

Learning from CELIM Study to Determine the Timing of Hepatectomy

CELIM

Key eligibility criteria
- Nonresectable CRC liver metastases
- Karnofsky performance status ≥80(ie, ECOG performance status 0-1)
- No previous EGFR-targeting therapy
- No previous CHT(except adjuvant CHT ≥6 months)

R 1:1

Neoajuvant CHT + targeted therapy (eight cycles in 4 months)

FOLFOX + cetuximab n=56

FOLFOX + cetuximab n=55

Additional CHT + targeted therapy (Four cycles in 2 mouths)

Technically nonresectable

may be continued up to 2 years

Evaluation of respectability (every 2 months)

Technically resectable

36 patients R0 resected

Resection

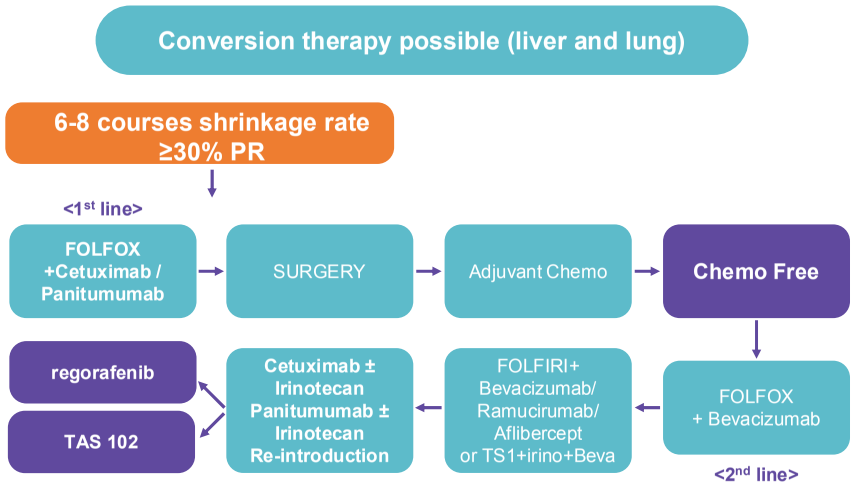
Postoperative CHT + targeted therapy (six cycles in 3 months)

FU

The results indicated that the effect of anti-EGFR plus FOLFOX on tumor size is achieved at around 3 months (6-8 cycles)

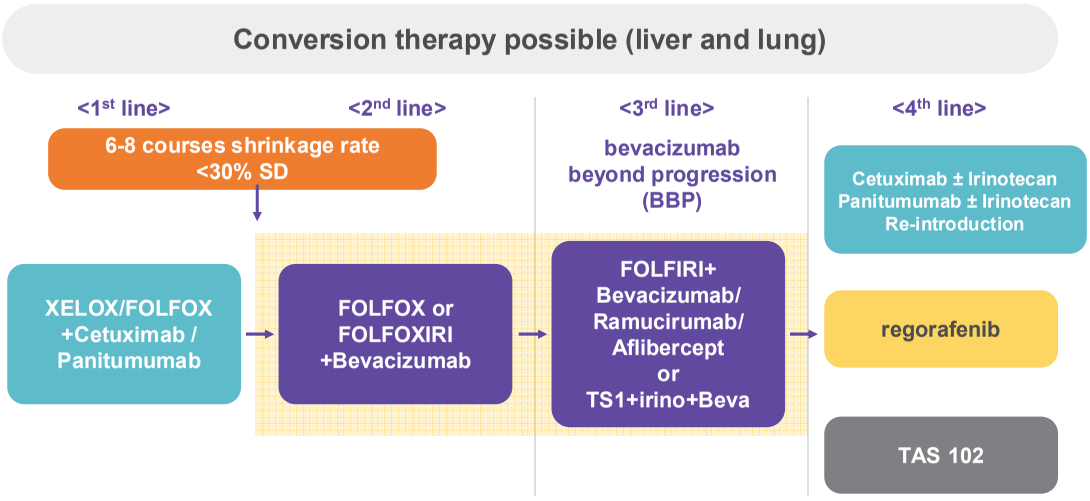
Annals of Oncology 25: 1018 – 1025, 2014

Personalized Medicine for RAS wild-type disease
Determining conversion therapy after 6-8 courses of anti-EGFR



- Patients with RAS wild-type disease should undergo 6-8 courses of therapy with anti-EGFR plus FOLFOX.
- If tumor shrinkage shows a PR, these patients should continue on this same therapy.
- It is possible to perform conversion therapy (surgery) in patients with unresectable or borderline resectable liver and lung mCRC

Personalized Medicine for RAS wild-type disease
Determining conversion therapy after 6-8 courses of anti-EGFR



- Patients with RAS wild-type disease should undergo 6-8 courses of therapy with anti-EGFR plus FOLFOX.
- If tumor shrinkage shows a SD, patients may be switched to therapy with anti-VEGF plus FOLFOX to provide a maintenance dose of the therapeutic agent

Learning from Taiwan Consensus

Taiwan Society of Colon and Rectal Surgeons (TSCRS) Consensus for Cytoreduction Selection in Metastatic Colorectal Cancer

Chun-Chi Lin, MD[1,2], Te-Hung Chen, MD[3], Yu-Chung Wu, MD[4], Chuan-Yin Fang, MD[5], Jaw-Yuan Wang, MD, PhD[6], Chou-Pin Chen, MD[7], Kai-Wen Huang, MD, PhD[8], and Jeng-Kai Jiang, MD, PhD[1,2]

[1]Division of Colon and Rectal Surgery, Department of Surgery, Taipei Veterans General Hospital, Taipei, Taiwan; [2]School of Medicine, National Yang-Ming University, Taipei, Taiwan; [3]Department of Surgery, China Medical University Hospital, Taichung, Taiwan R.O.C.; [4]Division of Thoracic Surgery, Department of Surgery, Taipei Veterans General Hospital, Taipei, Taiwan; [5]Division of Colorectal Surgery, Department of Surgery, Chia-Yi Christian Hospital, Chia-Yi City, Taiwan; [6]Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan; [7]Division of Colorectal Surgery, Taichung Veterans General Hospital, Taichung, Taiwan; [8]Department of Surgery and Hepatitis Research Centre, Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan

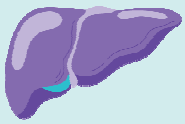
Ann Surg Oncol (2021) 28:1762 – 1776

Taiwan Society of Colon and Rectal Surgeons (TSCRS) Consensus for Cytoreduction

- Sequence: systemic treatment → cytoreductive surgery → systemic treatment
- Evaluation of potential cytoreduction patients:
  1. CT plays the most important role
  2. Positron emission tomograpy(PET)is also used to determine potential for cytoreduction
  3. Base on the response evaluation criteria in solid tumors(RECIST), patients achieving partial response(PR)or complete response(CR)
  4. Tumor shrinking and ability to conduct surgery
  5. Tumor markers: CEA drop
  6. Other factors, such as trends in performance status and symptoms, and patient's condition, such as weight and appetite
- Based on Taiwan reimbursed guideline, it is recommended to evaluate tumor response after 3 months(six cycles of targeted therapy)
- Treatment of choice after R0 resection: Adjuvant treatment is needed, but it depends upon patient's reimbursed application status, effectiveness of neoadjuvant therapy, and patient's acceptance
- Treatment for a recurrence after R0 resection: It is based on time to recurrence and location of recurrence

Ann Surg Oncol (2021) 28:1762 – 1776

Taiwan Society of Colon and Rectal Surgeons (TSCRS) Consensus Recommended criteria for hepatic resection



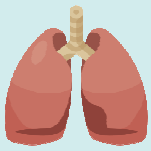
1. 30% future liver remnant (FLR) or remnant "liver:body weight" ratio should be > 0.5
2. R0 resections of liver metastases must be performed independently of margin width
3. In tumors with large size or tumors close to blood vessel/s, neoadjuvant chemotherapy is recommended initially for downsizing
4. Other criteria are absence of cirrhosis (Child B), hepatitis B virus (HBV), hepatitis C virus (HCV), fatty liver, or accumulated chemotoxicity. An indocyanine clearance study is recommended to evaluate liver function
5. Multidisciplinary team discussion is essential for the liver resection decision-making

Preoperative evaluation

Shift in criteria from
"what will be removed" to "what will remain."

Ann Surg Oncol (2021) 28:1762 – 1776

Taiwan Society of Colon and Rectal Surgeons (TSCRS) Consensus Recommended criteria for defining lung potential resectable patient



1. Number of metastases should be between two and three
2. Metastases should be located centrally
3. Metastases should have same tissue histopathology as colorectal primary (except if it is single metastasis; then resection can be done without determining histopathology type)
4. Enough safe margin and good future lung remnant should be possible
5. Speed of growth of tumor, measured as "doubling time after chemotherapy progression."
6. Patient should be surgically fit
7. Patient should present adequate pulmonary function and absence of lung comorbidities such as asthma or COPD
8. Multidisciplinary team discussion is essential for the lung resection decision-making

Speed of growth of tumor is critical

"doubling time after chemotherapy progression." If the progression is fast, tumor is not considered resectable.

Ann Surg Oncol (2021) 28:1762 – 1776

Take home message

- OS is better with secondary surgery, Resectable / resected > Resectable / Not-resected
- For sake of tumor shrinkage, anti-EGFR + chemotherapy can be used in right side RAS/BRAFwt mCRC
- Similary PFS/OS but improved ORR
- Consider not using it in R't side bulky (mean > 3.5cm) disease
- Reevaluate every 2-3 month (maximal tumor shrinkage in 200days) for resectability

Cancer Med. 2019 May 15. Taiwan CRC Registry (2022 ESMO abstract) Hsu et al Cancer medicine 2019 2. Annals of Oncology (2022) 33 (suppl_7): S136-S196. 10.1016/annonc/annonc1048 INTERNATIONAL JOURNAL OF ONCOLOGY 52: 1391-1400, 2018