Selection and Sequencing of Therapies for Relapsed Gastric/GEJ Cancer; Novel Investigational Approaches

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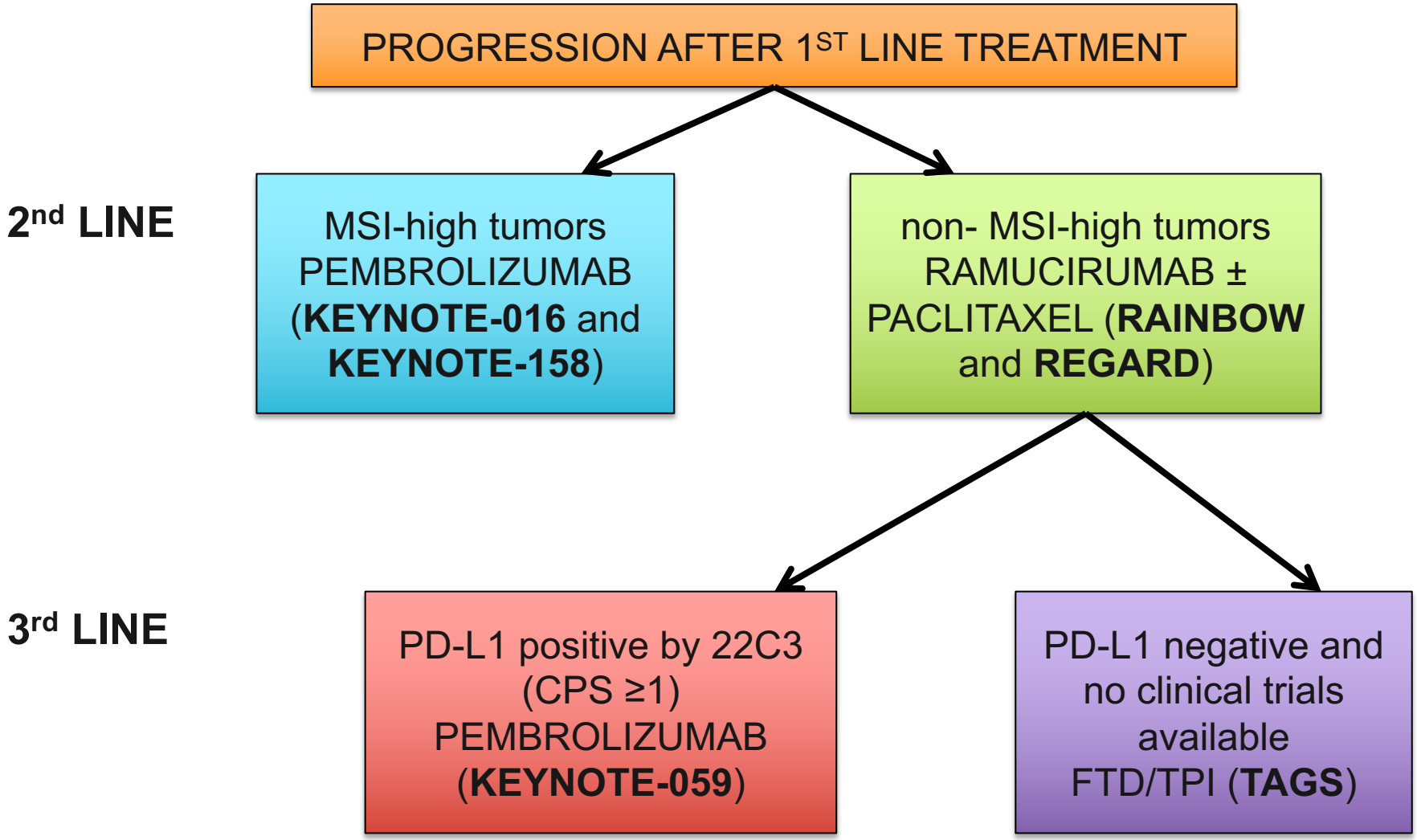
Current landscape of treatment after failure of 1L treatment for gastric/GEJ cancers

Courtesy of Rutika Mehta, MD, MPH

What after progression on 1st line treatment?



Marabelle et al., JCO 2020. Wilke et al., Lancet Oncol 2014. Fuchs et al., Lancet 2014. Fuchs et al., JAMA Oncol 2018. Shitara et al. Lancet Oncol 2018.

Courtesy of Rutika Mehta, MD, MPH

Integration of ramucirumab into the treatment of gastric/GEJ cancers

Courtesy of Rutika Mehta, MD, MPH

Integration of ramucirumab in metastatic gastric/GEJ cancer treatment

FIRST-LINE TREATMENT	
REST OF THE WORLD	**ASIA**
RAINFALL	**RAINSTORM**
5-FLUOROURACIL PLUS CISPLATIN ± RAMUCIRUMAB	S-1 PLUS OXALIPLATIN ± RAMUCIRUMAB FOLLOWED BY RAMUCIRUMAB PLUS PACLITAXEL
Phase 3 randomized study with N=645	Phase 2 randomized study with N=189

Fuchs et al. Lancet Oncol 2019. Yoshikawa et al., JAMA Netw Open 2019.

Courtesy of Rutika Mehta, MD, MPH

Integration of ramucirumab in gastric/GEJ cancer treatment

FIRST LINE TREATMENT	
REST OF THE WORLD	**ASIA**
RAINFALL	**RAMUCIRUMAB**
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Phase 3 randomized study with N=645	Phase 2 randomized study with N=189

NO PFS OR OS BENEFIT

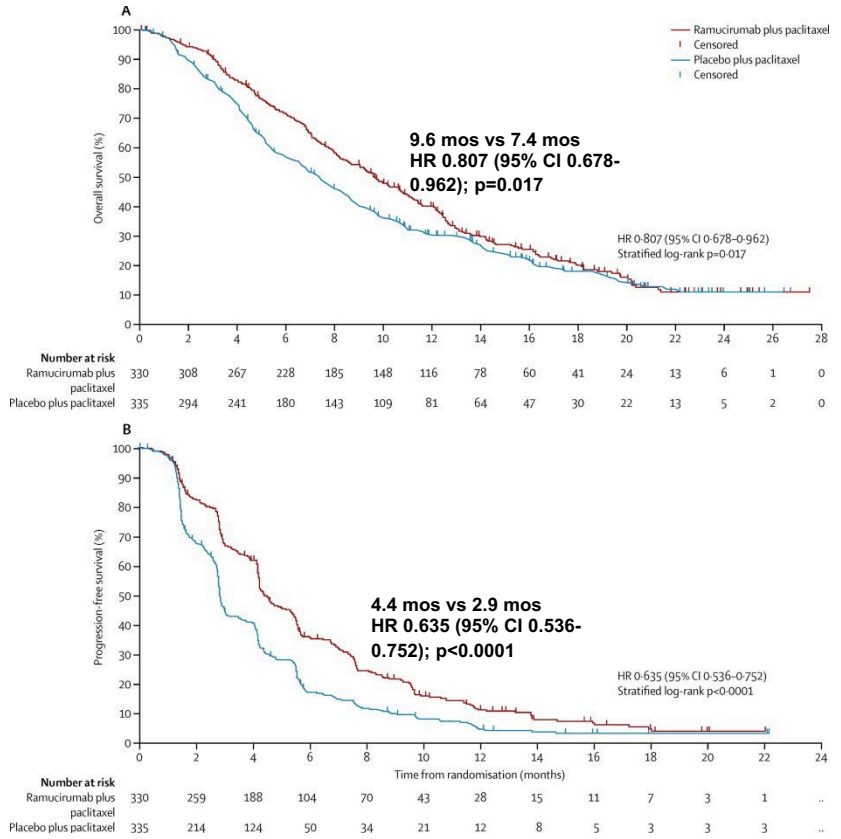
Fuchs et al. Lancet Oncol 2019. Yoshikawa et al., JAMA Netw Open 2019.

Courtesy of Rutika Mehta, MD, MPH

Where has ramucirumab really been beneficial?

RAINBOW

- Gastric/GEJ patients who have progressed on 1st line therapy with fluoropyrimidine or platinum
- Ramucirumab (8 mg/kg D1 & D15) + paclitaxel (80 mg/m^2 D1, D8 and D15) every 28 days vs placebo + paclitaxel
- N=665
- Objective response rate 28% vs 16%
- Disease control rate 80% vs 64%



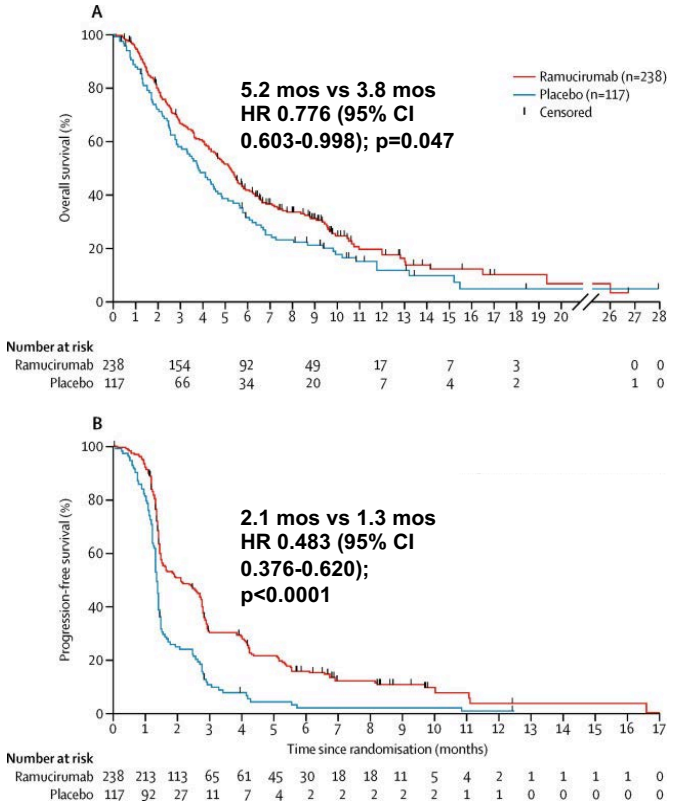
Wilke et al., Lancet Oncol 2014.

Courtesy of Rutika Mehta, MD, MPH

Where has ramucirumab really been beneficial?

REGARD

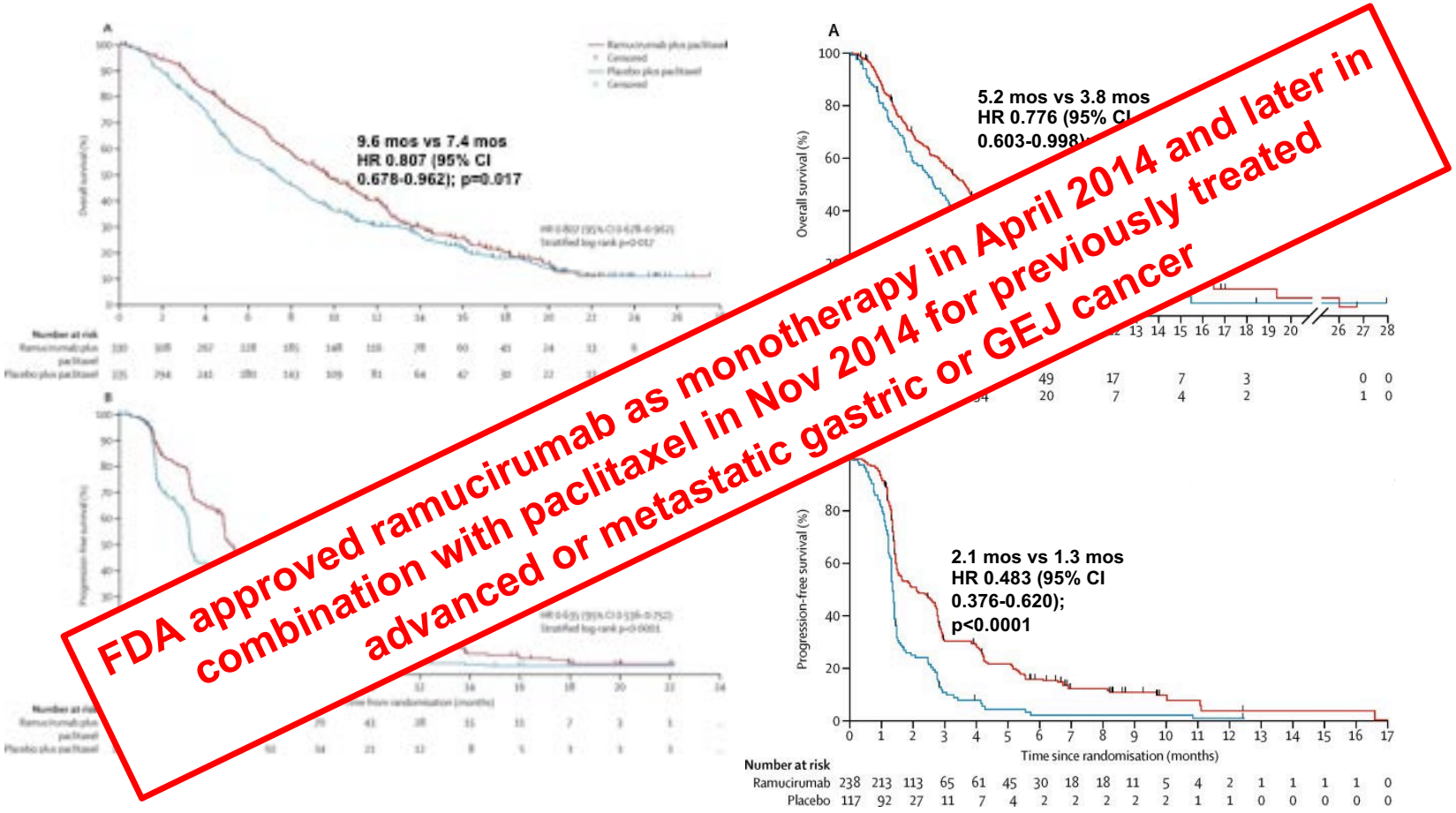
- Gastric/GEJ patients who have progressed on 1st line therapy with fluoropyrimidine or platinum
- Ramucirumab (8 mg/kg D1 & D15) vs placebo
- N= 355
- Objective response rate 3% vs 3%
- Disease control rate 49% vs 23%



Fuchs et al., Lancet 2014

Courtesy of Rutika Mehta, MD, MPH

FDA approved use of ramucirumab



Courtesy of Rutika Mehta, MD, MPH

Why are the new combinations with ramucirumab being studied?

- Neuropathy is a significant adverse effect of first-line chemotherapy that can affect QoL for gastric/GEJ cancer patients
- With first-line platinum based treatment, all grade neuropathy can range from 21-62% and grade 3-4 neuropathy can range from 2-14%.
- With the ramucirumab/paclitaxel combination, grade 1-2 neuropathy rates are 38% and grade 3 is 8% which is comparable to single agent paclitaxel.
- Therefore, novel combinations with ramucirumab are desirable that can offset the side effects of neuropathy.

Kim et al. Eur J Cancer 2012. Al-Batran SE et al. J Clin Oncol 2008.

Courtesy of Rutika Mehta, MD, MPH

Ramucirumab combinations

	With Irinotecan			
Study	**Klempner et al.**	**Vogl et al.**	**Park et al.***	**RAMIRIS***
Study type	Retrospective	Retrospective	Phase 2 single arm	Phase 2/3 randomized
Ramucirumab combination	FOLFIRI + ramucirumab	FOLFIRI + ramucirumab	Ramucirumab + irinotecan	FOLFIRI plus ramucirumab
Comparator	N/A	Ramucirumab + paclitaxel	N/A	Ramucirumab + paclitaxel
N	29	16	40 (planned)	111 (in Ph2)
Gastric/GEJ cancer %	>59%	100%	100%	-
mOS	13.4 mos	8.3 mos	-	6.8 mos vs 7.6 mos
mPFS	6 mos	5.9 mos	-	3.9 mos vs 3.7 mos
ORR	23%	23.1%	25% (based on interim analyses of 20 patients)	22% vs 11%

*- Ongoing study. Preliminary data only available so far. Klempner et al. Oncologist 2019. Vogl et al. JGO 2020. Park et al. Annals of Oncol 2020. Thuss-Patience et al. Annals of Oncol 2020

Courtesy of Rutika Mehta, MD, MPH

Combining ramucirumab with immunotherapy

- In the hypoxic microenvironment of solid tumors, vascular endothelial growth factor (VEGF) influences immunosuppressive Tregs, TAMs and MDSCs
- These secrete immunosuppressive cytokines IL-10, TGF-β
- Combining VEGF blockade with immunotherapy attempts to restore this balance by inducing antitumor immune response.

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Other combinations with ramucirumab

	Hara et al.	Herbst et al.	Bang et al.	Bando et al.
Combination	ramucirumab plus nivolumab	ramucirumab plus pembrolizumab	ramucirumab plus durvalumab	ramucirumab plus nab-paclitaxel
Study type	Single arm Ph1/2	Single arm multi-cohort Ph1a/b	Single arm multi-cohort Ph1	Single arm Ph2
N	44	41	29	43
mOS	17.05 mos	5.9 mos	12.4 mos	NR
mPFS	2.89 mos	2.5 mos	2.6 mos	7.6 mos
ORR	26.7%	7%	21%	54.8%

Hara et al. J Clin Oncol 2019. Herbst et al. Lancet Oncology 2019. Bang et al. Eur J Cancer 2020. Bando et al. Eur J Cancer 2018.

Courtesy of Rutika Mehta, MD, MPH

Other ramucirumab-based ongoing clinical trials

- Rucaparib plus ramucirumab ± nivolumab
- Olaparib plus ramucirumab
- Ramucirumab plus FTD/TPI (TAS-102)

Courtesy of Rutika Mehta, MD, MPH

Pembrolizumab in gastric/GEJ cancers

Courtesy of Rutika Mehta, MD, MPH

Pembrolizumab studies in gastric/GEJ cancers

KEYNOTE-061	KEYNOTE-059

• Phase III randomized study of pembrolizumab versus paclitaxel as 2nd line treatment.
• N= 592
• PD-L1 positive (CPS ≥1): 395 (196 in pembrolizumab and 199 in paclitaxel group)
• OS by CPS
  • ≥1: 9.1 mos vs 8.3 mos
  • ≥5: 10.4 mos vs 8.3 mos
  • ≥10: 10.4 mos vs 8.0 mos
• PFS by CPS
  • ≥1: 1.5 mos vs 4.1 mos
  • ≥5: 1.6 mos vs 4.0 mos
  • ≥10: 2.7 mos vs 4.0 mos
• ORR by CPS
  • ≥1: 16.3% vs 13.6%
  • ≥5: 20% vs 14.3%
  • ≥10: 24.5% vs 9.1%
	• Phase II nonrandomized multicohort study. Cohort 1 administered pembrolizumab after 2 or more prior lines of treatment
	• N=259
	• PD-L1 positive (CPS ≥1): 148
	• mOS: 5.6 mos
	  • PD-L1 positive: 5.8 mos
	  • PD-L1 negative: 4.9 mos
	• mPFS: 2.0 mos
	• ORR: 11.6%
	  • PD-L1 positive: 15.5%
	  • PD-L1 negative: 6.4%

Shitara et al. Lancet 2018. Fuchs et al. JAMA Oncol 2018.

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Pembrolizumab studies in gastric/GEJ cancers

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PEMBROLIZUMAB FAILED TO SHOW SURVIVAL BENEFIT AS 2ND LINE TEATMENT

FDA APPROVED USE OF PEMBROLIZUMAB AS 3RD LINE OR BEYOND TREATMENT FOR PD-L1 POSITIVE GASTRIC/GEJ CANCERS

Shitara et al. Lancet 2018. Fuchs et al. JAMA Oncol 2018.

Courtesy of Rutika Mehta, MD, MPH

Role of FTD/TPI (TAS-102) in gastric cancer

Courtesy of Rutika Mehta, MD, MPH

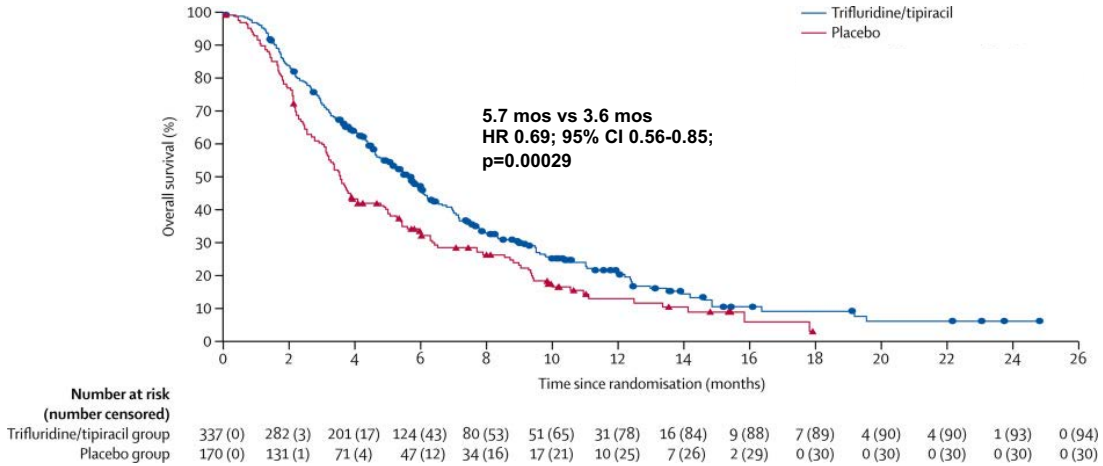
What is FTD/TPI?

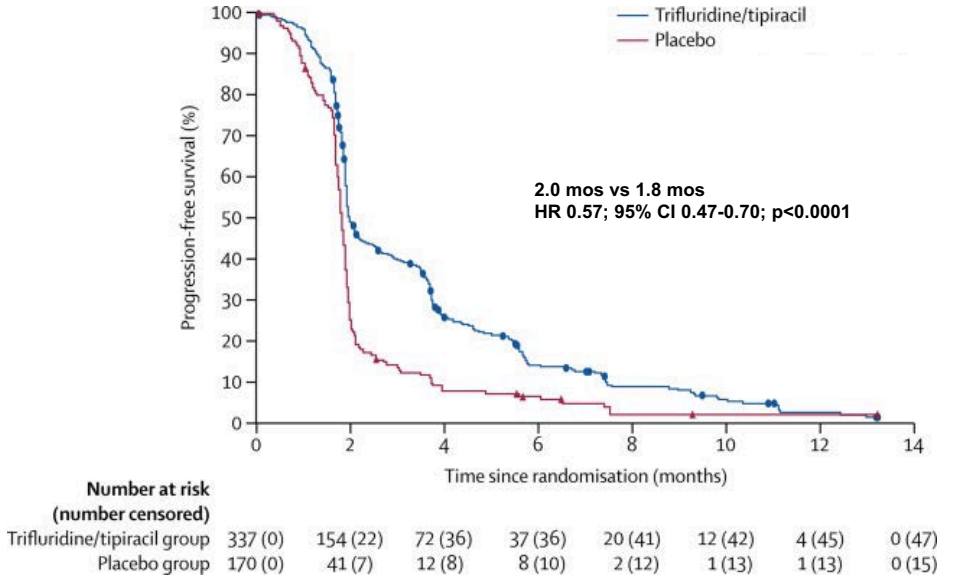
- Trifluridine/tipiracil (FTD/TPI) is a novel oral cytotoxic chemotherapy consisting of a thymidine-based nucleoside analogue, trifluridine, and a thymidine phosphorylase inhibitor, tipiracil.
- FTD/TPI has a unique mechanism of action in which trifluridine is incorporated into DNA, resulting in DNA dysfunction, and tipiracil blocks trifluridine degradation by thymidine phosphorylase, increasing trifluridine bioavailability.

Courtesy of Rutika Mehta, MD, MPH

The TAGS study

- Randomized Phase 3 trial of FTD/TPI vs placebo
- ≥2 prior lines of treatment
- Gastric or GEJ cancers
- N=507
- ORR 4% vs 2%
- Median time to deterioration of ECOG PS ≥2: 4.3 mos vs 2.3 mos; p=0.00053.
- ≥ Gr3 AEs 80% vs 58%





Shitara et al. Lancet Oncol 2018.

Courtesy of Rutika Mehta, MD, MPH

How do I use FTD/TPI in clinical practice?

- Outside of clinical trial settings, I typically do not use FTD/TPI for gastric/GEJ cancer patients
- Patients are unable to tolerate hematological toxicities and experience severe fatigue
- At about 3rd line setting, the performance status also declines which makes them ineligible for this treatment
- If they are of good performance status, I would offer them a clinical trial.

Courtesy of Rutika Mehta, MD, MPH

Claudin 18.2 in gastric cancer

Courtesy of Rutika Mehta, MD, MPH

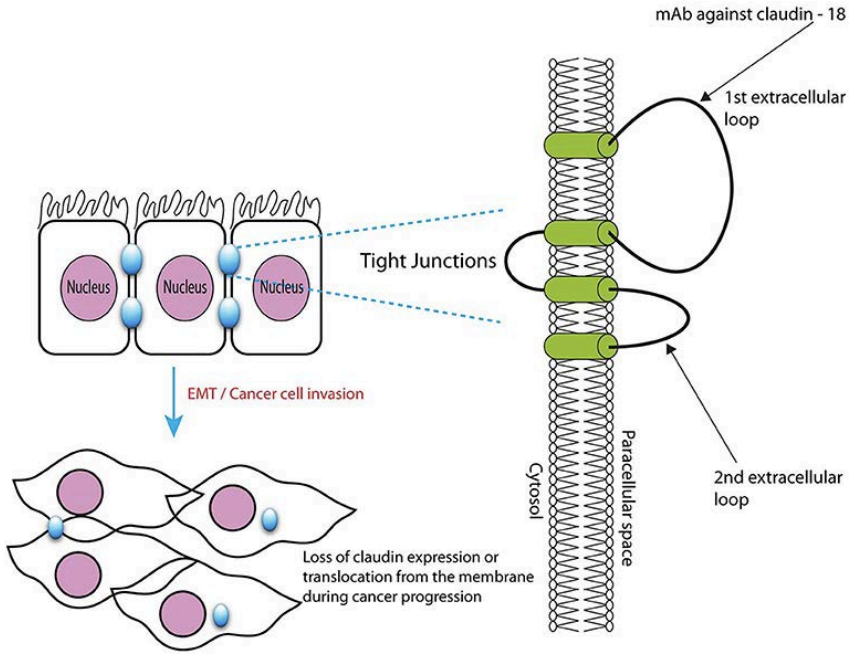
Claudin 18.2

- Claudin 18.2 is an isoform of the claudin-18 protein, and claudins are structural components of tight junctions present in the paracellular region.
- It is overexpressed in 70% of gastric cancers
- High protein expression defined as 2+ intensity in at least 60% of cells was found in 56% of gastric cancers.
- Only 14% of Claudin 18.2 positive tumors are also HER-2 positive.

Courtesy of Rutika Mehta, MD, MPH

Zolbetuximab

- It is a first-in-class novel chimeric idealized IgG1 monoclonal antibody
- Targets only tumor cells and has a lower toxicity profile than other anti-cancer monoclonal antibodies
- It activates ADCC and complement-dependent cytotoxicity.



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Clinical efficacy of zolbetuximab in gastric/GEJ cancer

- In a single arm Phase 2 study of zolbetuximab, 54 patients with gastric/GEJ cancers were treated
- Of the 43 evaluable patients, response rate was 9%, stable disease 14% for a disease control rate of 23%
- In patients with moderate-high intensity of Claudin 18.2 in ≥ 70% cells, the response rate was 14%
- This has led to large Phase 3 studies in the 1L setting in combination with chemotherapy.

Tureci et al. Ann Oncol 2019.

Courtesy of Rutika Mehta, MD, MPH

Other agents in gastric/GEJ cancers

Courtesy of Rutika Mehta, MD, MPH

Other agents

- FGFR2 inhibitors
  - Futibatinib (ongoing)
- Targeting DDR alterations
  - Niraparib in DDR deficient gastric/GEJ cancers (ongoing)
  - Paclitaxel + pembrolizumab + olaparib (ongoing)
- Combination of TKIs and immunotherapy
  - LEAP-005: lenvatinib + pembrolizumab; ORR 10%
  - Cabozantinib + durvalumab (ongoing)

Courtesy of Rutika Mehta, MD, MPH

Patient Case #1

62 y/o male with HER-2 negative, MMR proficient, PD-L1 positive (CPS 15) gastric cancer had durable response to 1L chemotherapy with FOLFOX for 6 months after which he had progressive disease. He did experience grade 2 neuropathy. ECOG PS0. He had gained 10 lbs during the 1st line treatment and had recovered much of the weight he had lost prior to the diagnosis. His appetite was good. Unfortunately, a clinical trial was unavailable at that time. He worked as a cook and the neuropathy was debilitating. He started single agent ramucirumab with a plan to add paclitaxel after the first cycle after reassessment of his neuropathy. Patient elected to try paclitaxel. He showed response to treatment. At 4 months of response, he began to notice increased dysphagia. EGD now revealed deep ulcerations at the site of the tumor with no evidence of perforation. CT imaging shortly after that showed evidence of progression and decision was made to switch therapy.

Courtesy of Rutika Mehta, MD, MPH

Patient Case #2

55 y/o male with HER-2 negative, MMR proficient, PD-L1 positive (CPS 6) was diagnosed with GEJ adenocarcinoma metastatic to retroperitoneal lymph nodes. He achieved significant clinical and radiological response to FOLFOX and then underwent consolidative chemoradiation. Within 3 months of completion, he had a single site of recurrence in the liver - biopsy confirmed. He started a clinical trial with ramucirumab plus FTD/TPI. However, due to non-compliance and then significant hematological adverse events, patient opted to come off the trial. He then started pembrolizumab. Imaging performed before starting this therapy showed re-emergence of retroperitoneal adenopathy. Patient tolerated pembrolizumab well and at first re-staging scans showed improvement in disease burden. At 8 months, there was just one lymph node that was evident on imaging at 1.2 cm. At 18 months, he continues on pembrolizumab without any adverse events and near complete response.

Courtesy of Rutika Mehta, MD, MPH