Advances in Systemic Therapy for Gastroesophageal Cancers

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Outline

- Non-metastatic/Locally Advanced Disease
- Metastatic Disease – Current Options
- Metastatic Disease – Future Landscape

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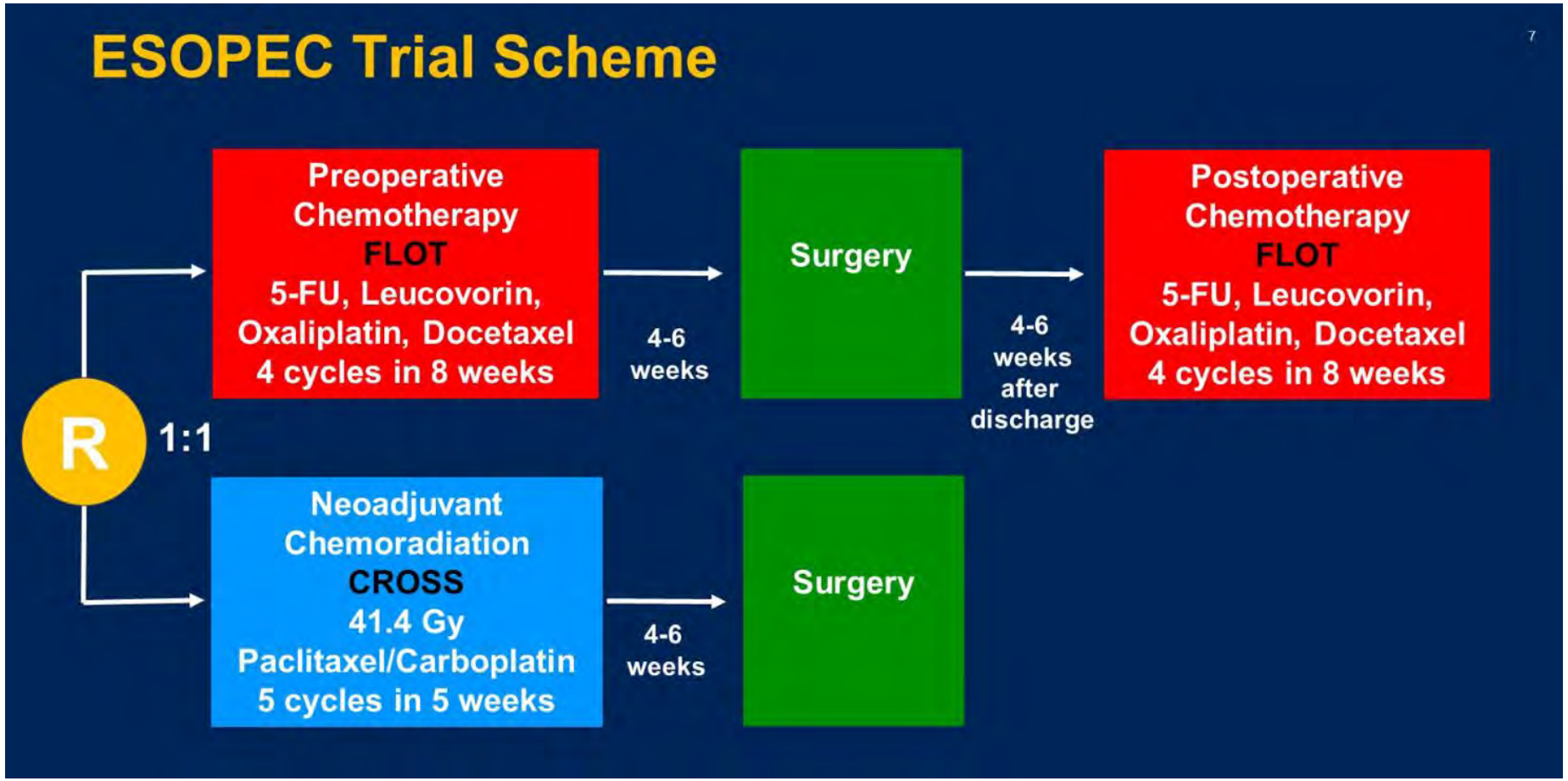
Non-Metastatic GEJ Cancers

- Until June 2024/ASCO, neoadjuvant chemoRT followed by surgery (CROSS) was widely accepted as a standard approach for locally advanced, resectable GEJ cancers

- ESOPEC Trial: Phase 3 randomized trial in patients with esophagus and GEJ adenocarcinoma – neoadjuvant chemoRT (CROSS) vs. perioperative chemotherapy (FLOT)

Non-Metastatic GEJ Cancers – ASCO 2024



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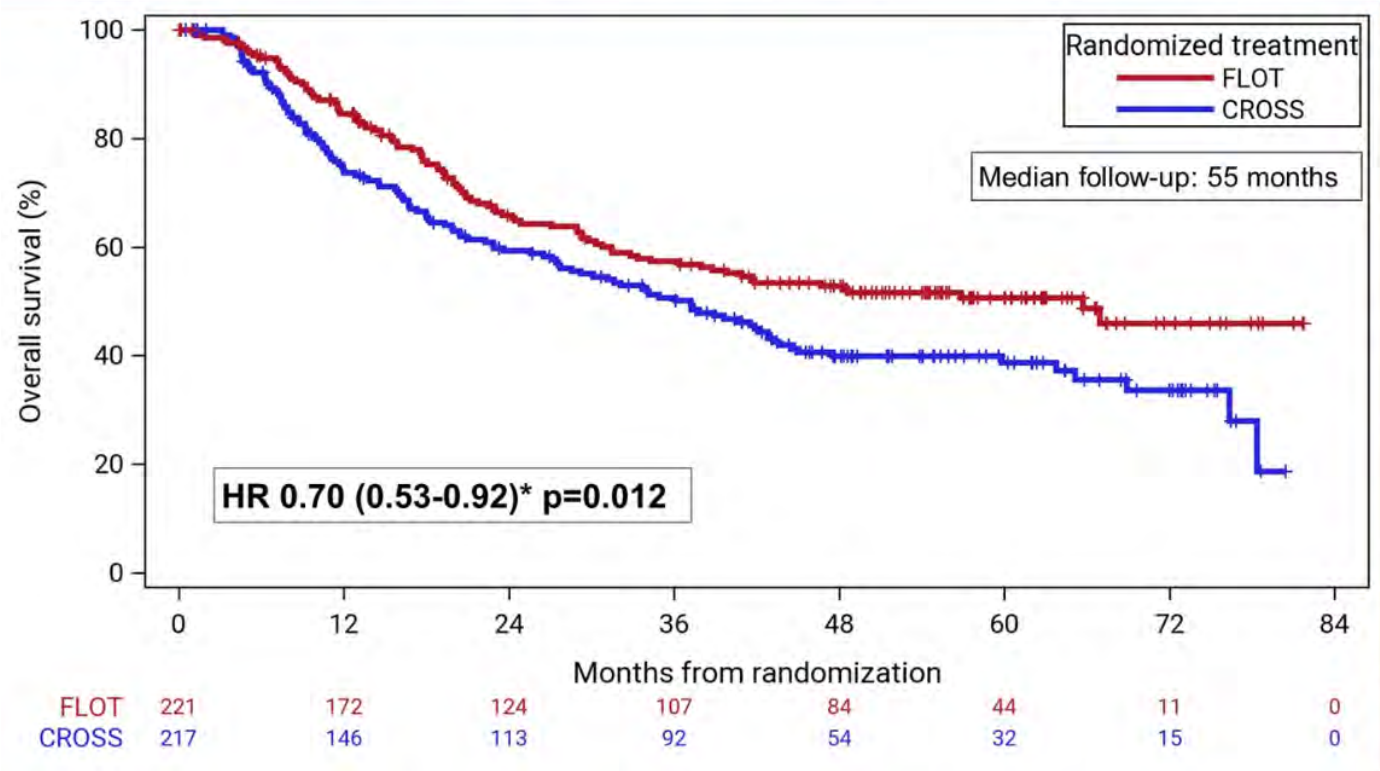
Non-Metastatic GEJ Cancers – ASCO 2024

Overall Survival - ITT Population

13



	FLOT	CROSS
Events	97	121
Median OS time (months)	66 95% CI 36 – n.e	37 95% CI 28 – 43
3-year OS rate	57.4%	50.7%
5-year OS rate	50.6%	38.7%

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Non-Metastatic GEJ Cancers – ESMO 2024

Proffered paper session 2: GI tumours, upper digestive

LBA58 - A randomized phase III trial of perioperative chemotherapy (periop CT) with or without preoperative chemoradiotherapy (preop CRT) for resectable gastric cancer (AGITG TOPGEAR): Final results from an intergroup trial of AGITG, TROG, EORTC and CCTG

Date

14 Sep 2024

Session

Proffered paper session 2: GI tumours, upper digestive

Topics

Tumour Site

Gastric Cancer; Gastro-Oesophageal Junction Cancer

Presenters

Trevor Leong

Citation

Annals of Oncology (2024) 35 (suppl_2): 1-72. 10.1016/annonc/annonc1623

Authors

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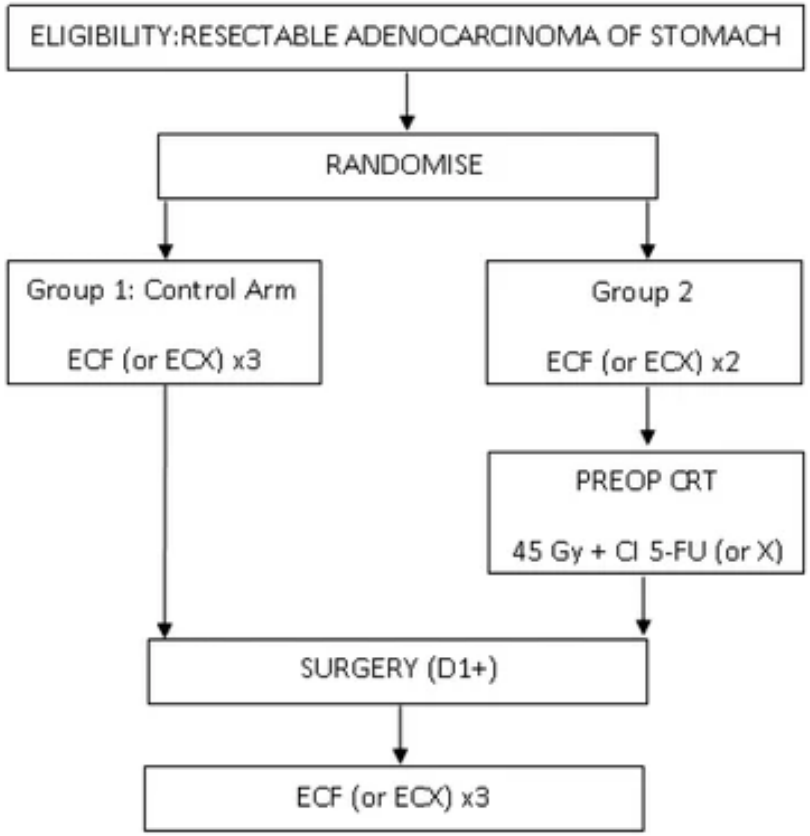

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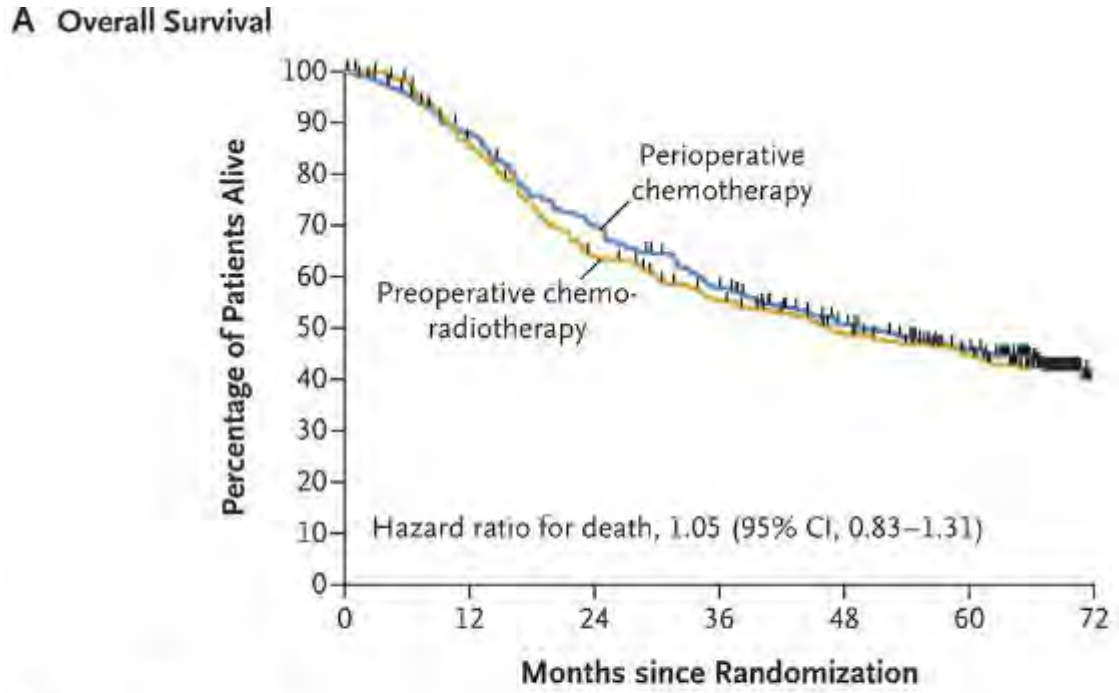
Non-Metastatic GEJ Cancers- ESMO 2024



No. at Risk							
Perioperative chemotherapy	288	241	191	154	122	94	8
Preoperative chemo-radiotherapy	286	235	174	143	117	89	9

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Non-Metastatic GEJ cancer

- Perioperative FLOT chemotherapy is the new standard for resectable GEJ cancers

- ChemoRT remains a standard approach for patients with esophageal SCC, who would not tolerate periop chemo and those unlikely to undergo resection.

- Role of adjuvant immunotherapy? CheckMate 577 evaluated adjuvant Nivolumab following neoadjuvant chemoRT and surgery

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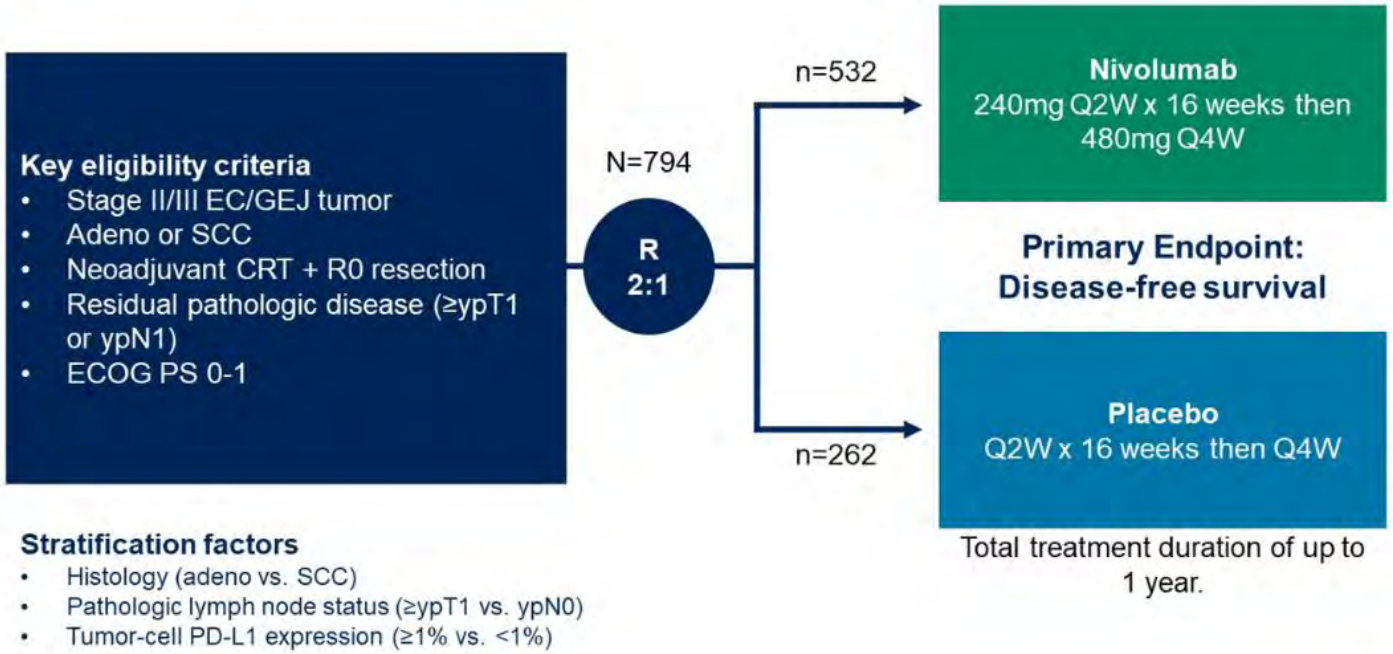
Non-Metastatic GEJ Cancers

CheckMate 577: Adjuvant Nivolumab in Resected Esophagus or GEJ Cancer



Kelly JR. ASCO Annual Meeting, 2021.

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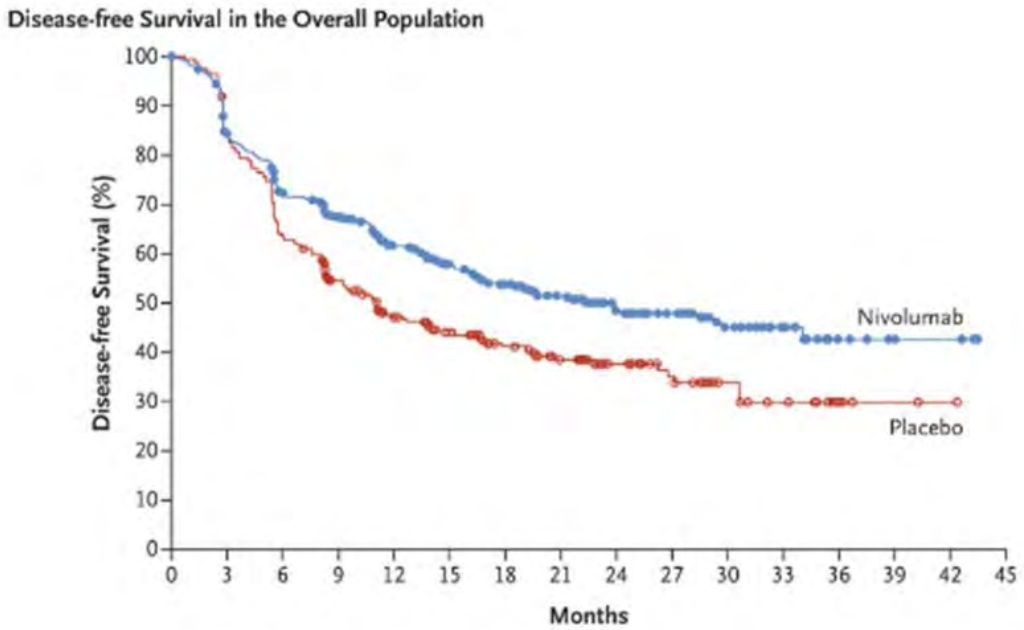
Non-Metastatic GEJ Cancers

CheckMate 577: Adjuvant Nivolumab in Resected Esophagus or GEJ Cancer



Median Disease-Free Survival	
Nivolumab n=532	**22.4mo** (95% CI 16.6-34.0)
Placebo N=262	**11.0mo** (95% CI 8.3-14.3)

HR 0.69
96.4% CI 0.56 0.86); P<0.001

In patients with residual disease following chemoRT + surgery, adjuvant nivolumab prolongs disease-free survival.

- **Doubled median disease-free survival**
- **31% reduction in the risk of recurrence or death**

Kelly JR et al. NEJM 2021.

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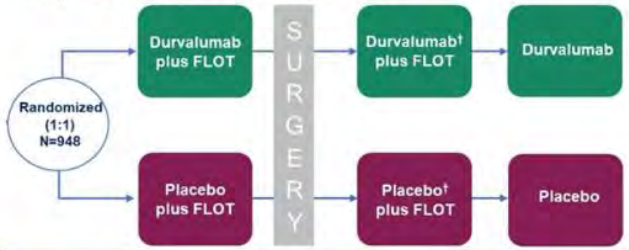
Non-Metastatic GEJ Cancers – Adjuvant Immunotherapy

Role of checkpoint inhibitors in the management of non-metastatic gastric and GEJ cancers: Ongoing trials

MATTERHORN: Phase 3, randomized, placebo-controlled trial

Eligibility not limited by PD-L1 status



Primary endpoint: EFS

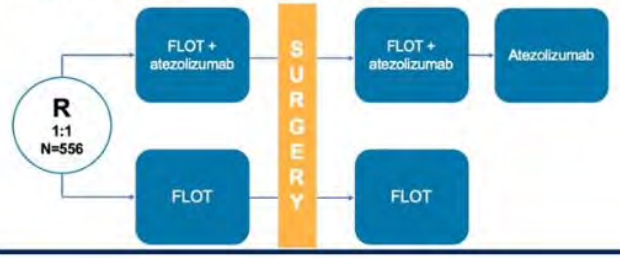
Interim analysis: PathCR rate: 19% vs. 7%

(95% CI 2.03-4.67; p<0.00001)

Janjigian Y. ASCO GI Symposium, 2024.

DANTE: Phase 2/3, randomized, open-label trial

Phase 2 eligibility not limited by PD-L1 status



Primary endpoint: EFS

Ph 2: PathCR rate: 24% vs. 15%

(descriptive)

Al-Batran SE. ASCO Annual Meeting, 2022.

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Metastatic Disease – Standard Therapy

- 1st line – FOLFOX/CAPOX + PDL-1 inhibitor (CPS score)

- 2nd line and beyond – Paclitaxel + Ramucirumab
  Irinotecan
  Trifluridine/Tipiracil PO

	CHECKMATE-649	RATIONALE-305	KEYNOTE 859
Anti-PD-1	Nivolumab	Tislelizumab	Pembrolizumab
Chemotherapy	Oxaliplatin + 5FU	Oxaliplatin + 5FU	Oxali or cis + 5FU
PD-L1 endpoints	CPS ≥5 28.8	TAP ≥5 SP263	CPS ≥ 1 & ≥10 223C
% PD-L1 CPS ≥5 or 10	60%	~55%	35% (*gastric)
OS	All HR 0.80 CPS ≥ 1 HR 0.77 **CPS ≥ 5 HR 0.71** **CPS ≥ 10 HR 0.66**	**TAP ≥ 5 HR 0.74**	All HR 0.78 CPS ≥ 1 HR 0.73 **CPS ≥ 10 HR 0.64**

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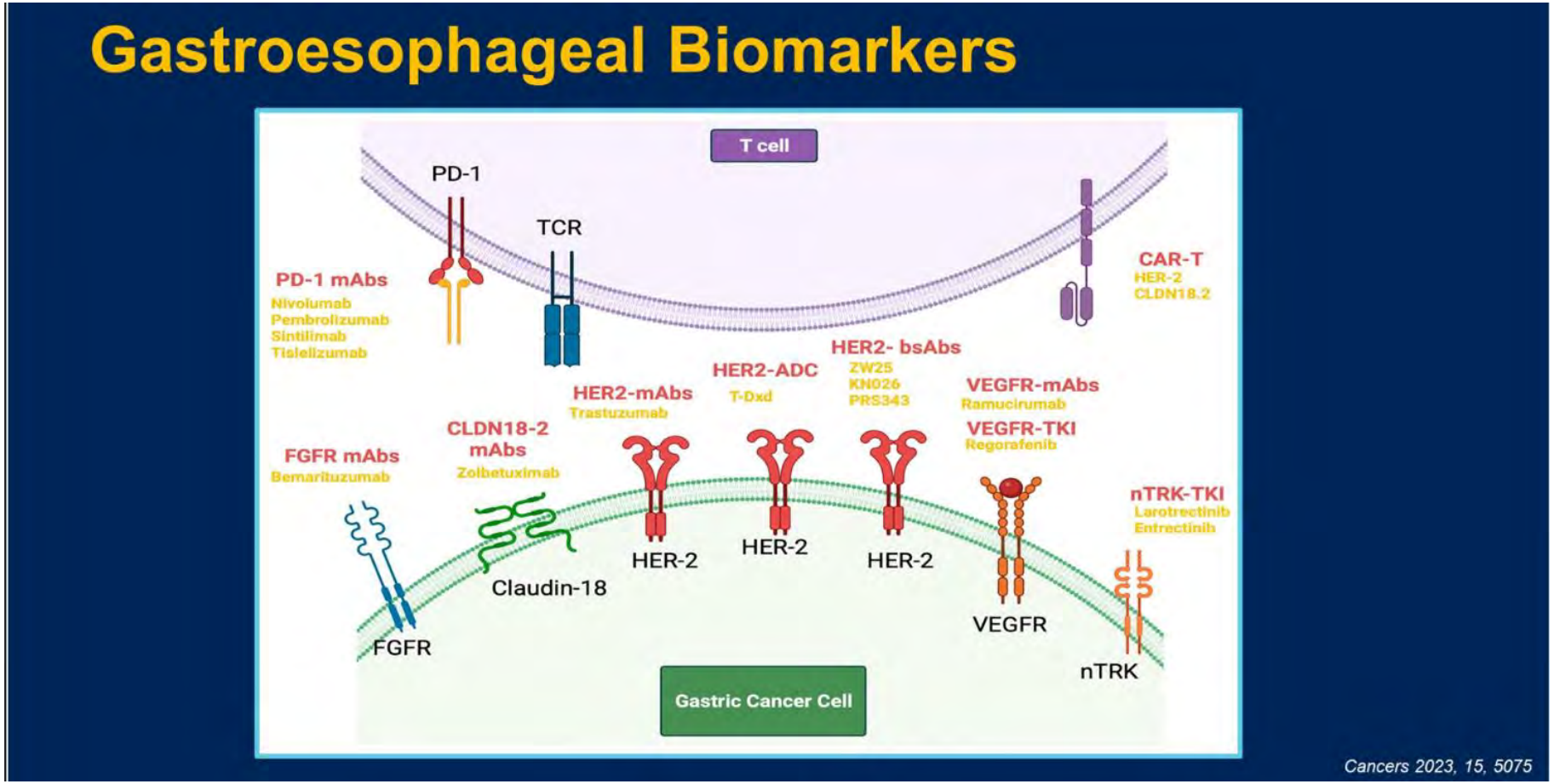
Metastatic Disease



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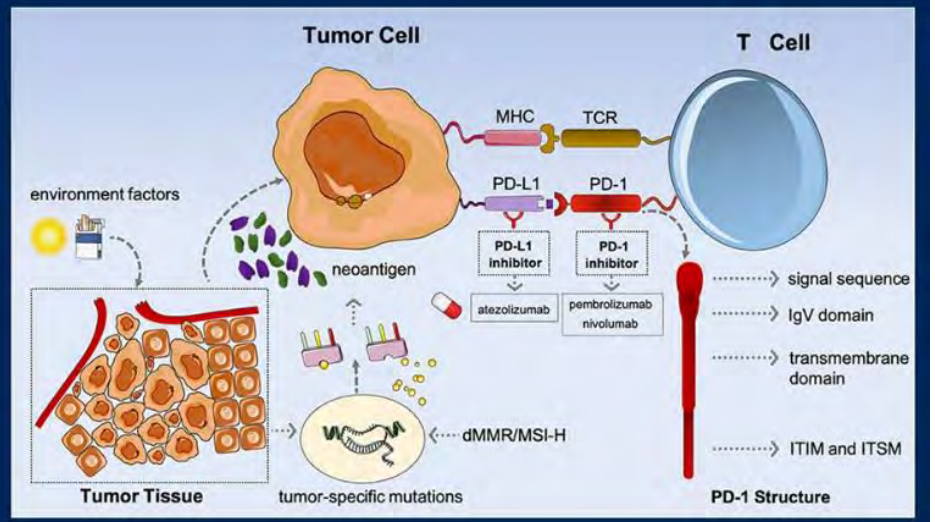
Metastatic Disease

Gastroesophageal Biomarkers – Immune

- MSI-H/dMMR
  - First tissue agnostic predictive biomarker approved by the FDA
  - Multiple methods for analysis
- PD-L1
  - FDA-approved biomarker
  - Combined Positive Score (CPS)
    - PD-L1 staining in both tumor cells and tumor-associated immune cells
- TMB
  - Mutations per megabase of DNA
  - Correlated with MSI-H
  - Comprehensive genomic profiling using NGS
  - Use currently evolving



Front. Oncol. **11**:650481 (2021)

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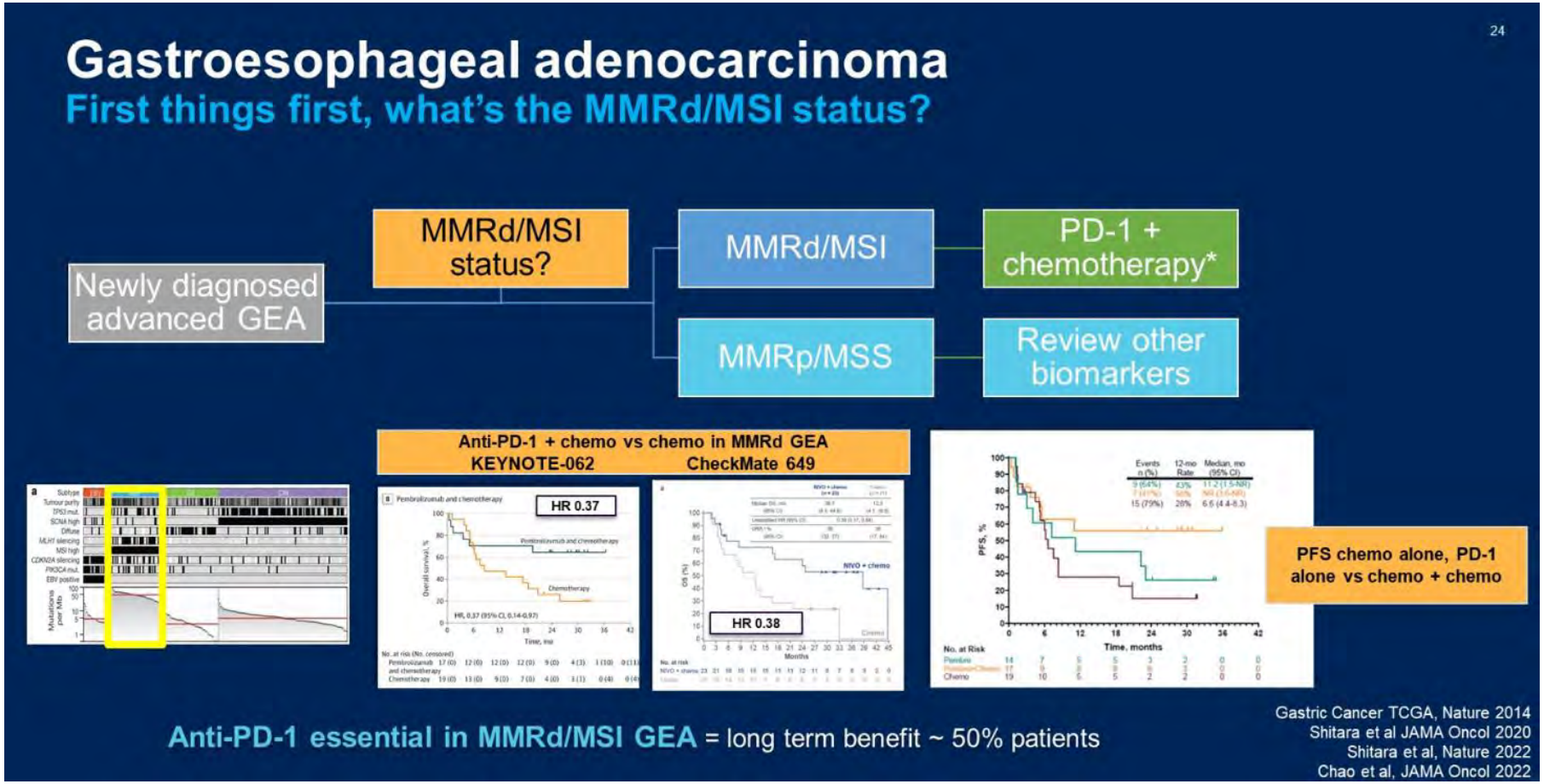
Metastatic Disease – MSI-High



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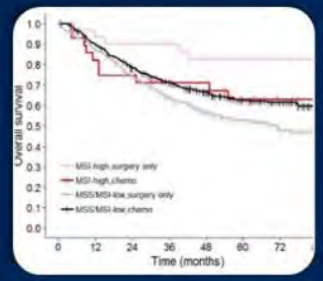
MSI-High

Operable gastroesophageal adenocarcinoma

First things first, what's the MMR/MSI status?



Newly diagnosed Operable GEA

MMRd/MSI status?

MMRd/MSI

- Surgery alone
- Neoadjuvant chemotherapy (FLOT) or chemoradiotherapy (Es)
- Neoadjuvant PD-1/CTLA4*

AIO DANTE MSI patients FLOT (n=13)	
pCR	38%

	NEONIPIGA nivolumab + ipilimumab		INFINITY Durvalumab + tremilimumab		
Mandard	n	%	Becker	n	%
1	17	59%	1a	9	60%
2	4	14%	1b	3	20%
3	2	7%	2	2	13%
4 -5	4	21%			

MMRd operable tumours

- Excellent survival with surgery alone
- If chemo and no ICI, include a taxane
- Organ sparing approach in development

Pietrantonio et al, JCO 2019
Lorenzen et al, JCO 2024
Andre et al, JCO 2023
Pietrantonio et al, ASCO GI 2023

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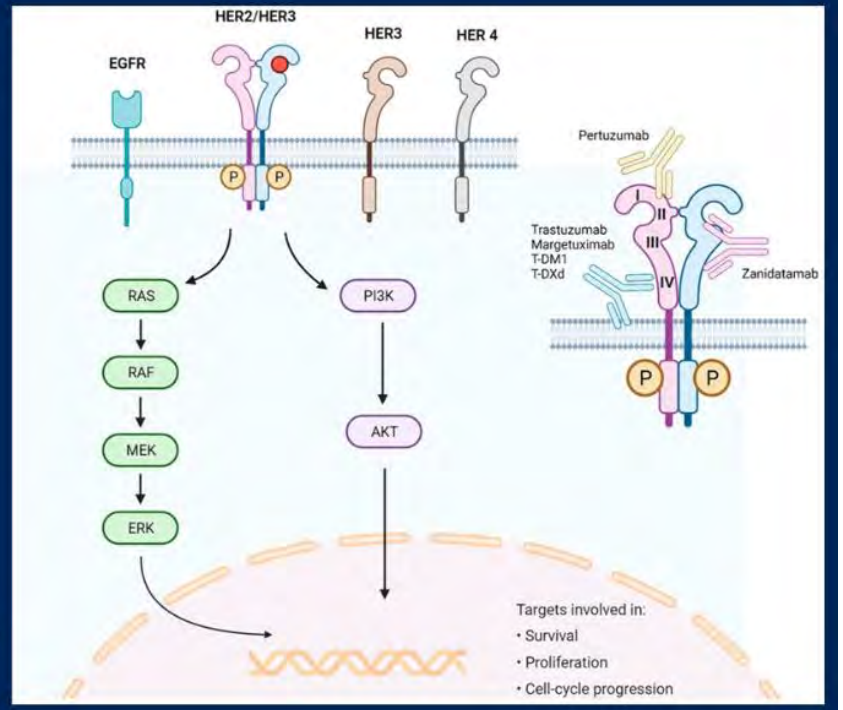
Metastatic Disease – Her2

Gastroesophageal Biomarkers – HER2

- Receptor tyrosine kinase amplified/overexpressed in ~15-20% of gastric & GE junction adenocarcinomas
- HER2-positive gastric cancers:
  - Worse prognosis
  - Increased tumor aggressiveness
  - Higher rates of metastasis
  - Lower overall survival rates
- HER2 expression in gastric cancer often heterogeneous, complicating diagnostic testing requiring comprehensive testing methods
- Serves as a predictive biomarker for the response to HER2-targeted therapies



Int. J. Mol. Sci. 2023, 24(14), 11403

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Metastatic Disease – Her2

Advanced gastroesophageal adenocarcinoma

Rapid developments in HER2 positive cancer

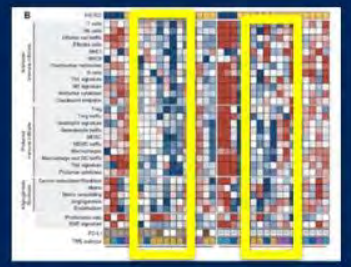
HER2 positive
IHC3+/IHC2+ FISH ratio >2.0

What's the PD-L1?

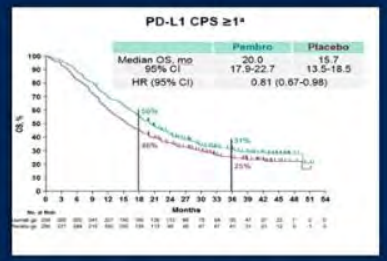
- PD-L1 positive → Chemotherapy + trastuzumab + pembrolizumab
- PD-L1 negative → Chemotherapy plus trastuzumab

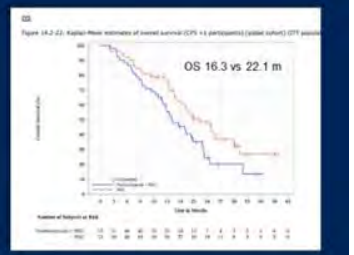
KEYNOTE 811
1L HER2+ve GEA

- Chemo-trastuzumab vs chemo-trastuzumab pembrolizumab
- Efficacy of pembrolizumab predicated on presence of PD-L1



HER2 positive GEA primed to respond to ICI





OS benefit for double biomarker only:HER2 and PD-L1 positive
Negative impact on OS in HER2+ve PD-L1 negative

Kim et al, Cancer Discovery 2021
Janjigian et al, Lancet 2023
EMA pembrolizumab EPAR

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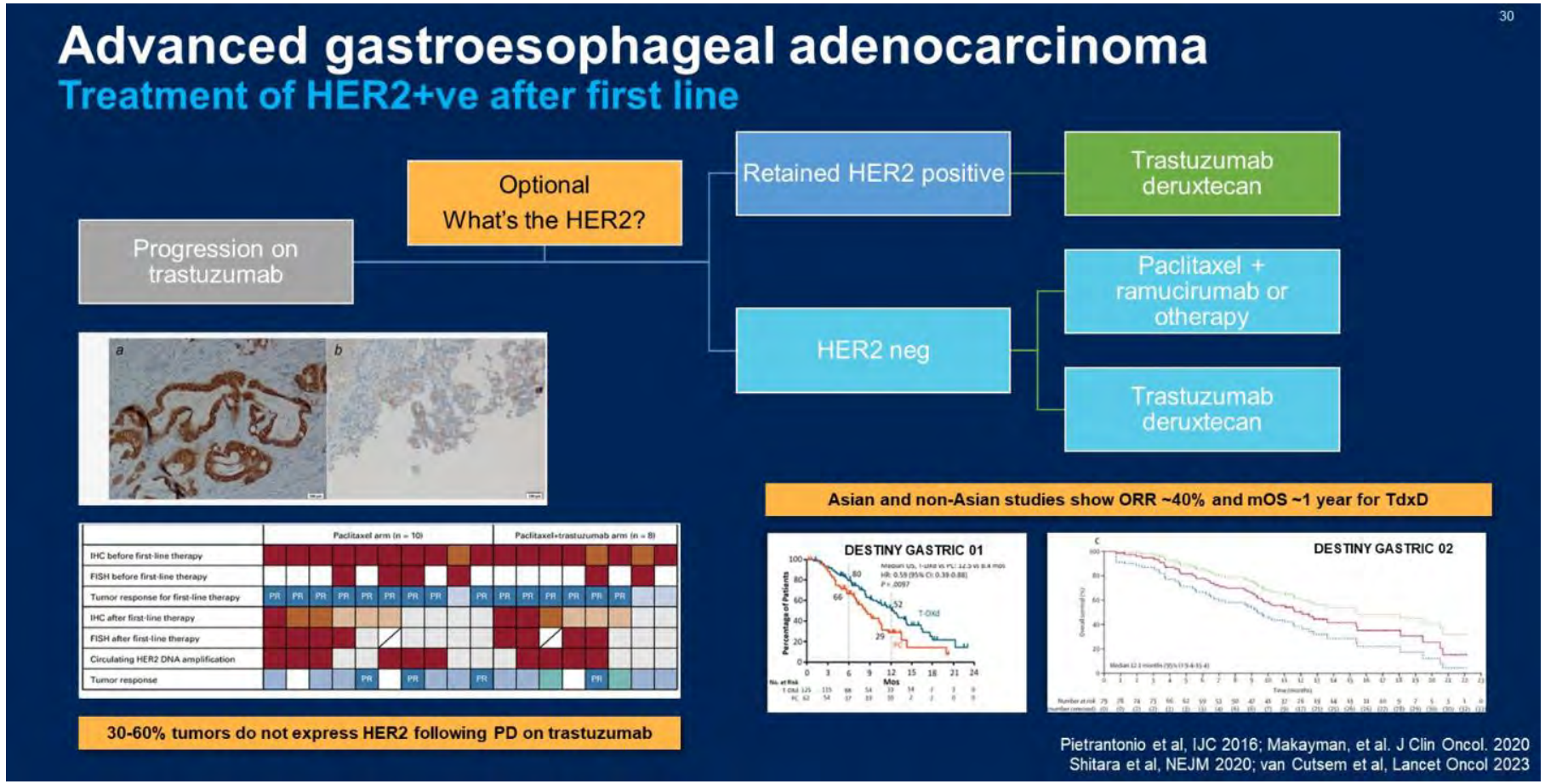
Metastatic Disease – Her2



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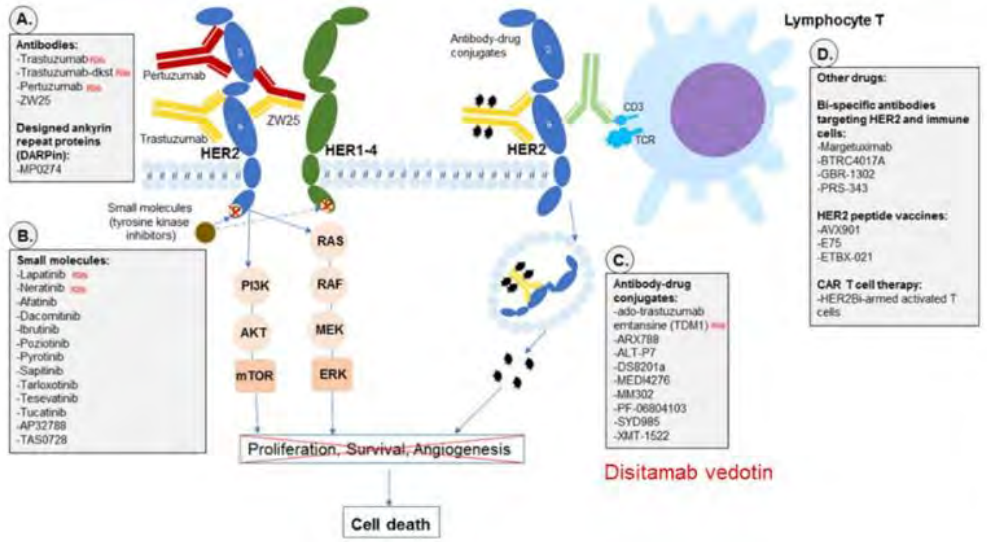
Metastatic Disease – Her2

Multiple Anti-HER2 Therapies in Development



Meric-Bernstam et al. CCR. 2019

- Targeting HER2 signaling
  - Monoclonal antibodies
    - Trastuzumab, pertuzumab
    - Emerging agents: eg Zanidatamab
    - May also have ADCC effects?
  - Small molecule inhibitors
    - Tucatinib, lapatinib, neratinib
    - Selective eg Zongertinib, ZN-1041, IAM-H1
    - Pan-HER: TAS2940, BAY 2927088,
- Targeting HER2 for immune strategies
  - Bispecific engagers
  - CARTs
  - Vaccines
- Targeting HER2 by ADCs
  - Cytotoxic payloads
  - Other payloads

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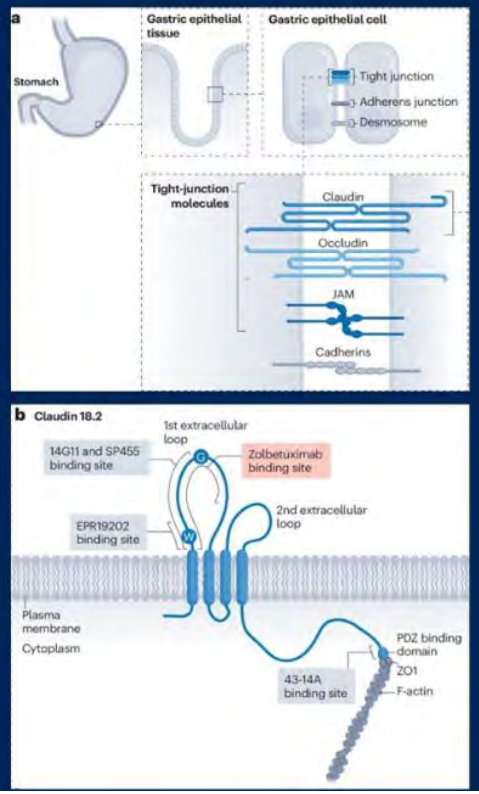
Metastatic Disease

Gastroesophageal Biomarkers – Claudin 18.2

- Tight junction protein highly specific:
  - Differentiated epithelial cells of normal stomach mucosa
  - High expression gastric adenocarcinomas and other malignancies
- Claudin 18.2 interacts with various signaling pathways involved in cell proliferation, migration, and survival
- Extracellular domain of Claudin 18.2
  - Ideal target for antibody-based therapies
  - Accessible to therapeutic antibodies
  - Elicit a robust immune response



Nat Rev Clin Oncol **21**, 354–369 (2024)

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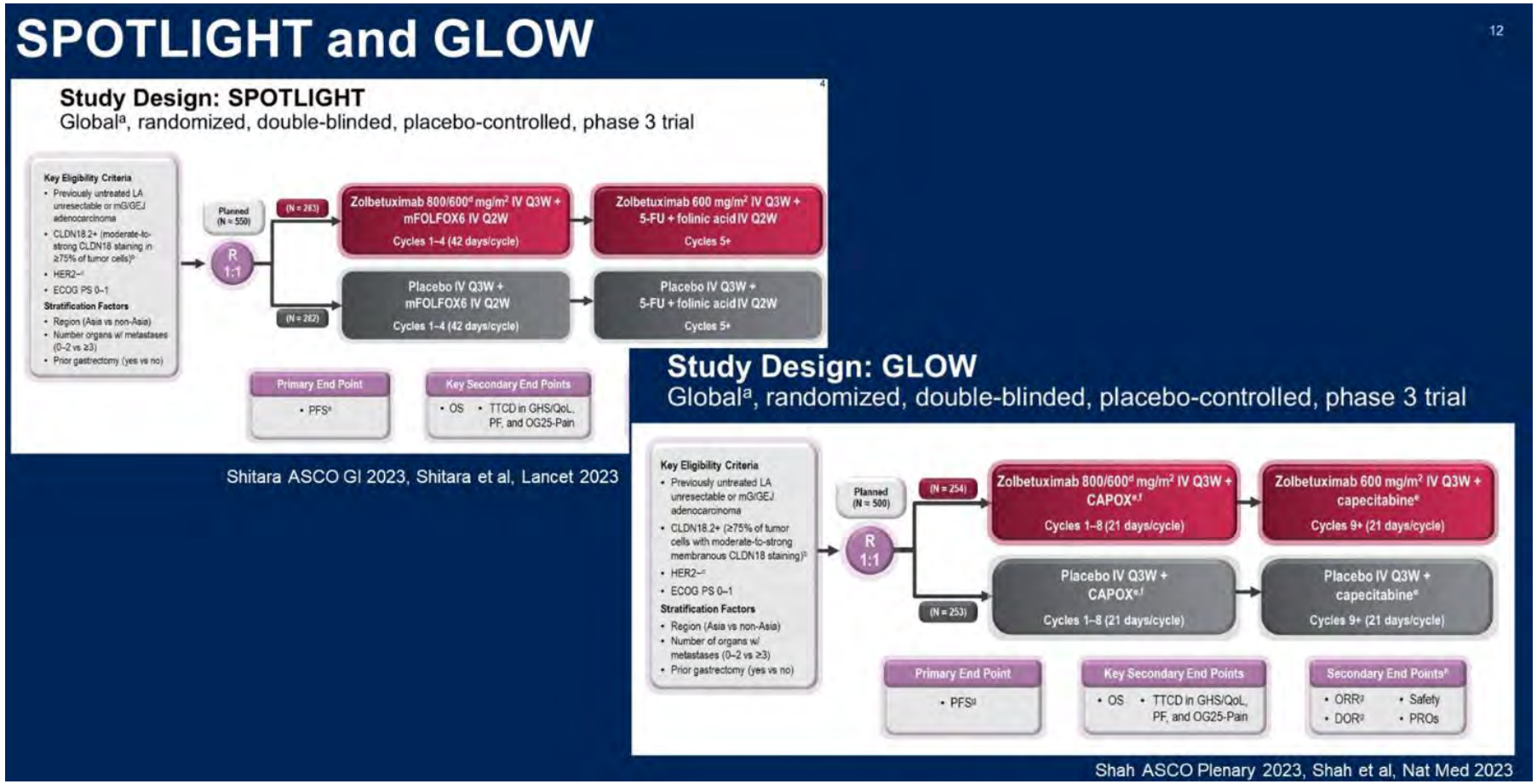
Metastatic Disease – Claudin 18.2



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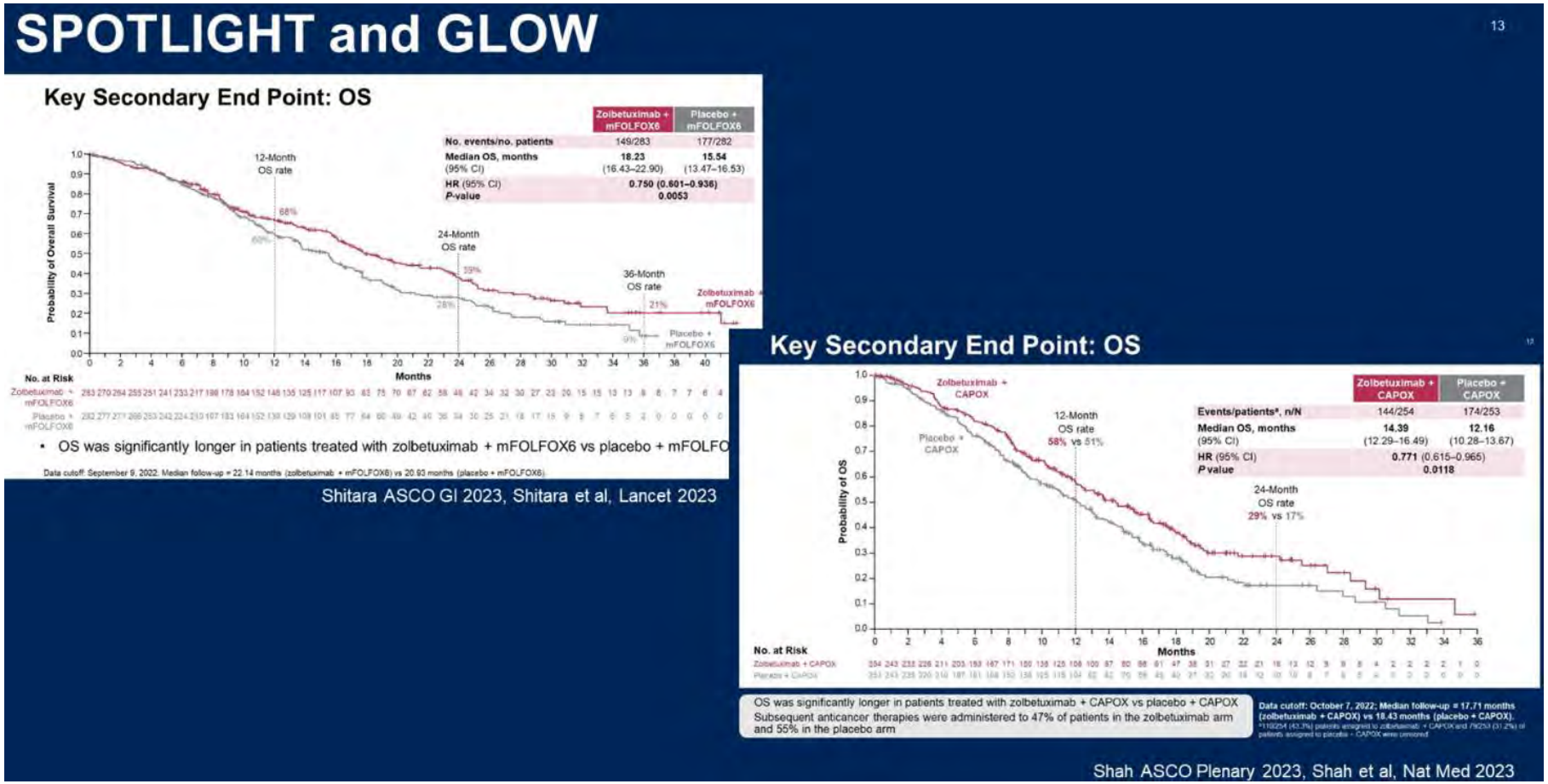
Metastatic Disease – Claudin 18.2



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Metastatic Disease – Open Questions

- Co-expression biomarkers – synergy vs antagonism
- Spatial and temporal heterogeneity
- Treatment sequencing
- Move into operable GEJ cancers

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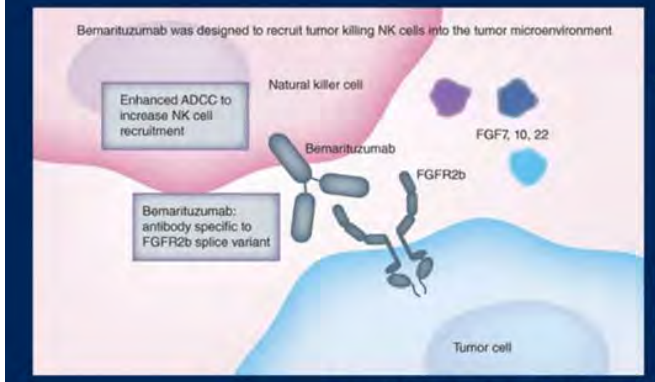
Metastatic Disease: Coming Soon

20

FGFR2b



Catenacci et al, Future Oncol 2019

FGFR2 amplification: ~5%
FGFR2b overexpression: ~30%

Wainberg et al, Lancet Oncol 2022

FIGHT Trial

Key Eligibility Criteria

- No prior therapy for unresectable, locally advanced or metastatic gastric/GEJ adenocarcinoma
- RECIST v1.1 evaluable disease
- FGFR2b overexpression and/or *FGFR2* gene amplification
- Not HER2-positive

Stratification Factors

- Geographic region
- Single dose of FOLFOX while screening
- Prior perioperative chemotherapy

Randomization 1:1

Bemarituzumab* + mFOLFOX6 (n = 77)

vs

Placebo + mFOLFOX6 (n = 78)

Primary endpoint
- PFS

Secondary endpoints
- OS
- Response rate

Treatment may continue until progression, unacceptable toxicity, or the patient meets other withdrawal criteria

Wainberg, ASCO GI 2021

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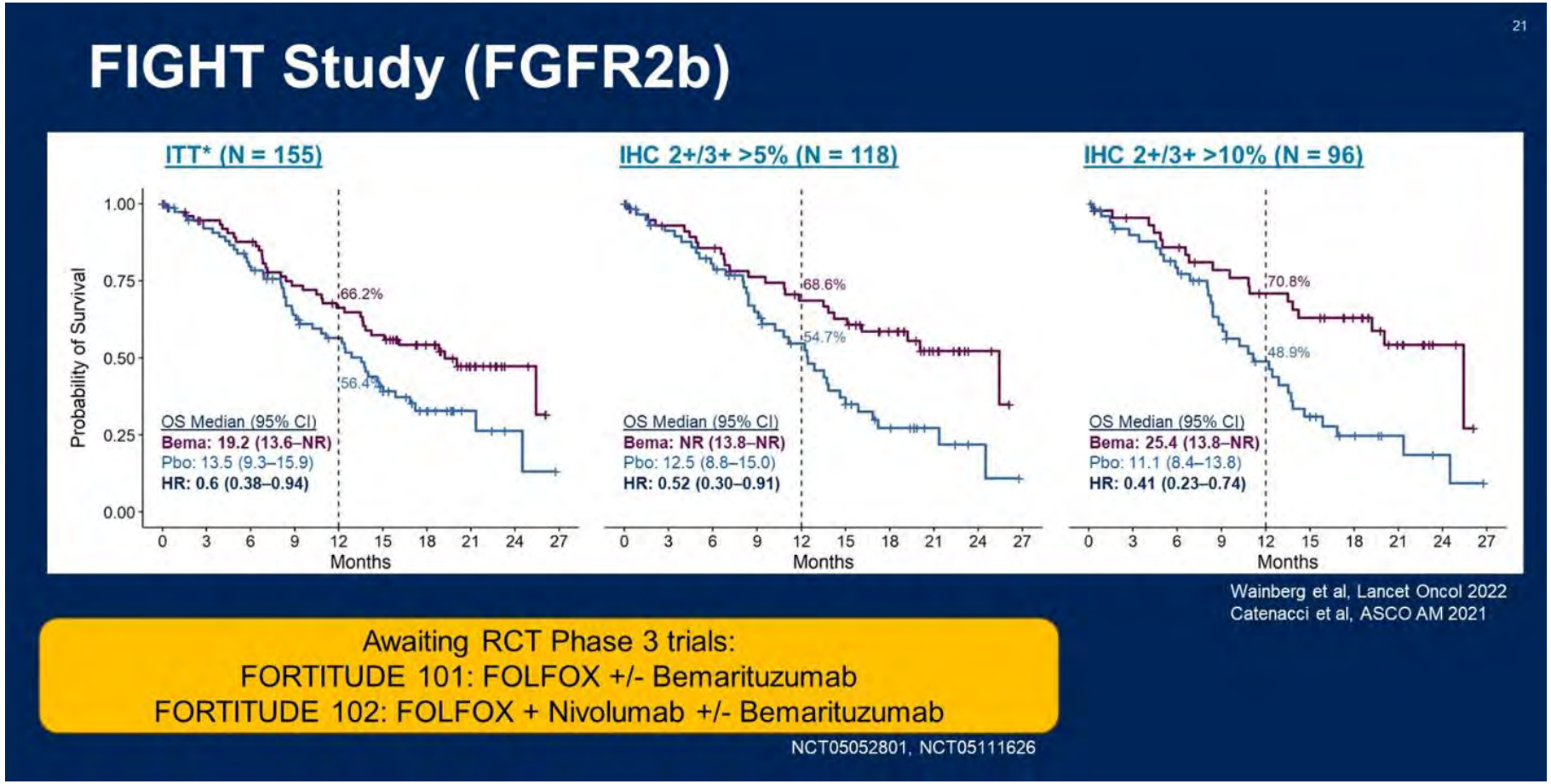
Metastatic Disease: Coming Soon



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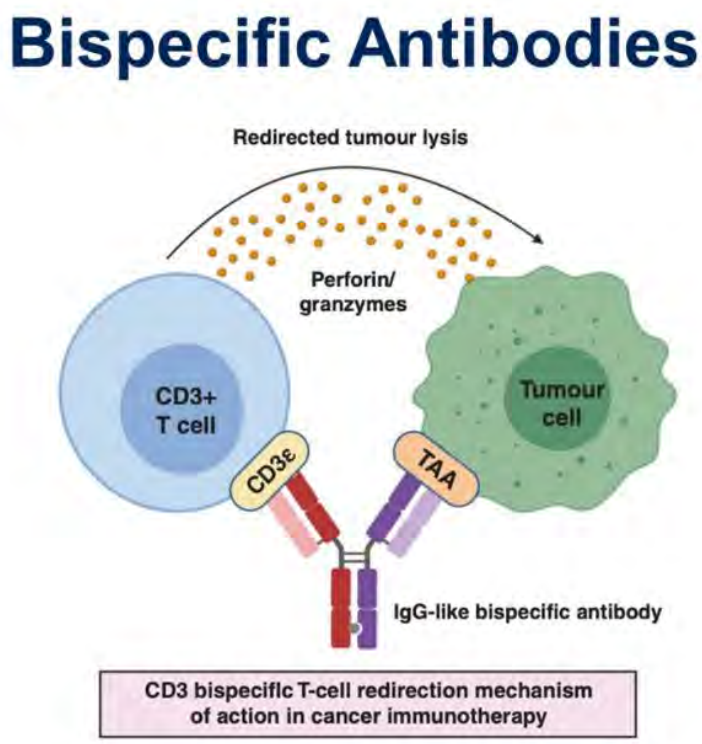
Metastatic Disease: Coming Soon



- More versatile than monoclonal antibodies
- Can recruit immune effector cells to cancer cells
- Target different signaling pathways with a single molecule
- Can exert multiple mechanism of actions at the same time

Singh A et al, 2021

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Metastatic Disease: Coming Soon

Bispecific Antibodies under investigation in gastroesophageal cancers

- HER2
  - Zanidatamab - ECD4 x ECD2
  - Anbenitamab – Domain IV x Domain II
- CLDN18.2
  - ASP2138, AZD5863, IBI389, QLS31905 – CLDN18.2 x CD3
  - Givastomig, PM1032 - CLDN18.2 x 4-1BB
  - PT886 - CLDN18.2 x CD47
  - Q-1802 – CLDN18.2 x PD-L1
- Retlirafusp alfa (SHR-1701) – PD-L1 x TGFβ

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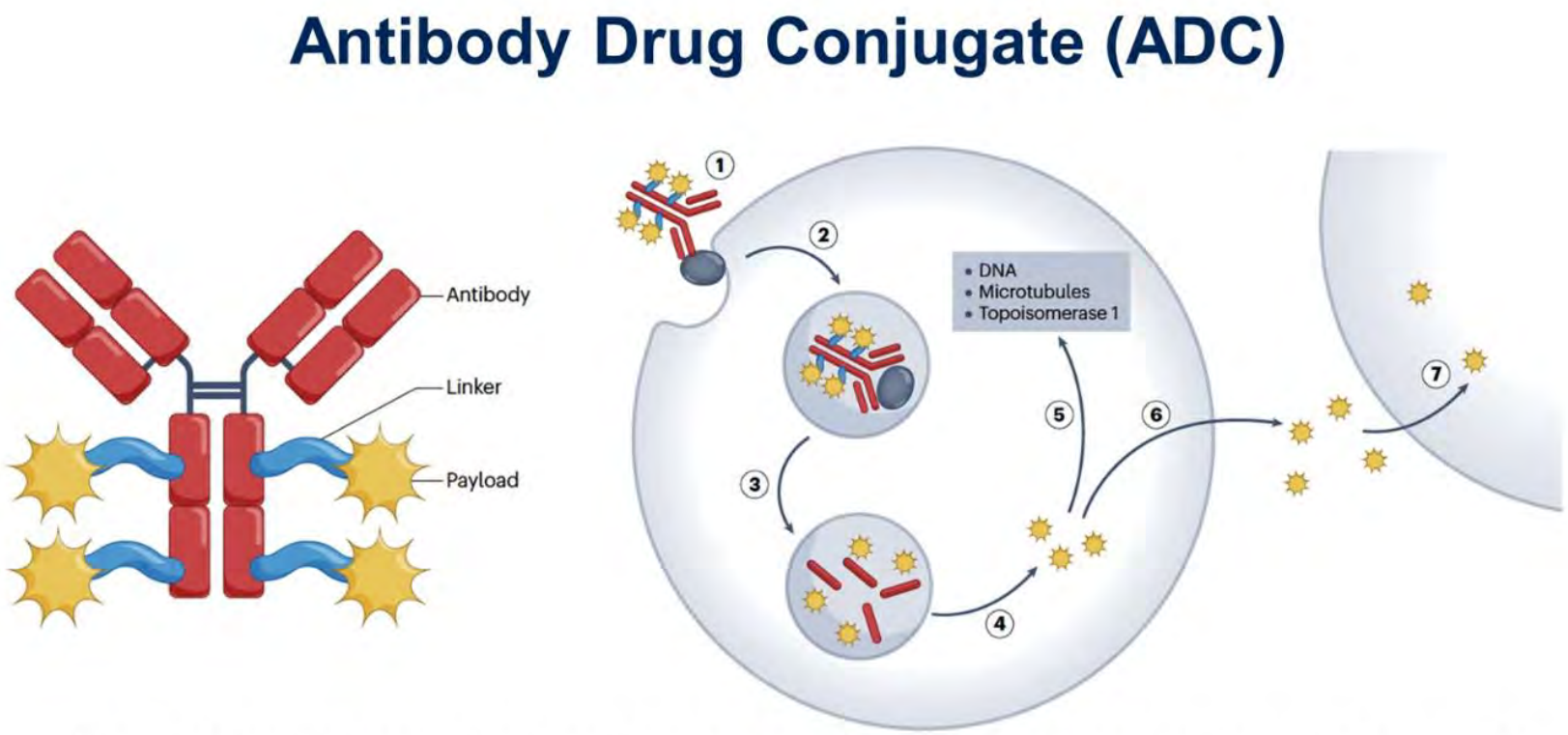
Metastatic Disease: Coming Soon



"Magic bullets" of cancer treatment due to ability to combine tumor targeting properties of an antibody AND potency of cytotoxic agents

Dumontet C et al, 2023

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Metastatic Disease: Coming Soon

ADCs under investigation in gastroesophageal cancers

CDLN18.2	• BMS-986476/TPX-4589/LM-302/RC118/CMG901 (MMAE) • EO-3021/SYSA1801/ATG-022 (MMAE) • SOT102 (PNU-159682) • IBI343 (topo I inhibitor)
HER2	• Trastuzumab deruxtecan (topo I inhibitor) • CMH902 (MMAE) • ARX788 (tubulin inhibitor) • RC48 (MMAE)
B7H3	• I-DxD (topo I inhibitor)
NECTIN-4	• EV-202 (topo 1 inhibitor)
TROP-2	• SKB264 (topo I inhibitor)

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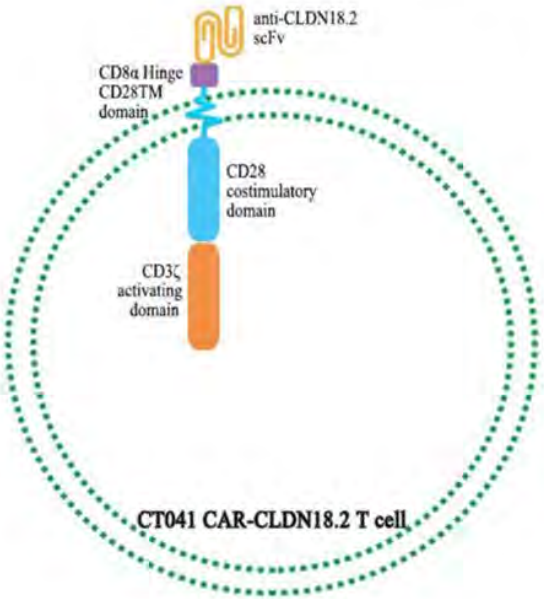
Metastatic Disease: Coming Soon

Chimeric Antigen Receptor T-cell (CAR-T) Targeting CLDN18.2



- CT041 contains genetically engineered autologous T cells that express the CLDN18.2-targeted CAR
- The CAR structure consists of the following:
  - Humanized anti-CLDN18.2 single-chain variable fragment
  - CD8α hinge region
  - CD28 co-stimulatory domain
  - CD3ζ signaling domain

Qi C ASCO 2022

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Conclusions

- Establish goals
- Tailor approach to each patient
- Balance efficacy and toxicity
- Right biomarker testing can guide therapy
- Refer for clinical trial

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Thank You!