Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Comprehensive Oncology Review: Colorectal Cancer - Metastatic

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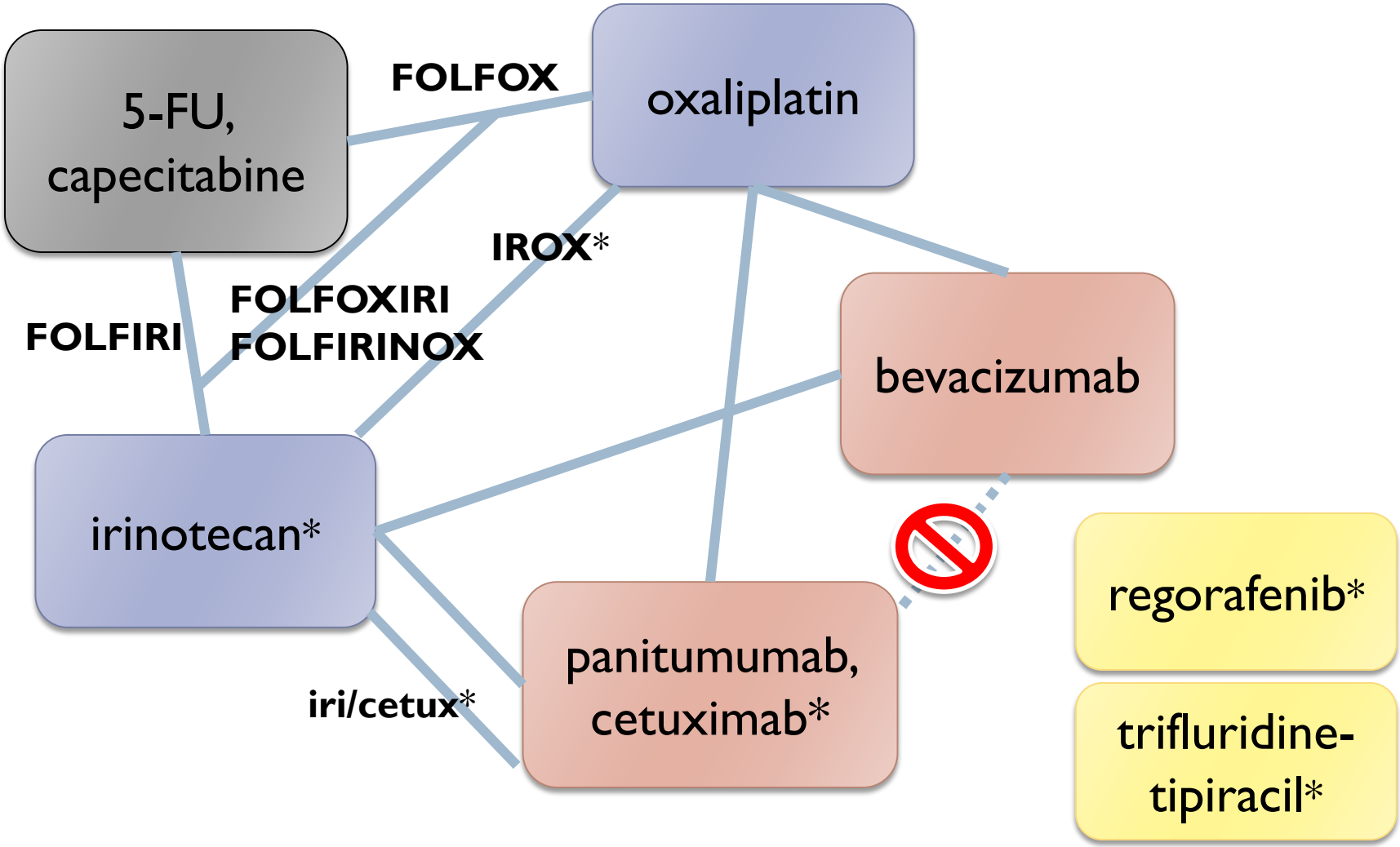
Outline

- Standard cytotoxic chemotherapy
- Tailored chemotherapy strategies
- Targeting molecular alterations

Standard cytotoxic chemotherapy

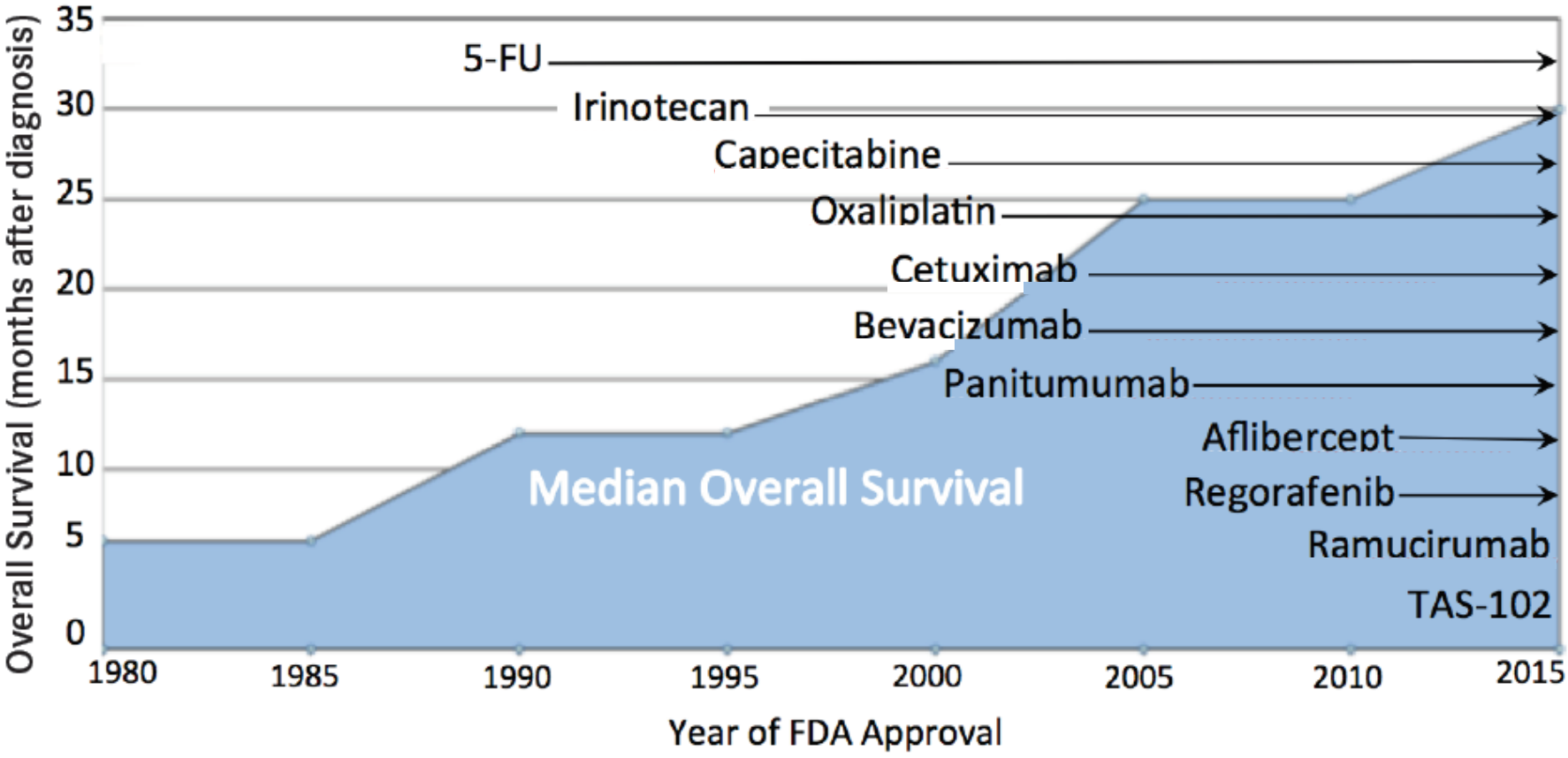
Multiple chemotherapy options



*Has activity without 5-FU

Growing repertoire of drug choices

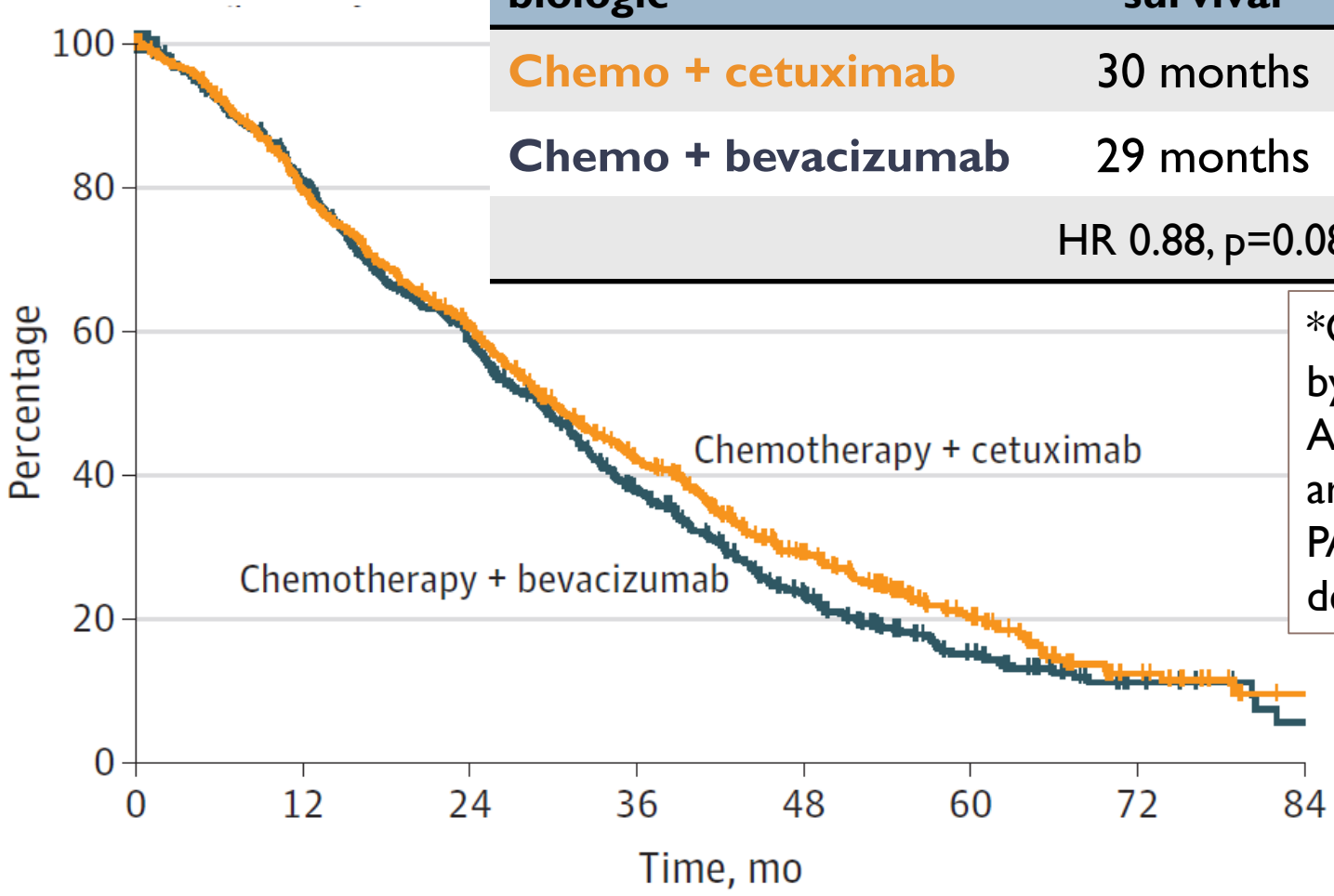
- Increase in drug options has improved mOS to ~30 mo



- Mody, *Am J Hematol Oncol* 2017

Optimal first-line therapy in KRASwt: CALGB/SWOG 80405

FOLFOX/FOLFIRI + biologic*	Overall survival	Progression-free survival
Chemo + cetuximab	30 months	10.5 months
Chemo + bevacizumab	29 months	10.6 months
	HR 0.88, p=0.08	HR 0.95, p=0.45



*Chemo backbone by physician choice. Additional bev/cetux arm dropped after PACCE, CAIRO-2 demonstrated harm

- Venook, *JAMA* 2017

Differences by side?

- Updated analysis classifying patients by left (distal/rectal) vs. right (proximal) primary colon site

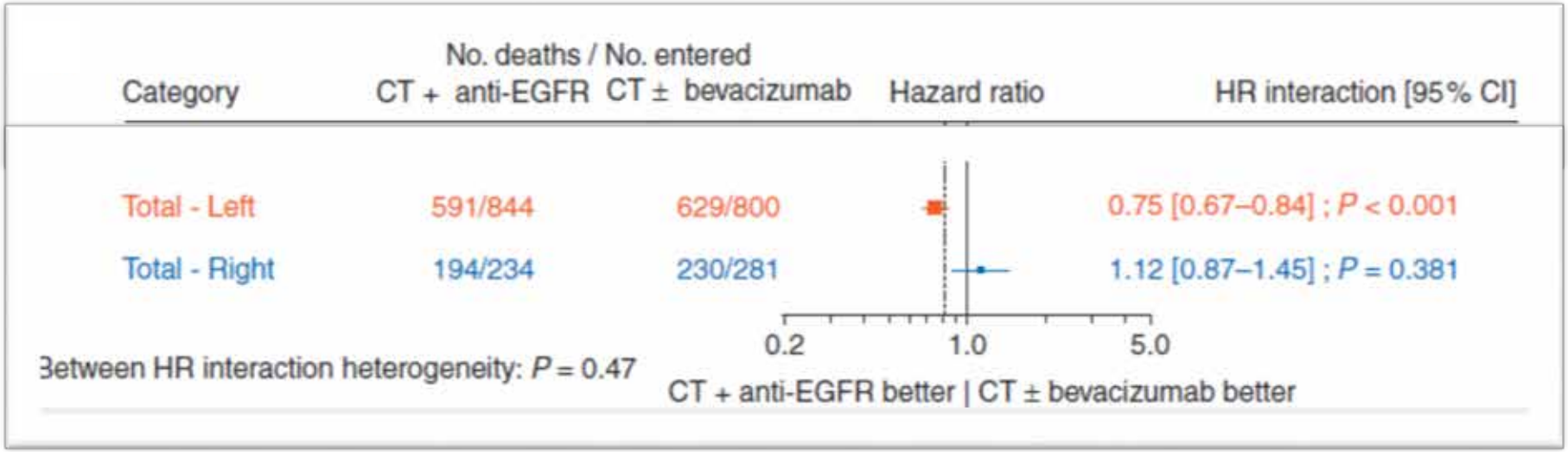
OS (months)	Overall
Left	33
Right	19
	p<0.0001

- Likely driven by different molecular profiles
  - But no difference when accounting for age, race, gender, synch/metachronous, MSI, *BRAF*, *RAS*, CMS

Venook, *ASCO* 2016, *ASCO* 2017

Differences by side?

- Pooled analysis of 80405 and 5 other RCT, classified by left (distal/rectal) vs. right (proximal) primary site

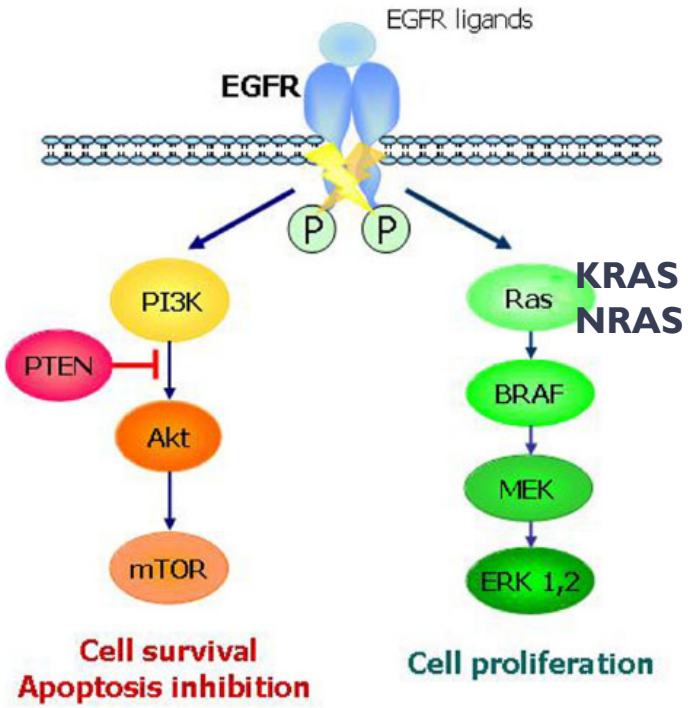


Thus, when *RAS* status is known…

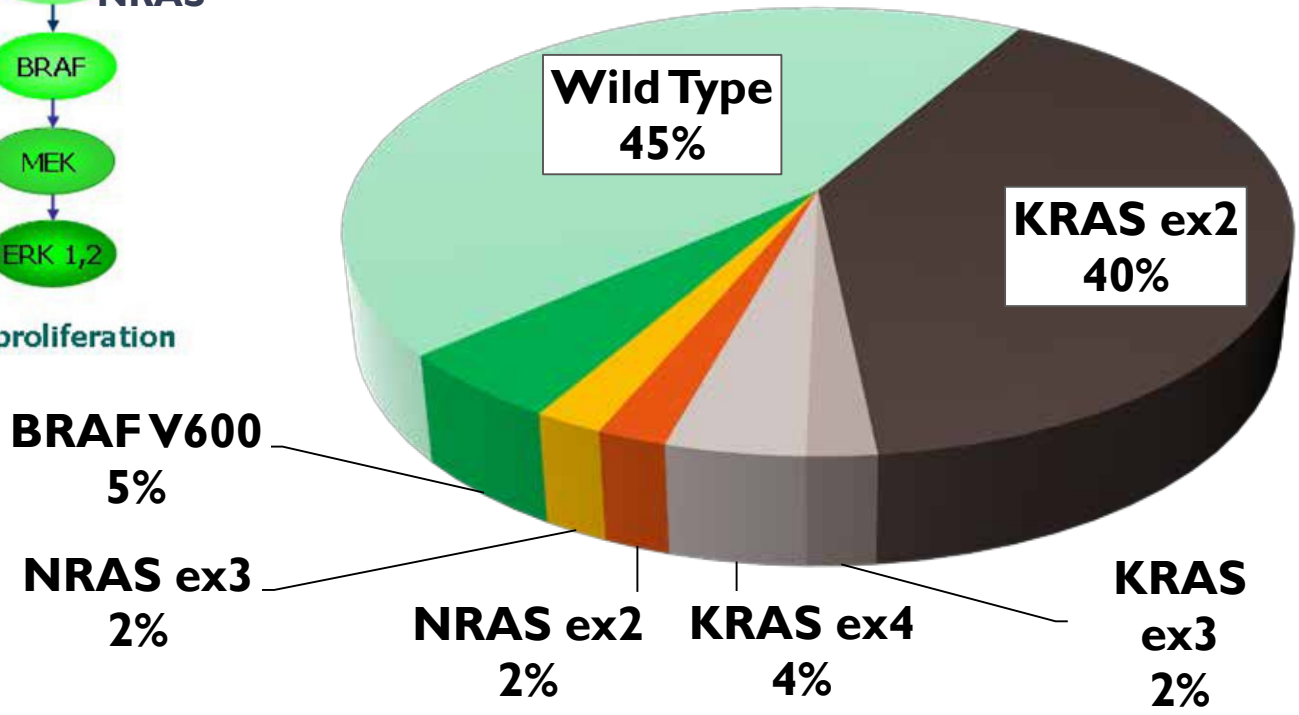
- Left-sided: consider starting with EGFR-targeted therapy
- Right-sided: may use EGFR therapy, but reserve for later line

Arnold, *Ann Oncol* 2017

Anti-EGFR: no benefit in RAS mutants



- Mut KRAS does not respond to silencing by EGFR inhibition (cetuximab, panitumumab)

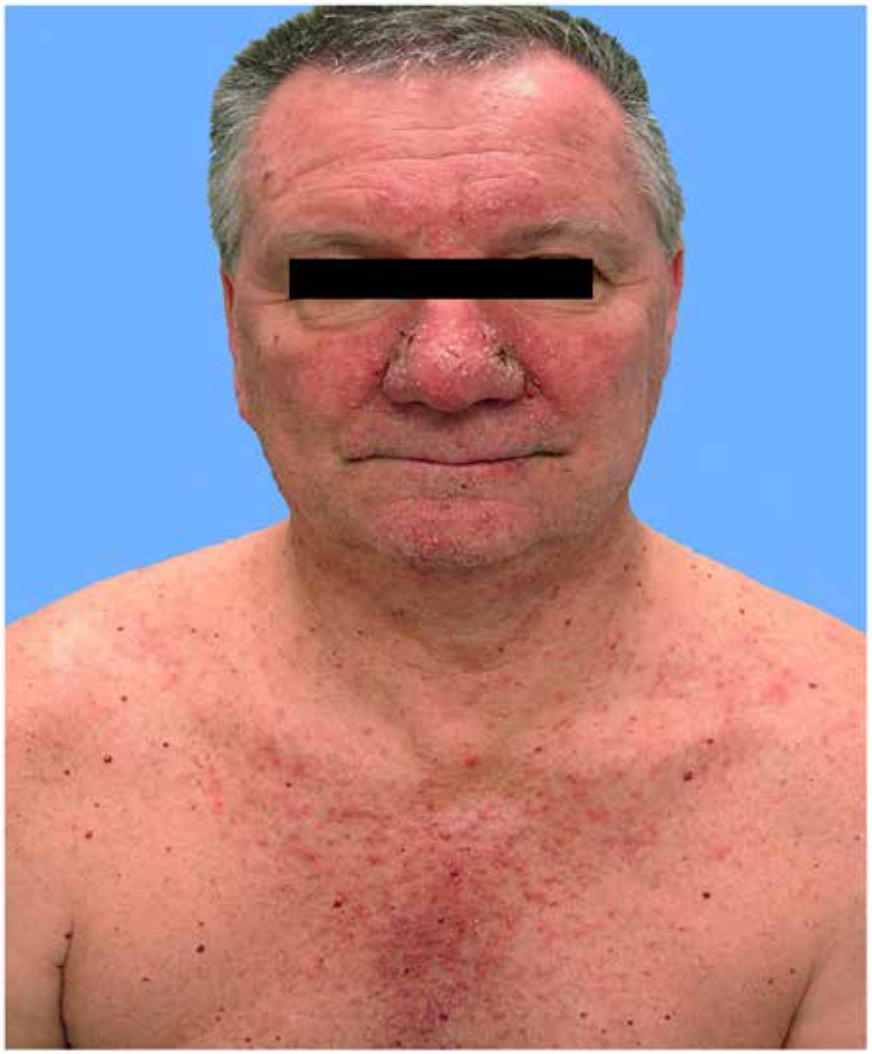


15-17% wild-type for KRAS exon 2 have a different *RAS/RAF* mut

- Saletti, *GI Cancer: Targets and Therapy* 2015; Douillard, *NEJM* 2013; Heinemann, *Lancet Onc* 2014

EGFR inhibitor-induced rash

Cetux	Pani
Any rash: 85%	Any rash: 90%
Grade 3: 10%	Grade 3: 16%

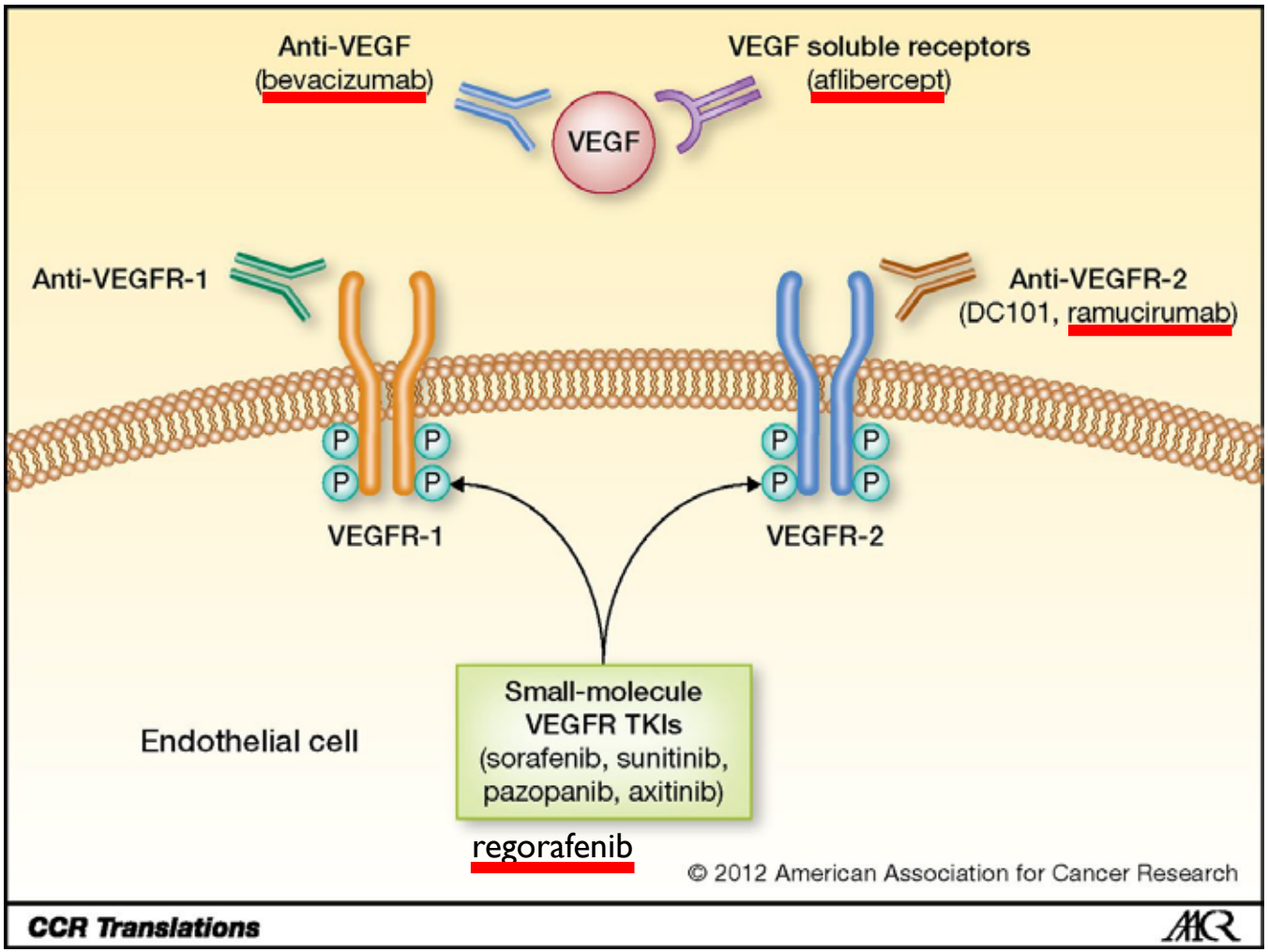


Prevention:

- Sunscreen
- Topical hydrocortisone 1%
- Oral doxycycline or minocycline

- Lacouture, *Br J Derm* 2006; Shepherd, *NEJM* 2005; Rosell, *Ann Onc* 2008; Van Cutsem, *JCO 2007*; Geyer, *NEJM* 2006

Anti-VEGF therapy: no biomarkers



- Bevacizumab
  1st or later line
- Aflibercept
  2nd line
- Ramucirumab
  2nd line
- Regorafenib
  3rd line

- Trials: NO16966, TREE-2; VELOUR; RAISE; CORRECT

Should we be using a triplet?

- FOLFOXIRI / FOLFIRINOX
  - Improved response rate, progression-free survival
  - BUT…
    - Increased toxicity
    - Benefit on OS lacking (until TRIBE2)
    - And how do you approach second-line therapy?

- There is increasing support. Especially consider for patients with (*my opinion*):
  - Excellent performance status
  - Patient wants aggressive care
  - And/or need for significant down-staging (i.e. attempt to convert metastases to resectable disease)

Cremolini, *Lancet Oncol* 2015; Cremolini, *Lancet Oncol* 2020; Gruenberger, *Ann Oncol* 2015; Sastre, *ASCO* 2019

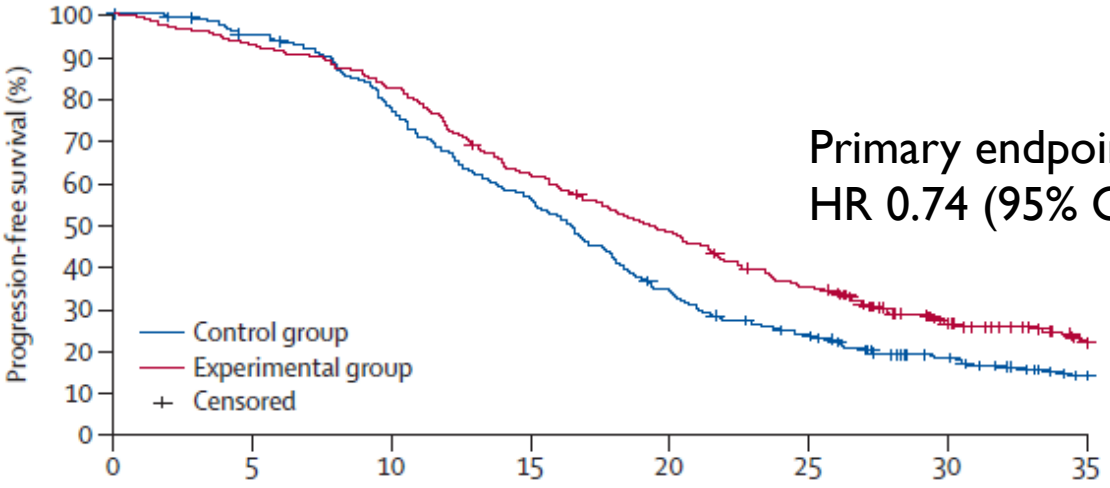
Growing support for triplet therapy

- TRIBE-2 study
  - Phase 3 of 679 patients

12.0 mo 19.2 mo

FOLFOXIRI + bev x8	5-FU + bev maint	FOLFOXIRI + bev
FOLFOX + bev x8	5-FU + bev maint	FOLFIRI + bev

9.8 mo 16.4 mo



Primary endpoint: PFS2
HR 0.74 (95% CI: 0.63-0.88), p=0.0005

Cremolini, *Lancet Oncol* 2020

Second-line therapy

- All of the same options
  - FOLFOX with bevacizumab or cetuximab*
  - FOLFIRI with bevacizumab or cetuximab*

* RAS wildtype

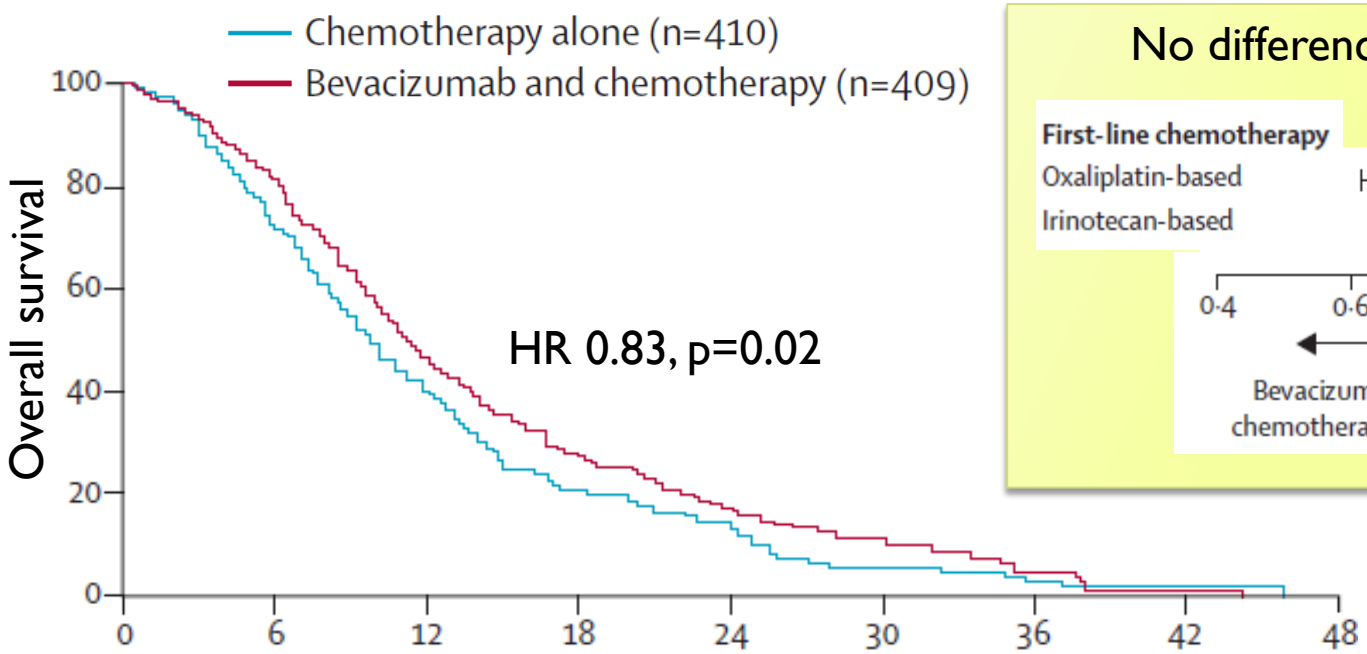
- Sequencing trials show no "correct" order

- Evidence supports continuation of biologic at progression
  - Ex. FOLFOX + bev → FOLFIRI + bev
    FOLFIRI + cetux* → FOLFOX + cetux*

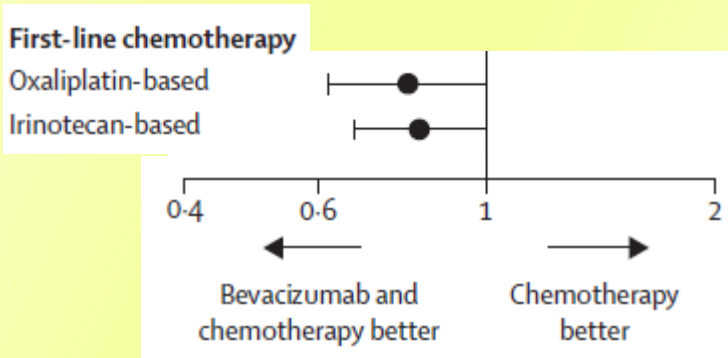
Tournigand, *JCO* 2004; Seymour, *Lancet* 2007; Grothey, *JCO* 2008; Ciardiello, *Ann Onc* 2015

Bevacizumab at progression

- ML 18147: randomized to **continuation of bevacizumab** at progression vs. **chemotherapy alone**
  - All switched FOLFOX ⇔ FOLFIRI
  - Capecitabine allowed



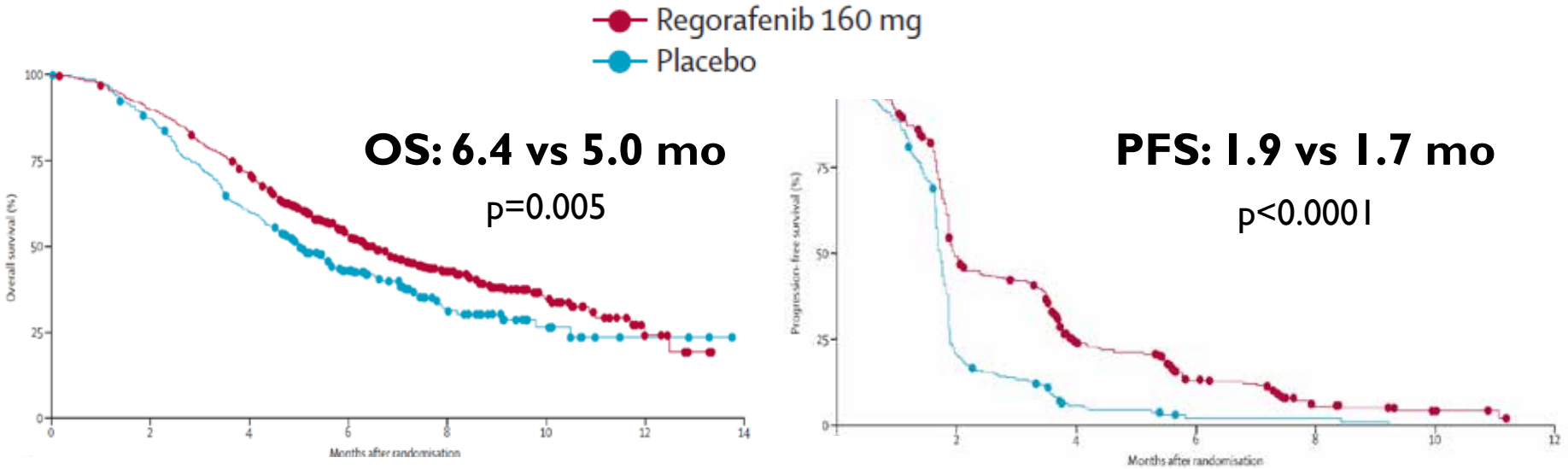
No difference in subgroups:



Bennouna, *Lancet Onc* 2013

Regorafenib

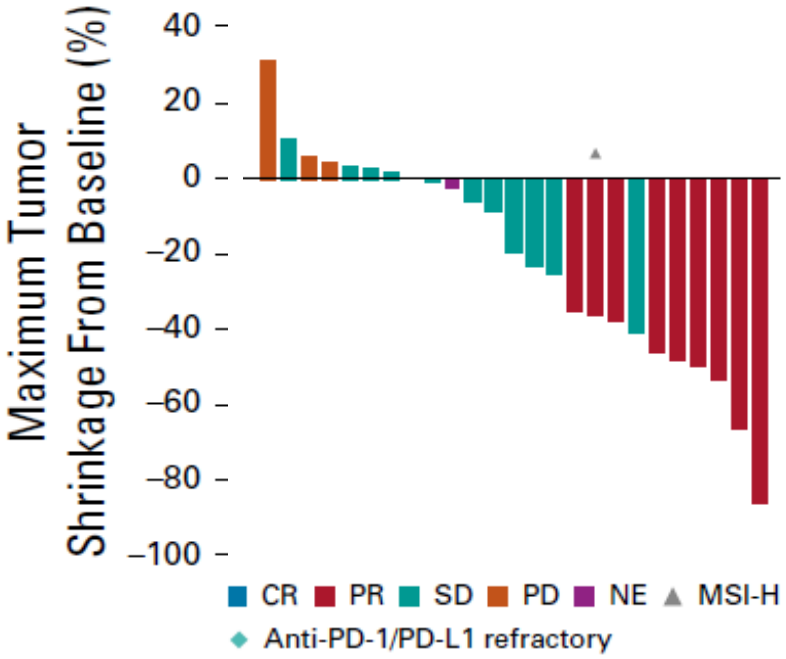
- Oral multi-kinase inhibitor (approved dose: 160mg)
  - REDOS: rPh2 80mg escalated to 160mg vs. upfront 160mg
    - Superior OS, PFS with starting at a lower dose, less toxicity
- CORRECT: RCT 2:1 to **regorafenib** vs. **placebo**
  - 53% grade 3/4 toxicity: hand-foot syndrome, fatigue, HTN, rash, GI

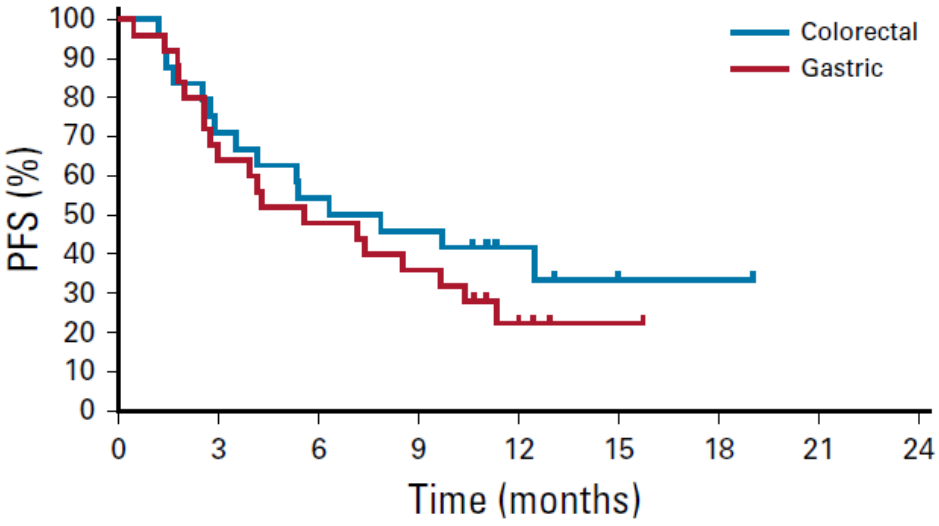


CORRECT: Grothey, *Lancet* 2013; Bekaii-Saab, *Lancet Oncol* 2019

Regorafenib with immunotherapy

- Phase I studies suggest benefit when combining regorafenib 80mg with nivolumab





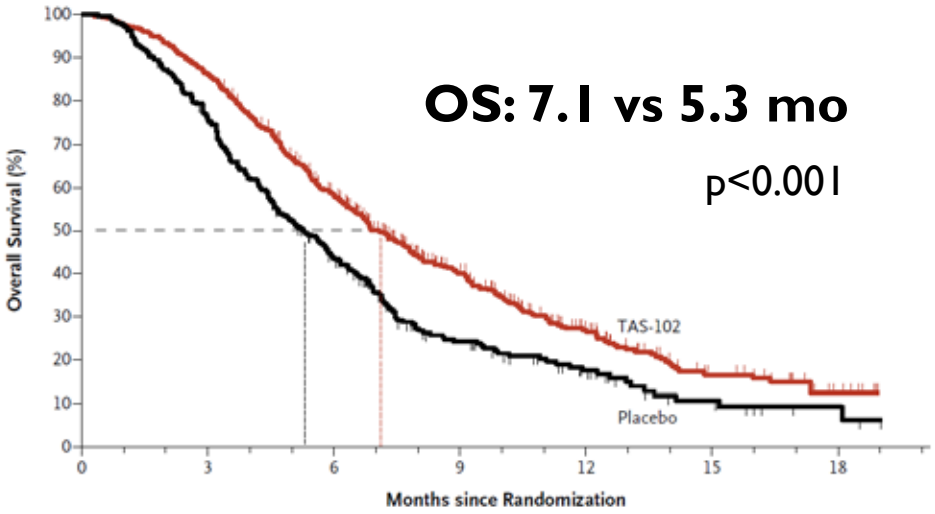
PFS 7.9 mo
1-year PFS: 42%

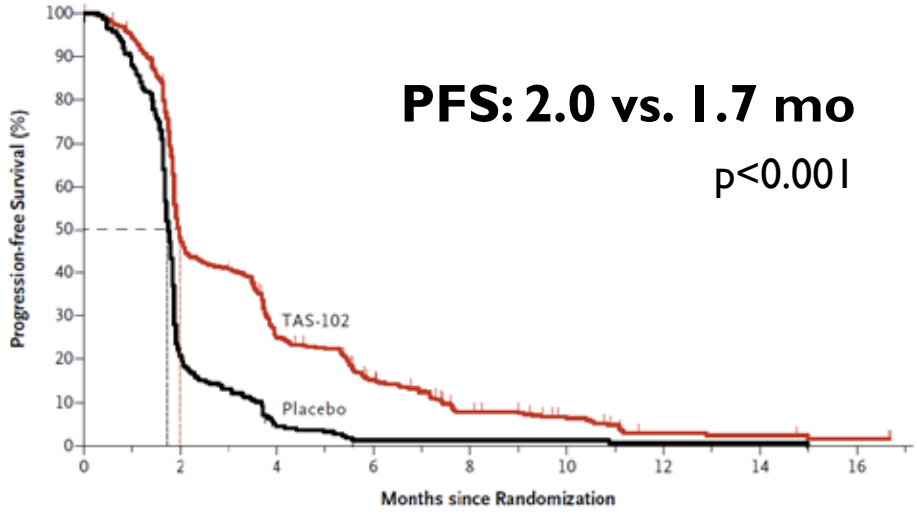
Fukoka, *J Clin Oncol* 2020; Kim, *ESMO GI* 2020

Trifluridine-tipiracil (TAS-102)

- Oral thymidine analog

- RECOURSE: RCT 2:1 to **TAS-102** vs. **placebo**
  - >90% 5-FU-refractory
  - Benefit irrespective of prior regorafenib
  - 38% neutropenia; low rates of hand-foot syndrome

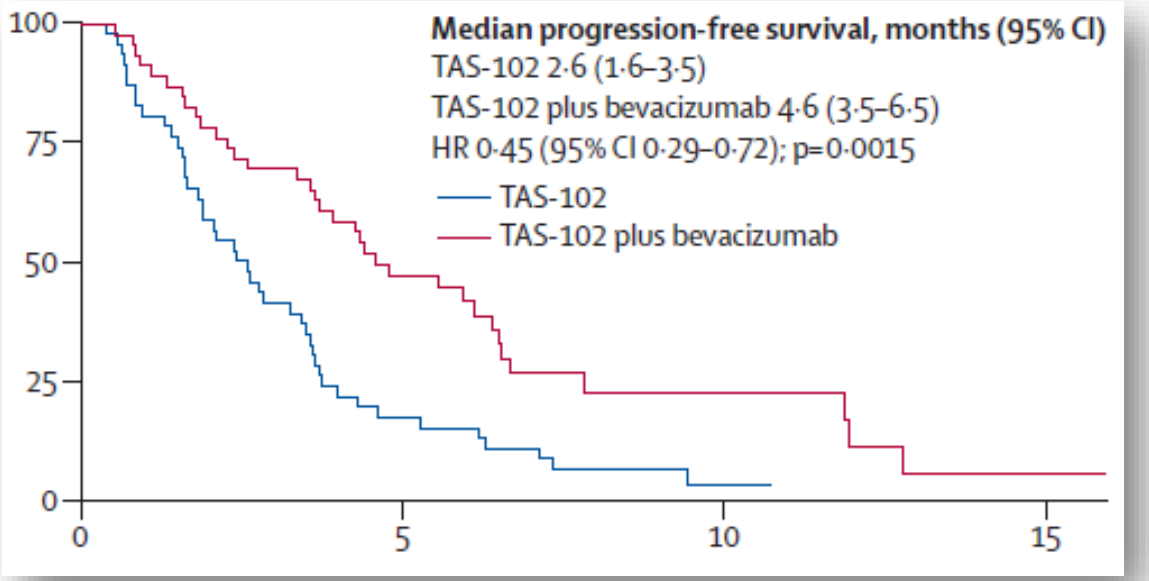




- Mayer, *NEJM* 2015

Trifluridine-tipiracil combinations

- C-TASKFORCE
  - Improved benefit in combination with bevacizumab



- Anticipate that it will be evaluated earlier in treatment and/or combination with other agents
  - Ex. trifluridine/tipiracil + irinotecan ± bevacizumab

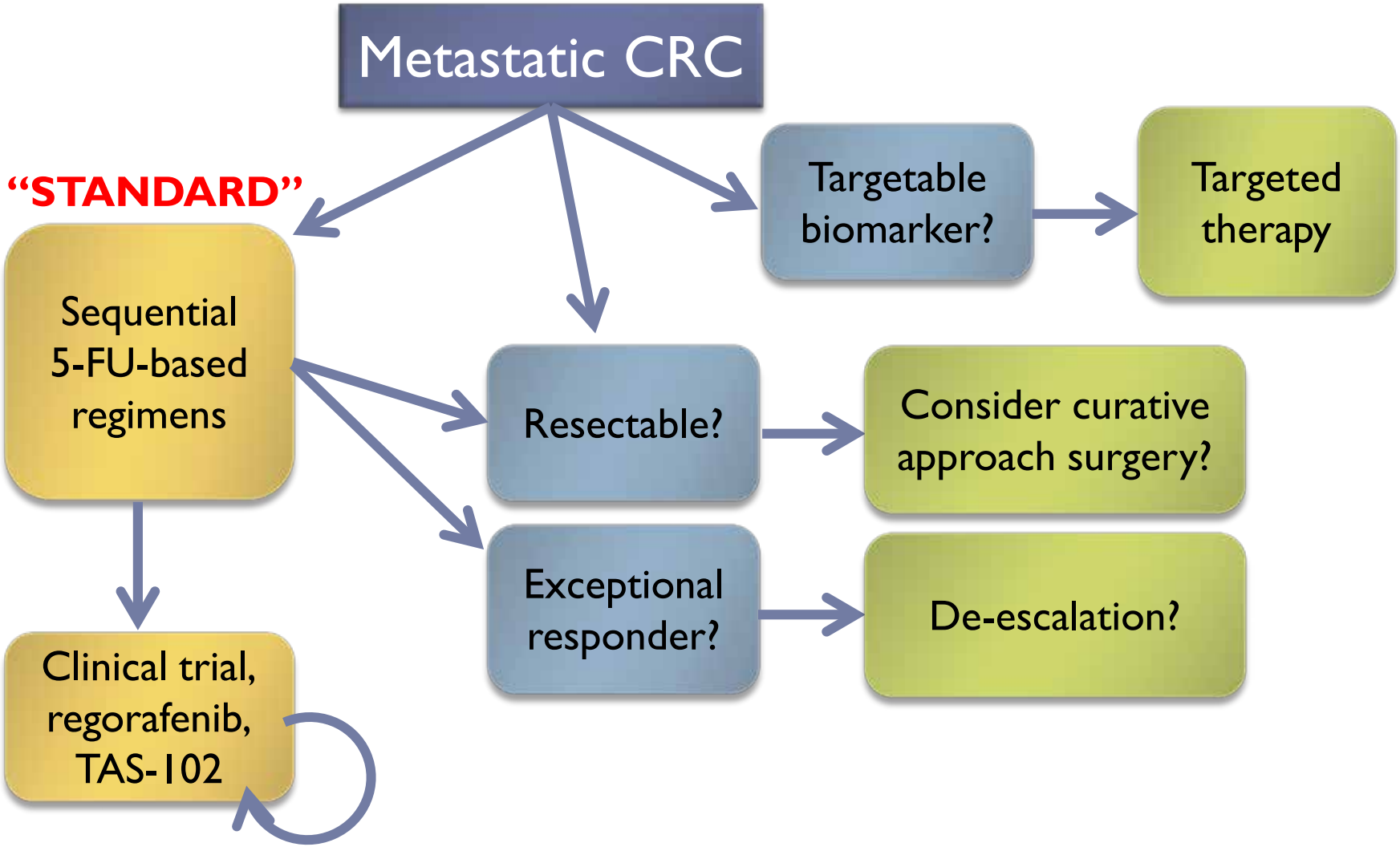
Pfeiffer, *Lancet Oncol* 2020

Key points

- No "correct" first-line chemotherapy regimen
  - Any chemo doublet (or triplet) + biologic is acceptable
  - Cetuximab may be less effective for right-sided tumors
- Extended RAS + BRAF testing should be part of every stage IV CRC work-up
- Regorafenib and TAS-102 are approved, but of limited clinical benefit (OS ~2 months) as monotherapy

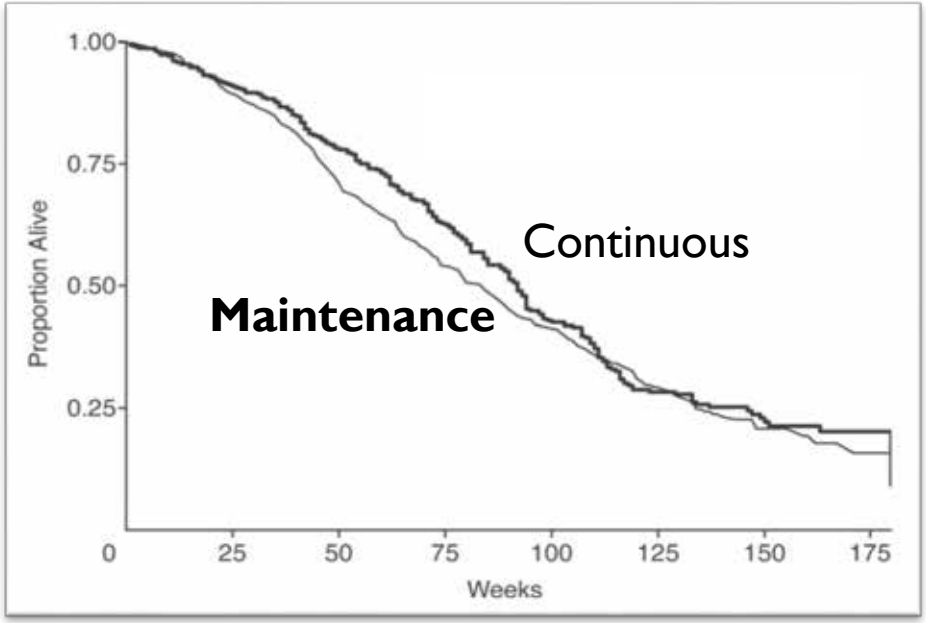
Tailored chemotherapy strategies

Approaches to longitudinal treatment



Maintenance / de-escalation

- OPTIMOX-1
  - RCT to de-escalating to **5-FU** vs. continuous FOLFOX
  - PFS, OS similar
  - Less toxicity with 5-FU



- Multiple "correct" maintenance strategies

5-FU + bevacizumab*	CAIRO3, AIO KRK 0207
Bevacizumab	AIO KRK 0207, PRODIGE-9
5-FU + panitumumab*	VALENTINO
Cetuximab	MACBETH, (PANAMA), (ERMES)

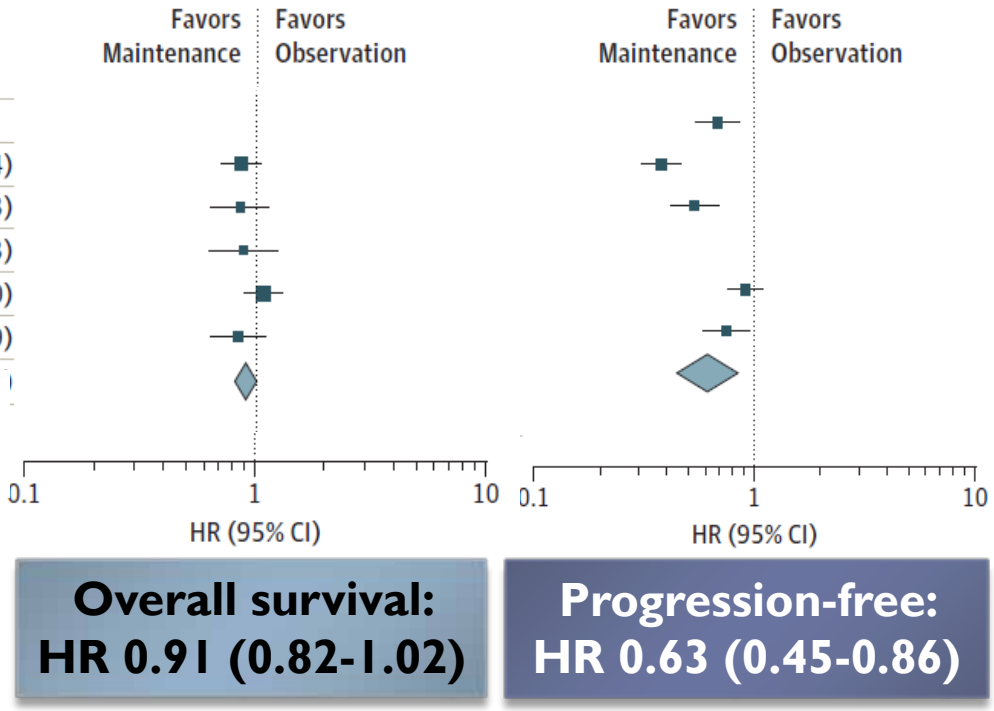
*Numerically, maintenance with 5-FU + biologic has best outcomes

Tournigand, *JCO* 2006; Simkens, *Lancet* 2015; Hegewisch-Becker, *Lancet Onc* 2015; Aparicio, *J Clin Oncol* 2018; Cremolini, *JAMA Oncol* 2018; Pietrantonio, *JAMA Oncol* 2019

Treatment holiday

- Meta-analysis

Hegewisch-Becker et al,[19] 2015	0	0	Not estimable
Simkens et al,[16] 2015	-0.1508	0.0978	0.86 (0.71-1.04)
Luo et al,[21] 2016	-0.1625	0.1448	0.85 (0.64-1.13)
Chibaudel et al,[7] 2009	-0.1278	0.1705	0.88 (0.63-1.23)
Aparicio et al,[14] 2018	0.0677	0.0997	1.07 (0.88-1.30)
Koeberle et al,[20] 2015	-0.1863	0.1407	0.83 (0.63-1.09)



Overall survival: HR 0.91 (0.82-1.02)

Progression-free: HR 0.63 (0.45-0.86)

- Complete treatment breaks often associated with worse short-term outcomes
- No clear detriment in the overall survival

Sonbol, *JAMA Oncol* 2019

Metastasectomy

- Retrospectives of carefully selected patients suggest improved 5-year OS: 25-58% (vs. 10% with just chemotherapy)
- Only 10-15% of stage IV patients qualify
  - Limited metastatic sites that are amenable to localized treatment (resection, ablation, etc.)
  - Thorough multi-disciplinary review
- Do not over-treat patients beforehand
  - Irinotecan: steatohepatitis
  - Oxaliplatin: sinusoidal obstructive syndrome
  - If upfront resectable, typically give ~2 months of chemo before reassessment and surgery

Folprecht, *Ann Onc* 2014; Karoui, *Ann Surg* 2006; Vauthey, *JCO* 2006; Adams, *HPB* 2013; Kim, *JKSS* 2011; Verwaal, *Ann Surg Onc* 2008

"Adjuvant" therapy after metastasectomy

- Controversial with limited data, but often done
- EORTC 40983: RCT to 6 cycles FOLFOX pre/post surgery vs. surgery alone

	Peri-op chemo	Surgery alone	
PFS	20.9 mo	12.5 mo	p=0.04
OS (all pt)	63.7 mo	55.0 mo	p=0.30
OS (resected)	77.5 mo	73.3 mo	p=0.35

- Like stage III, no demonstrated benefit to irinotecan or biologics
  - FOLFOX alone recommended

    (5-FU/capecitabine alone in an older person or residual neuropathy)
  - Guidelines allow for continuation of a biologic if it was helpful in converting to resectable disease

Nordlinger, *Lancet Onc* 2013; Primrose, *Lancet Onc* 2014

Key points

- Maintenance therapy is acceptable in good responders, without compromising PFS or OS
  - 5-FU/capecitabine ± biologic is recommended
- Full chemotherapy holidays compromise PFS, but may be appropriate for certain patients
- Curative intent treatment of oligometastatic disease greatly improves long-term survival in the correct patient

Targeting molecular alterations

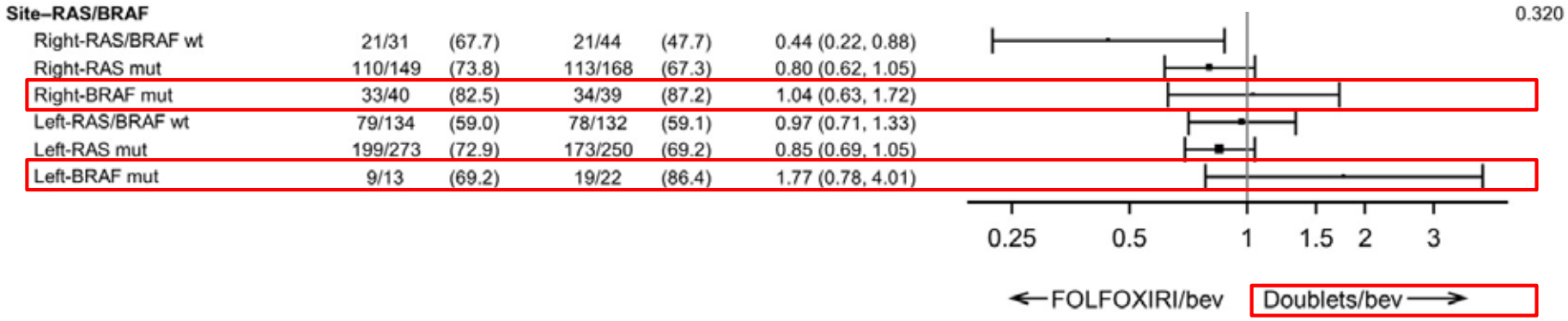
Tailoring to biomarkers

* BRAF	~~FOLFOXIRI~~ Encorafenib + cetuximab ~~Vemurafenib + irinotecan + cetuximab~~
* HER2	Trastuzumab + lapatinib Trastuzumab + pertuzumab Trastuzumb-deruxtecan
* MSI, hypermutation	PD-1 inhibitor, immune therapy
NTRK, ALK	Entrectanib, larotrectanib
ERCC1	~~Avoid oxaliplatin~~ → *Failed to show prospective difference*
CIMP (epigenetic hypermethylation)	Demethylating agents? Irinotecan-based regimen?

- Kopetz, *NEJM* 2019; Sartore-Bianchi, *Lancet Onc* 2015, MyPathway; Lenz, *ASCO 2016*; Overman, *Oncotarget* 2016, Shiovitz, *Gastro* 2014; Le, *NEJM* 2016; Drilon, *NEJM* 2018

BRAF+ colorectal cancer

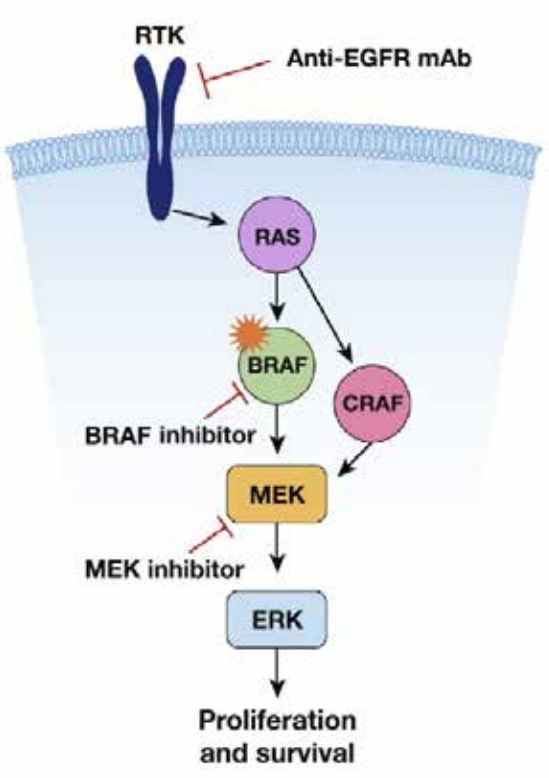
- Poor prognostic marker, resistant to anti-EGFR
- Benefit from more intensive first-line chemotherapy?
  - TRIBE trial suggested improved PFS from FOLFOXIRI/bev in the BRAF mutant subgroup
  - Meta-analysis of 5 trials (TRIBE, TRIBE2, CHARTA, OLIVIA, STEAM) was not supportive

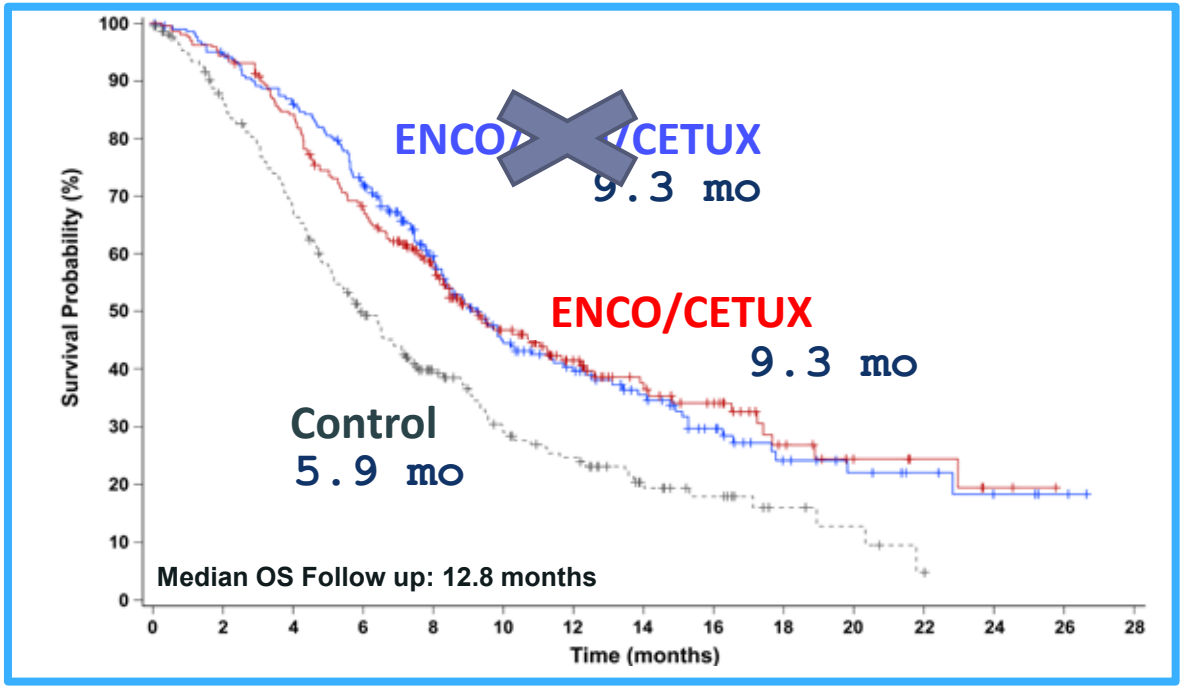


Cremolini, *ASCO* 2020

Targeted BRAF inhibition

- BRAF-inhibitor monotherapy ineffective
- Multi-pathway is necessary against BRAF and EGFR





New standard: encorafenib + cetuximab/panitumumab

MEK inhibition adds no meaningful benefit to BRAF/EGFR

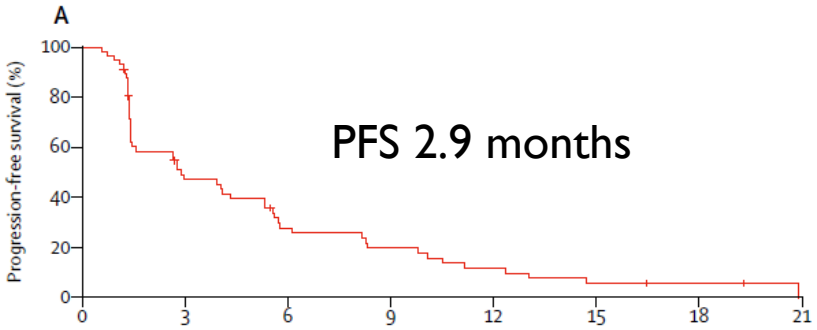
Future: BRAF/EGFR/PD1? BRAF/MEK/PDI?

Strickler, *Cancer Treat Rev* 2017; Kopetz, *NEJM* 2019; Kopetz, *ASCO* 2020

HER2 targeted therapy

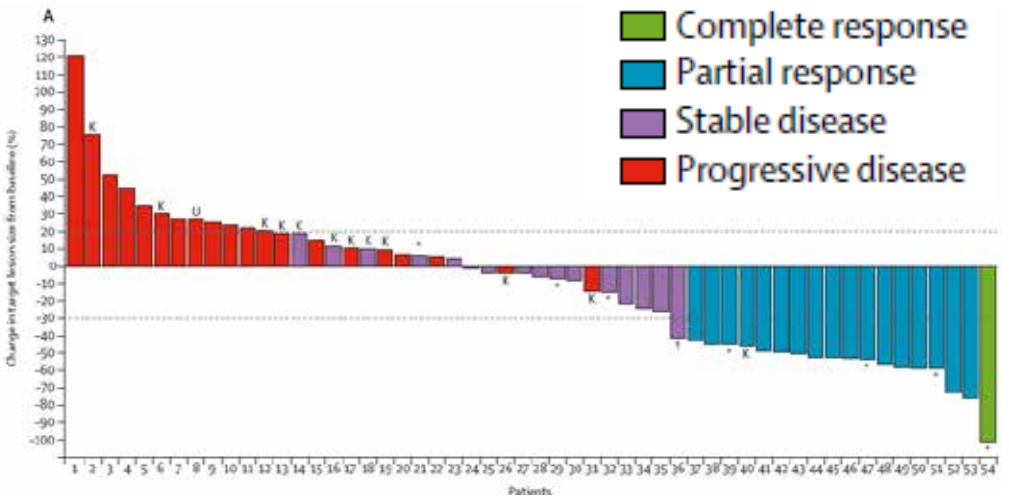
- 4-6% of mCRC; associated with MSI, wild-type RAS/RAF

- Trastuzumab + pertuzumab
  - ORR 14-32%



- Trastuzumab + lapatinib
  - ORR 30%

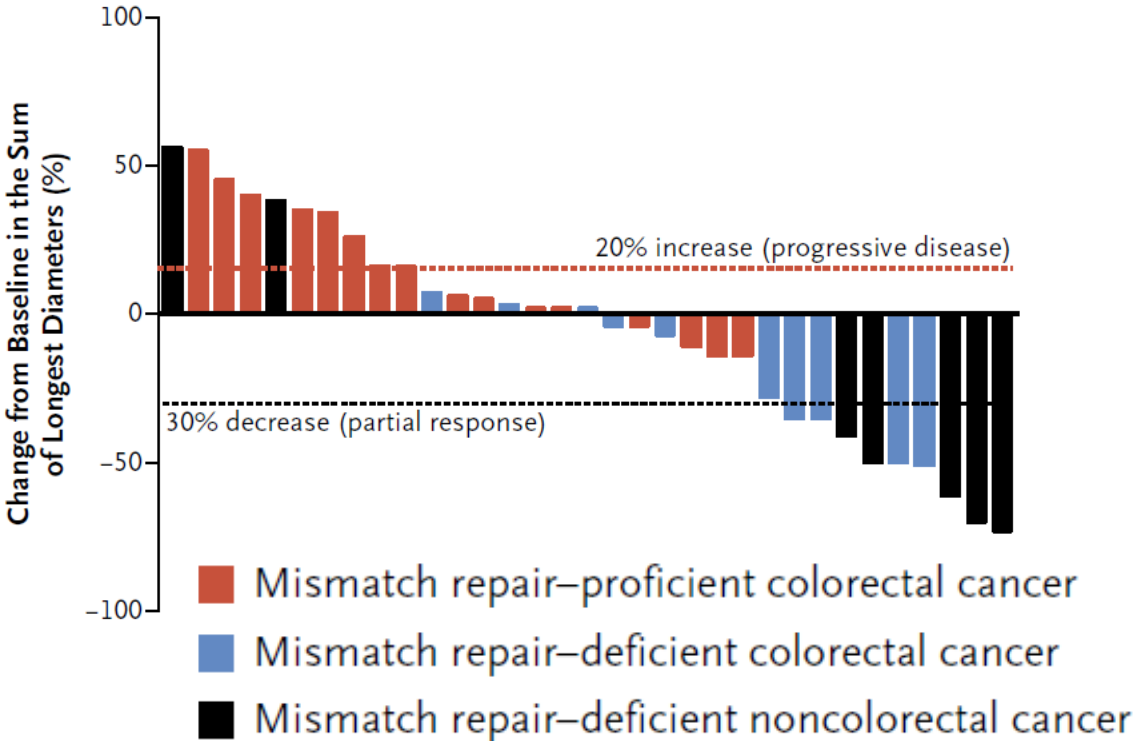
- Trastuzumab deruxtecan
  - ADC w/ topo-I derivative
  - ORR 45%



Meric-Bernstam, *Lancet Onc* 2019; Gupta, *ASCO GI* 2019; Sartore-Bianchi, *Lancet* 2016; Siena, *ASCO* 2020

Anti-PD1 therapy in MSI

- Phase 2 trial of pembrolizumab in mCRC or other cancers
- Response: MSI (MMR-deficient) >> MSS (MMR-proficient)

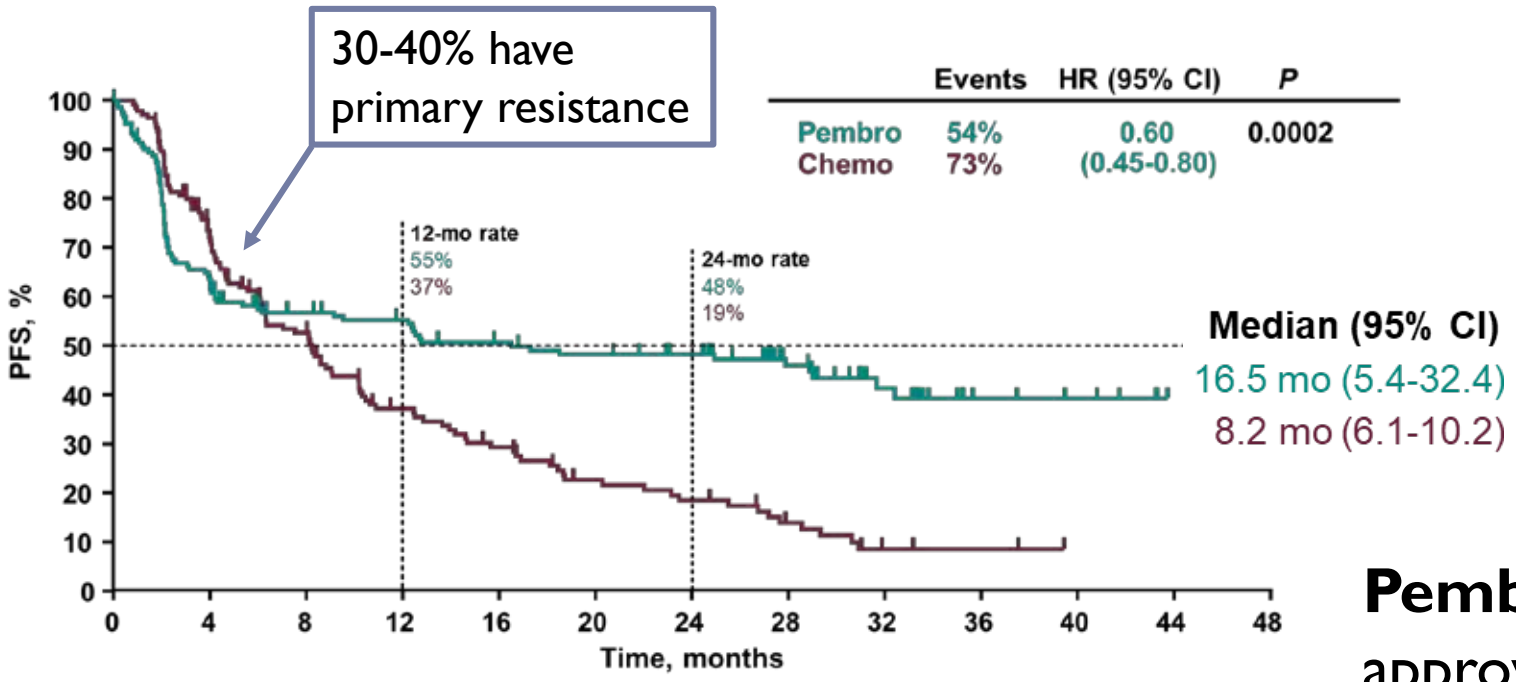


- Somatic MSI did better than germline (Lynch)
- **Pembrolizumab** approved 5/2017
- **Nivolumab** approved 8/2017
- **Nivo/ipilimumab** approved 8/2018

Le, *NEJM* 2015; Overman, *Lancet Onc* 2017

Use of anti-PD1 in first-line therapy

- Keynote-177
  - MSI CRC randomized to pembrolizumab vs. chemotherapy (any doublet ± biologic) allowed



Pembrolizumab approved 6/2020

Andre, *ASCO* 2020

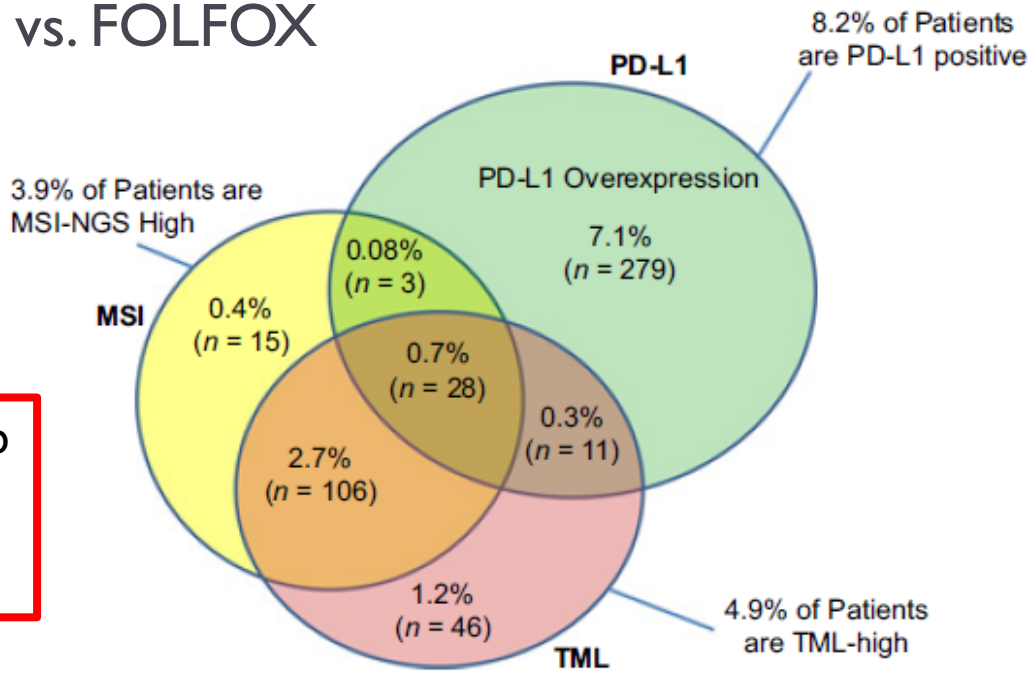
Ongoing investigation (examples)

- First-line therapy
  - SWOG 1610: atezolizumab vs. FOLFOX/bev/atezo vs. FOLFOX/bev
- Adjuvant therapy
  - ATOMIC: FOLFOX/atezo vs. FOLFOX

…but how to identify and/or induce MSS responders?

6/2020: FDA approves pembrolizumab for TMB ≥10 mut/Mb

… too low for CRC?



Salem, *Mol Cancer Res* 2018; Keynote-158: Marabelle, *J Clin Oncol* 2020

Key points

- Targeting BRAF requires multi-pathway blockade
  - At this point, encorafenib + cetuximab (panitumumab) is standard
- HER2 should be evaluated in RAS/RAFwt as targeted options are available
- MSI is a biomarker for response to immunotherapy
  - Now indicated in first or later line
  - Role in combination with chemotherapy is unproven