Case #1

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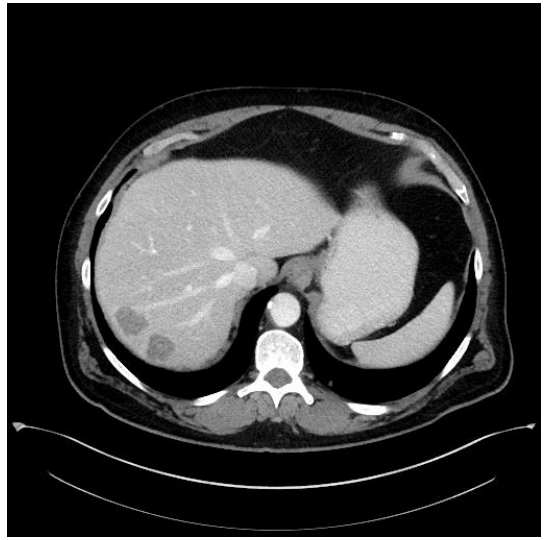
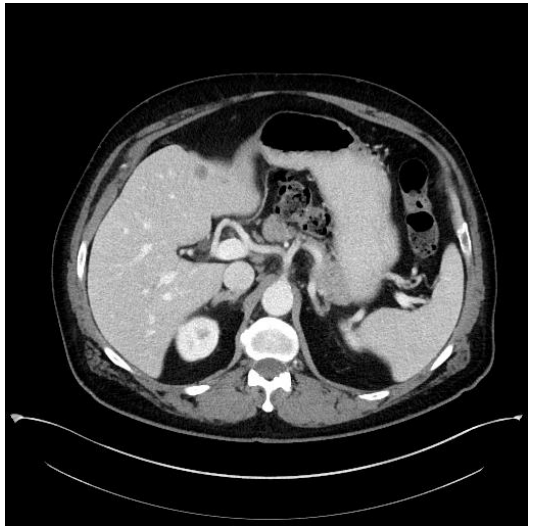
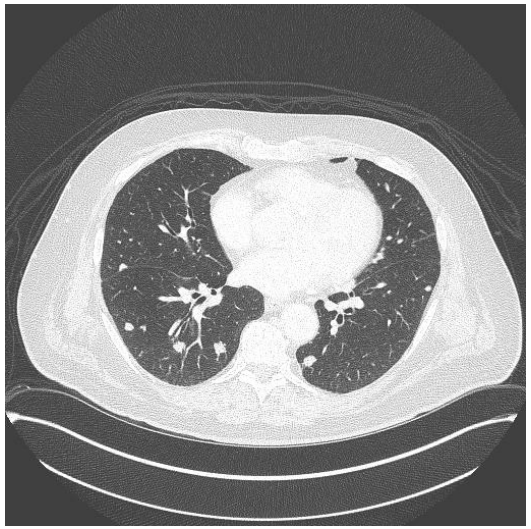
Case #1

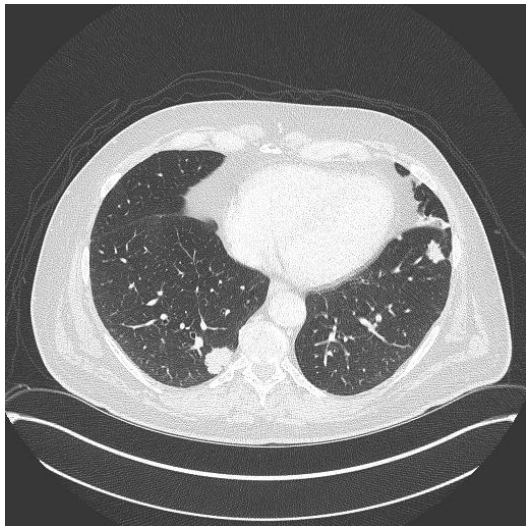
- 65 yo male h/o well-controlled HTN, hypothyroidism
- 1 month h/o altered bowel movements, 15 lb weight loss
- Colonoscopy with non-obstructing rectal mass and biopsy showing moderately differentiated adenocarcinoma
- Labs with CEA 348, normal lytes, AST = 45, ALT = 54, alk phos = 188, normal bilirubin
- Molecular Profiling: MSS, *KRAS G12V* MT, *TP53* MT, *APC* MT, TMB = 3

Case # 1 Radiology









CT Chest, Abdomen & Pelvis

Large rectal mass noted with extensive mesorectal fat stranding and prominent superior rectal lymphadenopathy

Extensive metastases seen in the liver and bilateral lungs

Case # 1

- Started on 1st line therapy with FOLFOX + bevacizumab but with severe infusion reaction to oxaliplatin after cycle 8. Scans with stable disease and drop in CEA (348 -> 52).
- Subsequently, switched to maintenance therapy with 5-FU + bevacizumab x 8 cycles until progression with new lung lesions and increase in liver lesions
- 2nd line therapy with FOLFIRI + bevacizumab with initial response followed by eventual progression after 12 cycles
- **What is the next best step?**
- (*Molecular profiling: RAS MT, RAF WT, MSS, Her-2neu-ve*)

What Is the Next Best Step?

(*Molecular profiling: RAS mut (G12V), RAF WT, MSS, Her-2neu-ve*)

- Re-treat with FOLFOX + bevacizumab
- Regorafenib
- TAS-102 plus bevacizumab
- Fruquintinib
- Clinical trial of cetuximab plus adagrasib

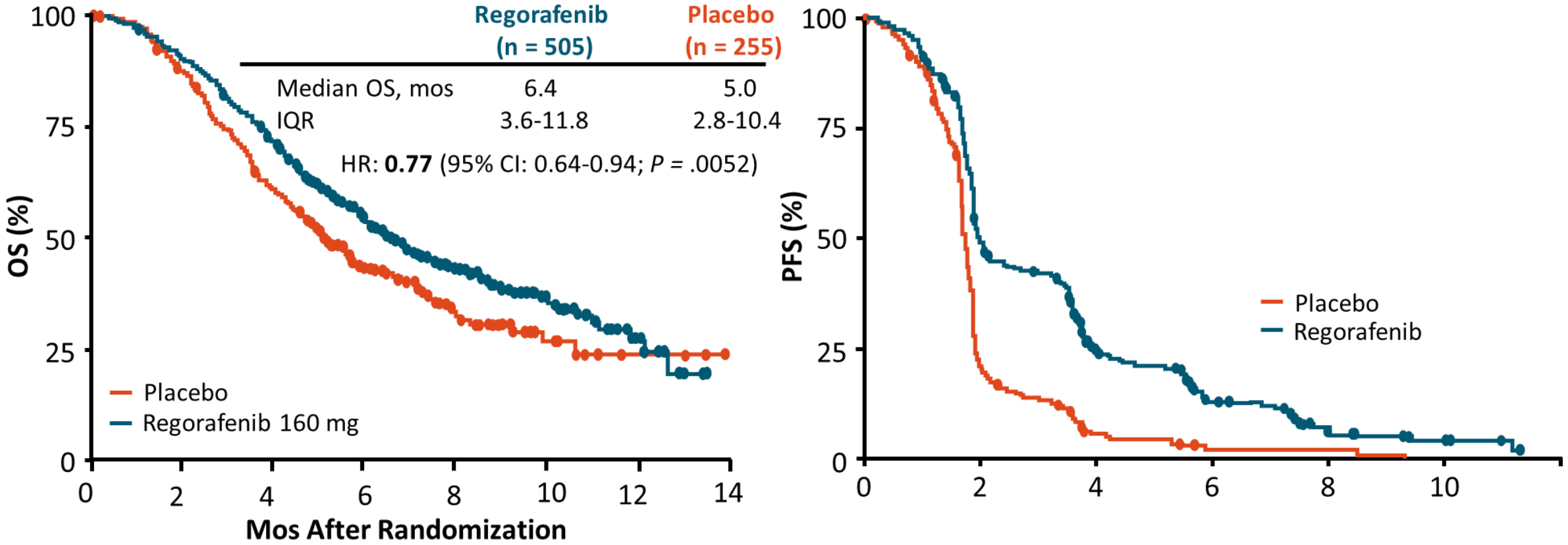
Anti-VEGF Agents in 2nd Line mCRC

Trial	Agent / Mechanism of Action	Chemo Combination	Prior Bev Exposure	Overall Survival Benefit	≥ Grade 3 AEs
TML (ML18147)	Bevacizumab / VEGF-A MoAb	FOLFOX or FOLFIRI	30.4%	+ 1.4 months; HR 0.81 (95% CI 0.69 – 0.94); *P* = 0.0062	57% vs 64%
VELOUR	Ziv-aflibercept / VEGF-receptors 1,2, Fc IgG1 Ig fusion protein; VEGF trap for VEGF-A, VEGF-B, placental growth factor	FOLFIRI	100%	+ 1.4 months; HR 0.817 (95% CI 0.713-0.937); *P* = 0.0032	62.5% vs 83.5%
RAISE	Ramucirumab / VEGFR2 MoAb	FOLFIRI	100%	+ 1.6 months; HR 0.844 (95% CI 0.73-0.966); *P* = 0.0219	62% vs 79%

Bennouna J et al. *Lancet Oncol*. 2013;14(1):29-37. Van Cutsem E et al. *J Clin Oncol*. 2012;30(28):3499-3506.
Tabernero J et al. *Lancet Oncol*. 2015;16(5):499-508.

Regorafenib (CORRECT Trial)

- Randomized, double-blind, phase III trial of regorafenib 160 mg PO QD vs placebo (both plus BSC) for patients with mCRC who progressed on or within 3 mos of previous therapy (N = 760)

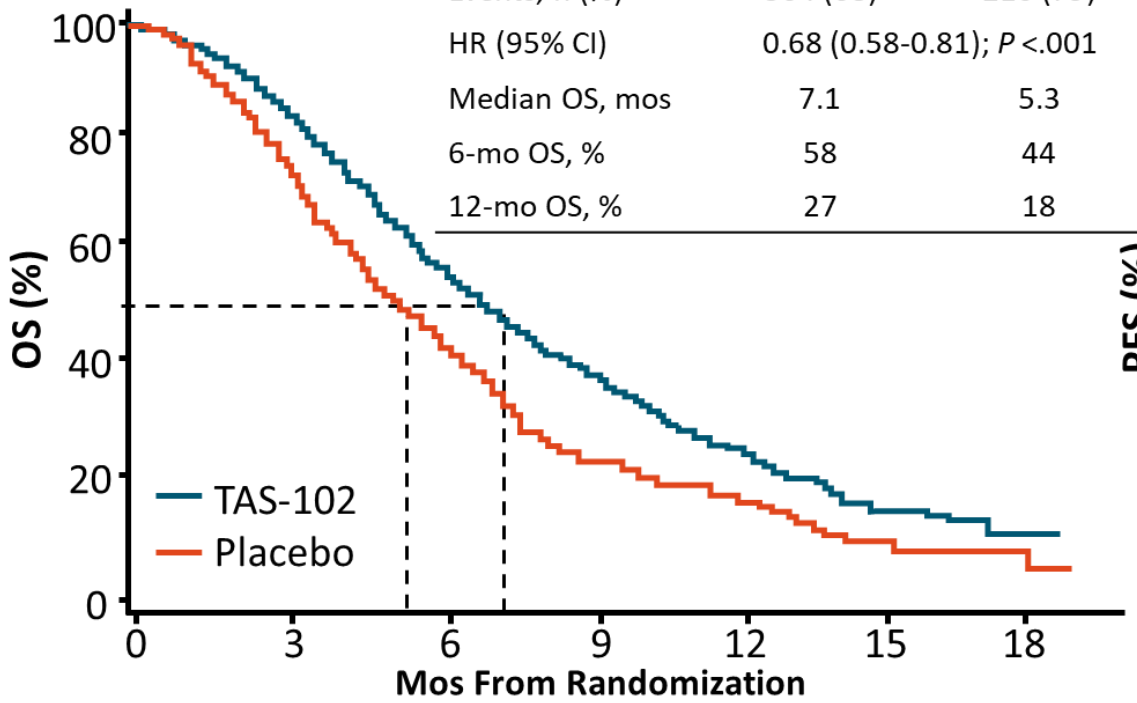


Grothey A et al. *Lancet*. 2013;381(9863):303-312.

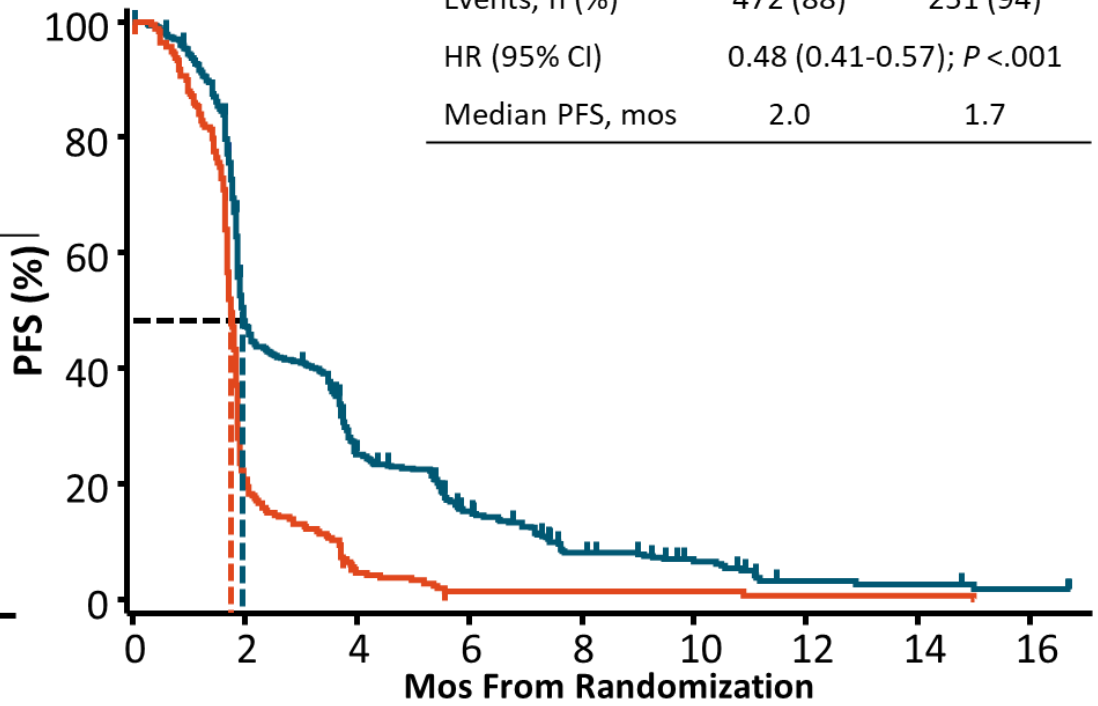
TAS-102 (RECOURSE Trial)

- Randomized phase III trial of TAS-102 35 mg/m^2 PO BID vs placebo (both plus BSC) for patients with mCRC and ≥2 prior lines of standard chemotherapy (N = 800)

	TAS-102 (n = 534)	Placebo (n = 266)
Events, n (%)	364 (68)	210 (79)
HR (95% CI)	0.68 (0.58-0.81); *P* <.001	
Median OS, mos	7.1	5.3
6-mo OS, %	58	44
12-mo OS, %	27	18



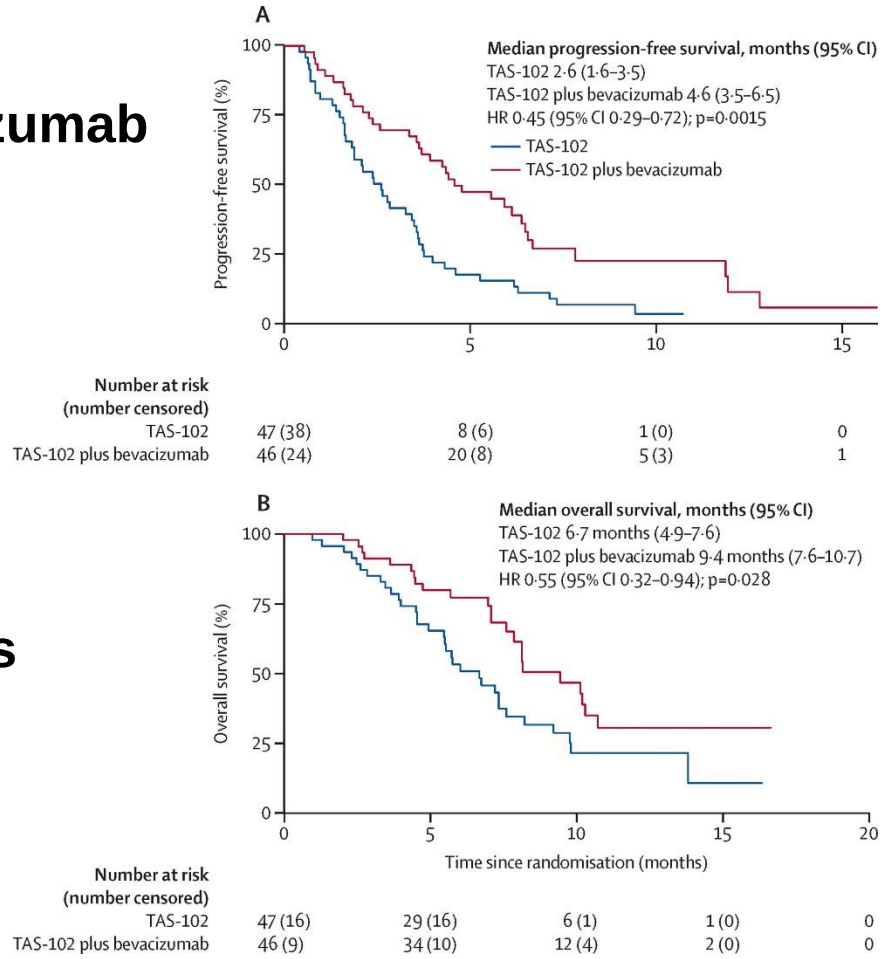
	TAS-102 (n = 534)	Placebo (n = 266)
Events, n (%)	472 (88)	251 (94)
HR (95% CI)	0.48 (0.41-0.57); *P* <.001	
Median PFS, mos	2.0	1.7



Mayer RJ et al. *N Engl J Med*. 2015;372(20):1909-1919.

TAS-102 + Bevacizumab (Phase 2 Trial)

- **Phase 2 of TAS-102 + / - bevacizumab**
- **N = 93**
- **Primary Endpoint = PFS (investigator assessed)**
- **Secondary Endpoints = OS, AEs**



PFS: 4.6 vs 2.6 mos

HR = 0.45

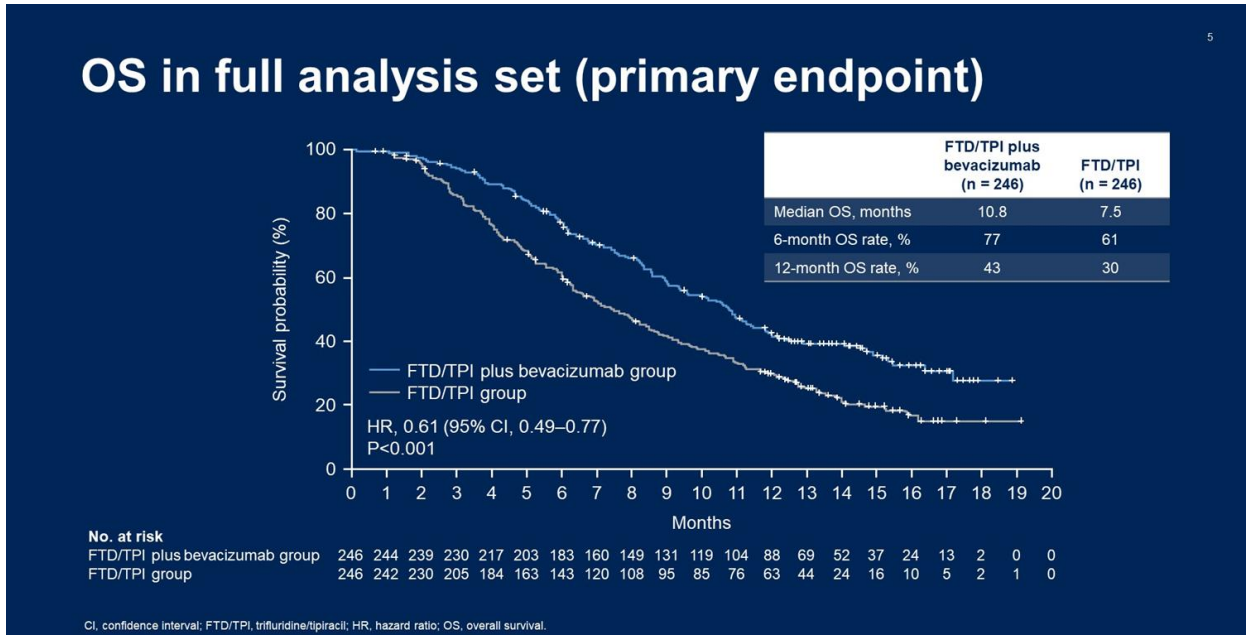
OS: 9.4 vs 6.7 mos

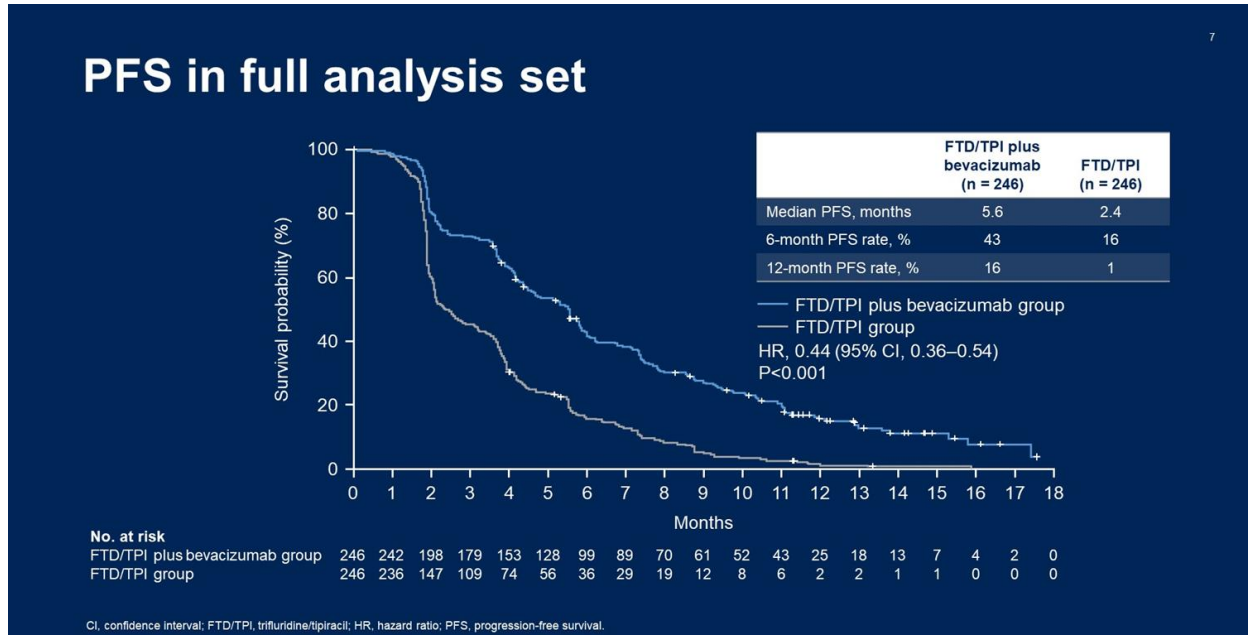
HR = 0.55

Pfeiffer P et al. *Lancet Oncol*. 2020;21(3):412-420.

TAS-102 + Bevacizumab (Phase 3 SUNLIGHT Trial)

- Open label randomized phase 3 trial of TAS-102 35 mg/m^2 PO BID + / - bevacizumab for patients with mCRC and ≥2 prior lines of standard chemotherapy (N = 490)

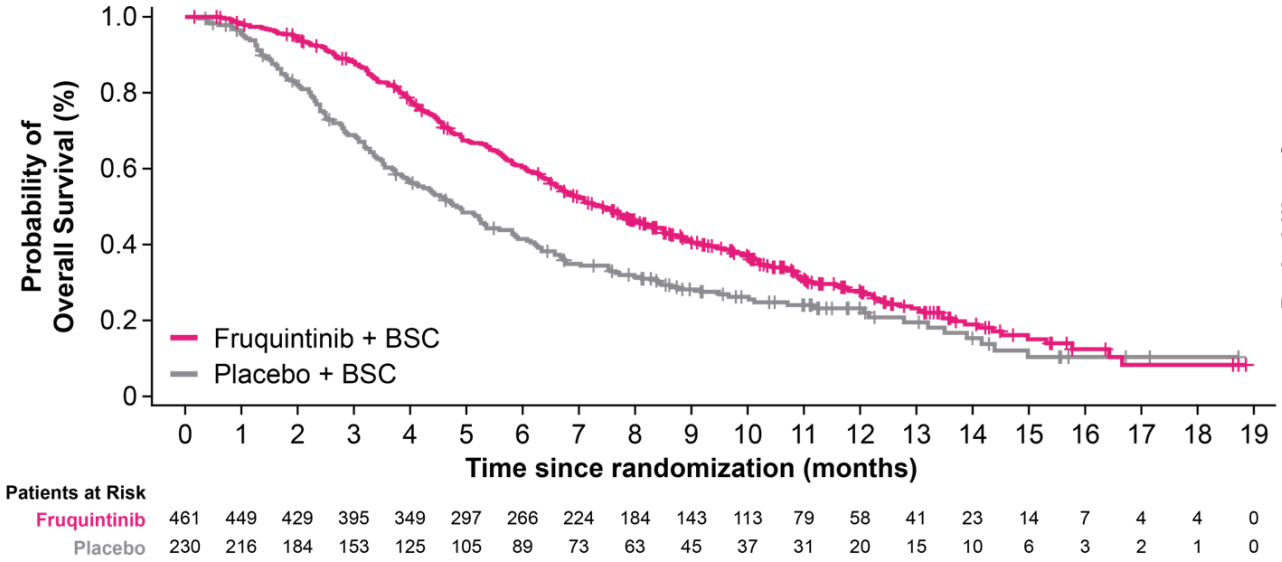


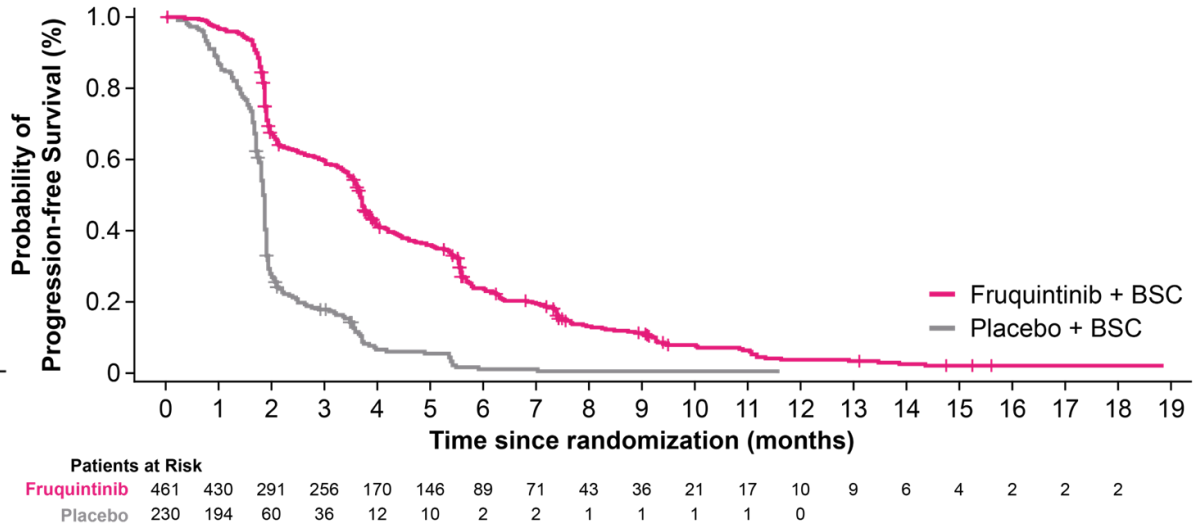


Prager GW et al. *N Engl J Med*. 2023;388(18):1657-1667.

Fruquintinib (FRESCO-2)

- Double blind randomized phase 3 trial of fruquintinib 5 mg po daily 3 weeks on, 1 week off vs placebo (both arms with BSC) for patients with refractory mCRC (N = 687)





Dasari A et al. *Lancet*. 2023;402(10395):41-53.