ESMO GUIDELINES:
REAL WORLD CASES

GASTRIC CANCER

Lizzy Smyth

Oxford University Hospitals NHS Foundation Trust

ESMO WEBINAR SERIES

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Programme

25 June 2024

10 min	**Welcome and introduction** Lizzy Smyth
10 min	**Case Presentation** Deniz Can Guven
20 min	**Presentation of the ESMO Clinical Practice Guideline for Critical Analysis of the Case** Kohei Shitara
10 min	**Considerations Related to Guideline Implementation in Everyday Clinical Practice and Discussion** Radu Vidra
10 min	**Live Q&A and Discussion** All speakers, Magnus Nilsson

Elizabeth (Lizzy) Smyth
Chair
Oxford University Hospitals NHS Foundation Trust

Deniz Can Güven
Speaker
Hacettepe University Cancer Institute

Kohei Shitara
Speaker
National Cancer Center Hospital East

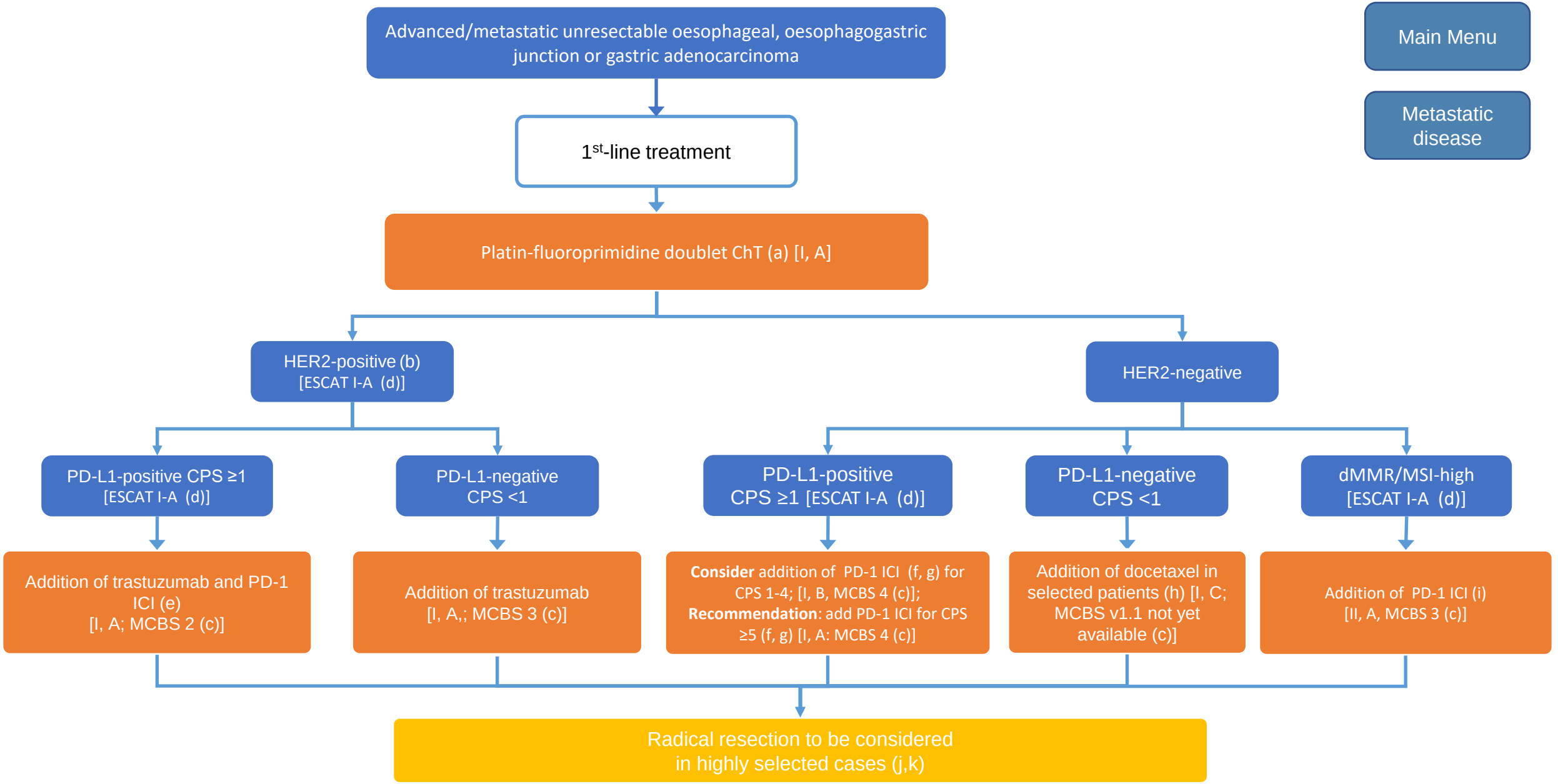
Radu Vidra
Speaker
Regional Institute of Gastroenterology and Hepatology "Prof. Dr. Octavian Fodor", Cluj-Napoca

Magnus Nilsson
Multidisciplinary Expert
CLINTEC, Karolinska Institutet

LEARNING OBJECTIVES

- Promote evidence-based quality cancer care by disseminating the ESMO Clinical Practice Guidelines (CPG) in the oncology community.
- Present a clinical case for each of the selected topics for discussion in the context of the ESMO CPG recommendations.
- Present and critically review the ESMO CPG recommendations for each selected cancer type.
- Discuss the case, the ESMO CPG recommendations, their impact on care and implementability in the daily practice setting under the guidance of a moderator senior expert, with participation of the guideline authors, practicing oncologists and young oncologists.
- Audit the fulfillment of the learning objectives and acceptability of the ESMO CPG recommendations by means of an online questionnaire.

Advanced/Metastatic Unresectable Oesophageal, Oesophagogastric Junction and Gastric Adenocarcinoma: First-line Therapy



ESMO GUIDELINES: REAL WORLD CASES

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ESMO GUIDELINES:
REAL WORLD CASES

ESMO GUIDELINES WEBINAR GASTRIC CANCER

Deniz Can Güven

ESMO YOC Member

Elazığ City Hospital, Elazığ, Turkey

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@DenizCanGuven1

Initial Presentation

- 41 y, Male
- Weight loss and anemia
- No additional comorbidity

- Endoscopy: Gastric adenocarcinoma (lesser curvature)

Reference

Initial Evaluation and Staging

- CT scan at diagnosis: Metastatic lesions in the right lobe of the liver

- Biomarker analysis: HER 2-, PD-L1 CPS 0, **loss of MLH1 and PMS2**
  - No NGS due to lack of reimbursement

Reference

1st Line Treatment

- CAPOX+Pembrolizumab was started

- **Questions**
  - Was NGS needed for the management?
  - Was the chemotherapy needed in this scenario (MSI-H mGC 1st line)?

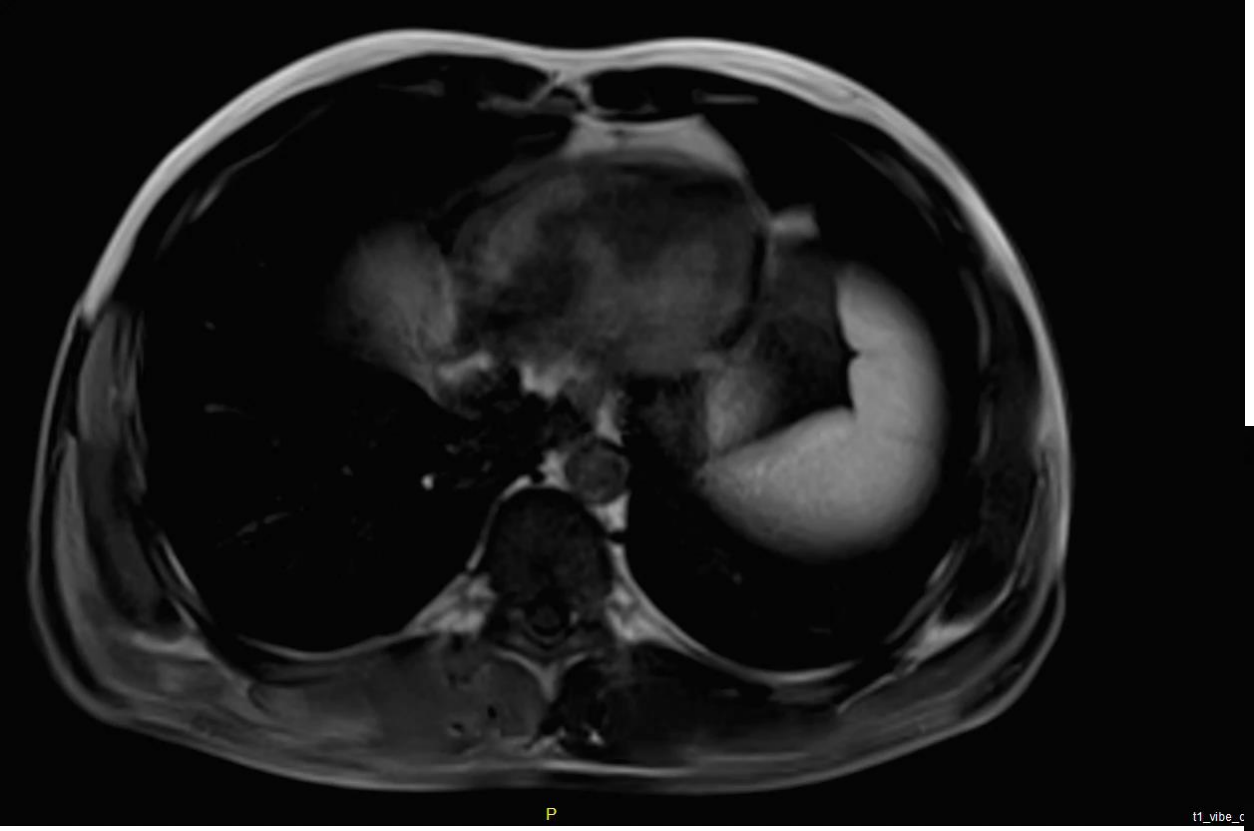
Reference

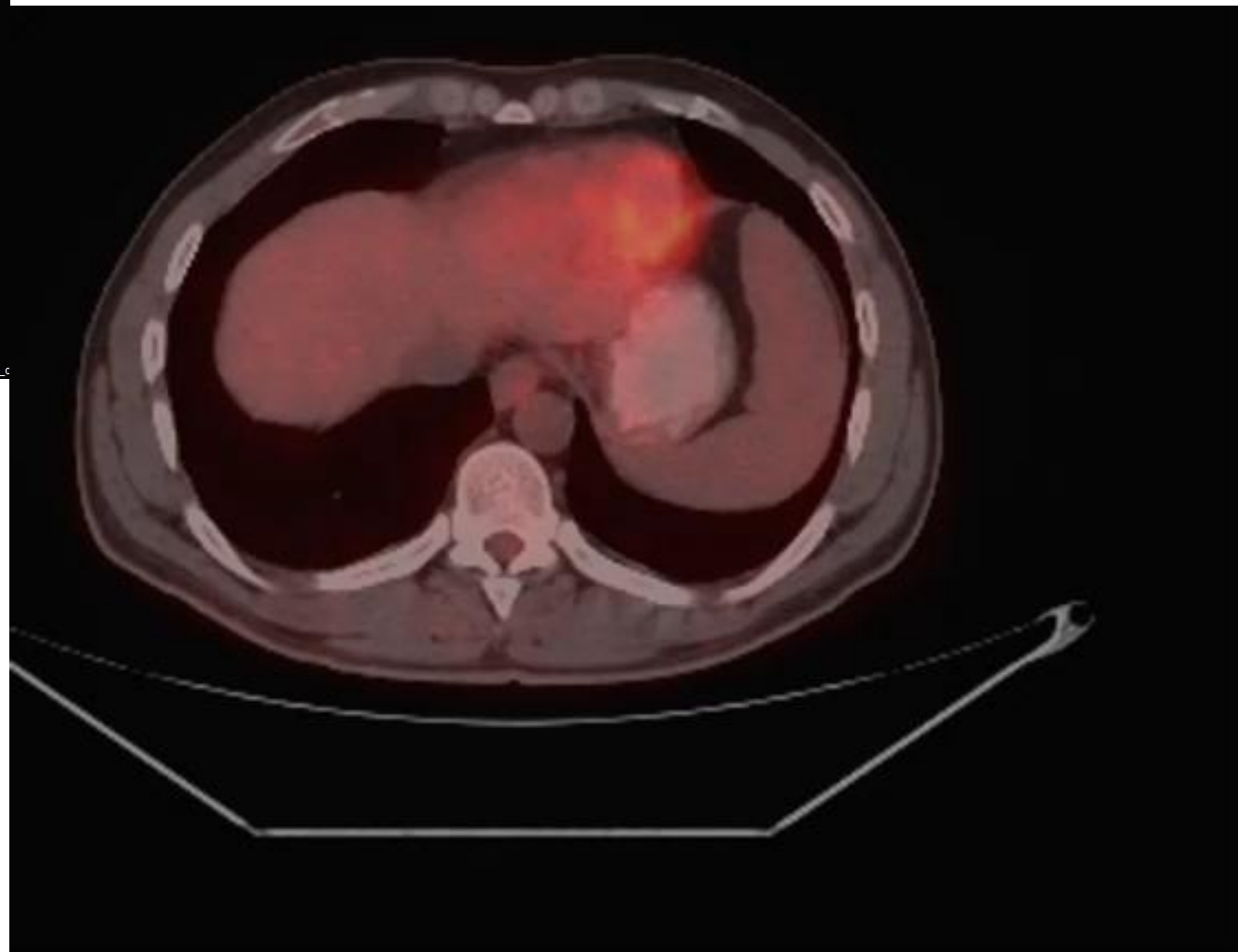
Response Evaluation

- Response evaluation (6 months)
  - Partial response
  - Complete resolution of the liver lesions

- MDT discussion: Surgery to primary and intraoperative US for liver lesions

Reference





Reference

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REAL WORLD CASES

Response Evaluation

- Pathology: pT4aN1, modified Ryan score 3

- **Question**
  - Could surgery be beneficial for mGC after response to 1st line treatment?

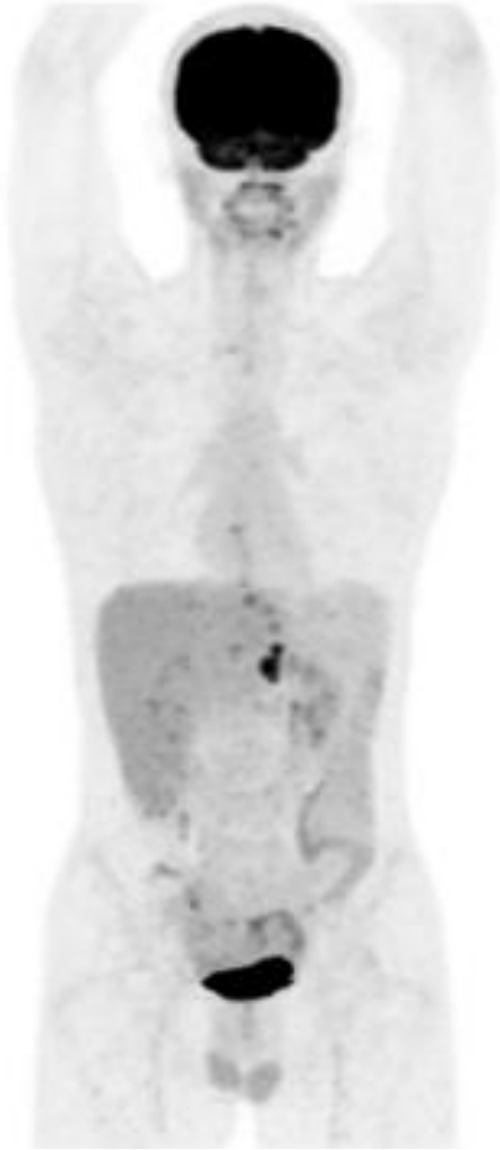
Reference

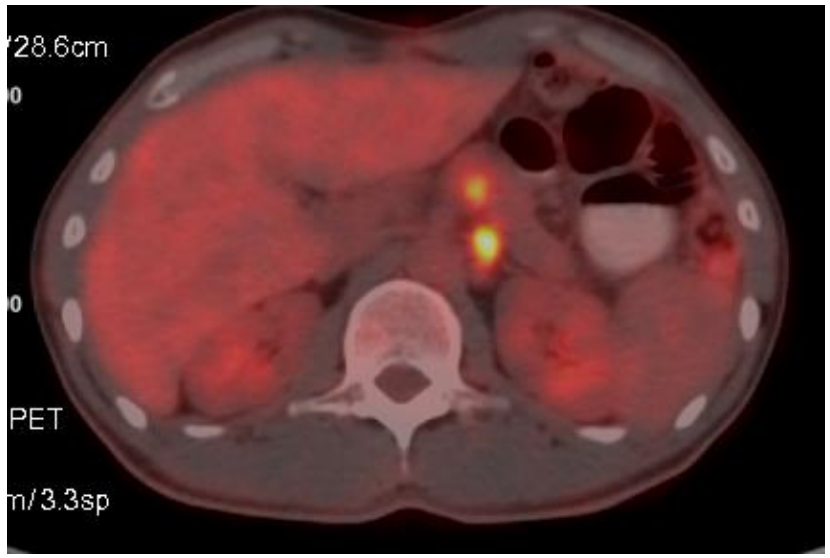
Follow-Up

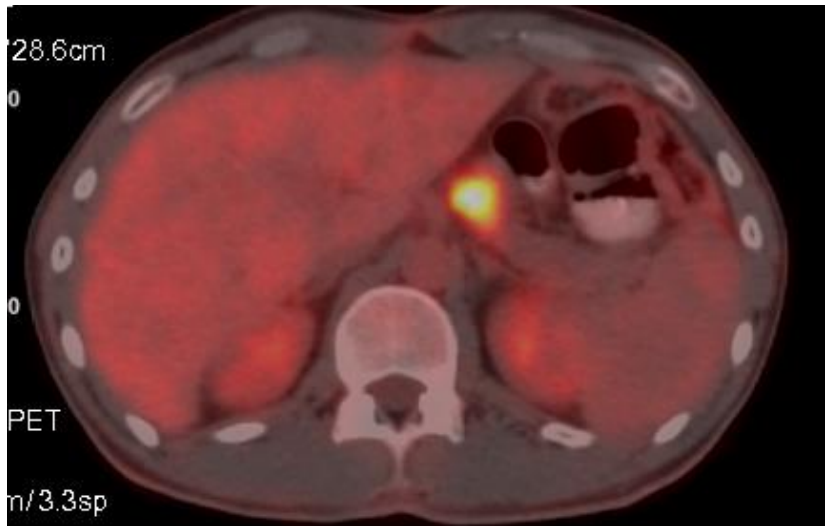
- Maintenance with capecitabine and pembrolizumab after surgery

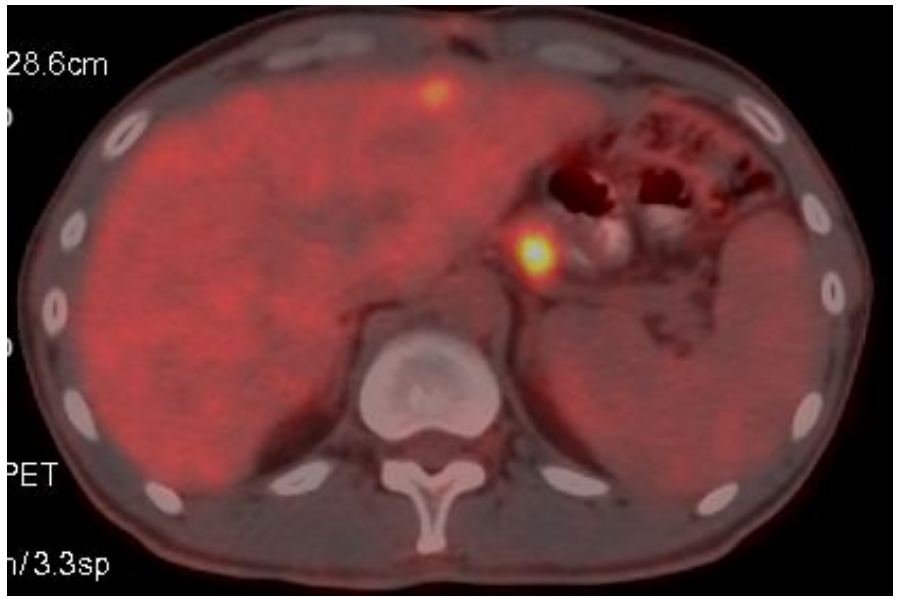
- Progression at the 54th week of treatment
  - Intraabdominal lymph nodes
  - New lesion in the liver

Reference









Reference

Follow-Up

- DCX was started→Progression in 6th month after the initial PR

- **Question**
  - **Was triplet necessary for the patient?**

Reference

Follow-Up

- Nivolumab plus ipilimumab in 3rd line
  - Out of pocket expense

- **Question**
  - **What is the available data regarding IO rechallenge in MSI-H mGC?**

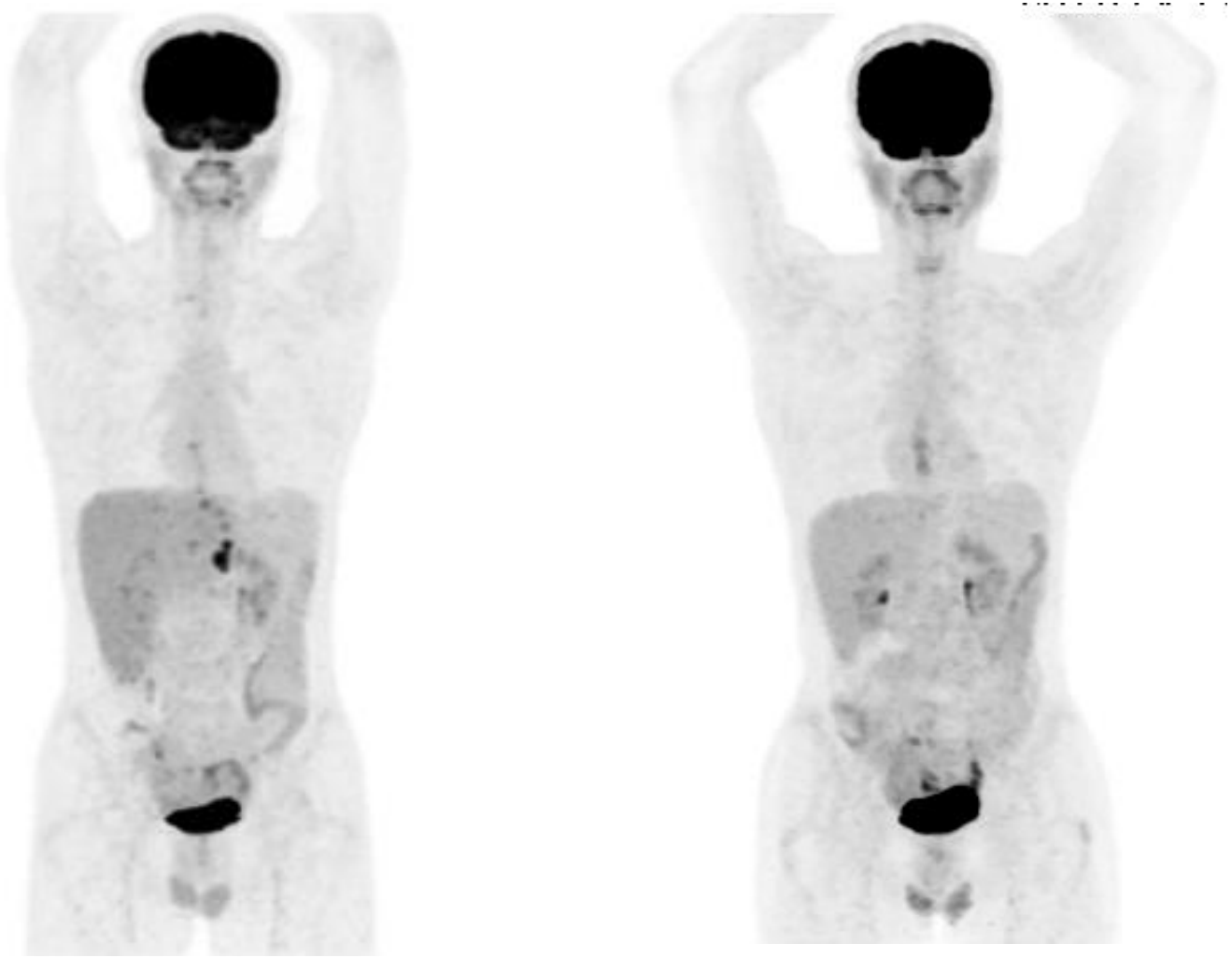
Reference

Follow-Up

- Complete metabolic response at PET scan (3rd month)

- Progression at the 9th month of the treatment
  - Left adrenal lesion
  - Bilateral supraclavicular and cervical lymph nodes

Reference



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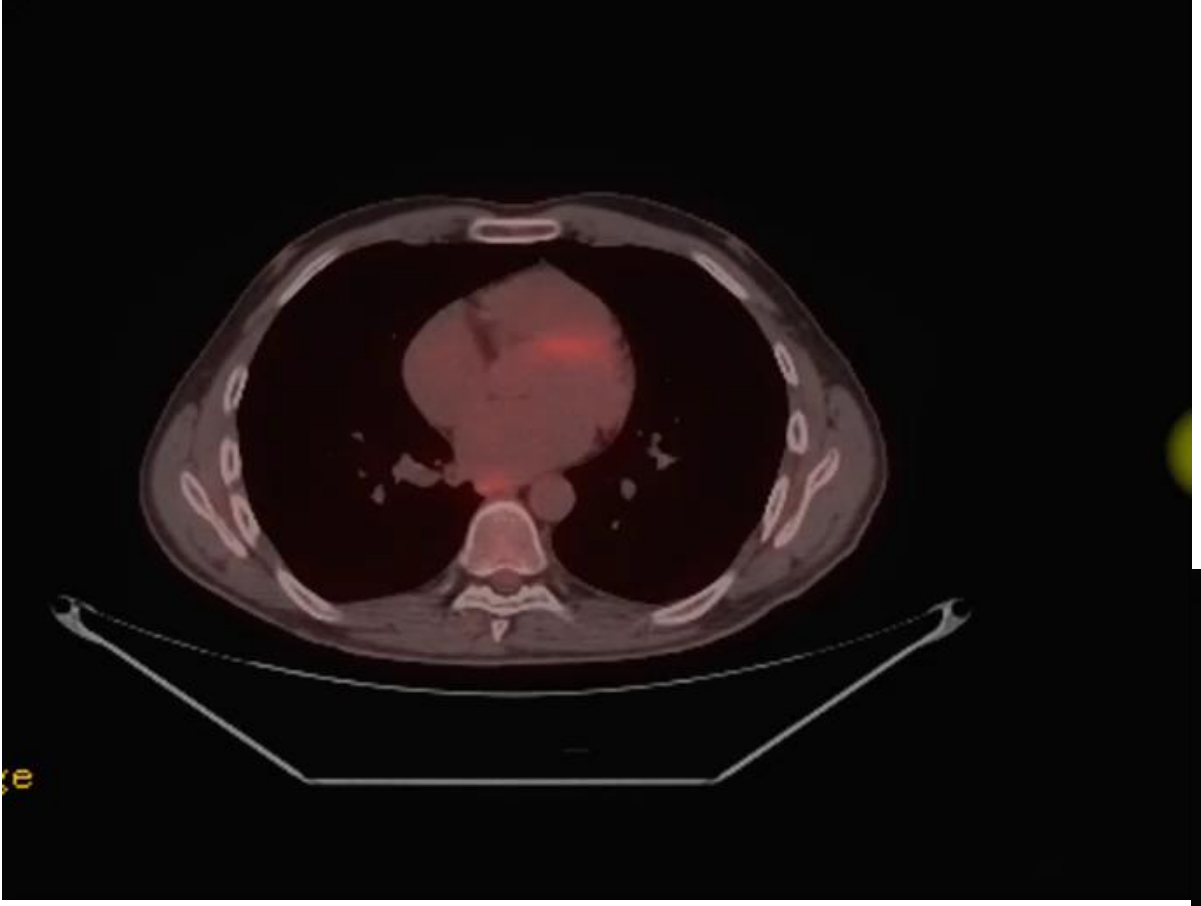

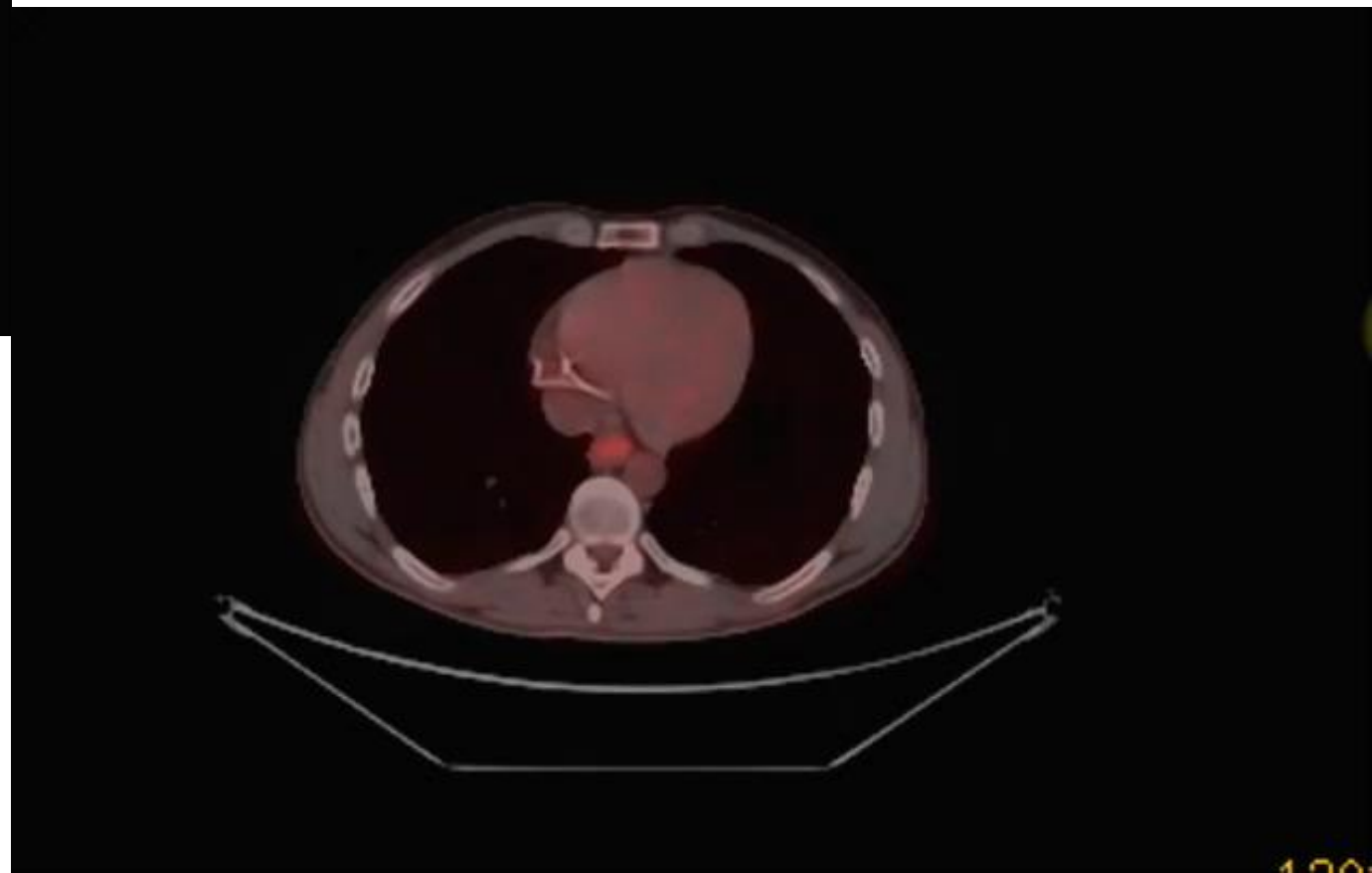

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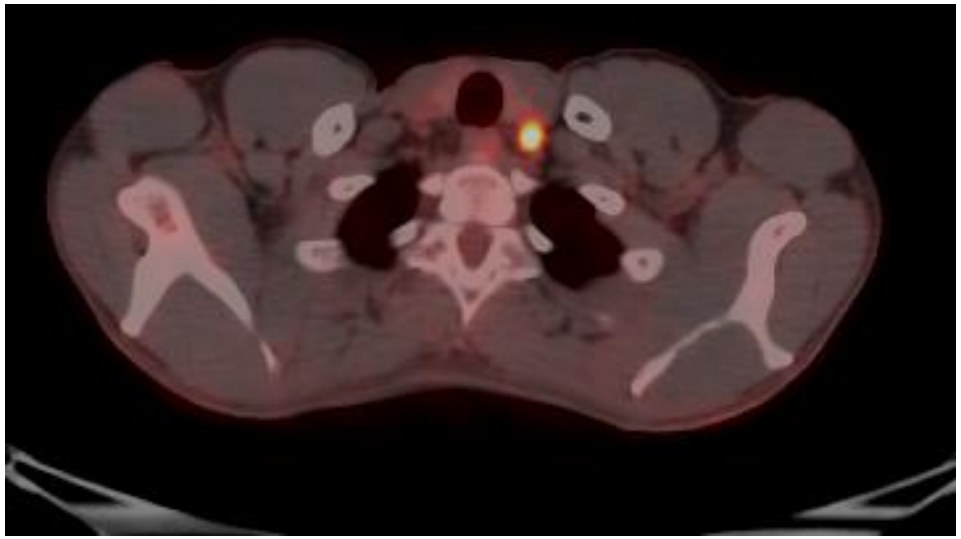
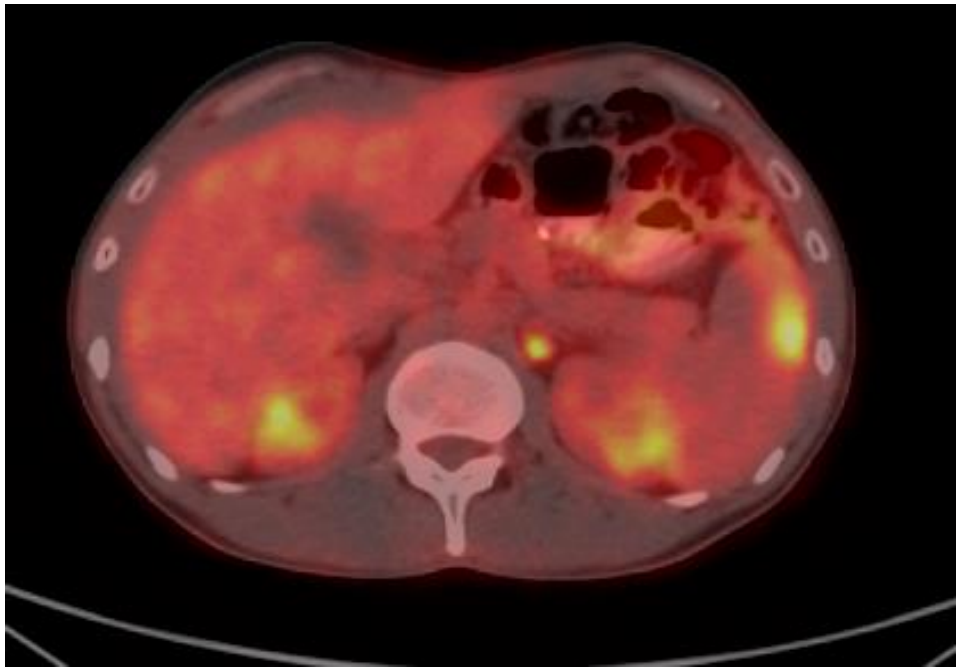
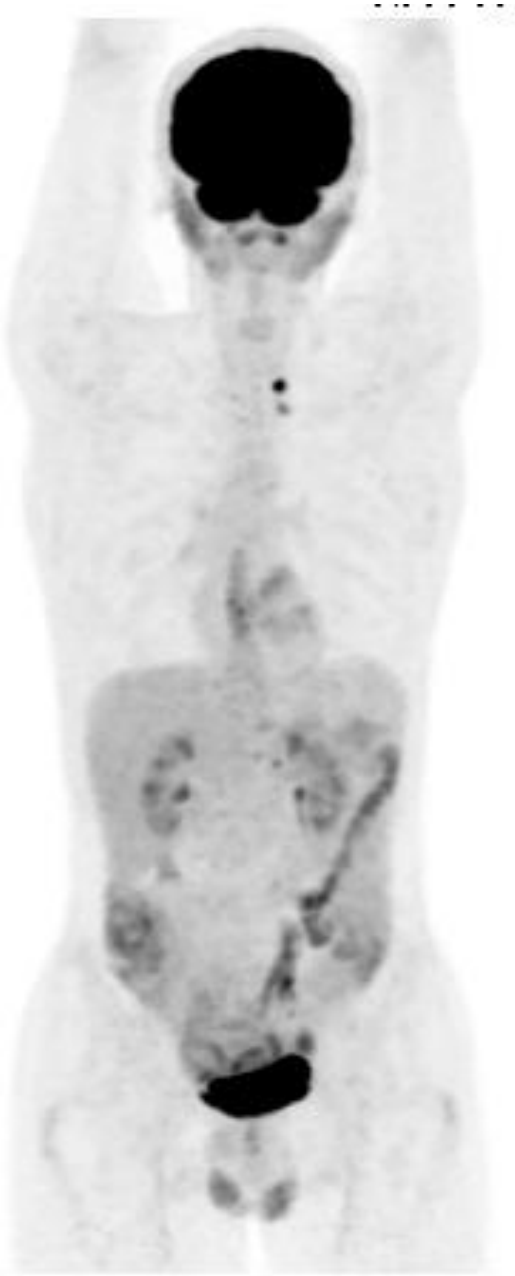
REAL WORLD CASES







Reference

Follow-Up

- Ramucirumab was unavailable (no reimbursement)
- Weekly paclitaxel was started
- Still under this treatment (4th week)

Reference

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Thank you very much for listening

ESMO GUIDELINES:
REAL WORLD CASES

ANALYSIS OF THE CASES

And guideline recommendations

Kohei Shitara
National Cancer Center Hospital East

DISCLOSURES

A position of a board member or advisor: Bristol Myers Squibb, Takeda, Ono Pharmaceutical, Novartis, Daiichi Sankyo, Amgen, Boehringer Ingelheim, Merck Pharmaceutical,Astellas,Guardant Health Japan, Janssen, AstraZeneca,Zymeworks Biopharmaceuticals, ALX Oncology Inc.,and Bayer

Honoraria for lectures: Bristol-Myers Squibb,Ono Pharmaceutical,Janssen, Eli Lilly,Astellas,and AstraZeneca

Clinical research grants: Astellas, Ono Pharmaceutical, Daiichi Sankyo, Taiho Pharmaceutical, Chugai, Merck Pharmaceutical, Amgen, Eisai, PRA Health Sciences and Syneos Health

PRESENTED CASES

41y Male, d-MMR, CPS0, liver metastases

Treated with

- CapeOX+pembro
- Surgery to primary f/w by cape+pembro
- Triplet chemo for recurrence
- Nivo+Ipi
- PTX

QUESTION RELATED TO PRESENTED CASES

- 1st-line for MSI-H pts
- Surgery after chemotherapy
- Triplet chemotherapy
- ICI rechallenge

ESMO GUIDELINE

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

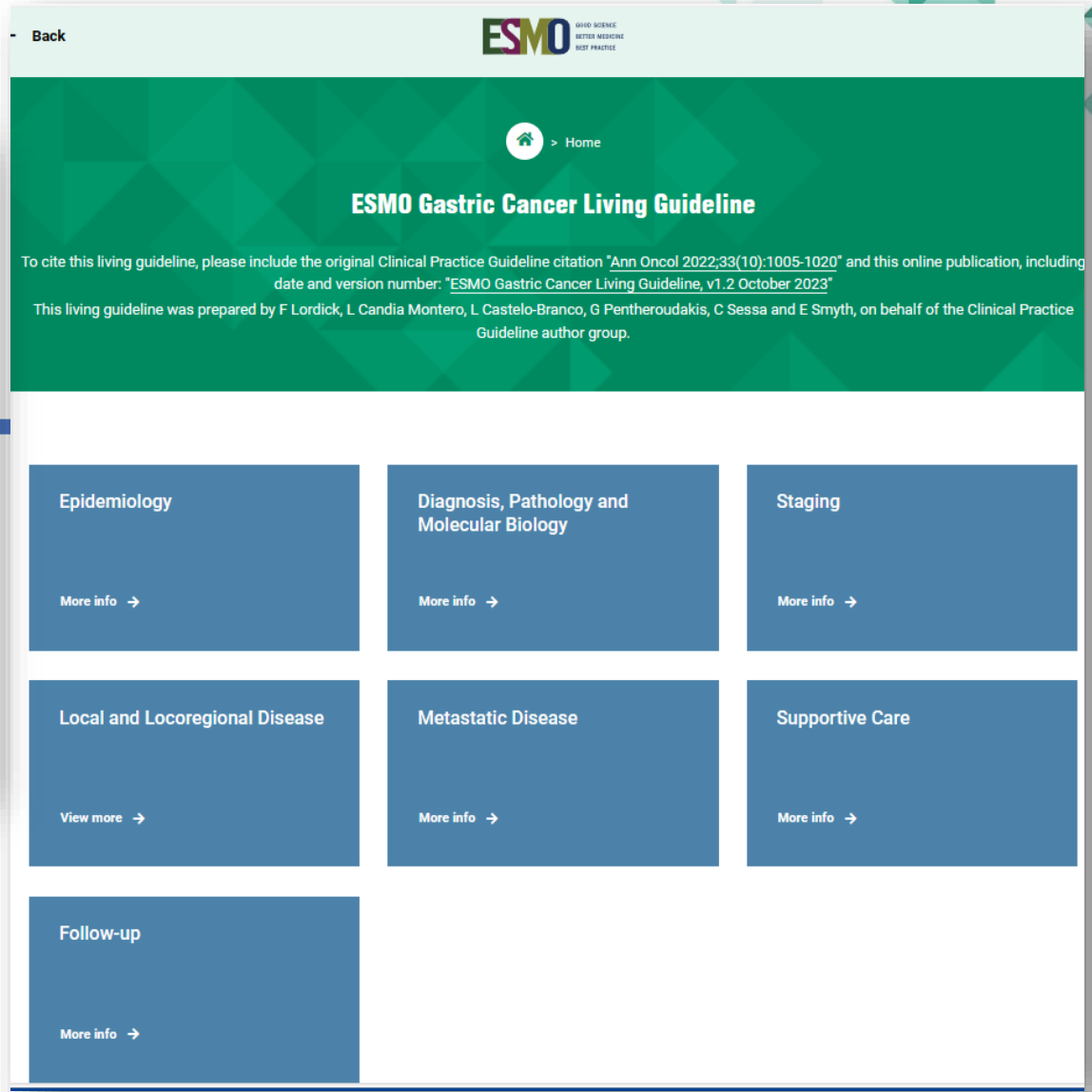
SPECIAL ARTICLE

Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

F. Lordick[1], F. Carneiro[2,3,4], S. Cascinu[5], T. Fleitas[6], K. Haustermans[7], G. Piessen[8,9,10,11], A. Vogel[12] & E. C. Smyth[13], on behalf of the ESMO Guidelines Committee*

[1]Department of Medicine II (Oncology, Gastroenterology, Hepatology, Pulmonology and Infectious Diseases), University Cancer Center Leipzig (UCCL), University Medical Center, Leipzig, Germany; [2]Department of Pathology, Centro Hospitalar Universitário de São João (CHUSJ), Porto; [3]Faculty of Medicine, University of Porto (FMUP), Porto; [4]Instituto de Investigação e Inovação em Saúde (i3S)/Institute of Molecular Pathology and Immunology, University of Porto (Ipatimup), Porto, Portugal; [5]Department of Medical Oncology, Comprehensive Cancer Center, Università Vita-Salute, IRCCS Ospedale San Raffaele, Milan, Italy; [6]Department of Medical Oncology, INCLIVA Biomedical Research Institute, University of Valencia, Valencia, Spain; [7]Department of Radiation Oncology, University Hospital Leuven, Leuven, Belgium; [8]University of Lille, UMR9020-U1277 - CANTHER - Cancer Heterogeneity Plasticity and Resistance to Therapies, Lille; [9]CNRS, UMR9020, Lille; [10]Inserm, U1277, Lille; [11]CHU Lille, Department of Digestive and Oncological Surgery, Lille, France; [12]Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany; [13]Department of Oncology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

Available online 29 July 2022



https://www.esmo.org/living-guidelines/esmo-gastric-cancer-living-guideline
Lordick F, et al. Ann Oncol 2022

PAGA GUIDELINE

- Consensus meeting on Aug 26, 2023
- 20 voting Asian experts from 10 societies

- 38 ESMO recommendations
  - Lack of agreement 23
  - Discussed 16

- Published online on Feb 3

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

SPECIAL ARTICLE

Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with gastric cancer

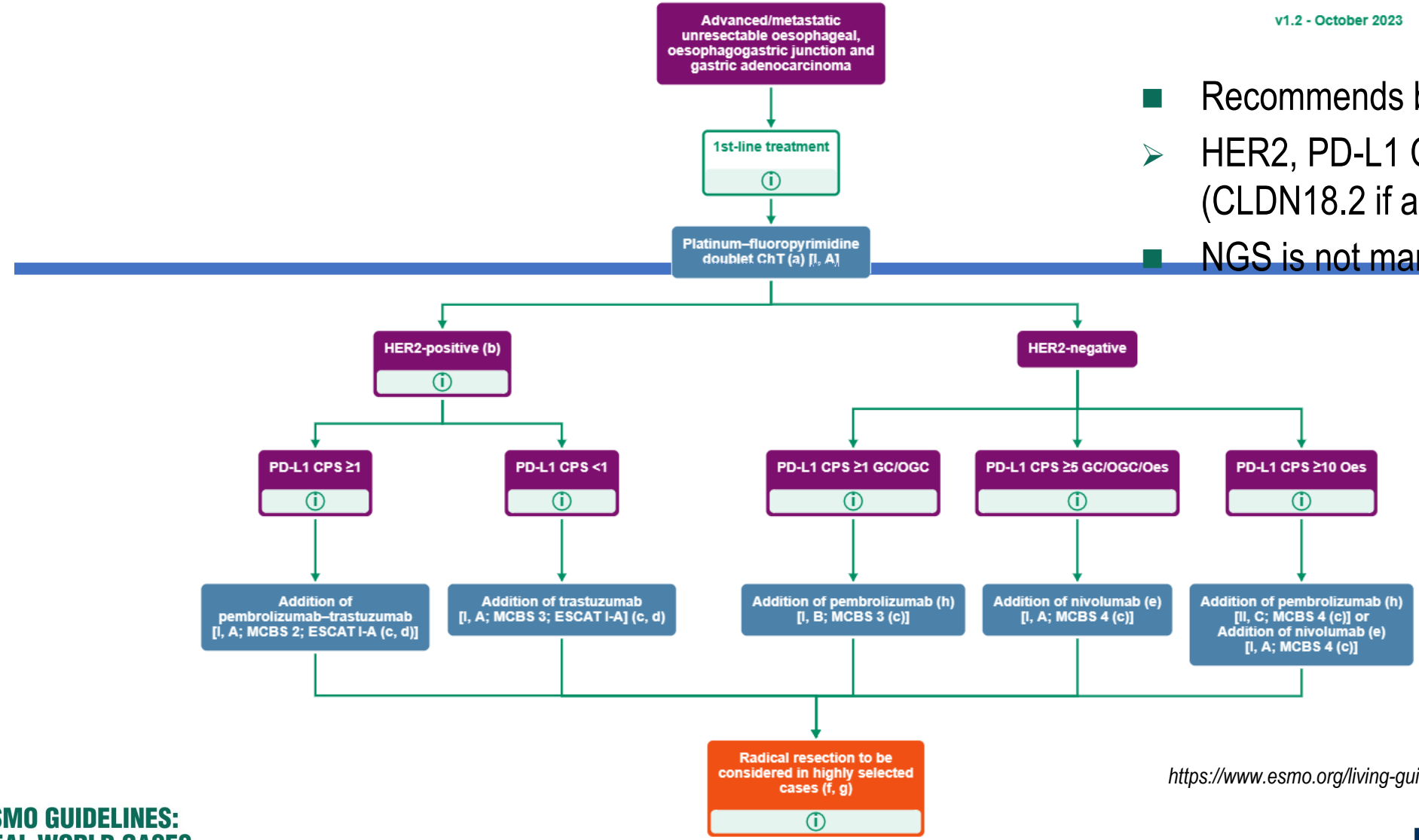
K. Shitara[1*], T. Fleitas[2], H. Kawakami[3], G. Curigliano[4,5], Y. Narita[6], F. Wang[7], S. O. Wardhani[8], M. Basade[9], S. Y. Rha[10], W. I. Wan Zamaniah[11], D. L. Sacdalan[12], M. Ng[13], K. H. Yeh[14,15], P. Sunpaweravong[16], E. Sirachainan[17], M.-H. Chen[18], W. P. Yong[19], J. L. Peneyra[20], M. N. Ibtisam[21], K.-W. Lee[22], V. Krishna[23], R. R. Pribadi[24], J. Li[25], A. Lui[26], T. Yoshino[1], E. Baba[27], I. Nakayama[28], G. Pentheroudakis[29], H. Shoji[30], A. Cervantes[31,32], C. Ishioka[33] & E. Smyth[34]

Shitara K, et al. ESMO open 2024

QUESTION RELATED TO PRESENTED CASES

- 1st-line for MSI-H pts
- Surgery after chemotherapy
- Triplet chemotherapy
- ICI rechallenge

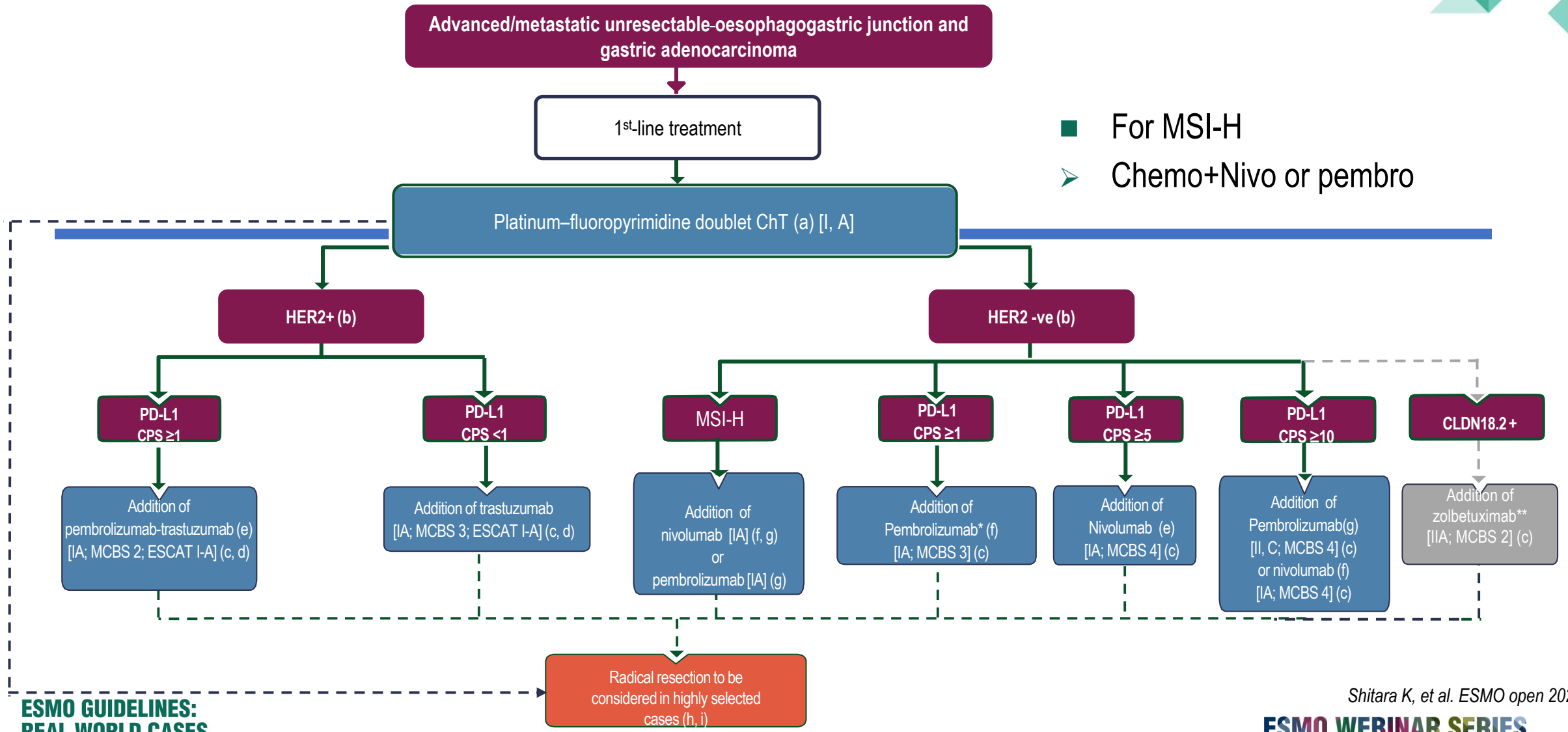
ESMO LIVING GUIDELINE: 1ST-LINE TREATMENT



- Recommends biomarker tests
  - HER2, PD-L1 CPS, MSI/MMR (CLDN18.2 if available)
- NGS is not mandatory/optional

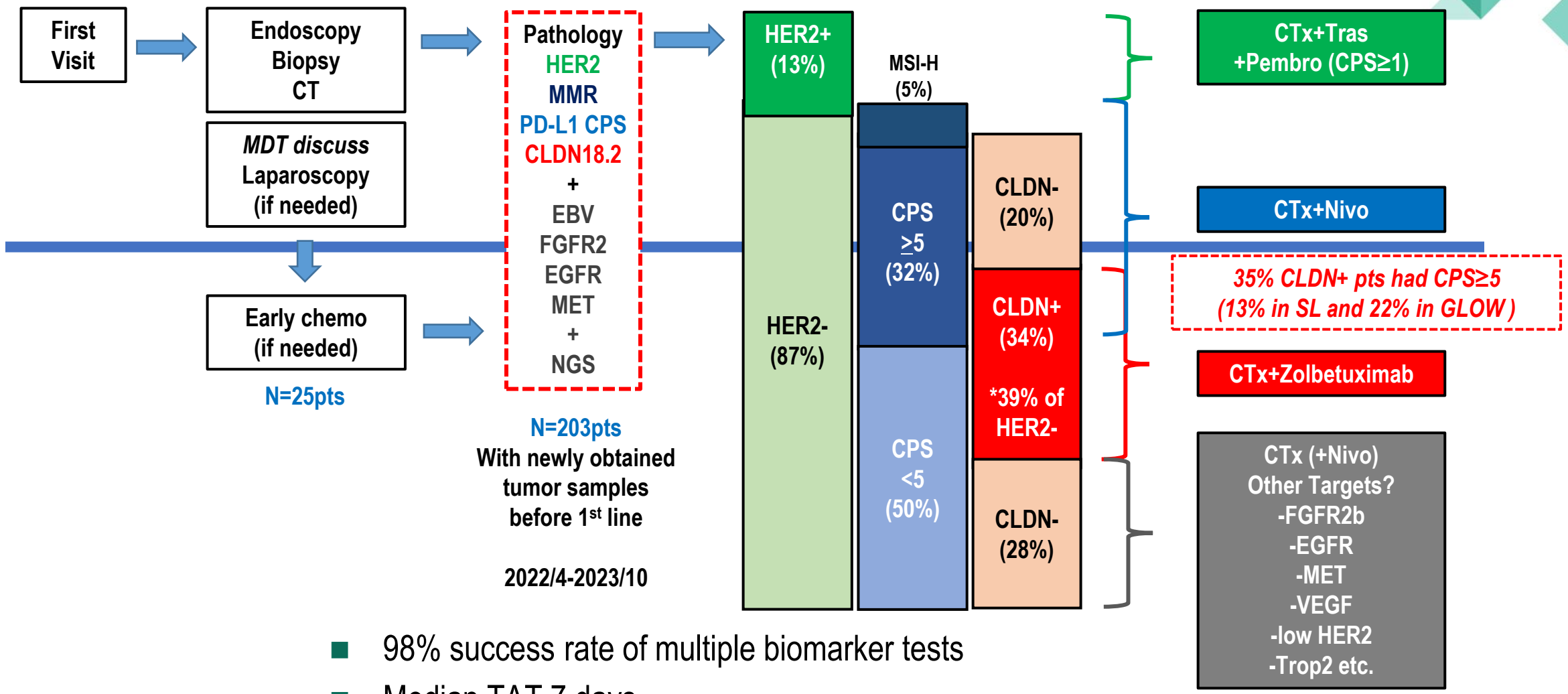
https://www.esmo.org/living-guidelines/esmo-gastric-cancer-living-guideline
Lordick F, et al. Ann Oncol 2022

PAGA: 1ST-LINE TREATMENT



Shitara K, et al. ESMO open 2024

NCCHE EXPERIENCE



- 98% success rate of multiple biomarker tests
- Median TAT 7 days
- 88% received chemo after obtaining biomarker results

Okazaki, Nakayama.Manuscript submitted

NCCN GUIDELINE: 1ST-LINE TREATMENT

First-Line Therapy

- Oxaliplatin is preferred over cisplatin due to lower toxicity.

Preferred Regimens

- HER2 overexpression positive[c]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin and trastuzumab[f]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, trastuzumab[f] and pembrolizumab for PD-L1 CPS ≥1 (category 1)[g,h,17-18]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), cisplatin and trastuzumab (category 1)[f,19]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), cisplatin, trastuzumab[f] and pembrolizumab for PD-L1 CPS ≥1 (category 1)[g,h,17-18]
- HER2 overexpression negative[c]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS ≥5) (category 1)[g,h,20]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and pembrolizumab for PD-L1 CPS ≥1[g,h,21] (category 1 for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS 1 to <10)
  - Fluoropyrimidine (fluorouracil[a] or capecitabine) and oxaliplatin[22-24]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), cisplatin, and pembrolizumab for PD-L1 CPS ≥1[g,h,21] (category 1 for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS 1 to <10)
  - Fluoropyrimidine (fluorouracil[a] or capecitabine) and cisplatin[22,25-27]
- MSI-H/dMMR tumors (independent of PD-L1 status)[c]
  - Pembrolizumab[g,h,28-30]
  - Dostarlimab-gxly[g,h,31]
  - Nivolumab and ipilimumab[g,h,20]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and nivolumab[g,h,20]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and pembrolizumab[g,h,29,30]

- Chemo+Nivo or pembro in MSI-H
- Pembro, Dostarlimab, Nivo+Ipi: No official FDA approval as 1st-line for GC nor MSI-H

NCCN guideline ver. 2 2024

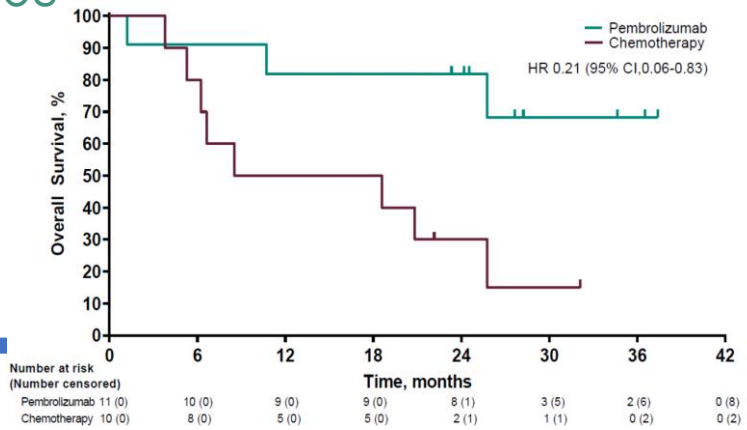
KN062, KN859 AND CM649: MSI-H SUBGROUP

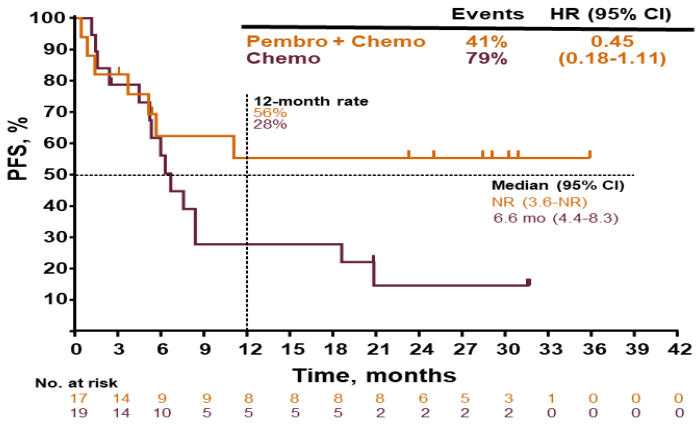
Pembro
ORR **57%**
OS HR 0.21
PFS HR 0.72

Pembro+Chemo
(KN062)
ORR **65%**
OS HR 0.45
PFS HR 0.45

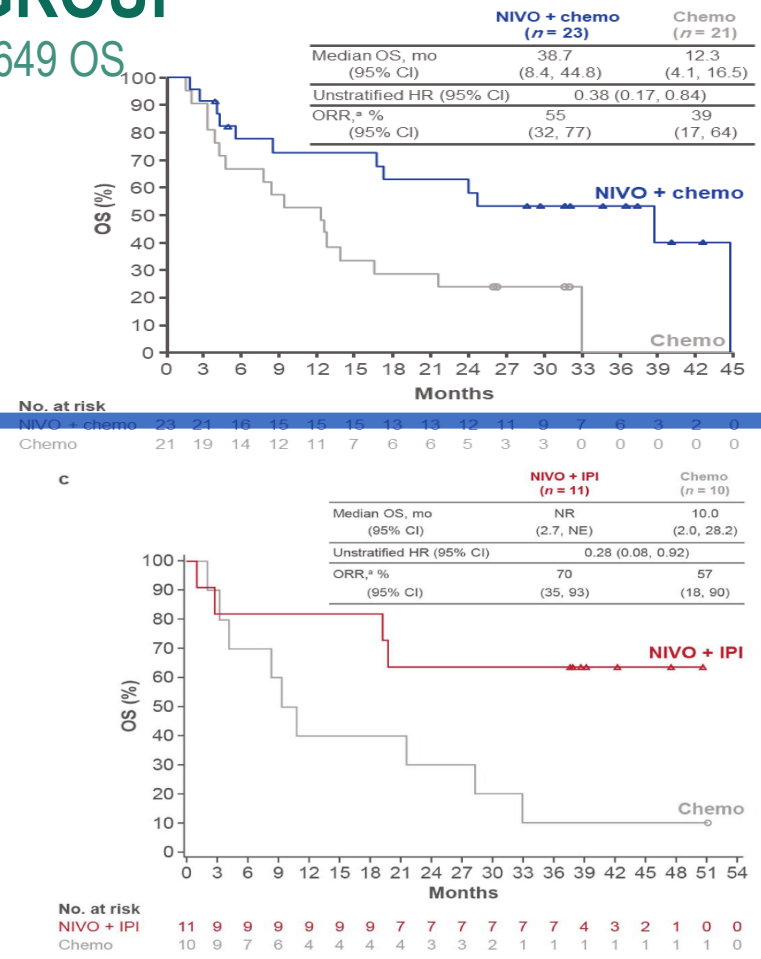
Pembro+Chemo
(KN859)
ORR **80%**
OS HR 0.34
PFS HR 0.27

KN062 OS





CM649 OS



Nivo+Chemo
ORR **55%**
OS HR 0.38

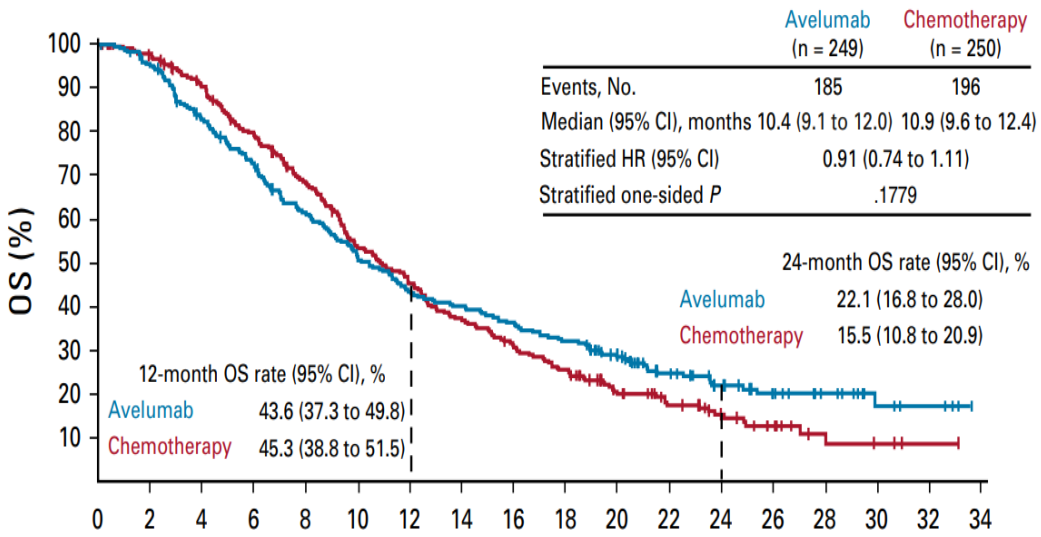
NivoIpi
ORR **70%**
OS HR 0.28

- 2-5% in trials
- OS HR 0.21-0.45
- No direct comparison of IO vs IO+chemo

Shitara K, et al. JAMA Oncol 2019; Nature 2021
Rha SY, et al. Lancet Oncol 2023
https://www.ema.europa.eu/en/medicines/human/EPAR/keytruda

IO ALONE AS MAINTENANCE

JAVELIN100 OS



	Avelumab (n = 249)	Chemotherapy (n = 250)
Events, No.	185	196
Median (95% CI), months	10.4 (9.1 to 12.0)	10.9 (9.6 to 12.4)
Stratified HR (95% CI)	0.91 (0.74 to 1.11)	
Stratified one-sided *P*	.1779	

- ITT: No OS benefit
- OS HR 0.27 in MSI-H

AIO Moonlight trial

Figure 2: Progression-free survival

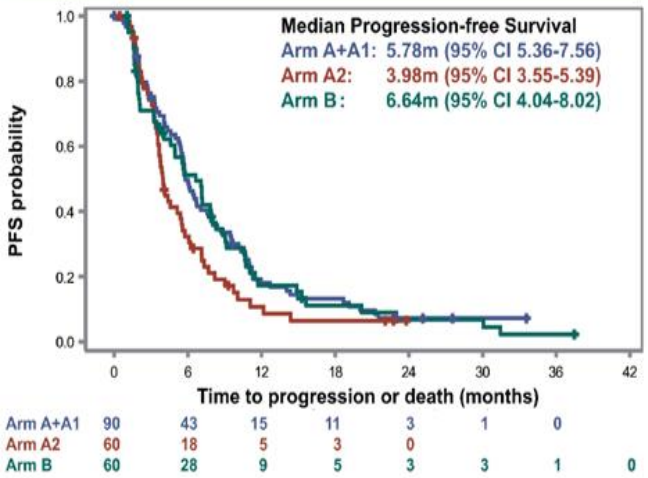
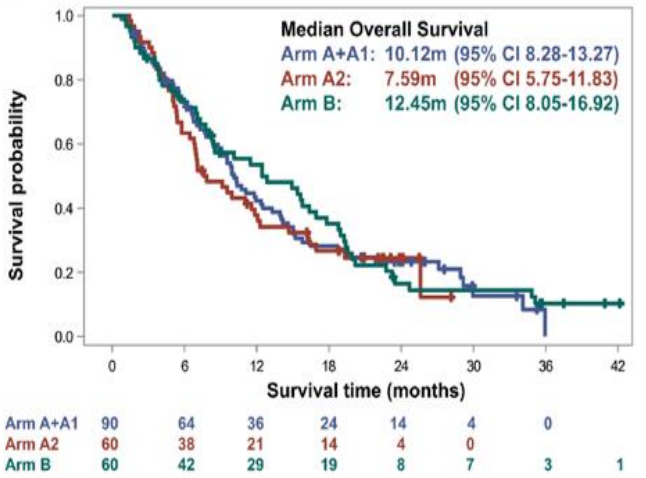


Figure 3: Overall survival

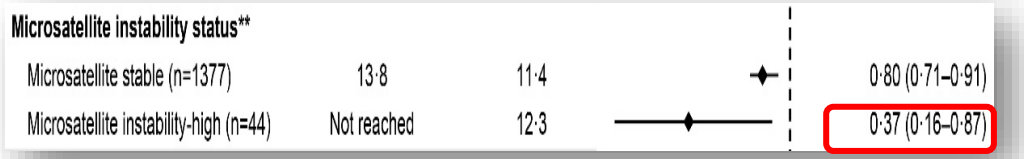


- FOLFOX f/w byNivo/Ipi (arm A2) seems to be inferior to FOLFOX alone (arm B)

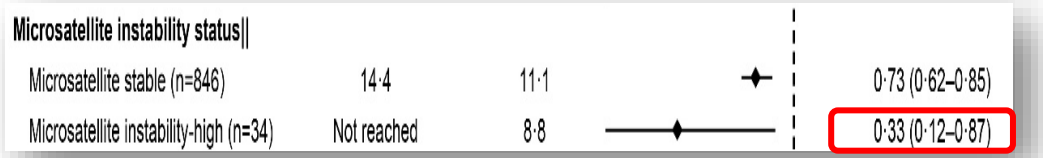
Shah MA, et al.ASCO 2024; Moehler M, et al. JCO 2020; Lorenzen S, et al. ASCO 2023

CPS IN MSI-H PATIENTS

OS of All pts in CM649

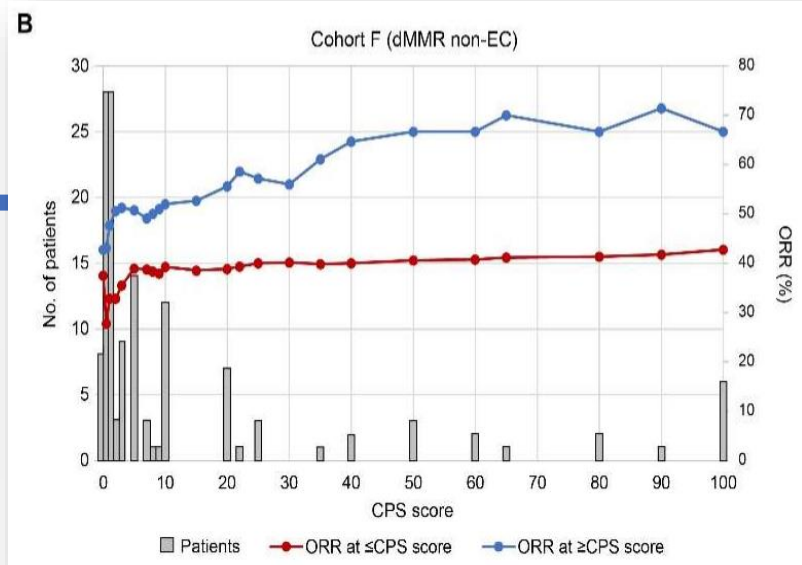


OS of CPS≥5 pts in CM649



- OS benefit in MSI-H regardless of CPS

CPS in GARNET study (dostarlimab for MSI-H tumor)



CPS score	Patients	Responders	ORR (%) at ≤CPS score	ORR (%) at ≥CPS score
0	8	3	37.50	42.76
<1	28	7	27.78	43.07
1	28	11	32.81	47.71
2	3	1	32.84	50.62
3	9	5	35.53	51.28
5	14	8	38.89	50.72
7	3	1	38.71	49.09
8	1	0	38.30	50.00
9	1	0	37.89	50.98
10	12	6	39.25	52.00
15	2	0	38.53	52.63
20	7	3	38.79	55.56
22	1	1	39.32	58.62
25	3	2	40.00	57.14
30	7	3	40.16	56.00
35	1	0	39.84	61.11
40	2	1	40.00	64.71
50	3	2	40.60	66.67
60	2	1	40.74	66.67
65	1	1	41.18	70.00
80	2	1	41.30	66.67
90	1	1	41.73	71.43
100	6	4	42.76	66.67

- ORR observed regardless of CPS

Shitara K, et al. Nautre 2022; Andre T, et al. JAMA Netw Open 2023

PRESENTED CASES

- 1st-line for MSI-H pts
- Surgery after chemotherapy
- Triplet chemotherapy
- ICI rechallenge

PAGA GUIDELINE: SURGERY FOR METASTATIC GC

PAGA

- Gastrectomy is not recommended in metastatic gastric cancer unless required for palliation of symptoms [I, D].
- Resection of metastases cannot be recommended in general, but might be considered as an individual approach in highly selected cases with oligometastatic disease and response to ChT [V, C].

Context

The phase II AIO-FLOT3 trial reported favourable outcomes in patients with oligometastatic disease after FLOT induction followed by gastrectomy plus resection of the metastatic site, but this study was not randomised. (Al-Batran, 2017)

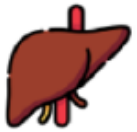
At the present time, data to support routine resection or ablation of oligometastases are limited. (Kataoka, 2017)

In case of limited peritoneal carcinomatosis, addition of HIPEC to cytoreduction has been reported to be safe and may be associated with some improved oncological outcomes, but is yet to be confirmed in larger trials. (Bonnot, 2019; Bonnot, 2021; Rau, 2021)

v1.2 - October 2023

- Still investigational
- Case by Case MDT discussion needed

OMEC project

	Oligometastatic disease (consensus)	Not oligometastatic disease (consensus)
omec	1 organ with ≤ 3 metastases *or* 1 involved extra-regional lymph node station	Organ metastases *and* extra-regional lymph node metastases
	No progression in number of metastases after ≥ 3 months of systemic therapy	Progression in number of metastases after ≥ 3 months of systemic therapy
	≤ 3 unilobar liver metastases	

- European consensus of oligo metastasis
  - 1 organ with ≤3 mets / stability on chemo (≥3ms)
  - Chemo followed by local treatment recommended

https://www.esmo.org/living-guidelines/esmo-gastric-cancer-living-guideline
Lordick F, et al. Ann Oncol 2022
Kroese TE, et al. Eur J Cancer 2022, 2024; ESMO gastrointestinal Oncology 2023

OS AFTER LIVER RESECTION ADN JGCA GUIDELINE

JGCA guideline

***CQ10* Is surgical treatment for oligo metastases recommended?**

Recommendation

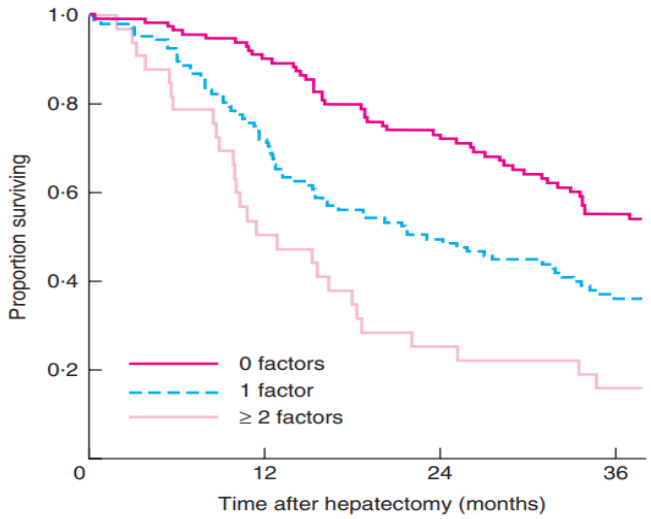
Surgical resection after neoadjuvant chemotherapy is weakly recommended for a small number of paraaortic lymph node metastases confined to No.16a2/b1. In addition, surgical resection is weakly recommended for solitary liver metastasis without other incurable factors (consensus rate 100%, 7/7, strength of evidence C).

***CQ11* Is conversion surgery recommended?**

Recommendation

Conversion surgery for patients with stage IV gastric cancer is weakly recommended with the condition that chemotherapy provides a certain antitumor effect, the response is maintained, and R0 resection is possible (consensus rate 100%, 7/7, strength of evidence D).

Upfront hepatectomy

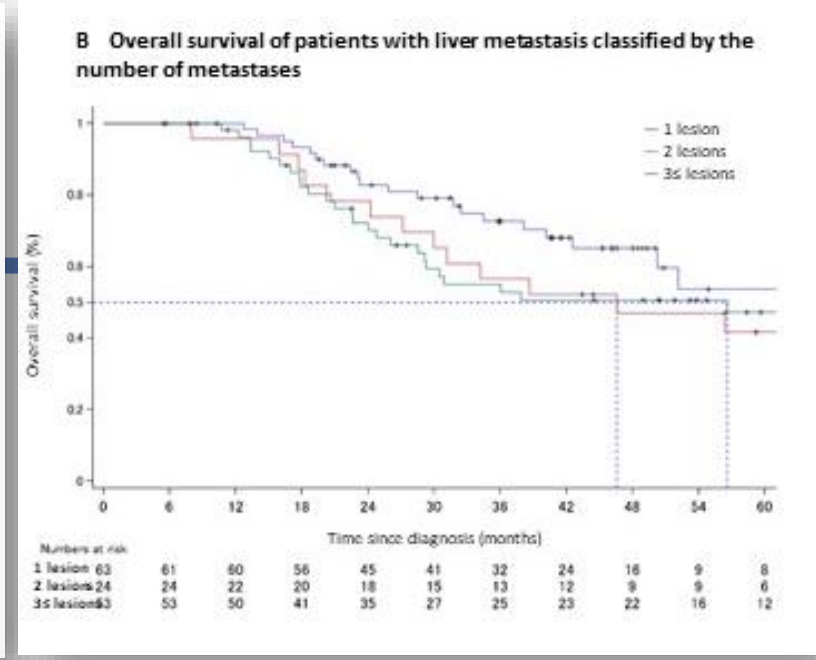


No. at risk

0 factors	115	97	75	53
1 factor	108	77	53	37
≥ 2 factors	33	16	8	5

	Hazard ratio	*P*
Serosal invasion of primary tumour	1·50 (1·10, 2·05)	0·012
No. of liver metastases ≥ 3	2·33 (1·62, 3·36)	< 0·001
Size of largest hepatic tumour ≥ 5·0 cm	1·62 (1·15, 2·28)	0·005

Conversion surgery (CONVO-GC01)



- Recommended in selected case

Kinoshita T, et al. British Journal of Surgery 2015; Yoshida K, et al. Ann Gastroenterol Surg. 2022; JGCA guideline ver. 6. 2023

PROSPECTIVE TRIALS FOR OLIGOMETASTASIS

Table 1. Overview of completed and ongoing trials in patients with oligometastatic esophagogastric cancer

	Author/sponsor name or clinicaltrials.gov ID	Primary tumor	Country	Study type	Maximum number of organs	Maximum number of metastases	Type of OMD	Staging	Treatment	Median overall survival
Completed	Zhao et al., 2023[11]	Esophageal SCC	China	Phase II NR	ns	5	Synchronous/ metachronous	ns	IO + ChT + SBRT	12.8 Months
	Cui et al., 2023[12]	Gastric AC	China	Phase II NR	1	Organ-specific	Synchronous	CT or laparoscopy	ChT + surgery + ChT	Not reached
	Liu et al., 2020[13]	Esophageal SCC	Chins	Phase II NR	ns	3	Metachronous	CT or ^{18}F-FDG PET	SBRT +/− ChT	24.6 Months
	Al-Batran et al., 2017[14]	Gastric AC or EGJ AC	Germany	Phase II NR	1 + RPLN	Organ-specific	Synchronous	CT/MRI or ^{18}F-FDG PET	ChT + surgery	31.3 Months
Ongoing	NCT04510064 (Fudan University)[15]	Gastric AC or EGJ AC	China	Phase II NR	1	Organ-specific	Synchronous	CT or MRI	IO + ChT + surgery	NA
	NCT04248452 (ECOG-ACRIN Cancer Research Group)[16]	Esophageal AC and gastric	USA	Phase III R	ns	3	Synchronous	CT or MRI	ChT + SBRT versus ChT	NA
	NCT03904927 (Fudan University)[17]	Esophageal SCC	China	Phase II R	2	4	Synchronous/ metachronous	CT	ChT + SBRT/Surgery versus ChT	NA
	NCT03161522 (M.D. Anderson Cancer Cancer)[18]	Esophageal AC	USA	Phase II NR	1	3	Synchronous	^{18}F-FDG PET/CT	ChT + SBRT/surgery	NA
	NCT03399253 (Sun Yat-sen University)[19]	Gastric AC	China	Phase II-III R	2	Organ-specific	Synchronous	CT	ChT + surgery versus ChT	NA
	NCT02578368 'FLOT5' (Krankenhaus Nordwest)[20]	Gastric AC or EGJ AC	Germany	Phase III R	1 + RPLN	Organ-specific	Synchronous	CT/MRI or ^{18}F-FDG PET	ChT + surgery versus ChT	NA
	NCT04512417 (Zhejiang Cancer Hospital)[21]	Esophageal SCC or AC	China	Phase II R	ns	4	Synchronous/ metachronous	ns	IO + ChT + SBRT versus IO + ChT	NA
	NCT03042169 'Surgigast' (University Hospital Lille)[22]	Gastric AC or EGJ AC	France	Phase III R	1 + RPLN	Organ-specific	Synchronous	CT/MRI or ^{18}F-FDG PET	ChT + surgery versus ChT	NA

- How about the role of surgery in pts with chemo response?

Kroese TE, et al. ESMO gastrointestinal Oncology 2023

AIO FLOT-5 STUDY (RENAISSANCE)

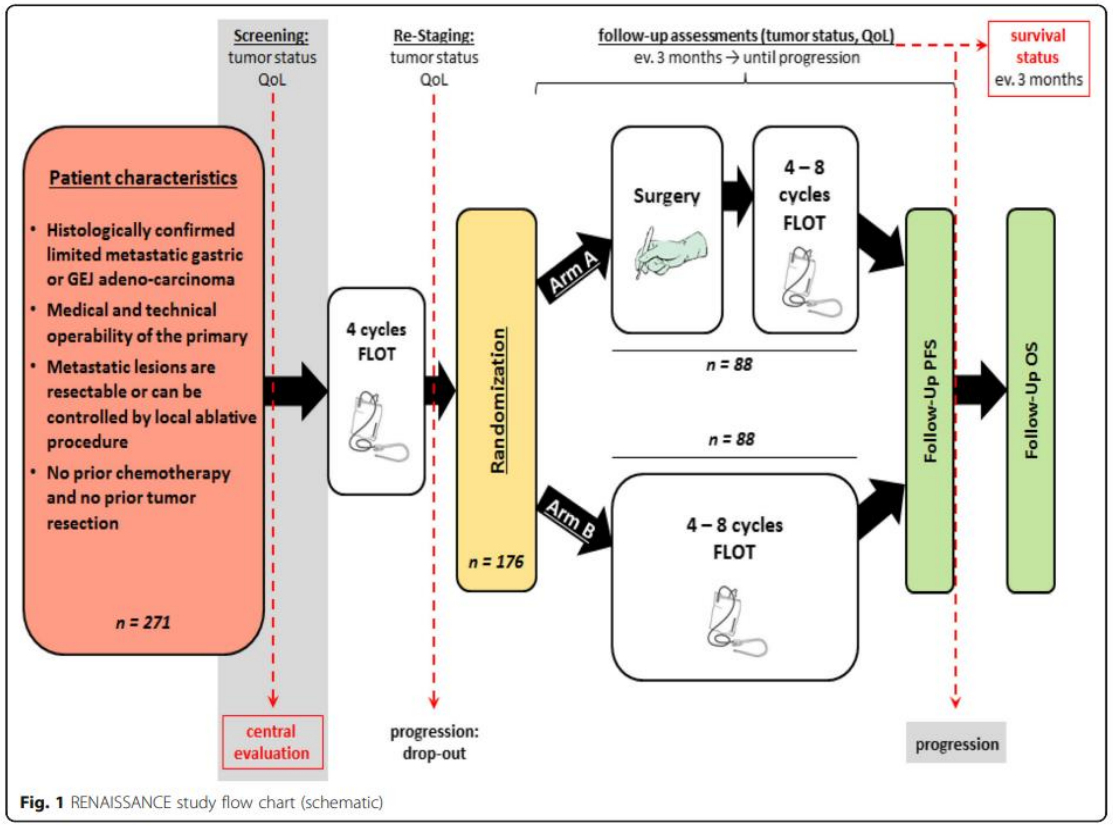
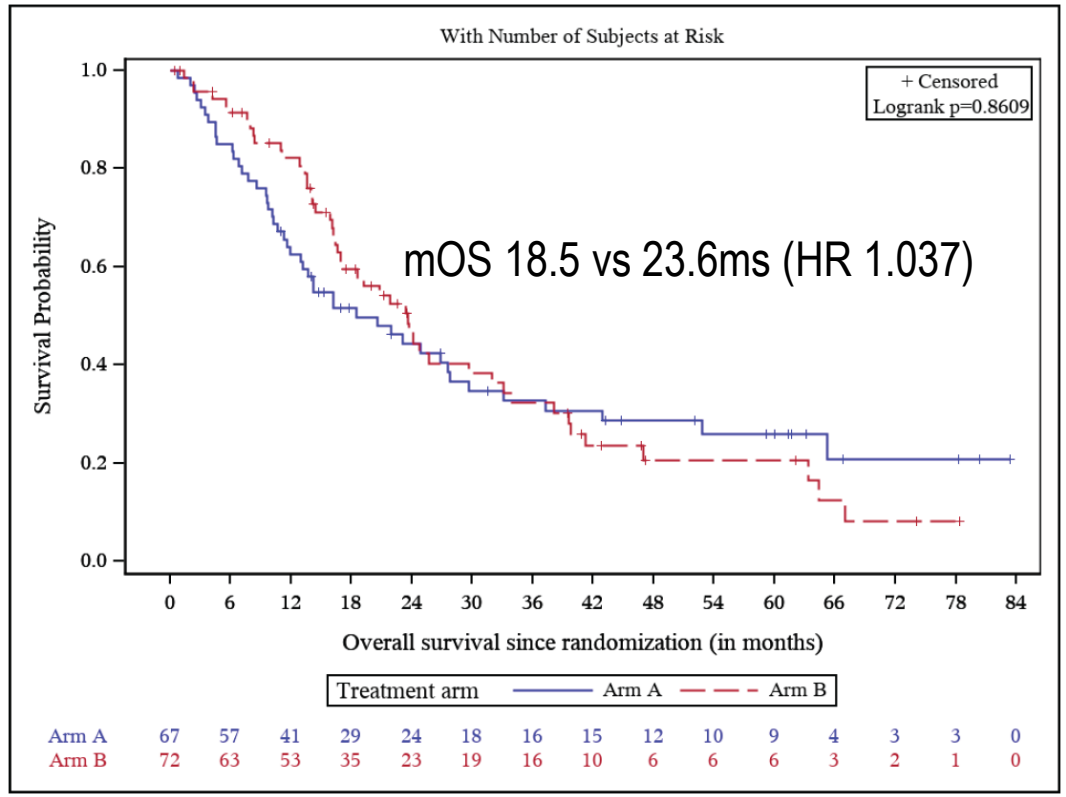


Fig. 1 RENAISSANCE study flow chart (schematic)



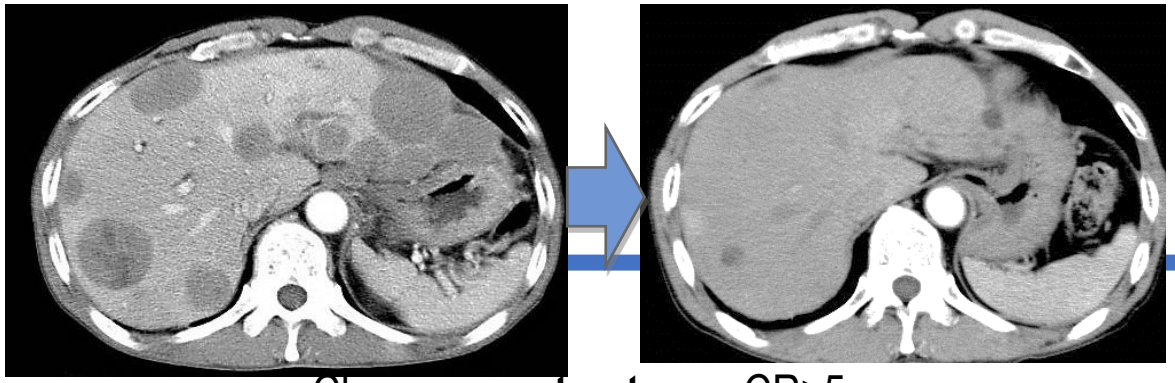
- No OS benefit by adding surgery
  - Suggested benefit only in RPLN mets
  - No clear benefit in liver mets
  - Detrimental in peritoneal mets

Al-Batran SE, et al. ASCO 2024

MY PATIENTS: WHO EXACTLY NEEDS SURGERY?

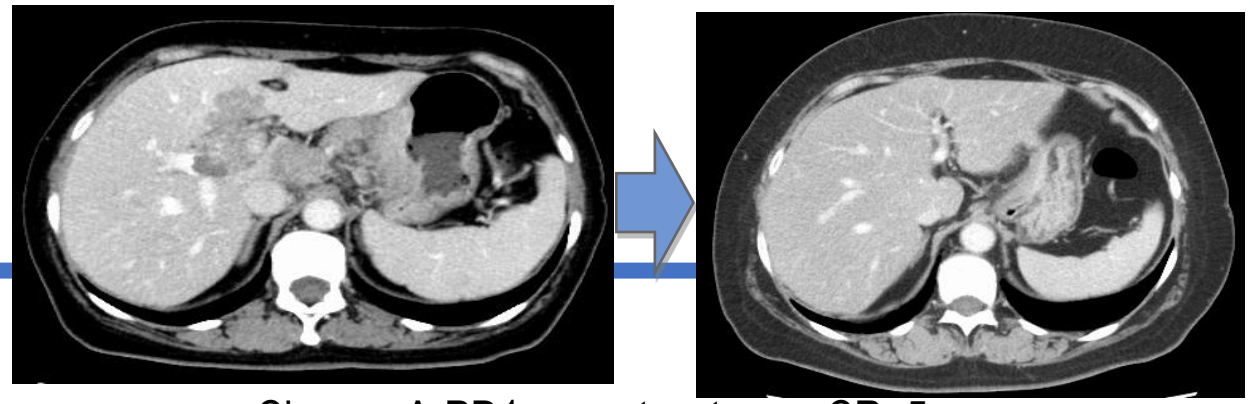
Cured patients with chemo+surgery

MSI unknown



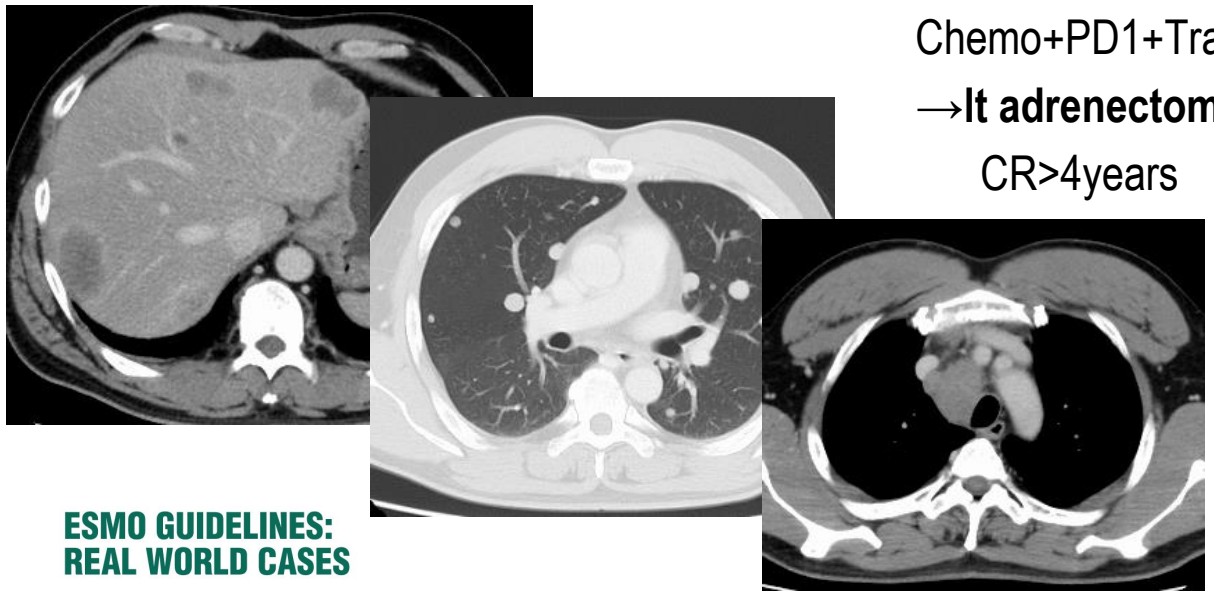
Chemo→**gastrectomy**: CR>5years

MSS

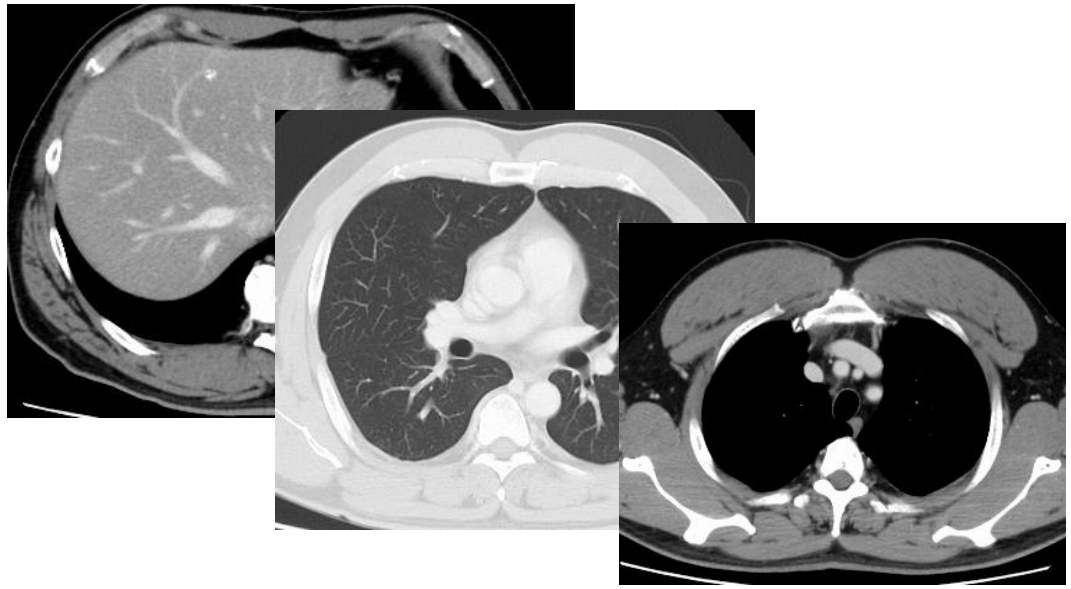


Chemo+A-PD1→**gastrectomy**: CR>5 years

HER2+



Chemo+PD1+Tras
→**It adrenectomy**
CR>4years



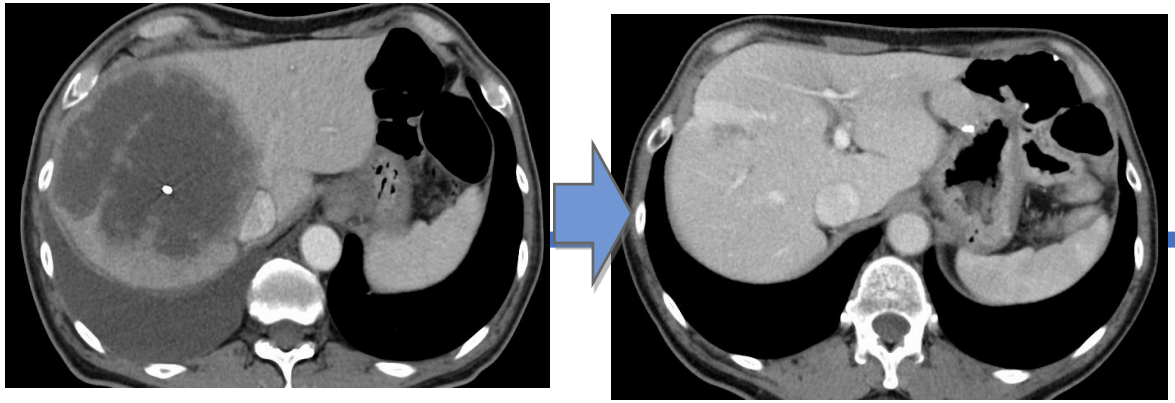
ESMO GUIDELINES: REAL WORLD CASES

NCCHE

MY PATIENTS: WHO EXACTLY NEEDS SURGERY?

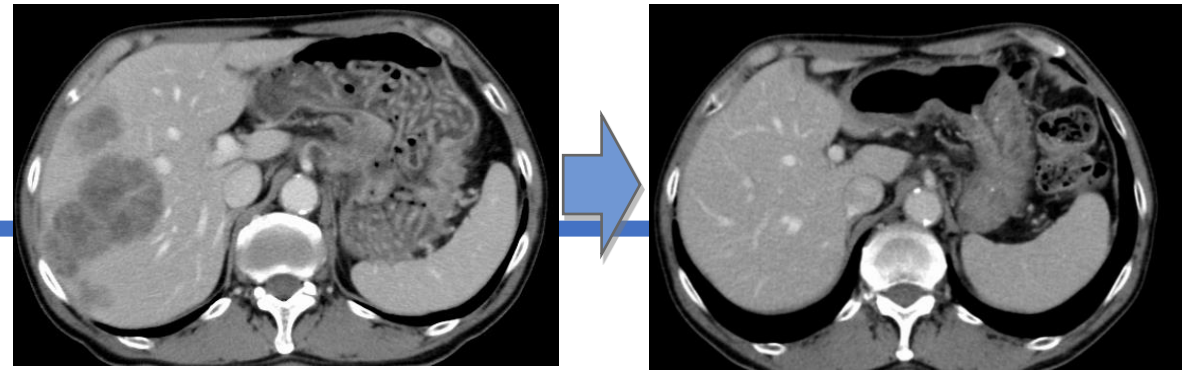
Cured patients without surgery

MSI-H



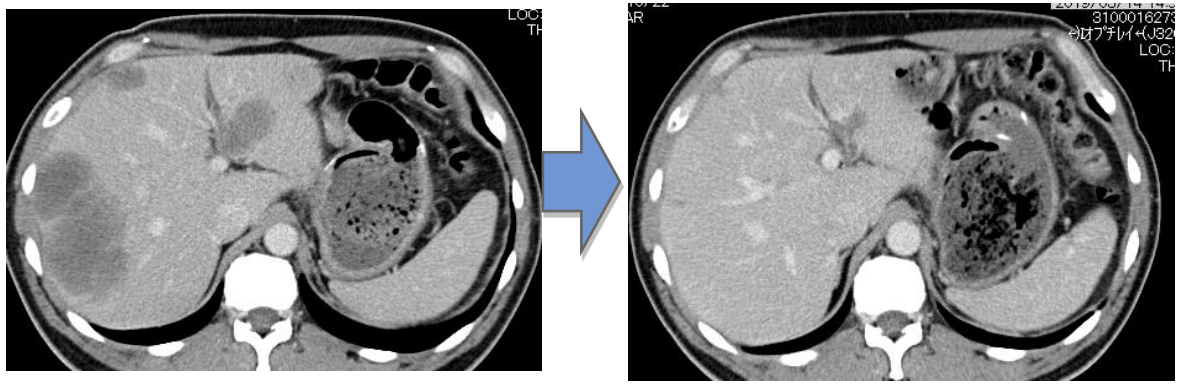
A-PD1 : CR>4 years

MSS



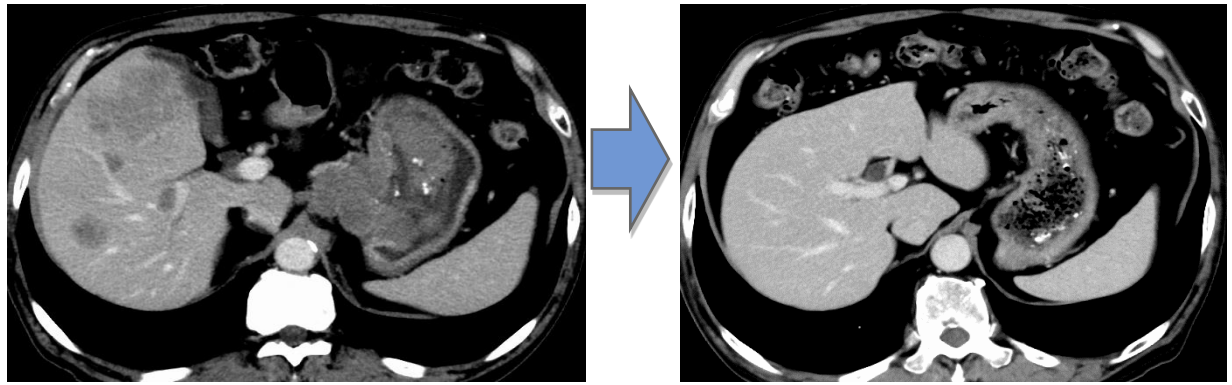
Chemo+A-PD1 : CR>5 years

MSS



Rego+Nivo: CR>5 years

MSS



Rego+Nivo: CR>5 years

NCCHE

Fukuoka S, Shitara K, et al. JCO 2020

PRESENTED CASES

- 1stline for MSI-H pts
- Surgery after chemotherapy
- Triplet chemotherapy
- ICI rechallenge

CONTROVERSY OF TRIPLET

ESMO living guideline

> ESMO Gastric Cancer Living Guideline > Metastatic disease > First Line > First-line Therapy

First-line Therapy

- First-line ChT with a platinum and fluoropyrimidine is recommended. Oxaliplatin is preferred, especially for older patients [I, A]. (Al-Batran, 2008) S-1 is commonly used in Asian patients [I, A]. (Koizumi, 2008)
- Due to higher levels of toxicity and uncertain survival benefit over recommended doublet regimens, first-line taxane-based triplet ChT is not recommended as a standard approach [I, C].
- Irinotecan–5-FU can be considered an alternative option for patients who do not tolerate platinum compounds [II, B]. (Dank, 2008; Giumbaud, 2014)

PAGA guideline

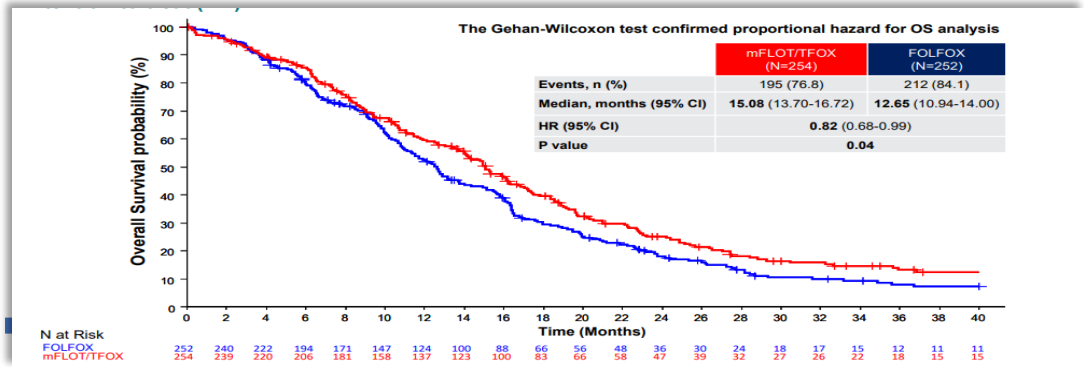
may be an option in this setting. In contrast, the Japanese JCOG1013 failed to demonstrate an improvement in OS for S-1 plus cisplatin plus docetaxel when compared with S-1 plus cisplatin.[53] However, when the low rate of use of subsequent ChT in the GASTFOX study, compared with Asian trials, is taken into account, the results are currently not applicable to the treatment of Asian patients.

- Generally not recommended
- Only for selected pts with fit, biomarker negative in area with low rate of 2nd-line use?

https://www.esmo.org/living-guidelines/esmo-gastric-cancer-living-guideline
Lordick F, et al. Ann Oncol 2022; Shitara K, ESMO open 2023

CONTROVERSY OF TRIPLET

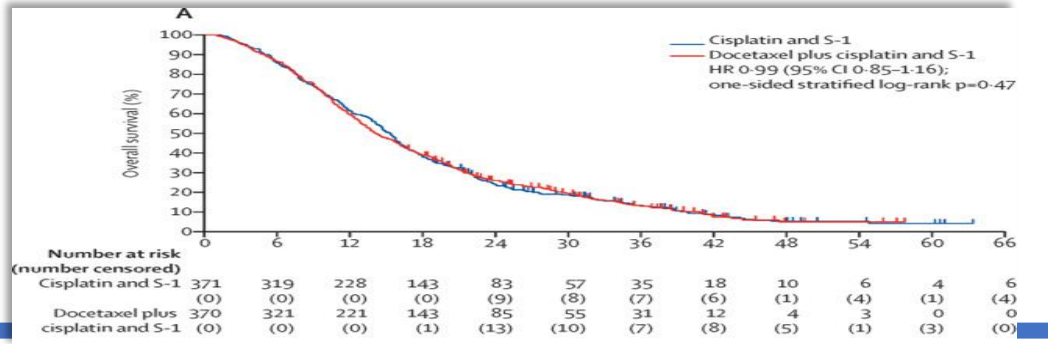
GASTFOX trial: mFLOT/TFOX vs FOLFOX



Prolong OS/ ↑ diarrhea, fatigue, neutropenia

2nd-line use ?

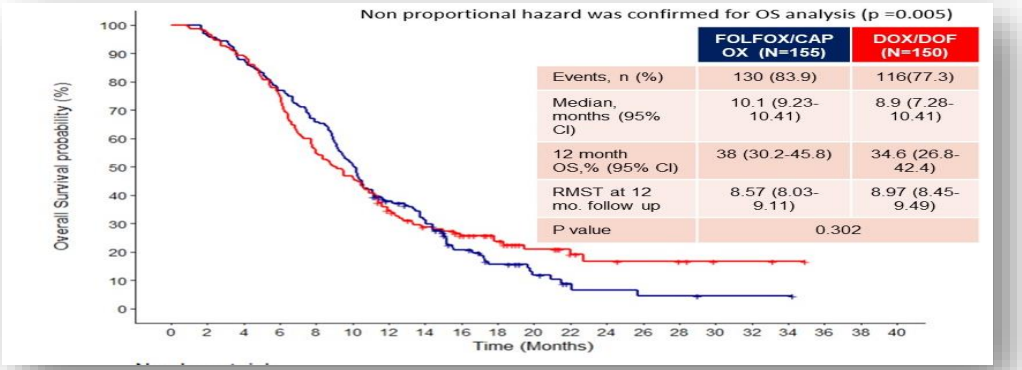
JCOG1013: DCS vs CS (S1+Cis)



Did not improve OS

2nd-line use: 77-79%

DOC-GC: DOC/F vs CapeOX/FOLFOX



No OS benefit

2nd-line use: 27-39%

- No consistent OS benefits
- Different proportions of 2nd-line use

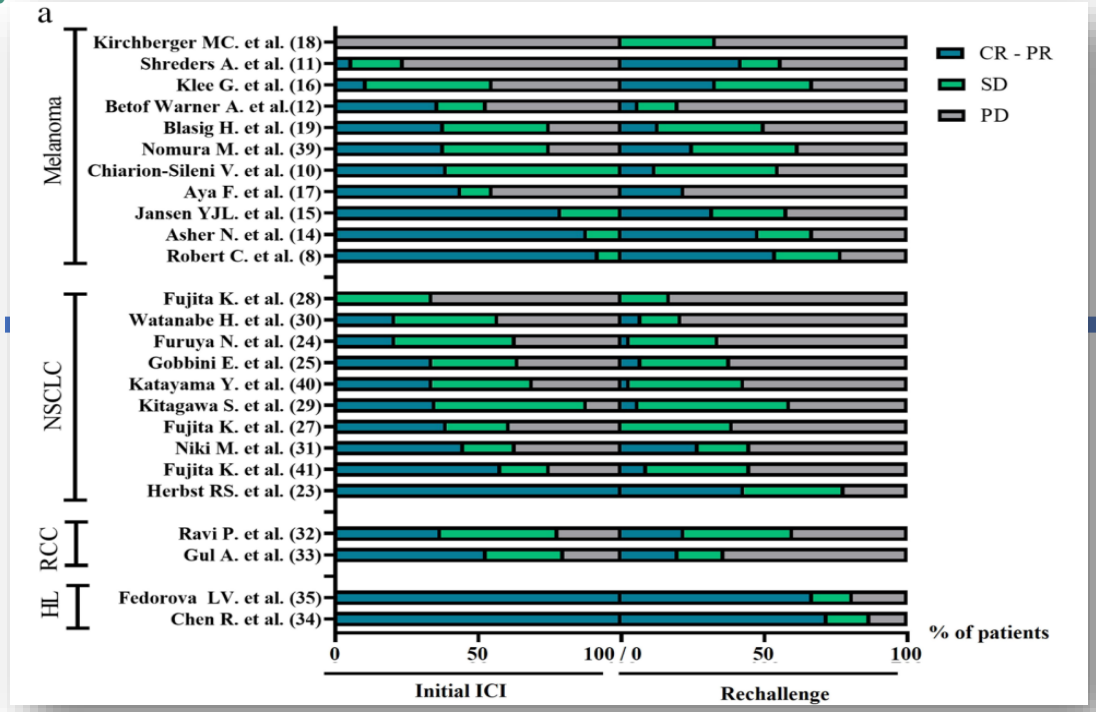
Zaanan A, et al. ESMO 2023; Yamada Y, et al. Lancet GH 202x, Ramaswamy A, et al. ASCO GI 2024

PRESENTED CASES

- 1stline for MSI-H pts
- Surgery after chemotherapy
- Triplet chemotherapy
- ICI rechallenge

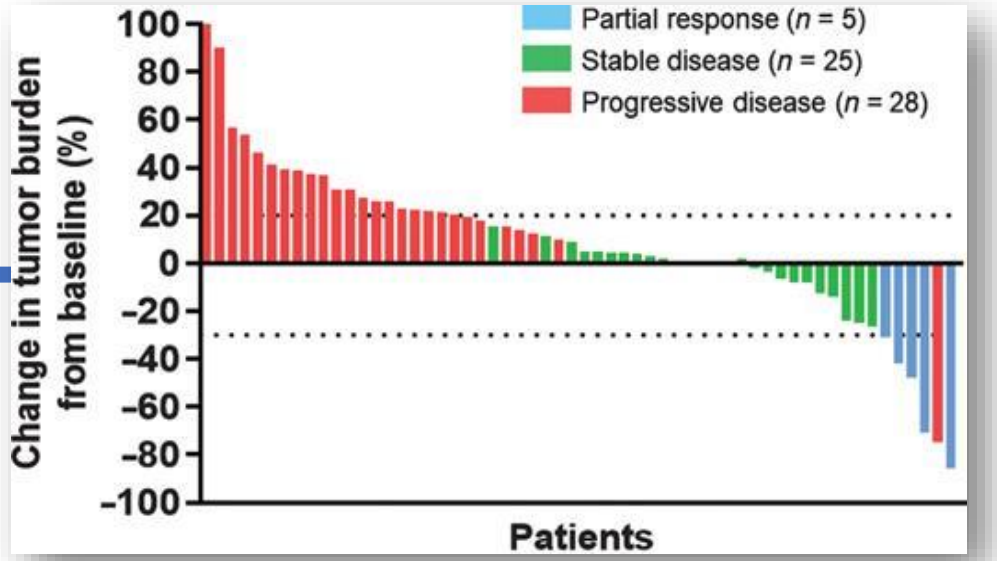
IO RECHALLENGE AFTER PREVIOUS PROGRESSION

Systematic review



- 32 researches (melanoma, NSCLC, RCC)
- Heterogenous results: ORR 0-54% / mPFS 1.5-12.9ms
- Favorable: better PS, longer initial ICI, d/c without PD, and combo with **different ICI**

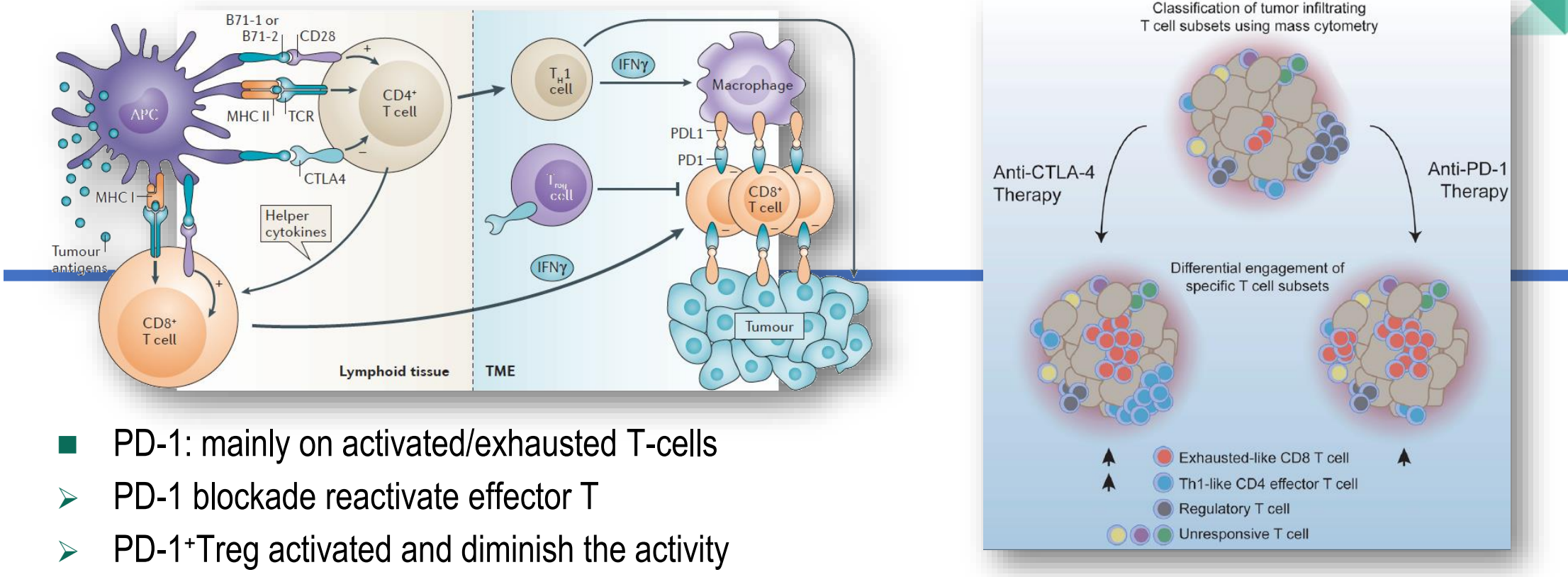
WJOG9616L (NSCLC)



- Eligible if pts with response f/w PD with prior IC and interval >2 months
- ORR 8.5% and mPFS 2.6ms
- ICI-free interval was only predictive

Plazy C, et al. Current Oncology Reports 2022; Akamatsu H, et al. CCR 2022

PD1 VS CTLA4: DIFFERENCE



- PD-1: mainly on activated/exhausted T-cells
  - PD-1 blockade reactivate effector T
  - PD-1^{+}Treg activated and diminish the activity
- CTLA4: mainly on CD4^{+} T-cells (activated by APC)
  - CTLA-4 blockade expand ICOS^{+} Th1-like CD4^{+} T cells
  - Inhibit and/or deplete Treg

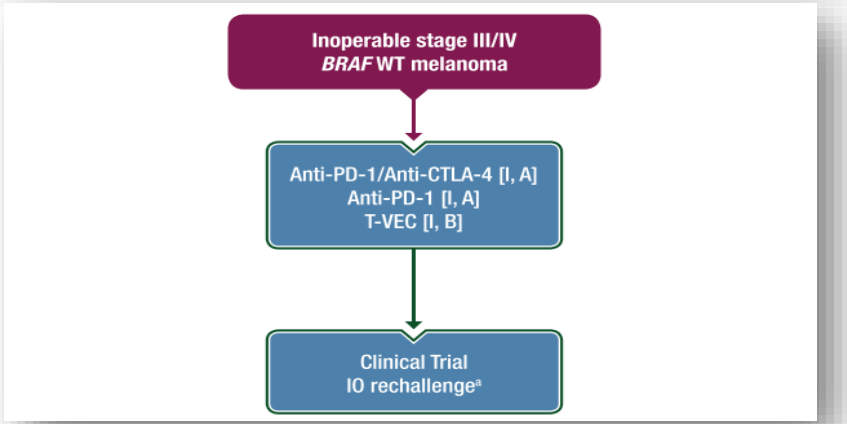
Topalian et al. Nat Rev Cancer 2016; Wei et al. Cell 2017; Kumagai S, et al. Nature Immunology 2020

A-PD1 RECHALLENGE WITH A-CTLA4 IN MELANOMA

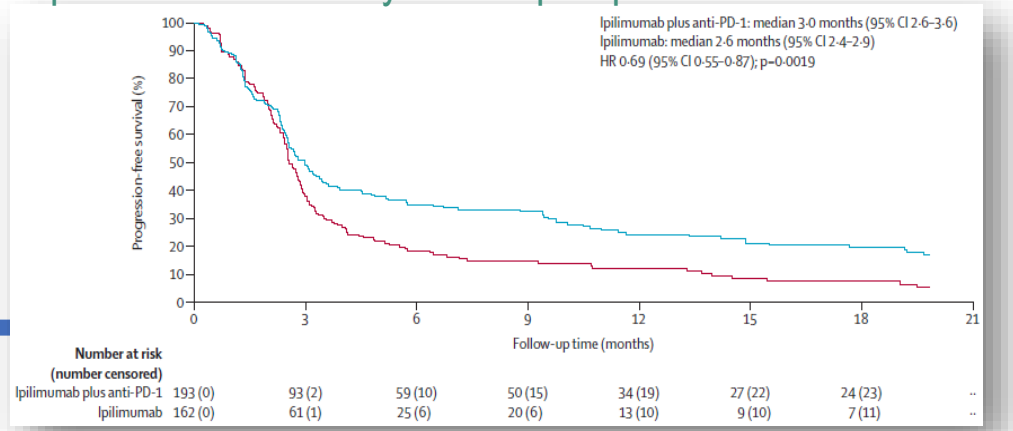
NCCN

- **BRAF V600 MUTATION *NOT* PRESENT**:
  - For patients with progression on anti-PD-1 monotherapy, consider the following options (if not already received):
    - ◊ Combination immunotherapy, options include:
      - – Clinical trials
      - – Anti-PD-1/ipilimumab (preferred)
      - – Nivolumab and relatlimab-rmbw
      - – T-VEC/ipilimumab therapy (for low burden of disease and injectable lesions)
    - ◊ Ipilimumab monotherapy (if prior progression on single-agent anti-PD-1 therapy)
    - ◊ Pembrolizumab/lenvatinib after progression on anti-PD-1/PD-L1

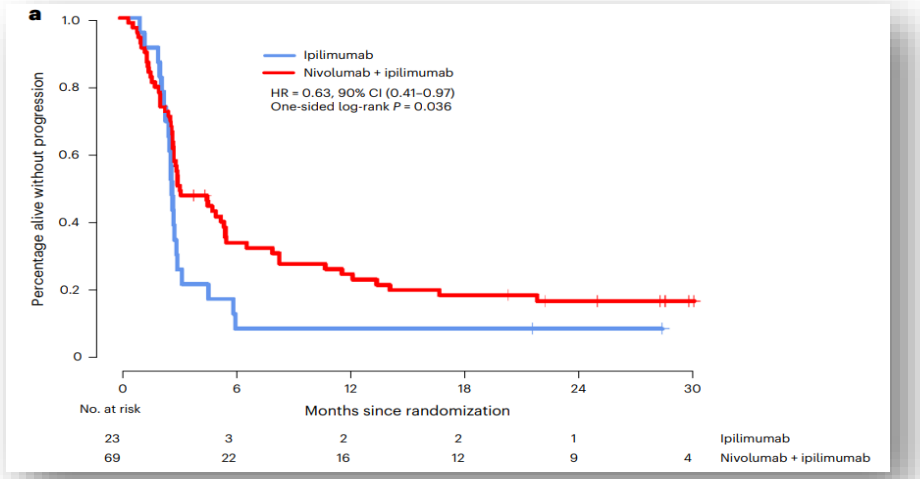
ESMO



Retrospective cohort study: Nivo+Ipi >Ipi



Randomized phase 2 : Nivo+Ipi >Ipi

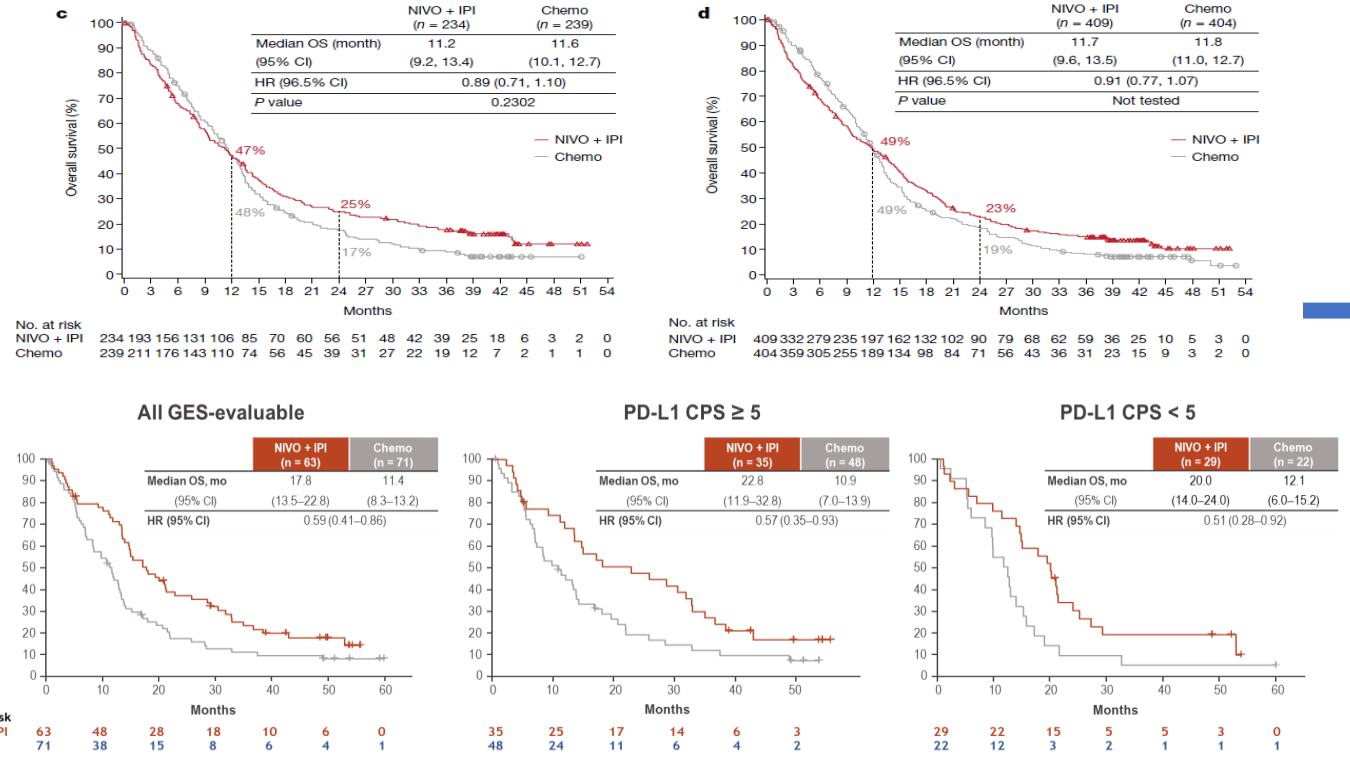


- Nivo+Ipi is considered as treatment option after A-PD1
- Supported by large retrospective study and rP2

NCCN guideline 2024 ver 2; Michielin O, et al, Ann Oncol 2019; VanderWalde A, et al. Nature Med 2023

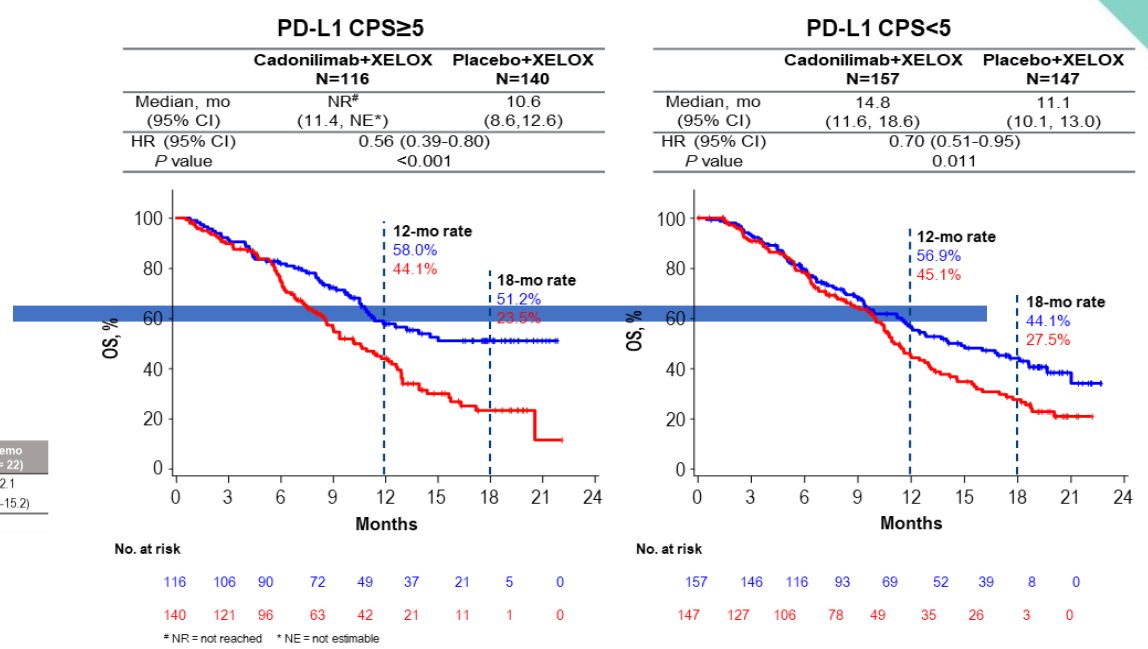
ROLE OF CTLA-4 IN GASTRIC?

CM-649 Nivo+Ipi



- Nivo+Ipi did not improve OS
- ORR 15% in CPS<1 (higher than A-PD1 mono?)
- Treg+ may predict benefit?

COMPASSION-15: Chemo+Cadonilimab



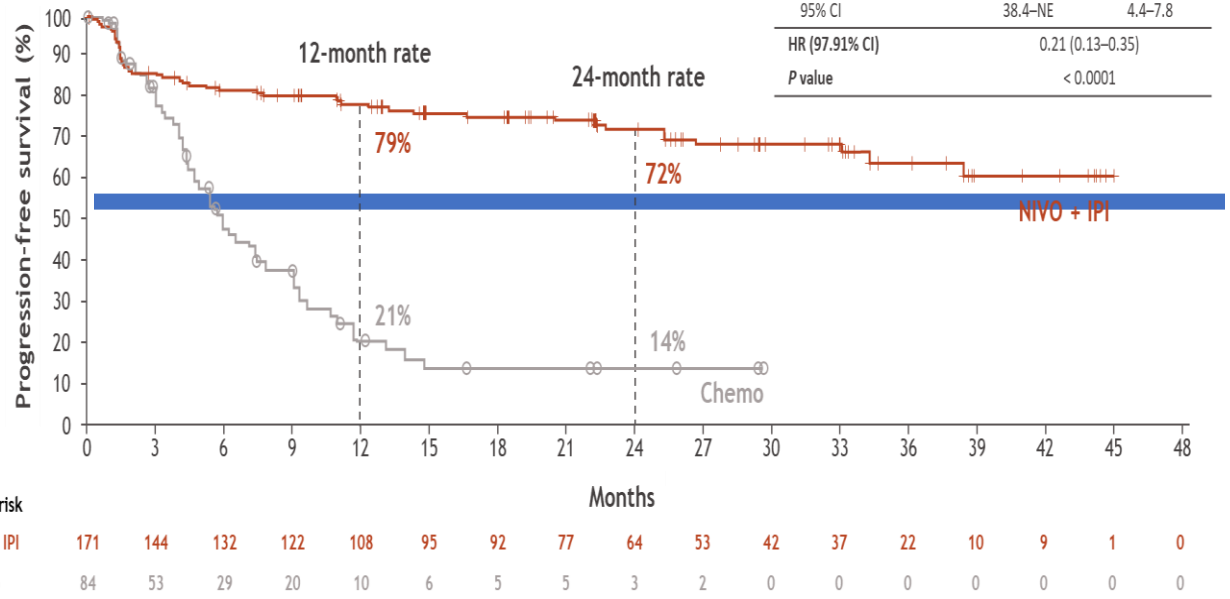
- Benefit even in CPS<5
- ATTRACTION-6 is also ongoing in Asia

Shitara K, et al. Nature 2022; Janjigian Y, et al. AACR 2023; Jiafu Ji et al. AACR 2024

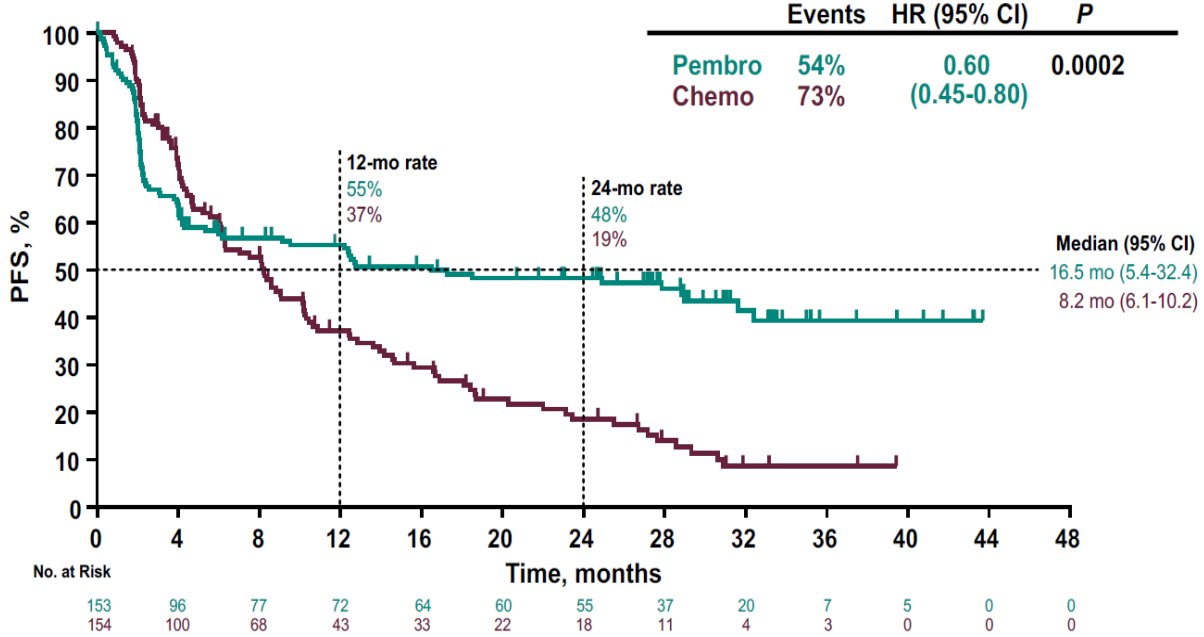
MSI-H CRC: 1ST-LINE

CheckMate 8HW: PFS

1L centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 171)	Chemo (n = 84)
Median PFS,[a,b] mo	NR	5.9
95% CI	38.4–NE	4.4–7.8
HR (97.91% CI)	0.21 (0.13–0.35)	
P value	< 0.0001	



KEYNOTE-177: PFS



- Nivo+Ipi vs Pembro (cross trial comparison)
  - 1y PFS: 79 vs 55% (+24%)
  - 2y PFS: 72 vs 48% (+24%)
- Nivo arm in CM8HW and biomarkers awaited

Andre T, et al. NEJM 2020; ASCO 2021; ASCO-GI 2024

MY PATIENT

59y M, MSI-H/MMR-D, CPS5

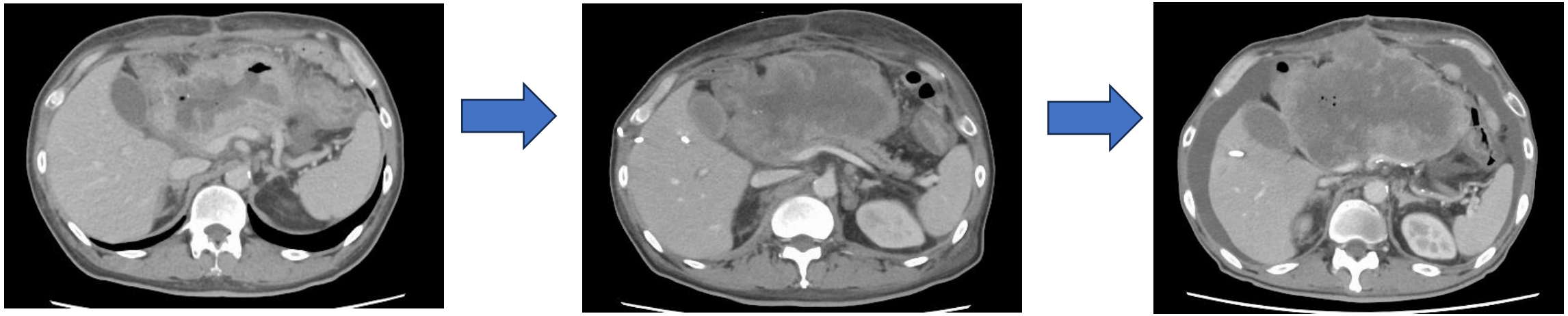
tTMB 74/mb, bTMB 100/mb, no PTEN/β2M mutations

post SOX, PTXRAM, Pembro, Irinotecan, TAS, and Irradiation

Previous Pembro
PR f/w by PD

Anti-PD1
+Investigational drug (trial)

Nivo
+Ipi



- More data needed to identify candidate

NCCHE

SUMMARY

- MSI-H testing is recommended before 1st-line
- A-PD1 based 1st-line is recommended for MSI-H (+/- chemo)
- Individual approach needed for surgery after chemo
- Triplet chemo is used only for selected pts
- More data is needed about ICI rechallenge in gastric cancer

ESMO GUIDELINES:
REAL WORLD CASES

CONSIDERATIONS RELATED TO ESMO GASTRIC GUIDELINE IMPLEMENTATION IN EVERYDAY CLINICAL PRACTICE

Radu Vidra, MD – Medical Oncologist

ESMO-Practicing Oncologists Working Group (POWG)

Regional Institute of Gastroenterology and Hepatology

Cluj-Napoca, Romania

ESMO WEBINAR SERIES

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

DISCLOSURE INFORMATION

-Speaker honoraria:

- Hoffmann la Roche, Eli Lilly, Bristol-Myers Squibb, Pfizer, Sandoz, Accord, Egis, Servier

- Advisory board:

- Sandoz, Accord, Servier

- Research funding (SI):

- Amgen, Bristol-Myers Squibb, Merck Sharp Dohme (MSD)

The ESMO POWG serves to identify the practice needs of oncologists who are hospital and office-based by developing educational services, practice tools and quality indicators that will facilitate the implementation of best practice at the point of care.

The POWG members are relevant stakeholders to the ESMO Guidelines Webinars as experts who are consulting and implementing the guidelines in their daily practices

For more information about the ESMO POWG visit **esmo.org**

ESMO > About ESMO > Organisational Structure > Educational Committee

ESMO PRACTISING ONCOLOGISTS WORKING GROUP

Don't miss:

- The «ESMO Checklists» on OncologyPRO

ESMO WEBINAR SERIES

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

GUIDELINE RECOMMENDATIONS

Diagnostic work-up

- Endoscopic examination & forceps biopsies – gold standard
  - Multiple (5- 8) biopsies
  - Narrow-band imaging or chromoendoscopy in combination with magnifying endoscopy
  - Endoscopic ultrasonography (EUS)
  - Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) may also be used for diagnosis.
- Molecular biology:
  - HER2 status
  - programmed death-ligand 1 (PD-L1) combined positive score (CPS)
  - MSI-H/mismatch repair deficiency (dMMR)
  - DYPD status
- Staging:
  - Contrast-enhanced CT scan of the thorax, abdomen pelvis
  - FDG-PET-CT is not routinely recommended
  - Diagnostic laparoscopy and peritoneal washings for cytology

F. Lordick et al. Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up
Annals of Oncology 2022 331005-1020DOI: (10.1016/j.annonc.2022.07.004)

ESMO CHECKLIST - GASTRIC CANCER

https://oncologypro.esmo.org/oncology-in-practice/practice-tools/esmo-checklists

ESMO Checklist: Gastric Cancer Patient Related Treatment Workflow*

Tick the box and insert the date as you have dealt with every task listed below, as appropriate. In case you use the template, you can also insert and save data directly on the PDF file.

PATIENT'S PERSONAL DATA	
Last Name:	First Name:
Date of birth: __/__/__	Gender:
DATE OF REFERRAL/1ST CONSULTATION: __/__/__	

- ☐ __/__/__ **MEDICAL HISTORY AND RISK FACTORS**
  - ☐ Past personal medical history and co-morbidities:
  - ☐ Past surgical history:
  - ☐ Concurrent medication:
  - ☐ Allergies:
  - ☐ Smoking history: __pack/y from age__ to age__
  - ☐ Alcohol consumption:

Normal weight:	Height:	BMI:

- ☐ __/__/__ **PRESENT MEDICAL CONDITIONS**
  - ☐ Main symptoms:
  - ☐ Weight loss:
  - ☐ ECOG Performance Status:
  - ☐ Nutritional Status:
  - ☐ Other relevant clinical conditions:
- ☐ __/__/__ **DIAGNOSIS AND CLINICAL STAGING**
  - ☐ __/__/__ Endoscopy
  - ☐ __/__/__ EUS
  - ☐ __/__/__ Thoraco-abdomino (+/- pelvic) CT scan
  - ☐ __/__/__ PET-CT scan
  - ☐ __/__/__ Laparoscopy + washings
  - ☐ __/__/__ TNM stage and grade
- ☐ __/__/__ **HISTOLOGICAL ANALYSIS**
  - ☐ Core biopsy of primary tumor
    - ☐ Adenocarcinoma
    - ☐ IHC, PD-L1 staining, method used:
    - ☐ IHC HER 2 and/or FISH HER 2
    - ☐ MSI or dMMR status
    - ☐ Tissue material available/stored for future molecular analyses ☐ YES ☐ NO
- ☐ __/__/__ **LAB TESTS**
  - ☐ FBC ☐ Liver Function ☐ Renal Function ☐ Iron Status
- ☐ **Timeline for further work-up has been checked and it is tight enough**

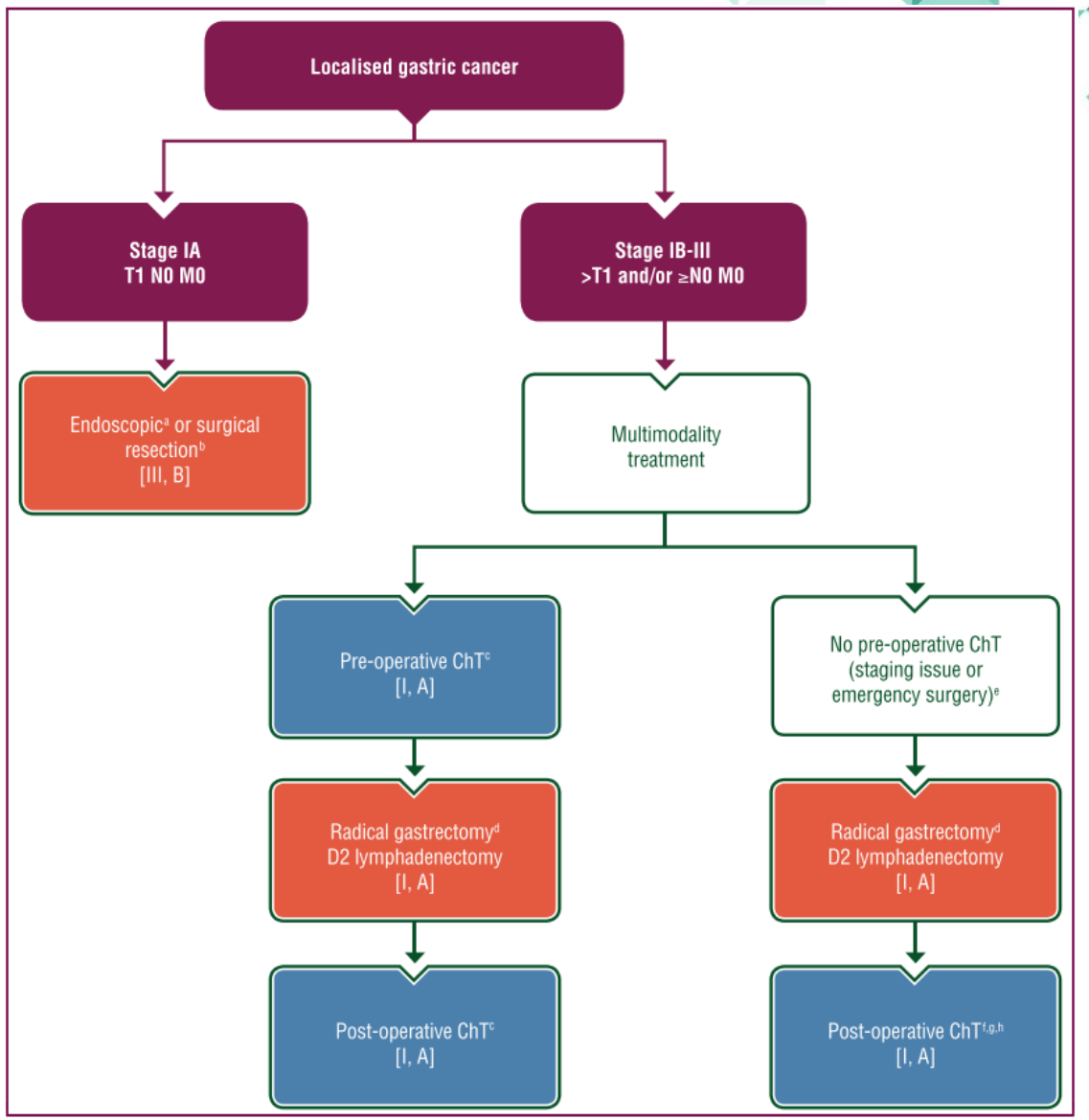
EVERYDAY CLINICAL PRACTICE

Guideline related approach

TREATMENT STRATEGY

Stage IB – III

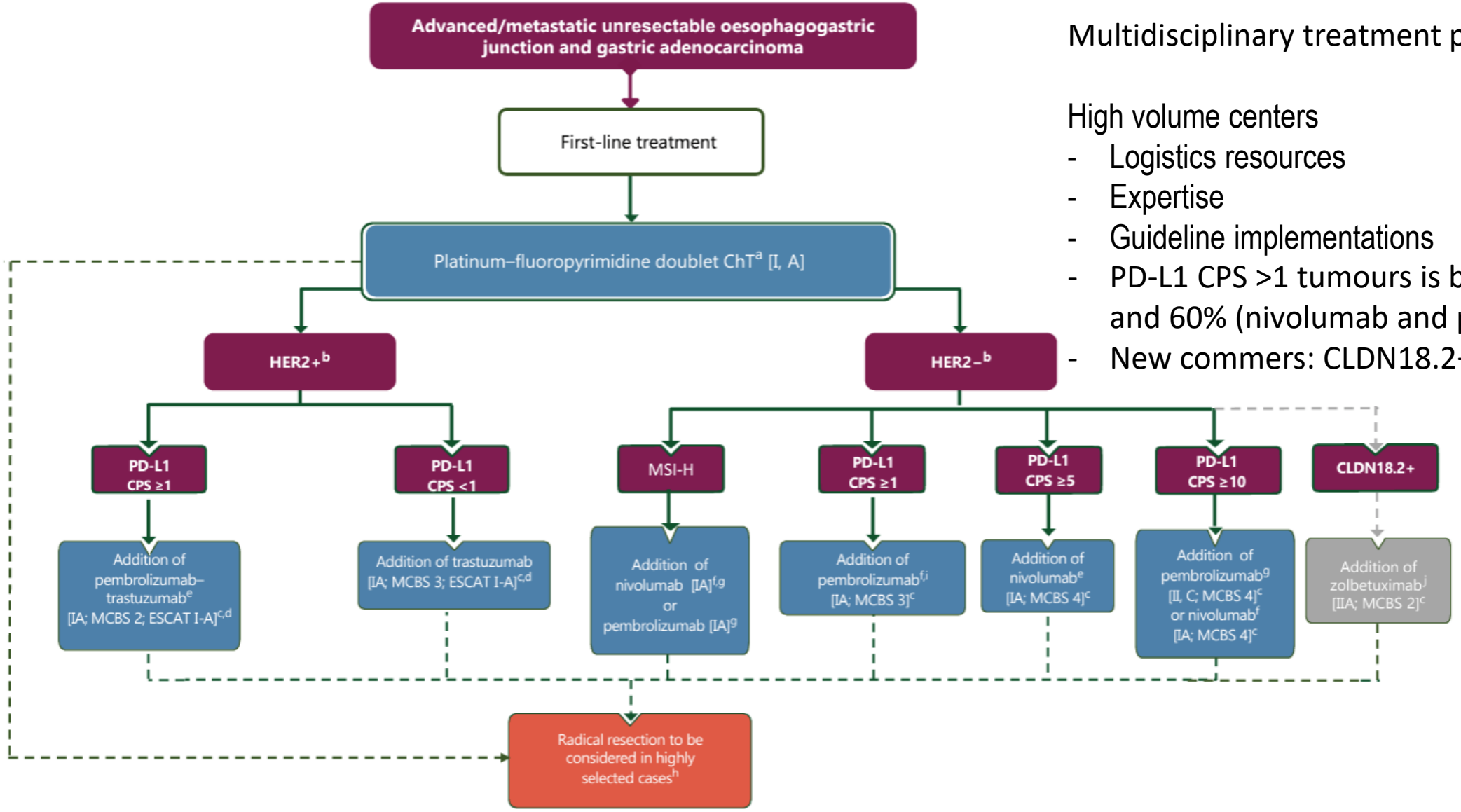
- Peri-operative therapy and radical gastrectomy is recommended
- Patients should undergo D2 resection in a high-volume surgical centre
- Peri-operative > stage IB: triplet ChT regimen
- FLOT is standard of care for patients who are able to tolerate a triple cytotoxic drug regimen
- Unfit patients: a combination of a fluoropyrimidine with cisplatin or oxaliplatin is recommended
- Adjuvant ChT is less well tolerated than neoadjuvant ChT



F. Lordick et al. Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up
Annals of Oncology 2022 331005-1020DOI:
(10.1016/j.annonc.2022.07.004)

TREATMENT STRATEGY

Stage IV – first line



Multidisciplinary treatment planning

High volume centers

- Logistics resources
- Expertise
- Guideline implementations
- PD-L1 CPS >1 tumours is between 50% and 60% (nivolumab and pembrolizumab)
- New commers: CLDN18.2+ (Zolbetuximab)

Shitara K, et al. ESMO open 2024

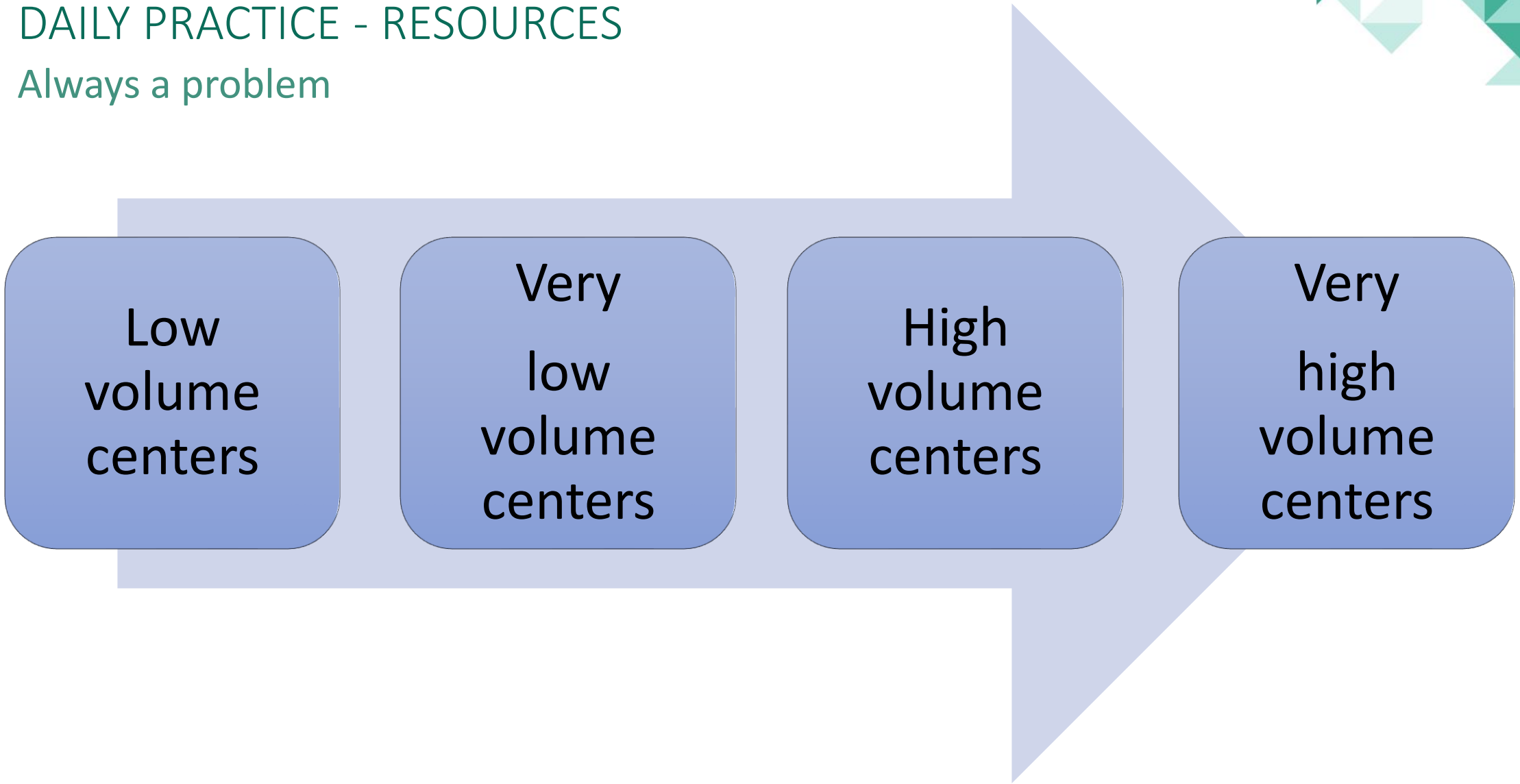
REIMBURSEMENT ISSUES

Europe 2024

Nivolumab 2024	Pembrolizumab 2024
Austria	Austria
Belgium	Belgium
Bulgaria	Bulgaria
Denmark	Denmark
Finland	Finland
France	France
Germany	Germany
Italy	Italy
Luxembourg	Luxembourg
Sweden	Sweden
Spain	Spain
Netherlands	Netherlands
United Kingdom	United Kingdom
13/50 countries	13/50

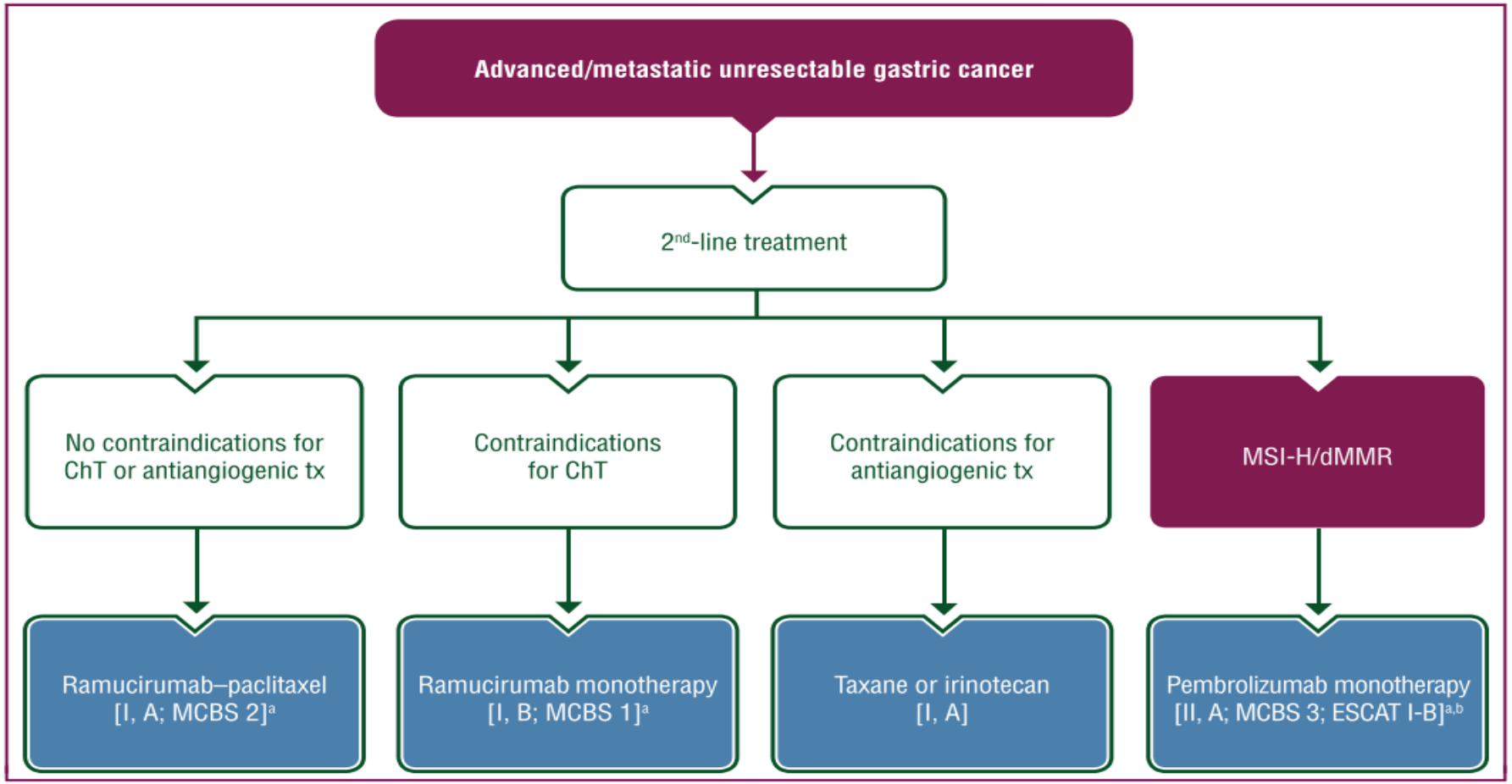
DAILY PRACTICE - RESOURCES

Always a problem



TREATMENT STRATEGY

Stage IV – second line



F. Lordick et al. Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up
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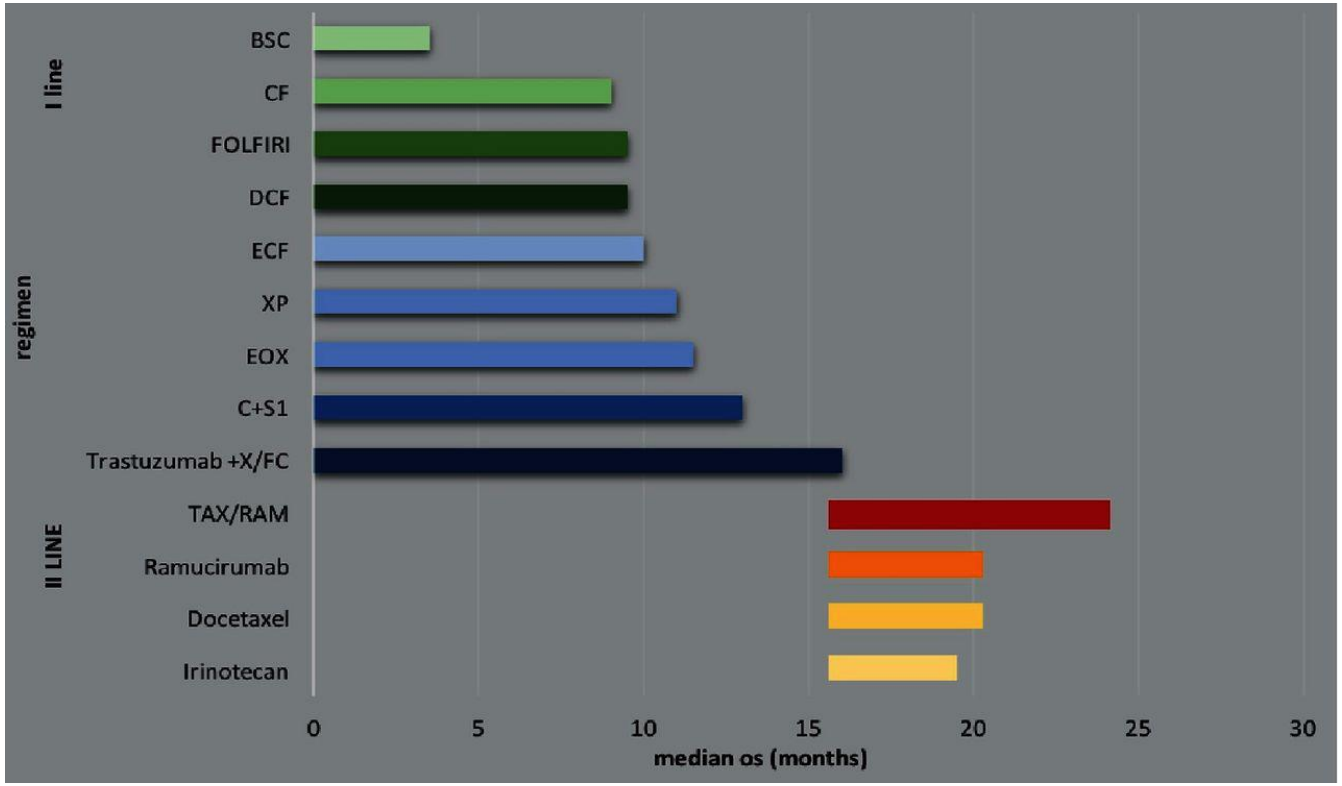
CONTINUUM OF CARE

First line: successes and disappointments[1]

- Only about 20% of patients went on to receive second-line therapy in historical studies[2]
- In more recent phase III trials the percentage of candidates has risen
  - From 40-50% in Europe[3]
  - Or high as 75% in Japan[4]



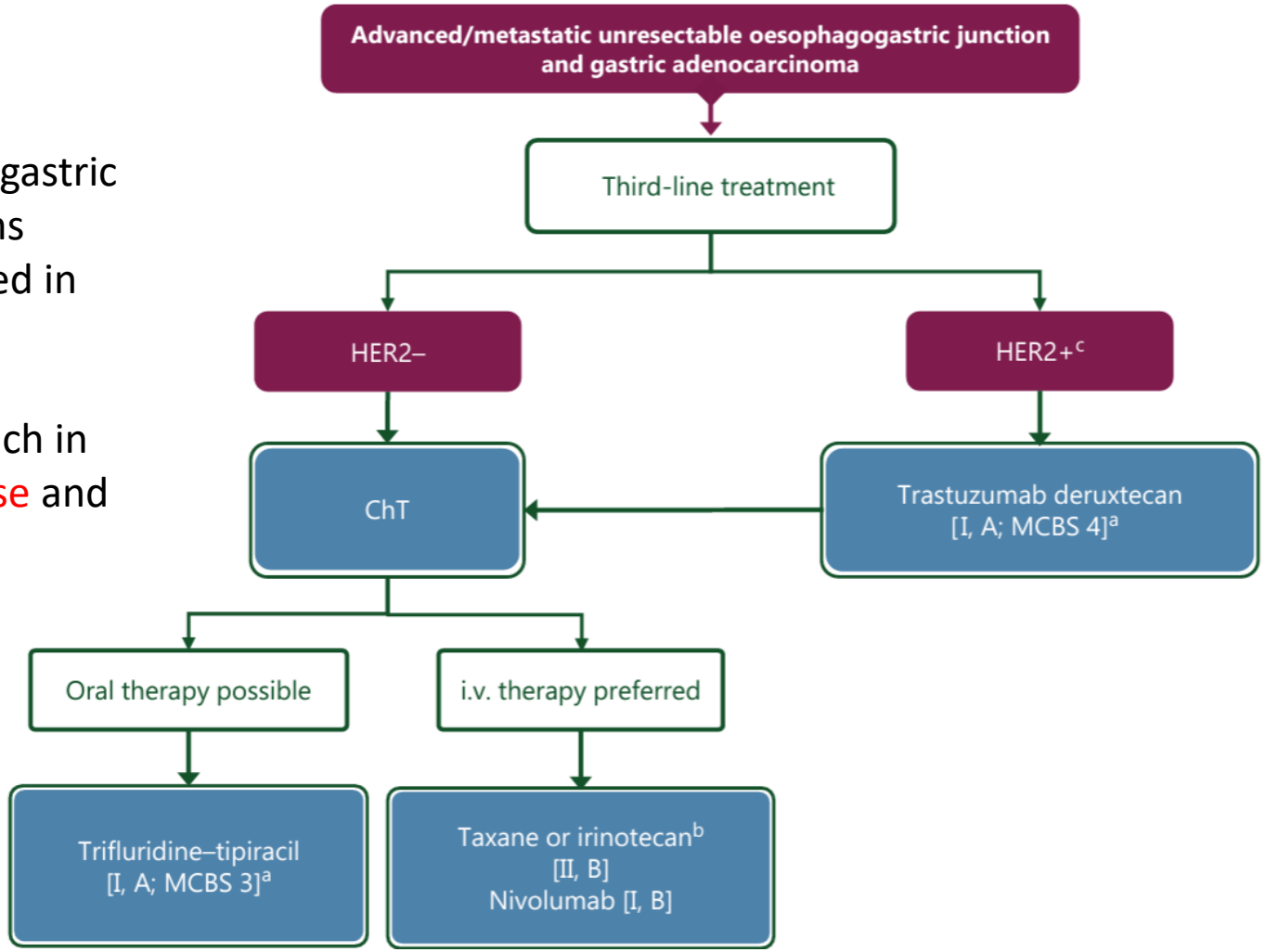
1. Salati M, et al . Second-line treatments: moving towards an opportunity to improve survival in advanced gastric cancer? ESMO Open. 2017 Jul 19;2(3):e000206. doi: 10.1136/esmoopen-2017-000206. PMID: 29209523; PMCID: PMC5703389.
2. Chau I. et al. *J Clin Oncol.* 2004; **22**: 2395-2403 doi:10.1200/JCO.2004.08.154
3. Catalano V. et al. *Br J Cancer.* 2008; **99**: 1402-1407 doi:10.1038/sj.bjc.6604732
4. Koizumi W. et al. *Eur J Cancer.* 2013; **49**: 3616-3624 doi:10.1016/j.ejca.2013.07.003

TREATMENT STRATEGY

Stage IV – third line

- Gastrectomy is not recommended in metastatic gastric cancer unless required for palliation of symptoms
- Resection of metastases cannot be recommended in general,

- But might be considered as an individual approach in highly selected cases with oligometastatic disease and response to ChT



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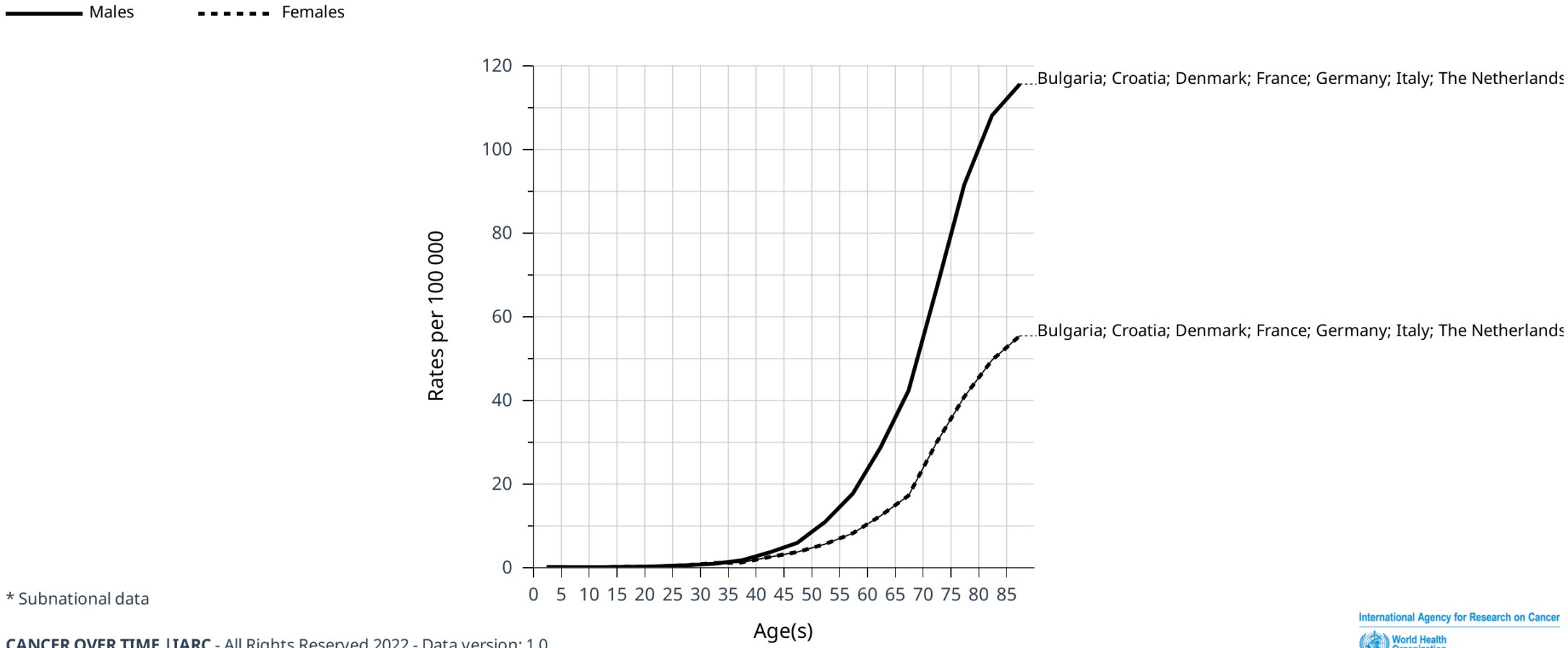
EVERYDAY CLINICAL PRACTICE

Patient related approach

Rates per 100 000, incidence, males and females, in 2012

Stomach

Bulgaria + Croatia + Denmark + France + Germany* + Italy* + The Netherlands + Norway + Poland* + Sweden + Switzerland* + UK, Northern Ireland + UK, England and Wales **



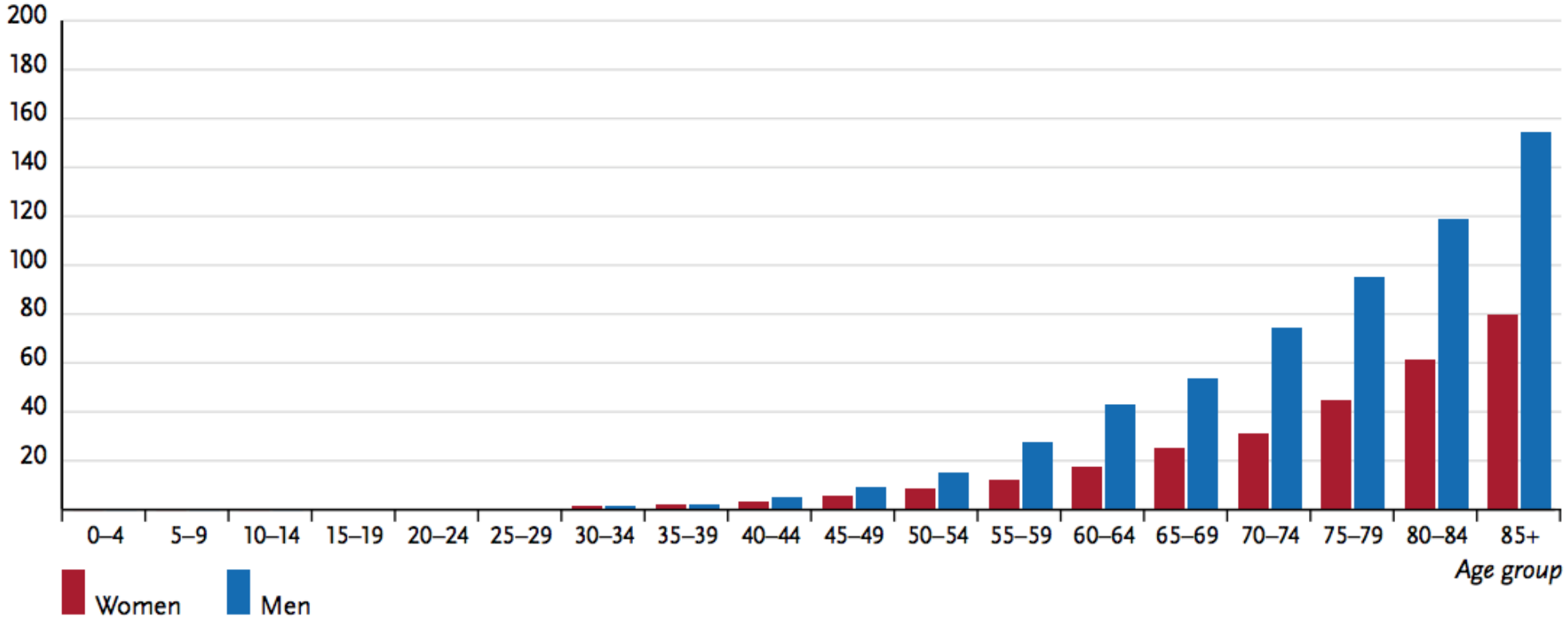
* Subnational data

International Agency for Research on Cancer
World Health Organization

AGE-SPECIFIC INCIDENCE

More than 50% pts are over 70ys old

Figure 3.4.2
Age-specific incidence rates by sex, ICD-10 C16, Germany 2015–2016
per 100,000



https://www.krebsdaten.de/Krebs/EN/Content/Publications/Cancer_in_Germany/cancer_chapters_2015_2016/cancer_c16.pdf?__blob=publicationFile

EXAMPLE FROM REAL LIFE

Geriatric assessment: symptoms, fitness, comorbidities, QoL, family support



M 60 ys old	**M 70 ys old**	**M 80 ys old**
ECOG PS 1	ECOG PS 1	ECOG PS 1
Arterial Hypertension	Arterial Hypertension + Hip replacement	Arterial Hypertension
Stage IV Gastric AC	Stage IV Gastric AC	Stage IV Gastric AC
3 liver lesions	3 liver lesions	3 liver lesions
1 previous lines of therapy	1 previous lines of therapy	1 previous lines of therapy
Lives alone, but independent	Lives alone, far from the hospital No relatives in the area	Lives with wife, close to the hospital and his children and their families

** Personal experience*

EVERYDAY CLINICAL PRACTICE

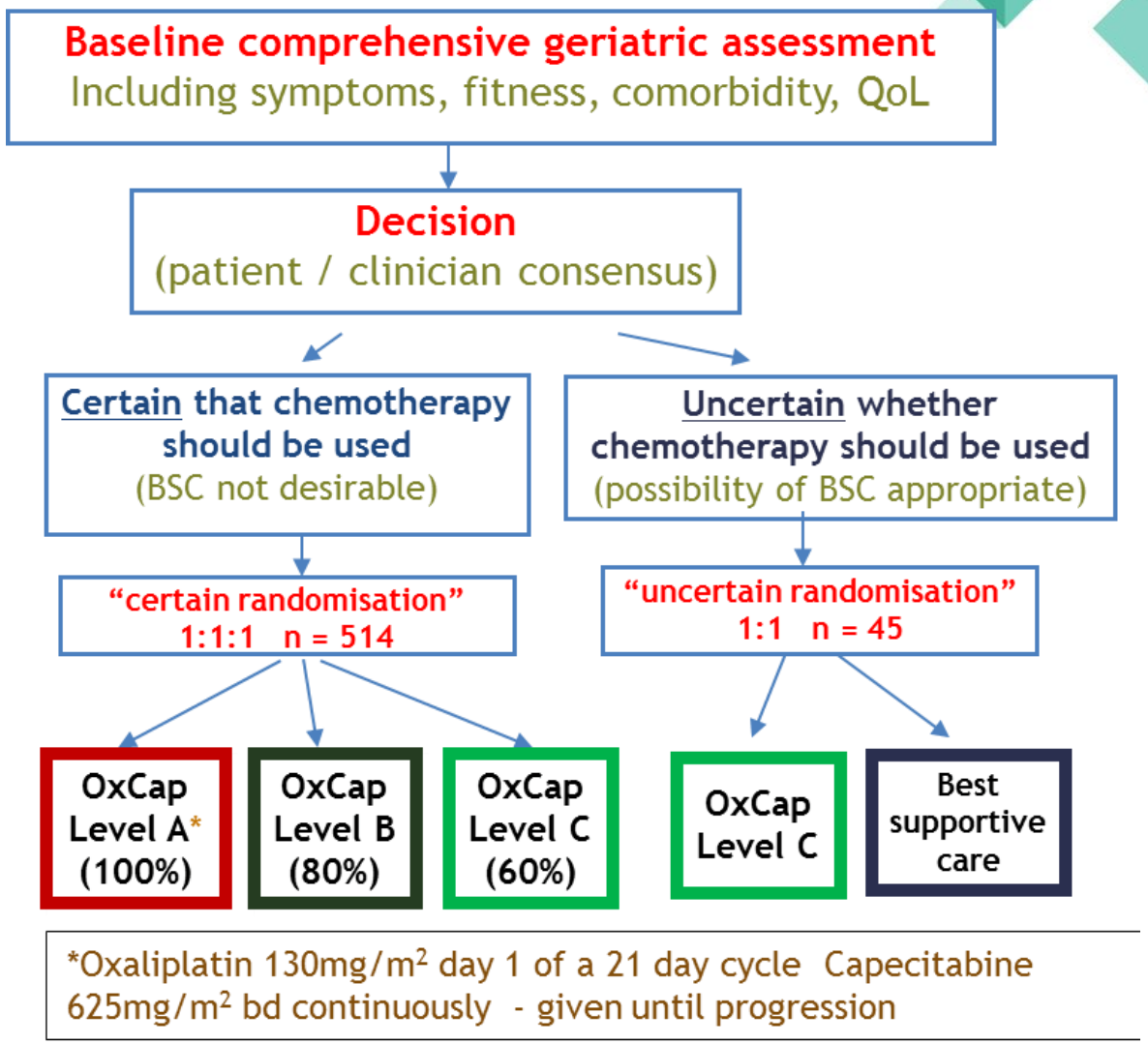
Erderly or less fit patients

ELDERLY OR LESS FIT PATIENTS

GO2 Study

- **Phase III, randomised, multi-centre, prospective, controlled, open label, non-inferiority trial**

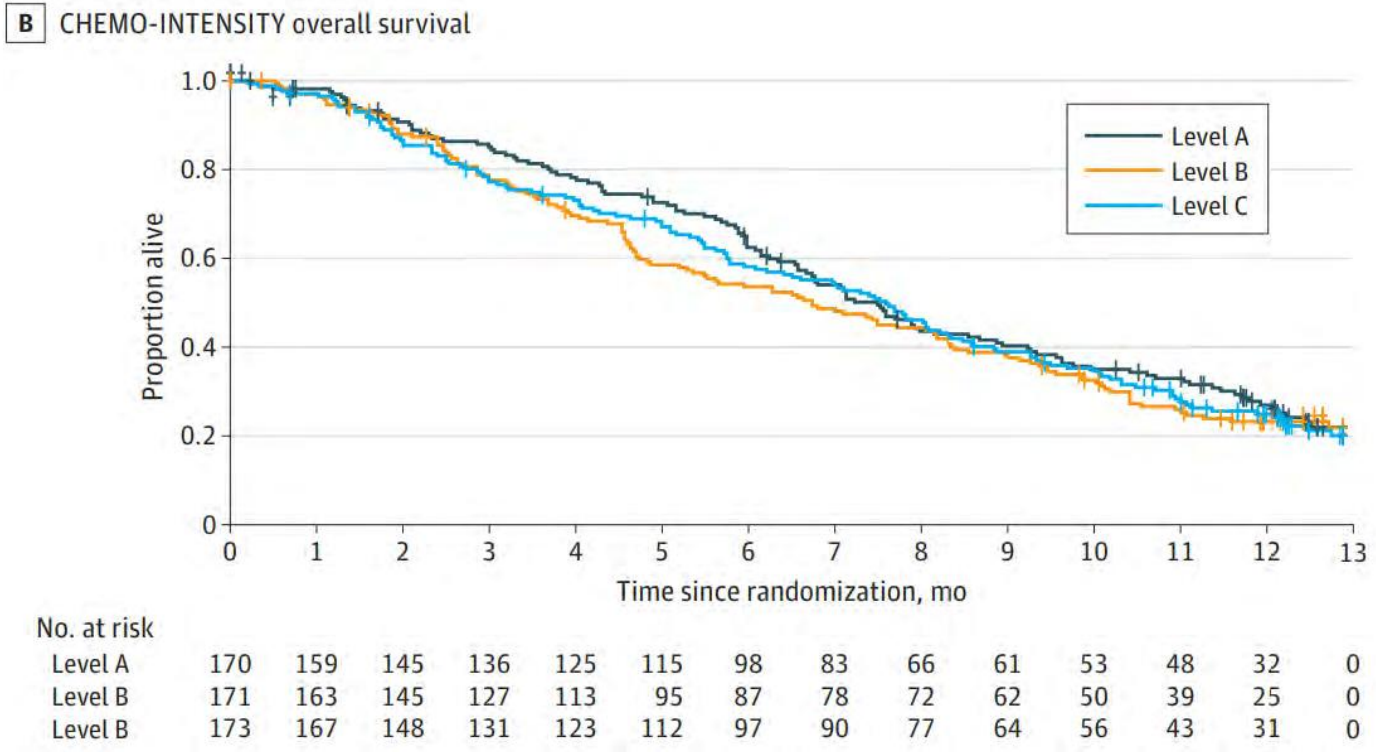
- Eligibility:
  - Not fit for full-dose 3-drug chemotherapy,
  - Suitable for reduced intensity chemotherapy.



Hall PS et al. *JAMA Oncol*. 2021 Aug 1;7(8):1249

ELDERLY OR LESS FIT PATIENTS

GO2 Study - Full vs Reduced-Intensity Chemotherapy



CapOx

Level A 100% of dose

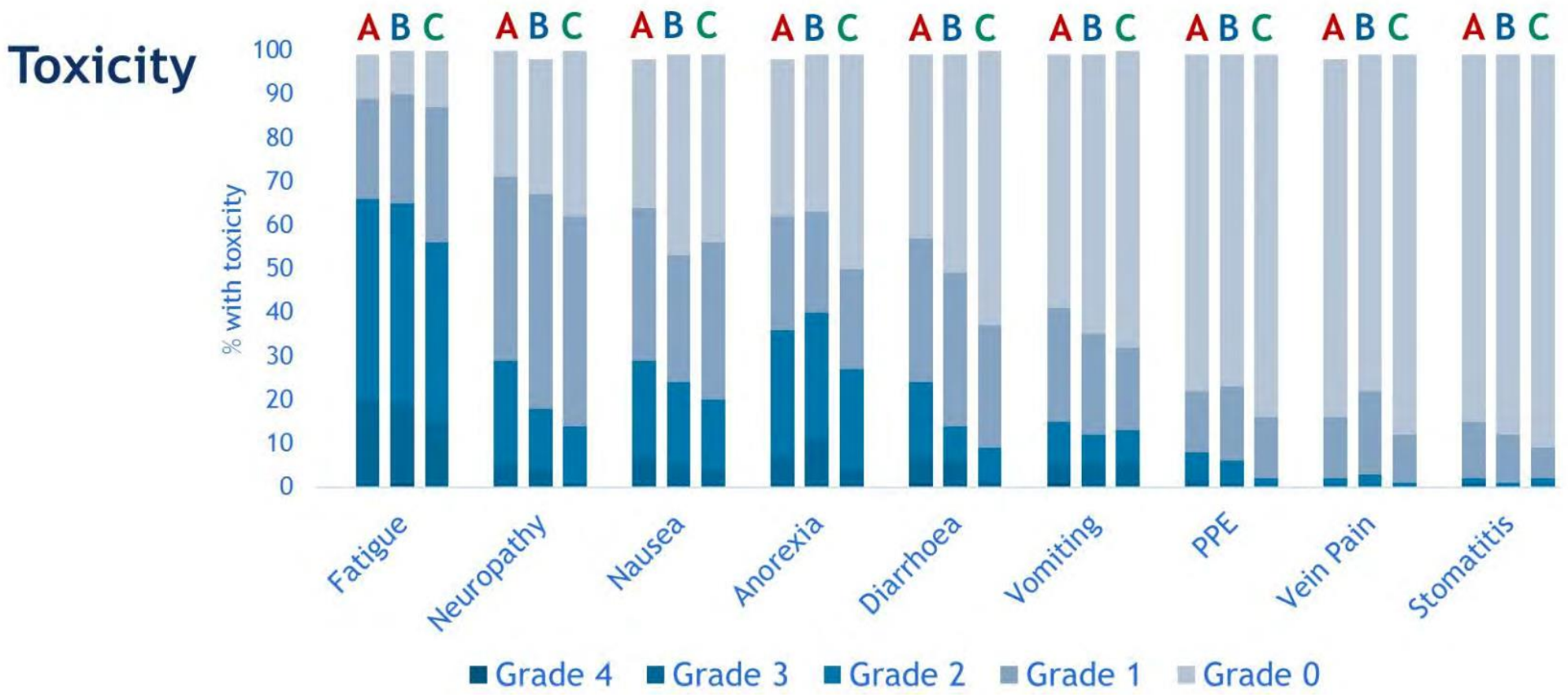
Level B 80% of dose

Level C 60% of dose

Hall PS et al. *JAMA Oncol*. 2021 Aug 1;7(8):1249

ELDERLY OR LESS FIT PATIENTS

GO2 Study - Full vs Reduced-Intensity Chemotherapy



Hall PS et al. *JAMA Oncol*. 2021 Aug 1;7(8):1249

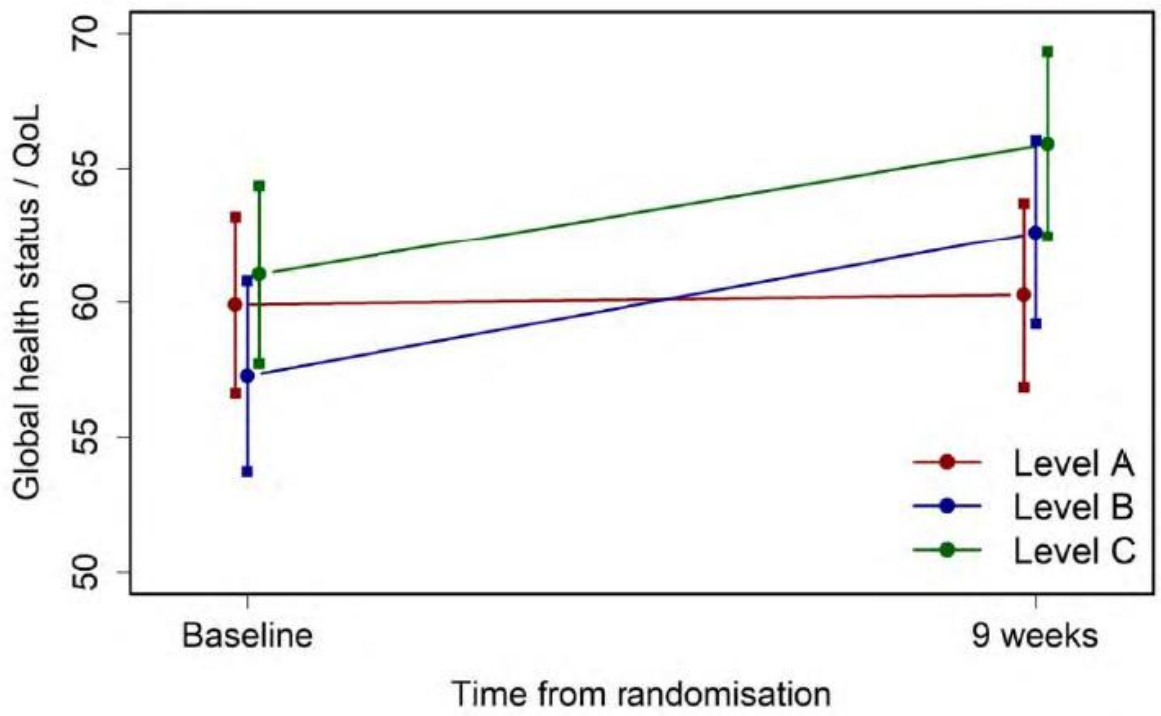
ELDERLY OR LESS FIT PATIENTS

GO2 Study - Full vs Reduced-Intensity Chemotherapy

- QoL improved at 9 week on treatment with Level B and C

- "We are not compromising on tumour/symptom control that may impact on QoL over the longer term by using the lower intensity regimens in this population" (Peter Hall)

- Consider upfront dose-reduction (80% -60%) in frail and elderly patients



Hall PS et al. *JAMA Oncol*. 2021 Aug 1;7(8):1249

TAKE HOME MESSAGES

TAKE HOME MESSAGES

- Multidisciplinary approach (new therapeutic options available)
- Dedicated tumor boards - molecular testing (PD-L1 CPS, MSI-H, Her2, CLDN18.2)
- Gastric cancer – more than 50% are elderly patients (doublet vs triplet)
- Geriatric assessment: symptoms, fitness, comorbidities, QoL, family support
- Only 45-50% patients in second line
- Large volume centers
- Treatment options – reimbursement policy

THANK YOU

For your attention ☺

ESMO GUIDELINES: REAL WORLD CASES

Thank you for your attention ☺

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