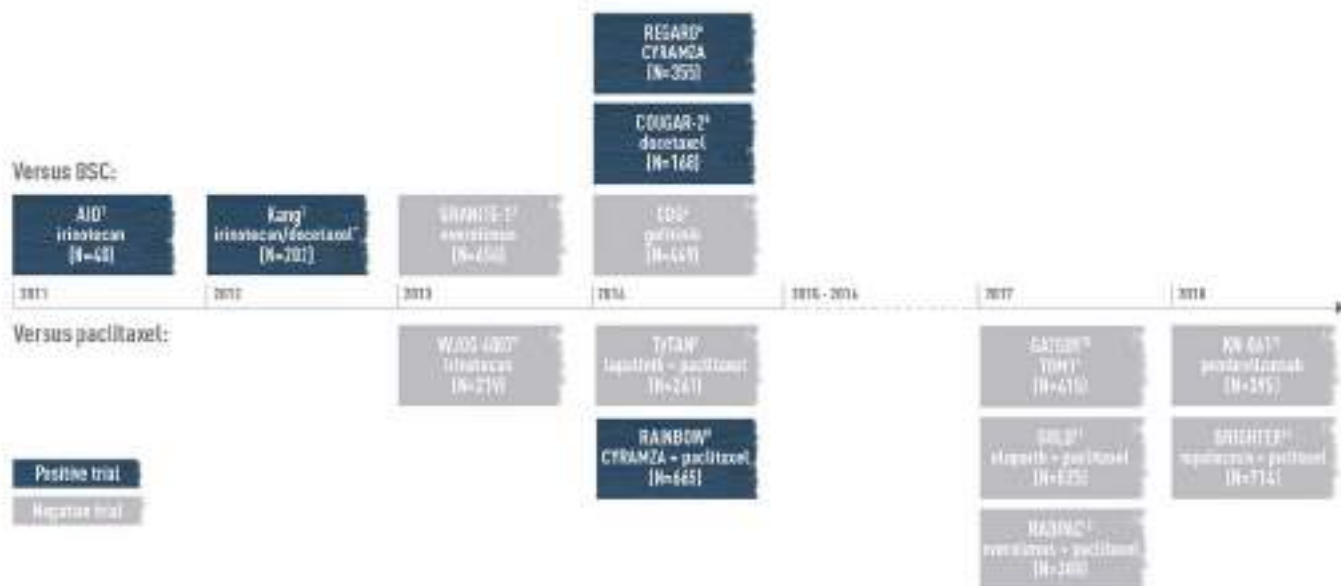




Tell me we've got a plan

Advanced Gastric Cancer Is Difficult to Treat

2nd-Line Phase 3 Clinical Studies



[†] No significant difference between the two treatment arms.

^{*} Docetaxel or paclitaxel could be used at the physician's discretion.

BSC=best supportive care.

References:

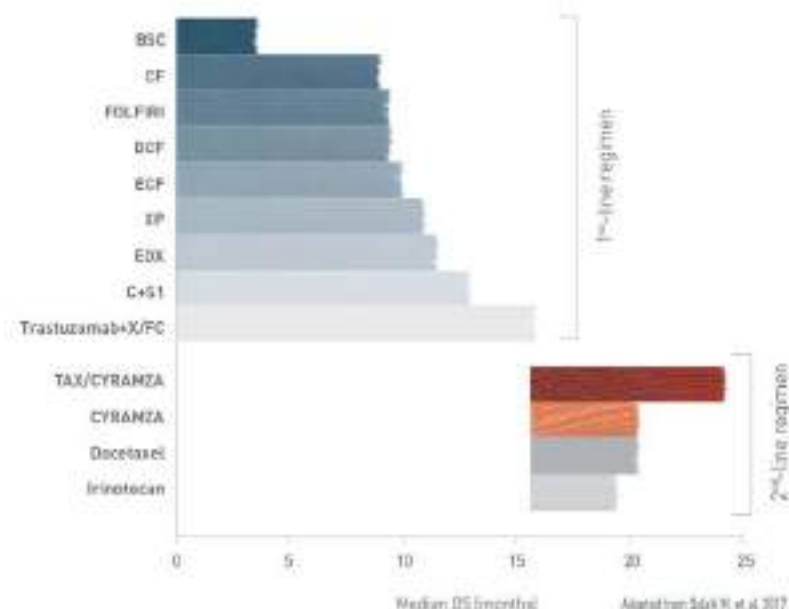
1. Thuss-Patience PC, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer – a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). *Eur J Cancer* 2011;47(15):2306–2314.
2. Kang JH, et al. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. *J Clin Oncol* 2012;30(13):1513–1518.
3. Ohtsu A, et al. Everolimus for previously treated advanced gastric cancer: results of the randomized, double-blind, phase III GRANITE-1 study. *J Clin Oncol* 2013;31(31):3935–3943.
4. Dutton SJ, et al. Gefitinib for oesophageal cancer progressing after chemotherapy (COG): a phase 3, multicentre, double-blind, placebo-controlled randomised trial. *Lancet Oncol* 2014;15(8):894–904.
5. Ford H, et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. *Lancet Oncol* 2014;15(1):78–86.
6. Fuchs CS, et al. Ramucicrumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* 2014;383(9911):31–39.
7. Hironaka S, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. *J Clin Oncol* 2013;31(35):4438–4444.
8. Satoh T, et al. Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of HER2-amplified advanced gastric cancer in Asian populations: TyTAN – a randomized, phase III study. *J Clin Oncol* 2014;32(19):2039–2049.
9. Wille H, et al. Ramucicrumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol* 2014;15:1224–1235.
10. Thuss-Patience PC, et al. Trastuzumab emtansine versus taxane use for previously treated HER2-positive locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma (GATSBY): an international randomised, open-label, adaptive, phase 2/3 study. *Lancet Oncol* 2017;18(5):640–653.
11. Bang YJ, et al. Olaparib in combination with paclitaxel in patients with advanced gastric cancer who have progressed following first-line therapy (SOLO): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol* 2017;18(12):1637–1651.
12. Lorenzen S, et al. A randomized, double-blind, multi-center phase III study evaluating paclitaxel with and without RAD001 in patients with gastric or esophagogastric junction carcinoma who have progressed after therapy with a fluoropyrimidine/platinum-containing regimen (RADPAC). *J Clin Oncol* 2017;34(15):4027.
13. Fuchs CS, et al. Pembrolizumab (pembro) vs paclitaxel (PTX) for previously treated advanced gastric or gastroesophageal junction (G/GEJ) cancer: Phase 3 KEYNOTE-061 trial. *J Clin Oncol*. 2018;36(suppl, abstr 4062).
14. Shah MA, et al. The BRIGHTER trial: A phase 3 randomized double-blind study of napabucasin (NAPA) plus paclitaxel (PTX) versus placebo (PBO) plus PTX in patients (pts) with pretreated advanced gastric and gastroesophageal junction (GEJ) adenocarcinoma. *J Clin Oncol*. 2018;36(suppl, abstr 4610).



Tell me we've got a plan



Median OS by Chemotherapy Regimens in 1st- and 2nd-line Treatment for Advanced Gastric Cancer¹



Among patients who received 1st-line treatment

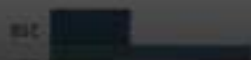
54%

also received 2nd-line treatment¹

¹BSC=best supportive care; C+S1=capecitabine and S1; CF=capecitabine and 5-FU; DCF=docetaxel, capecitabine and 5-FU; ECF=epirubicin, capecitabine and 5-FU; FOLFIRI=fluorouracil, oxaliplatin and irinotecan; XP=capecitabine and paclitaxel; EDX=epirubicin, docetaxel and 5-FU; TAX/CYRAMZA=paclitaxel and ramuciclib; CYRAMZA=ramuciclib; Docetaxel=docetaxel; Irinotecan=irinotecan

Tell me we've got a plan

Median OS by Chemotherapy Regimens in 1st- and 2nd-line Treatment for Advanced Gastric Cancer¹

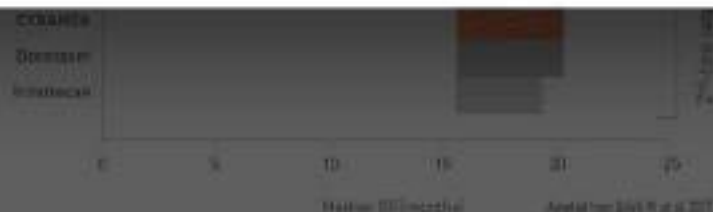


Among patients with
received 1st-line



References:

1. Salati M, et al. Second-line treatments: moving towards an opportunity to improve survival in advanced gastric cancer? *ESMO Open* 2017;2:e000206. doi:10.1136/esmoopen-2017-000206.
2. Hess LM, et al. Chemotherapy treatment patterns, costs, and outcomes of patients with gastric cancer in the United States: a retrospective analysis of electronic medical record (EMR) and administrative claims data. *Gastric Cancer* 2016;19(2):607-615.



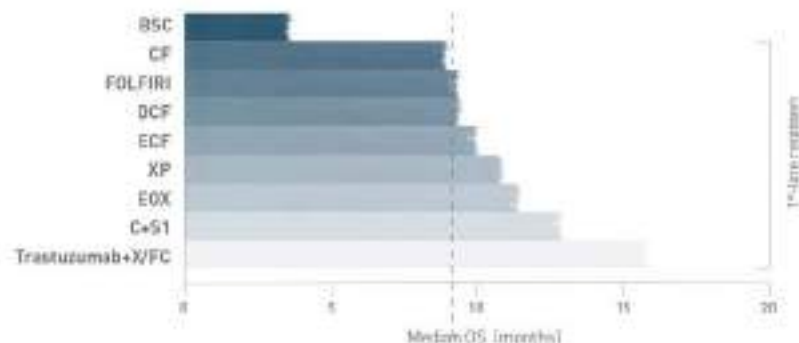
OS: overall survival; SOC: standard of care; Docetaxel: docetaxel; Irinotecan: irinotecan; FOLFIRI: fluorouracil, oxaliplatin, and irinotecan; SOC: standard of care; Docetaxel: docetaxel; Irinotecan: irinotecan; FOLFIRI: fluorouracil, oxaliplatin, and irinotecan.



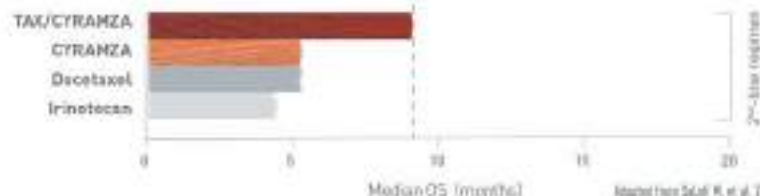
Tell me we've got a plan



Median OS by Chemotherapy Regimens in 1st- and 2nd-Line Treatment for Advanced Gastric Cancer¹



1st-line regimens



2nd-line regimens

Among patients who received 1st-line treatment

54%

also received 2nd-line treatment²

¹BSC=best supportive care; C+S1=cisplatin and S1; D=cisplatin and 5-FU; DCF=docetaxel, cisplatin and 5-FU; ECF=epidoxifen, cisplatin and 5-FU; FOLFIRI=fluorouracil, oxaliplatin and irinotecan; XP=capecitabine and cisplatin; EOX=epidoxifen, oxaliplatin and 5-FU; TCF=trastuzumab, capecitabine and 5-FU; Trastuzumab+X/FC=trastuzumab, capecitabine and 5-FU; TAX=paclitaxel; CYRAMZA=ramotexan; Docetaxel=docetaxel; Irinotecan=irinotecan; ²OS=overall survival; IM=irinotecan; RYC=capecitabine and 5-FU; XP=capecitabine and cisplatin

Tell me we've got a plan

Median OS by Chemotherapy Regimens in 1st- and 2nd-Line Treatment for Advanced Gastric Cancer¹



Among patients who received 1st line



References:

- Salati M, et al. Second-line treatments: moving towards an opportunity to improve survival in advanced gastric cancer? *ESMO Open* 2017;2:e000206. doi:10.1136/esmoopen-2017-000206.
- Hess LM, et al. Chemotherapy treatment patterns, costs, and outcomes of patients with gastric cancer in the United States: a retrospective analysis of electronic medical record (EMR) and administrative claims data. *Gastric Cancer* 2016;19(2):607-615.



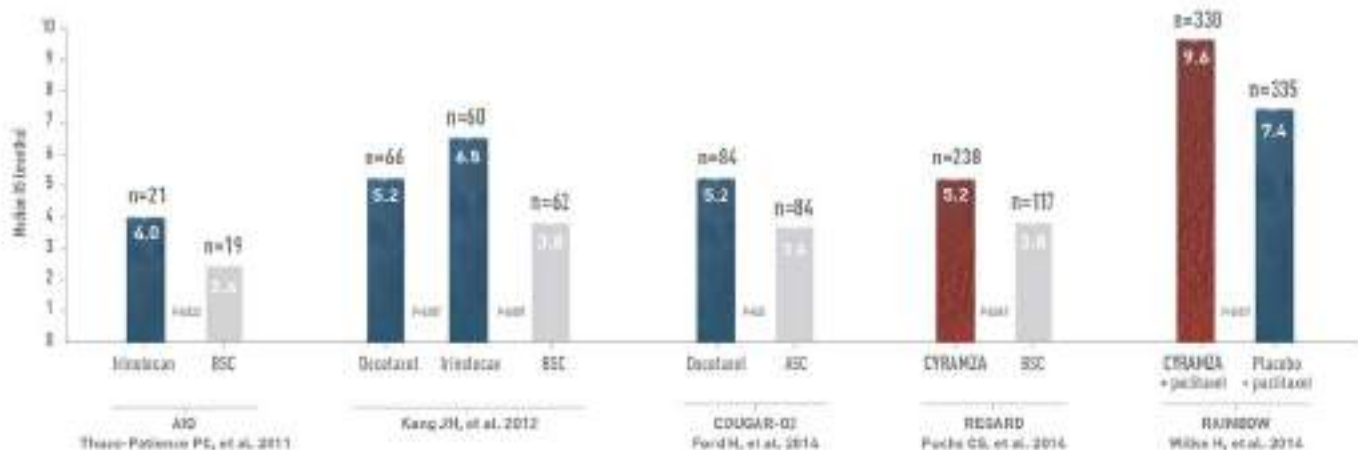
OS: overall survival; FOLFOX: fluorouracil, oxaliplatin; FOLFIRI: fluorouracil, irinotecan; FOLFIRI + cetuximab: fluorouracil, irinotecan, cetuximab; FOLFIRI + bevacizumab: fluorouracil, irinotecan, bevacizumab; FOLFIRI + ramucicab: fluorouracil, irinotecan, ramucicab; FOLFIRI + nivolumab: fluorouracil, irinotecan, nivolumab; FOLFIRI + pembrolizumab: fluorouracil, irinotecan, pembrolizumab; FOLFIRI + durvalumab: fluorouracil, irinotecan, durvalumab; FOLFIRI + tremelimumab: fluorouracil, irinotecan, tremelimumab; FOLFIRI + ipilimumab: fluorouracil, irinotecan, ipilimumab; FOLFIRI + nivolumab + ipilimumab: fluorouracil, irinotecan, nivolumab, ipilimumab; FOLFIRI + pembrolizumab + ipilimumab: fluorouracil, irinotecan, pembrolizumab, ipilimumab; FOLFIRI + durvalumab + tremelimumab: fluorouracil, irinotecan, durvalumab, tremelimumab; FOLFIRI + ipilimumab + nivolumab: fluorouracil, irinotecan, ipilimumab, nivolumab; FOLFIRI + nivolumab + pembrolizumab: fluorouracil, irinotecan, nivolumab, pembrolizumab; FOLFIRI + durvalumab + tremelimumab + ipilimumab: fluorouracil, irinotecan, durvalumab, tremelimumab, ipilimumab; FOLFIRI + ipilimumab + nivolumab + pembrolizumab: fluorouracil, irinotecan, ipilimumab, nivolumab, pembrolizumab; FOLFIRI + durvalumab + tremelimumab + ipilimumab + nivolumab + pembrolizumab: fluorouracil, irinotecan, durvalumab, tremelimumab, ipilimumab, nivolumab, pembrolizumab.



Tell me we've got a plan



Overall Survival (OS) by Treatment Arm – 2nd-Line Therapy¹⁻⁵



Overall Survival (OS) by Treatment Arm – 2nd-Line Therapy¹⁻⁵



References:

1. Thuss-Patience PC, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer — a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). *Eur J Cancer* 2011;47(15):2306–2314.
2. Kang JH, et al. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. *J Clin Oncol* 2012;30(13):1513–1518.
3. Ford H, et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. *Lancet Oncol* 2014;15(1):78–86.
4. Fuchs CS, et al. Ramucicrumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* 2014; 383(9911):31–39.
5. Wilke H, et al. Ramucicrumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol* 2014;15:1224–1235.



Tell me we've got a plan



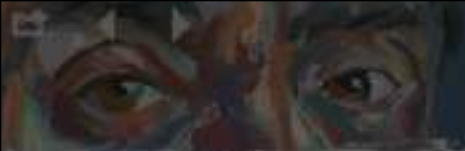
Optimizing Treatment Sequencing to Improve Patient Outcomes in Advanced Gastric Cancer¹

Locally Advanced – Initially Unresectable

- **Aim of treatment:**
tumour shrinkage to obtain resectability;
survival similar to initially resectable tumour
- **Preferred regimen:**
triplet including docetaxel or epirubicin

Metastatic

- **Aim of treatment:**
symptoms palliation, QoL, prolonged survival
- **Preferred regimen:**
fluoropyrimidine/platinum agent doublet



Tell me we've got a plan

Optimizing Treatment Sequencing to Improve Patient Outcomes in Advanced Gastric Cancer¹

Locally Advanced – Initially Unresectable



Reference:

1. Salati M, et al. Second-line treatments: moving towards an opportunity to improve survival in advanced gastric cancer? *ESMO Open* 2017;2:e000206. doi:10.1136/esmoopen-2017-000206.

Metastatic

- **Aim of treatment:**
symptoms palliation, QoL, prolonged survival

- **Preferred regimen:**
fluoropyrimidine/platinum agent doublet



Tell me we've got a plan



Considerations in the Right 1st-Line Choice for Optimal Treatment Sequencing

The standard 1st-line chemotherapy regimen is a doublet combination of a fluoropyrimidine with a platinum.¹

Triplet regimens including a taxane may be useful in select patients, however, they have been associated with a substantial increase in toxicity¹⁻³

Consider 1st-line regimens that combine good activity with good tolerability and fewer toxic effects to optimize the potential benefits of 2nd-line treatment⁴



Efficacy

Similar OS vs. doublet regimen²



Toxicity

Increased toxicity observed with triplet regimen [e.g., FLOT, DCF]¹



QoL

FLOT **adversely impacted QoL** and led to significant increases in individual toxicities including neutropenia, leukopenia, diarrhoea, and nausea²



TOXICITY TABLE



Toxicity

FLOT vs. FLO: Select Grade 3/4 Toxicity Comparison²

Toxicity	Grade 3/4	
	FLOT (5-FU, leucovorin, oxaliplatin, docetaxel) n=72	FLO (5-FU, leucovorin, oxaliplatin) n=70
Hematological toxicity		
Neutropenia	52.8%	12.9%
Leukopenia	29.2%	5.7%
Anemia	11.1%	4.3%
Thrombopenia	2.8%	2.9%
Gastrointestinal toxicity		
Nausea	20.8%	7.3%
Diarrhea	8.3%	1.5%
Vomiting	4.2%	2.9%
Mucositis	9.7%	2.9%
Neurosensory toxicity		
Sensorium	11.6%	19.4%

Tell me we've got a plan

Considerations in the Right 1st-Line Choice for Optimal Treatment Sequencing

Consider 1st-line regimens that combine good activity with good



References:

1. Van Cutsem E, et al. Gastric cancer. *Lancet* 2016;388:2654-2664.
2. Al-Batran S-E, et al. The feasibility of triple-drug chemotherapy combination in older adult patients with esophagogastric cancer: a randomised trial of the Arbeitsgemeinschaft Internistische Onkologie (FLOT65+). *Eur J Cancer* 2013;49:835-842.
3. Bittani A, et al. Three drugs vs two drugs first-line chemotherapy regimen in advanced gastric cancer patients: a retrospective analysis. *SpringerPlus* 2015;4:743.
4. Pericay C, et al. Positioning of second-line treatment for advanced gastric and gastroesophageal junction adenocarcinoma. *Cancer Med* 2016;5(12):3464-3474.

(e.g., FLOT, DCF)

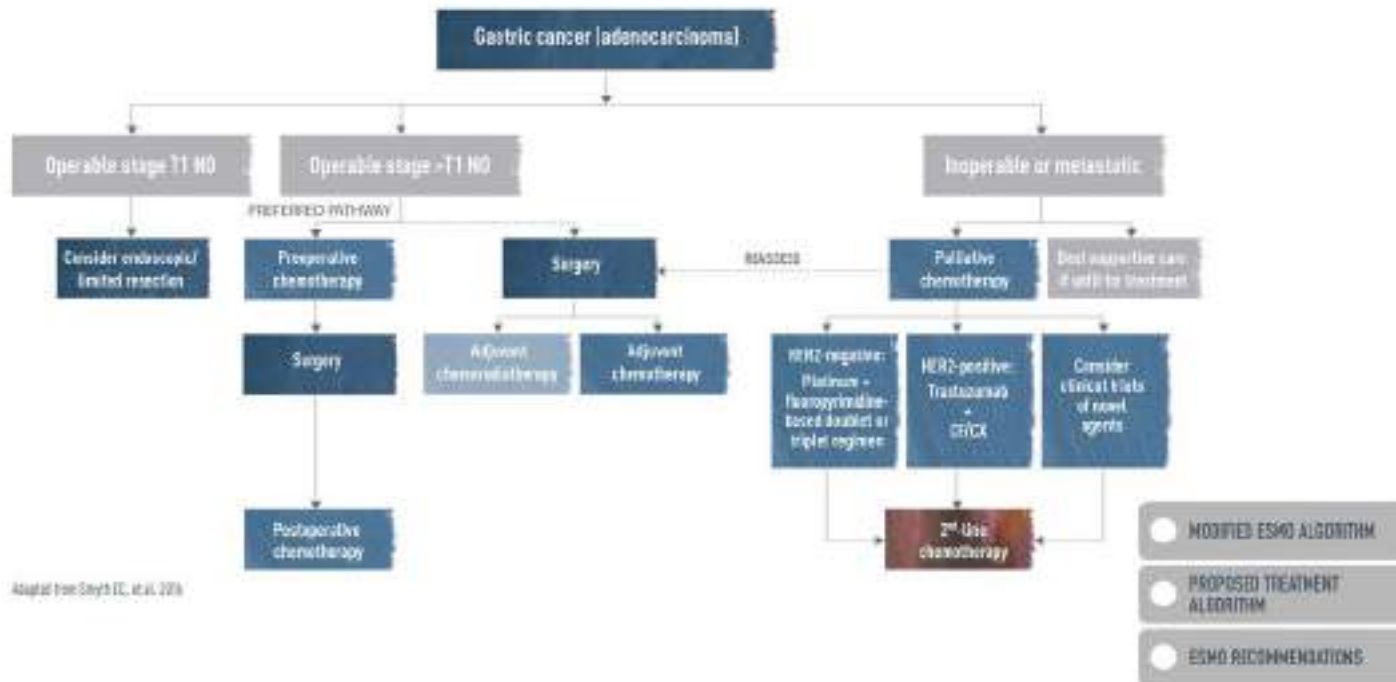
neutropenia, leukopenia, diarrhea, and fatigue²

TOXICITY TABLE



Tell me we've got a plan

Gastric Cancer Treatment Algorithm¹

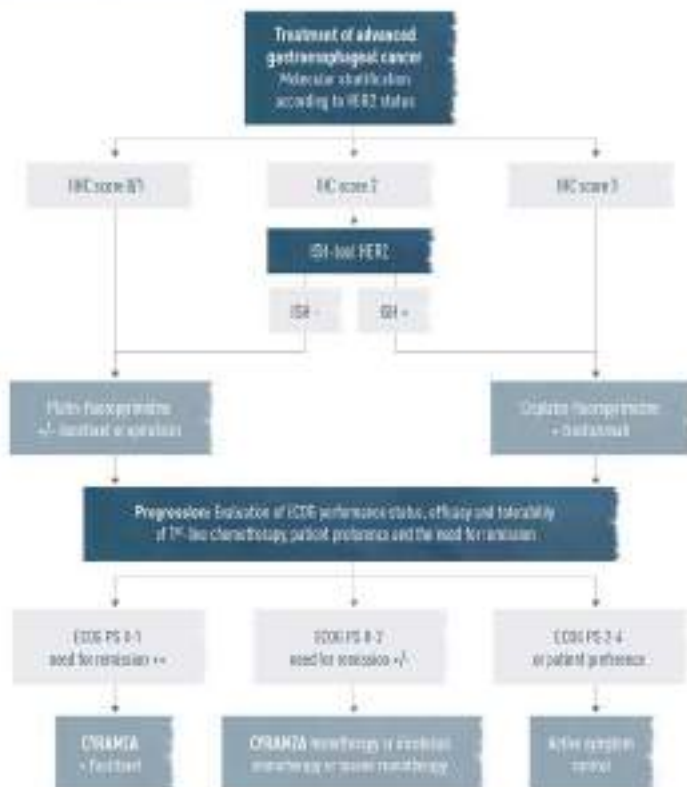


Tell me we've got a plan

Modified ESMO Advanced Gastric Cancer Treatment Algorithm²



Proposed Treatment Algorithm for Advanced Gastroesophageal Cancer Based on Published Recommendations³



ESMO CLINICAL PRACTICE GUIDELINES

Gastric Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up (2016)¹

- For use as a single agent as 2nd-line treatment (I, A)*
- In combination with paclitaxel as 2nd-line treatment (I, A)*

¹ **Level of Evidence I:** Evidence from at least one large, randomized, controlled trial of good methodological quality (low potential for bias) or meta-analysis of well-conducted randomized trials without heterogeneity. **Recommendation A:** Strong evidence for efficacy with a substantial clinical benefit, strongly recommended. CT=capecitabine and S-FU, O=oxipatin and capecitabine; HER2=human epidermal growth factor receptor 2.

Tell me we've got a plan

Gastric Cancer Treatment Algorithm¹

Gastric cancer (adenocarcinoma)



References:

1. Smyth EC, et al. ESMO Guidelines Committee. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2016;27(suppl 5):v38-v49.
2. Salati M, et al. Second-line treatments: moving towards an opportunity to improve survival in advanced gastric cancer? *ESMO Open* 2017;2:e000206. doi:10.1136/esmoopen-2017-000206.
3. Lordick F, Janjigian YY. Clinical impact of tumour biology in the management of gastroesophageal cancer. *Nat Rev Clin Oncol* 2016;13(6):348-360.

Preoperative
chemotherapy

2nd line
chemotherapy