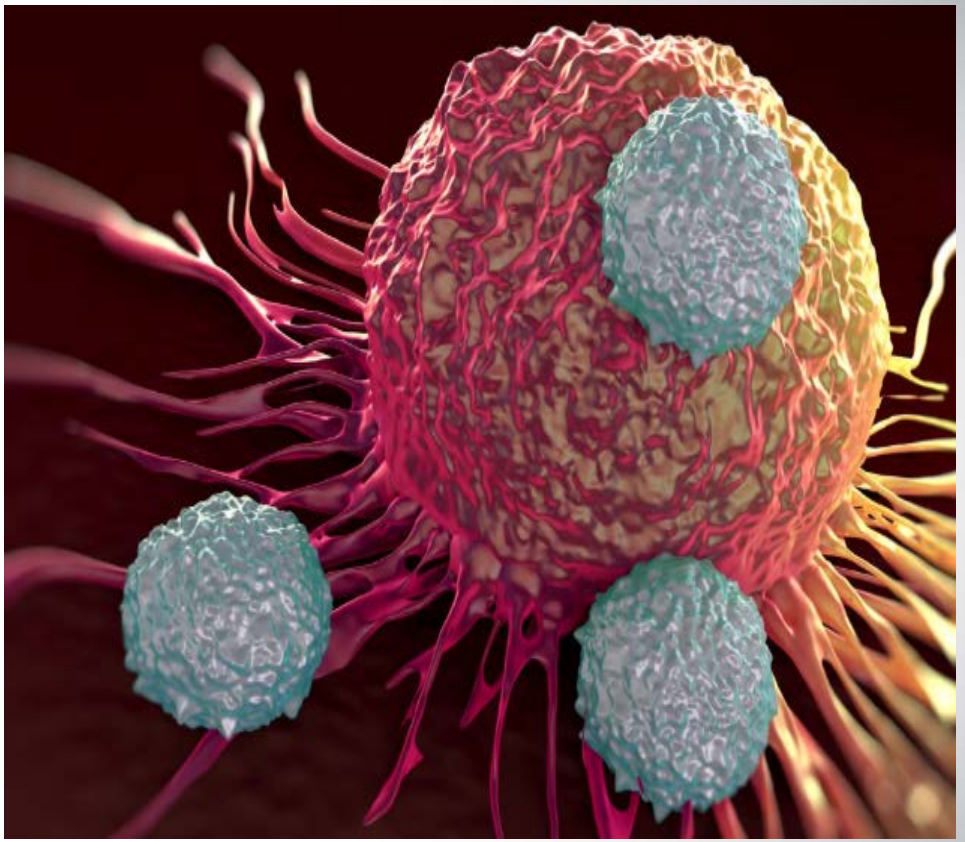
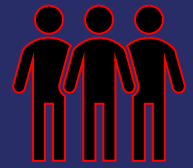
- ***Immunotherapy for Upper GI Cancers***
  - ***Esophageal Adenocarcinoma***
  - ***GE Junction Adeno***
  - ***Gastric Carcinoma***



Ahmed Zakari MD
Medical Director of GI Cancer Program , Florida Hospital Cancer Institute
Associate Professor University of Central Florida , College of Medicine

Esophageal Cancer : *Statistics, Risk Factors*

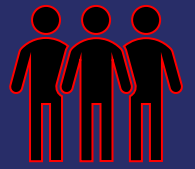


- The American Cancer Society estimates ***17290*** Esophageal cancer in the US for 2018
  - 13,480 in men and 3,810 in women
  - 15,850 deaths from esophageal cancer (12,850 in men and 3,000 in women)
- Esophageal cancer is more common among men than among women. The lifetime risk of esophageal cancer in the United States is about 1 in 132 in men and about 1 in 455 in women

- Age, Gender
- GERD
- Barrett's Esophagus
- Tobacco and ETOH
- Obesity
- Diet
- Achalasia
- Tylosis
- HPV (Asia, South America)

Presented by:

Gastric Cancer in the US: *STATS, Risk*

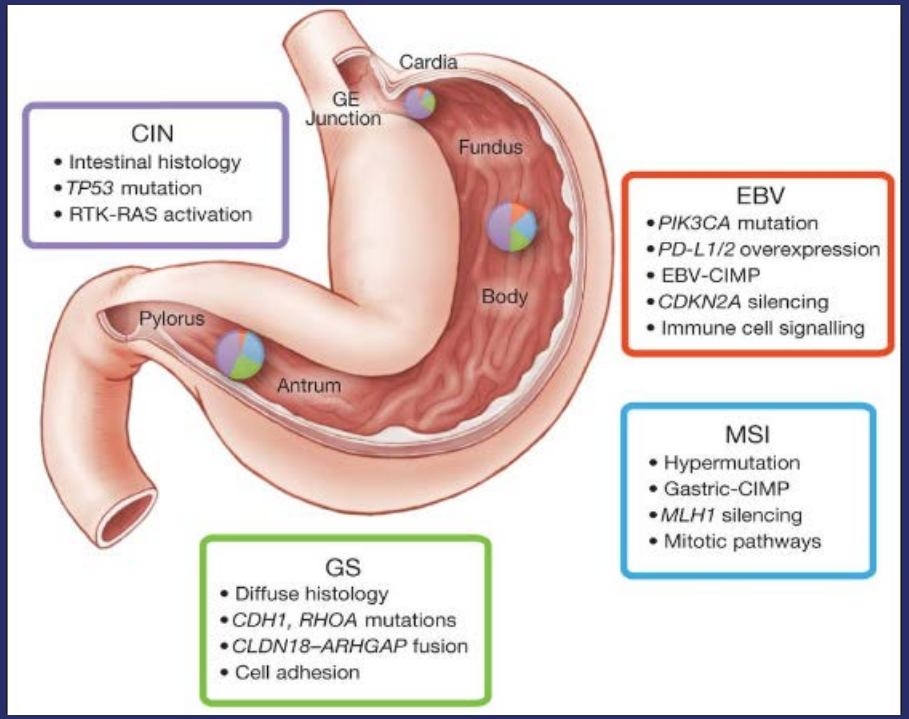


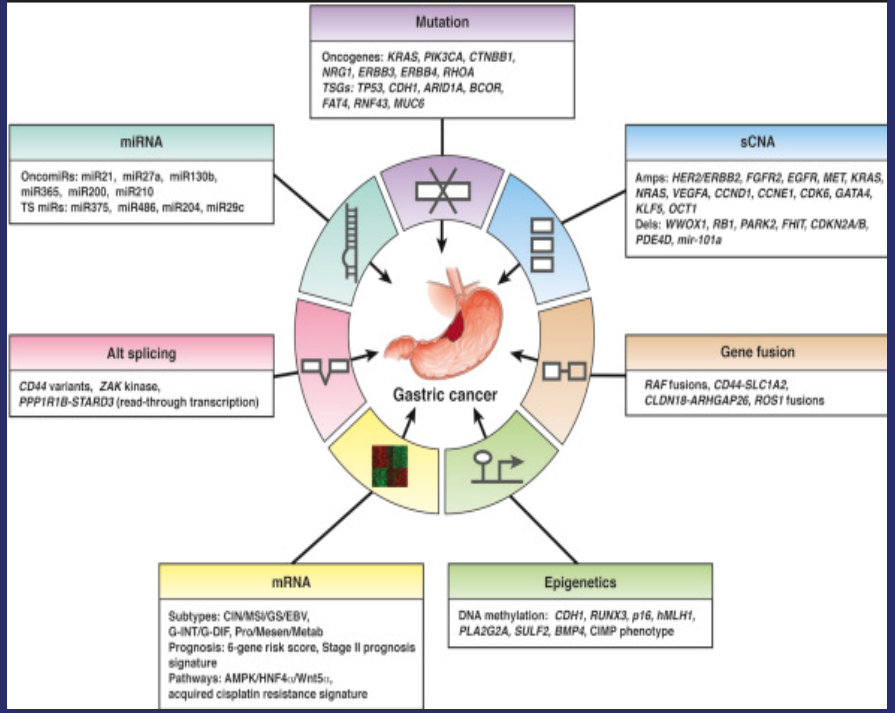
- The ACS estimates 26240 Gastric cancer in the United States for 2018
  - 16,520 in men and 9,720 in women
- About 10,800 people will die of Gastric cancer

- The risk that a man will develop Gastric cancer in their lifetime is about 1 in 95. For women the chance is about 1 in 154

- Age, Gender
- H. Pylori
- Tobacco Use
- Obesity
- Pernicious Anemia
- Inherited Syndromes
- Hereditary Diffuse Gastric Syndrome
  - HNPCC/ Lynch Synd.
  - FAP Syndrome
  - BRCA1/BRCA2
  - Li-Fraumeni syndrome
  - Peutz-Jeghers syndrome (PJS)

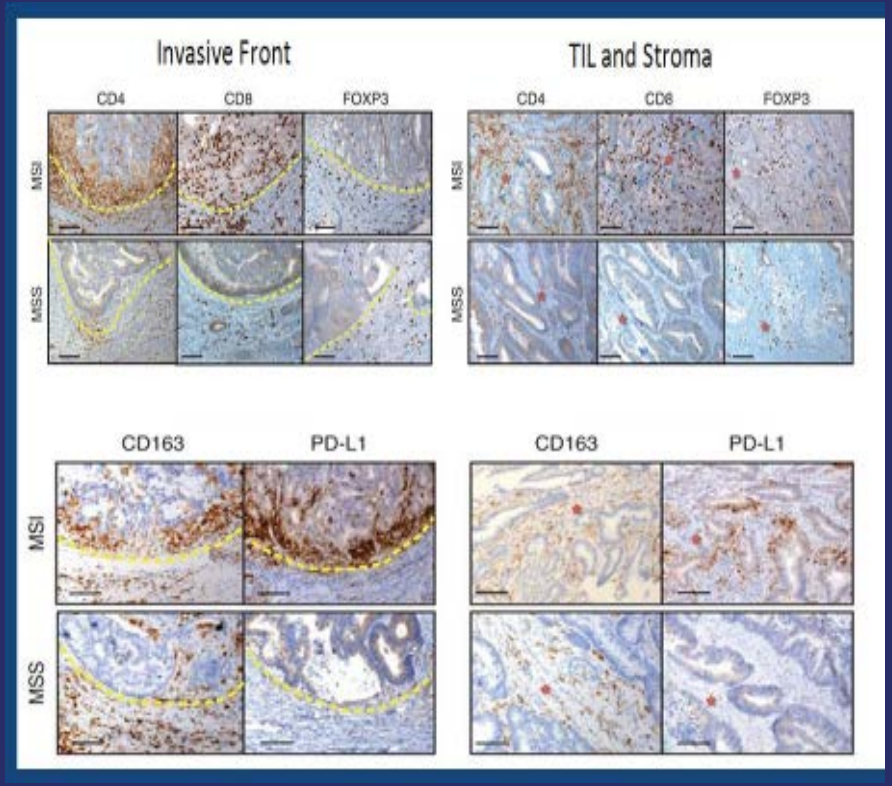
Gastro-Esophageal Oncogenesis and Biomarkers



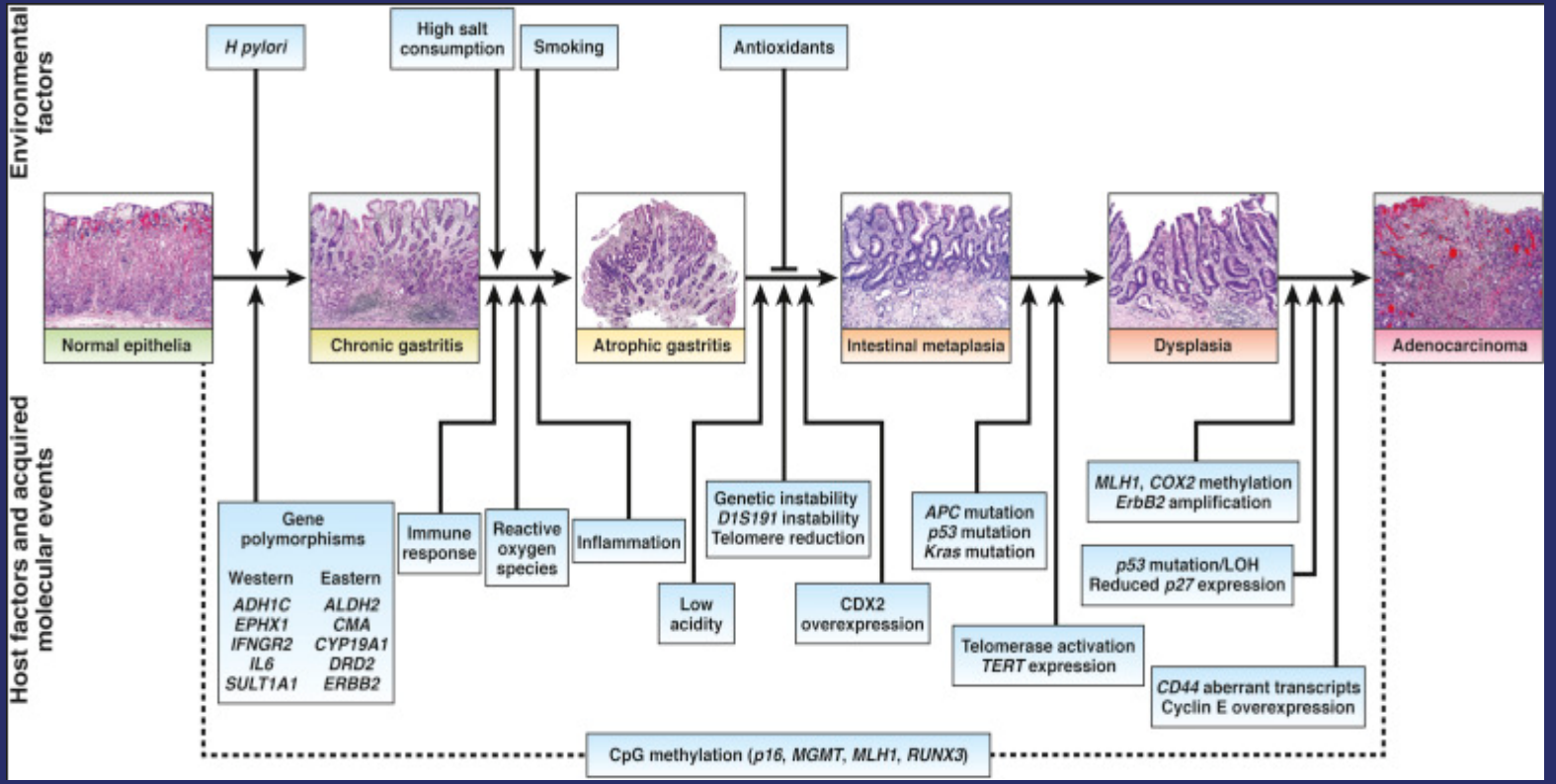


Gastro-Esophageal carcinoma : Biomarkers

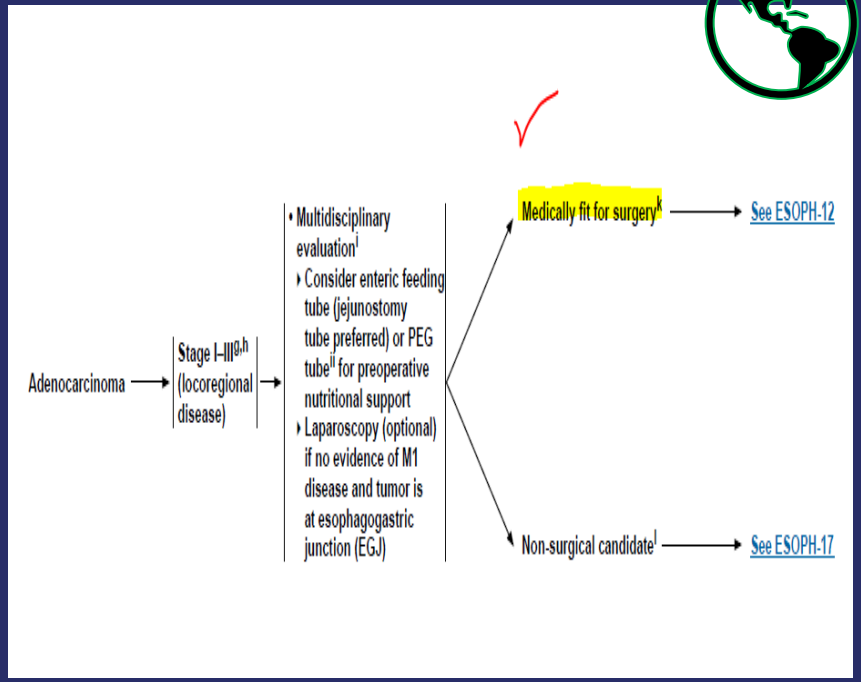
- Somatic Mutations are highly seen in GE presenting as truncated proteins
- Increased Lymphocyte infiltration in the tissue
- Checkpoint Ligand strongly expressed: PD1, PDL-1, LAG-3 and CTLA-4



Gastric carcinoma Pathogenesis : How do we get there?



Current Status of GE Cancers : AdenoCa. Recommendations
NCCN Guidelines 2018



National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2018
Esophageal and Esophagogastric Junction Cancers

NCCN Guidelines Table of Contents Discussion

PRINCIPLES OF SYSTEMIC THERAPY

Preoperative Chemoradiation
(Infusional fluorouracil can be replaced with capecitabine)

Preferred Regimens
- Paclitaxel and carboplatin (category 1)[1]
- Fluorouracil[a] and oxaliplatin (category 1)[2,3]

Other Recomended Regimens
- Fluorouracil and cisplatin (category 1)[4,5]
- Irinotecan and cisplatin (category 2B)[6]
- Paclitaxel and fluoropyrimidine (fluorouracil or capecitabine) (category 2B)[7]

Perioperative Chemotherapy
(Only for adenocarcinoma of the thoracic esophagus or EGJ)
(3 cycles preoperative and 3 cycle postoperative)

Preferred Regimens
- Fluoropyrimidine and oxaliplatin[b]
- Fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT)[8] (category 1)[c]

Other Recomended Regimens
- Fluorouracil and cisplatin (category 1)[9]

Preoperative Chemotherapy (2 cycles)
(Only for adenocarcinoma of the thoracic esophagus or EGJ)
- Fluorouracil and cisplatin (category 2B)[10]

Definitive Chemoradiation
Infusional fluorouracil can be replaced with capecitabine

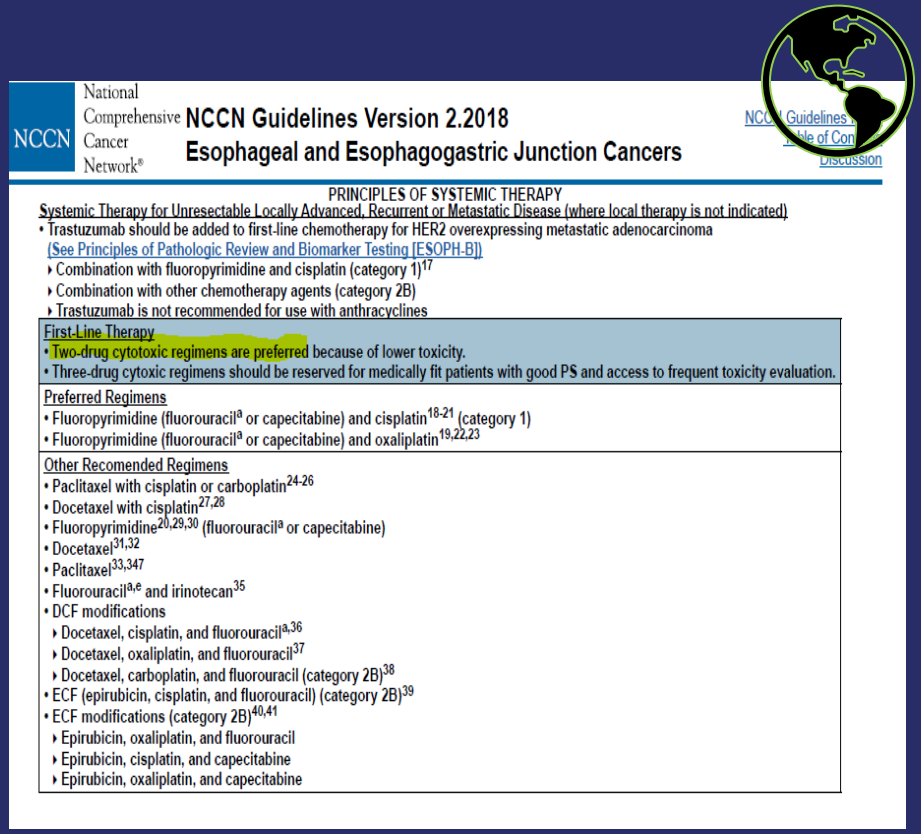
Preferred Regimens
- Fluorouracil and cisplatin (category 1)[11]
- Fluorouracil[a] and oxaliplatin (category 1)[2,3]
- Paclitaxel and carboplatin[1]

Other Recomended Regimens
- Cisplatin with docetaxel or paclitaxel[12-14]
- Irinotecan and cisplatin (category 2B)[6]
- Paclitaxel and fluoropyrimidine (fluorouracil or capecitabine) (category 2B)[7]

Postoperative Chemoradiation
- Fluoropyrimidine (infusional fluorouracil[a] or capecitabine) before and after fluoropyrimidine-based chemoradiation[15]

Postoperative Chemotherapy
- Capecitabine and oxaliplatin[d,16]

Approved Treatment Options for Advanced Esophageal / Gastric Cancers



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Esophageal and Esophagogastric Junction Cancers

NCCN Guidelines Table of Contents Discussion

PRINCIPLES OF SYSTEMIC THERAPY

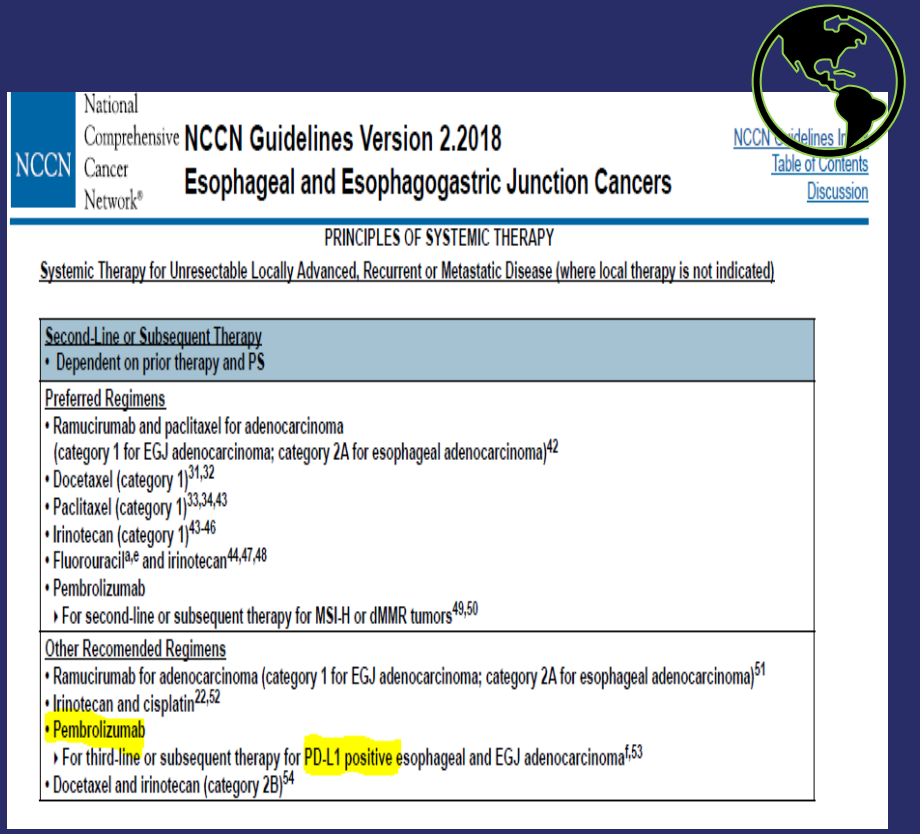
Systemic Therapy for Unresectable Locally Advanced, Recurrent or Metastatic Disease (where local therapy is not indicated)

- Trastuzumab should be added to first-line chemotherapy for HER2 overexpressing metastatic adenocarcinoma (See Principles of Pathologic Review and Biomarker Testing [ESOPH-B])
  - Combination with fluoropyrimidine and cisplatin (category 1)[17]
  - Combination with other chemotherapy agents (category 2B)
  - Trastuzumab is not recommended for use with anthracyclines

First-Line Therapy
- Two-drug cytotoxic regimens are preferred because of lower toxicity.
- Three-drug cytotoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation.

Preferred Regimens
- Fluoropyrimidine (fluorouracil[a] or capecitabine) and cisplatin[18-21] (category 1)
- Fluoropyrimidine (fluorouracil[a] or capecitabine) and oxaliplatin[19,22,23]

Other Recomended Regimens
- Paclitaxel with cisplatin or carboplatin[24-26]
- Docetaxel with cisplatin[27,28]
- Fluoropyrimidine[20,29,30] (fluorouracil[a] or capecitabine)
- Docetaxel[31,32]
- Paclitaxel[33,347]
- Fluorouracil[a,e] and irinotecan[35]
- DCF modifications
  - Docetaxel, cisplatin, and fluorouracil[a,36]
  - Docetaxel, oxaliplatin, and fluorouracil[37]
  - Docetaxel, carboplatin, and fluorouracil (category 2B)[38]
- ECF (epirubicin, cisplatin, and fluorouracil) (category 2B)[39]
- ECF modifications (category 2B)[40,41]
  - Epirubicin, oxaliplatin, and fluorouracil
  - Epirubicin, cisplatin, and capecitabine
  - Epirubicin, oxaliplatin, and capecitabine



NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2018
Esophageal and Esophagogastric Junction Cancers

NCCN Guidelines Table of Contents Discussion

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent or Metastatic Disease (where local therapy is not indicated)

Second-Line or Subsequent Therapy
- Dependent on prior therapy and PS

Preferred Regimens
- Ramucirumab and paclitaxel for adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)[42]
- Docetaxel (category 1)[31,32]
- Paclitaxel (category 1)[33,34,43]
- Irinotecan (category 1)[43-46]
- Fluorouracil[a,e] and irinotecan[44,47,48]
- Pembrolizumab
  - For second-line or subsequent therapy for MSI-H or dMMR tumors[49,50]

Other Recomended Regimens
- Ramucirumab for adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)[51]
- Irinotecan and cisplatin[22,52]
- Pembrolizumab
  - For third-line or subsequent therapy for PD-L1 positive esophageal and EGJ adenocarcinoma[f,53]
- Docetaxel and irinotecan (category 2B)[54]

Presented by:

FLOT4 Study Design

Randomized, multicenter, investigator-initiated, phase II/III study

- Gastric cancer or adenocarcinoma of the gastro-esophageal junction type I-III
- Medically and technically operable
- cT2-4/cN-any/cM0 or cT-any/cN+/cM0

STRATIFICATION

R

n=716

FLOT x4 - RESECTION - FLOT x4

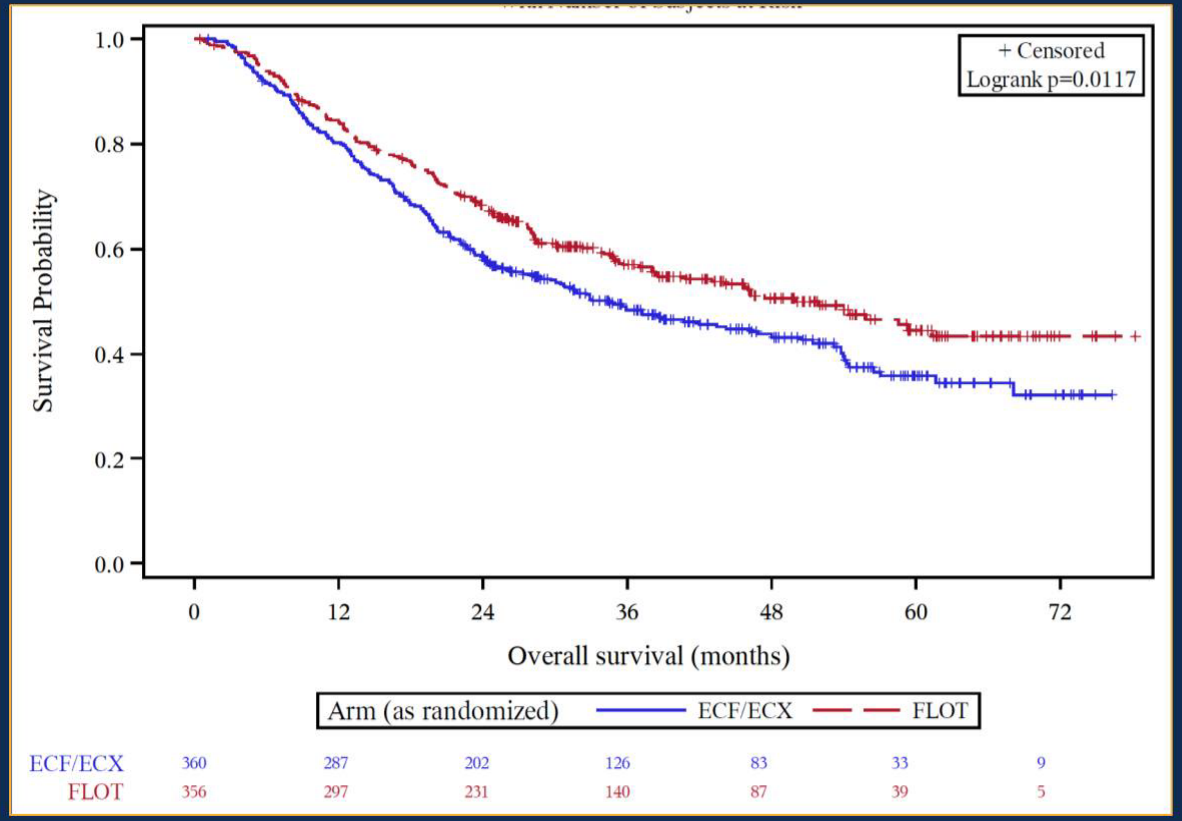
FLOT: docetaxel 50mg/m2, d1; 5-FU 2600 mg/m², d1; leucovorin 200 mg/m², d1; oxaliplatin 85 mg/m², d1, every two weeks

ECF/ECX x3 - RESECTION - ECF/ECX x3

ECF/ECX: Epirubicin 50 mg/m2, d1; cisplatin 60 mg/m², d1; 5-FU 200 mg/m² (or capecitabine 1250 mg/m² p.o. divided into two doses d1-d21), every three weeks

Stratification: ECOG (0 or 1 vs. 2), location of primary (GEJ type I vs. type II/III vs. stomach), age (< 60 vs. 60-69 vs. ≥70 years) and nodal status (cN+ vs. cN-).

FLOT4: Overall Survival



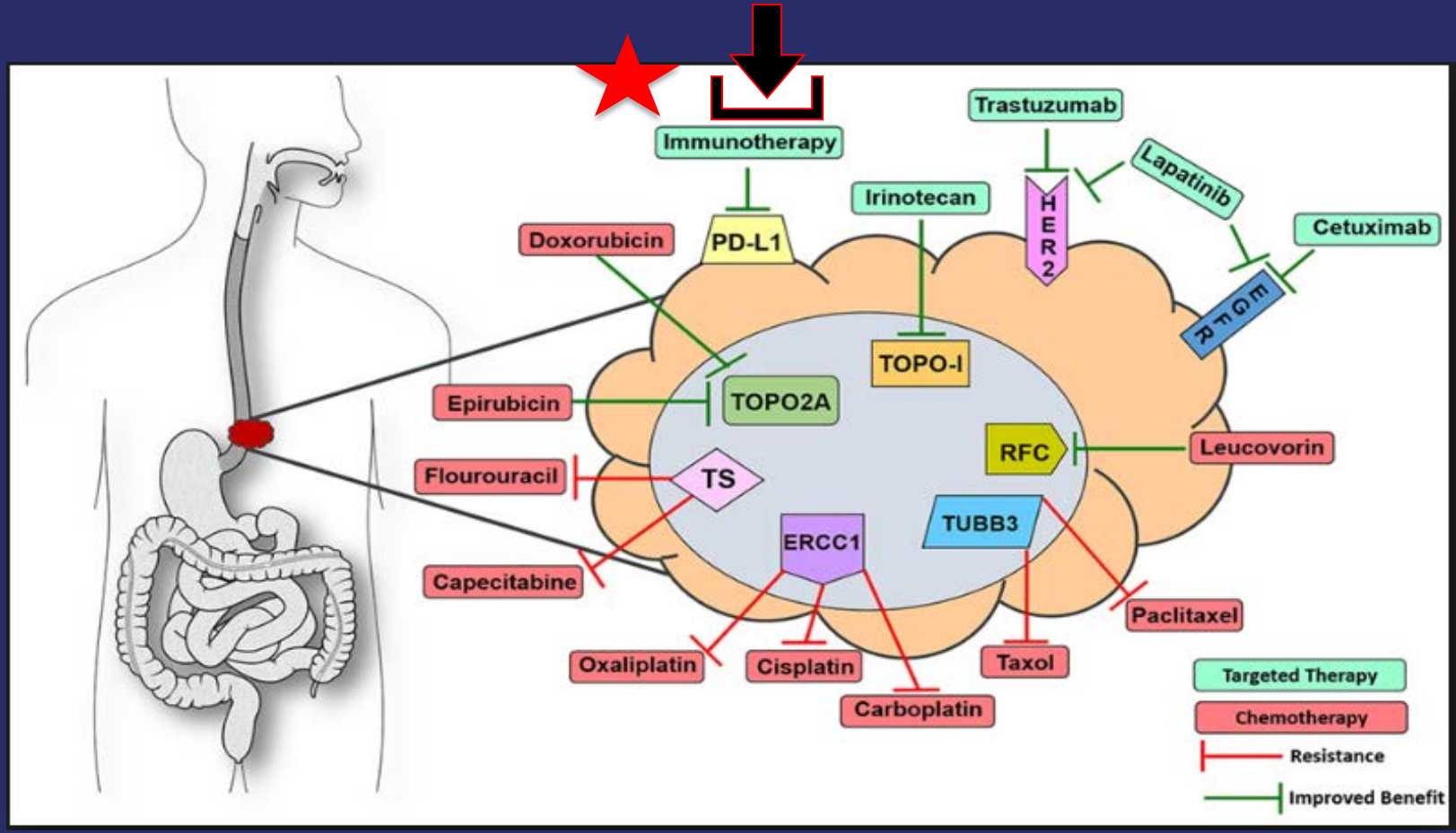
	ECF/ECX	FLOT
mOS months	35 months [27-46]	50 [38-na]

HR 0.77 [0.63 - 0.94]
p=0.012 (log rank)

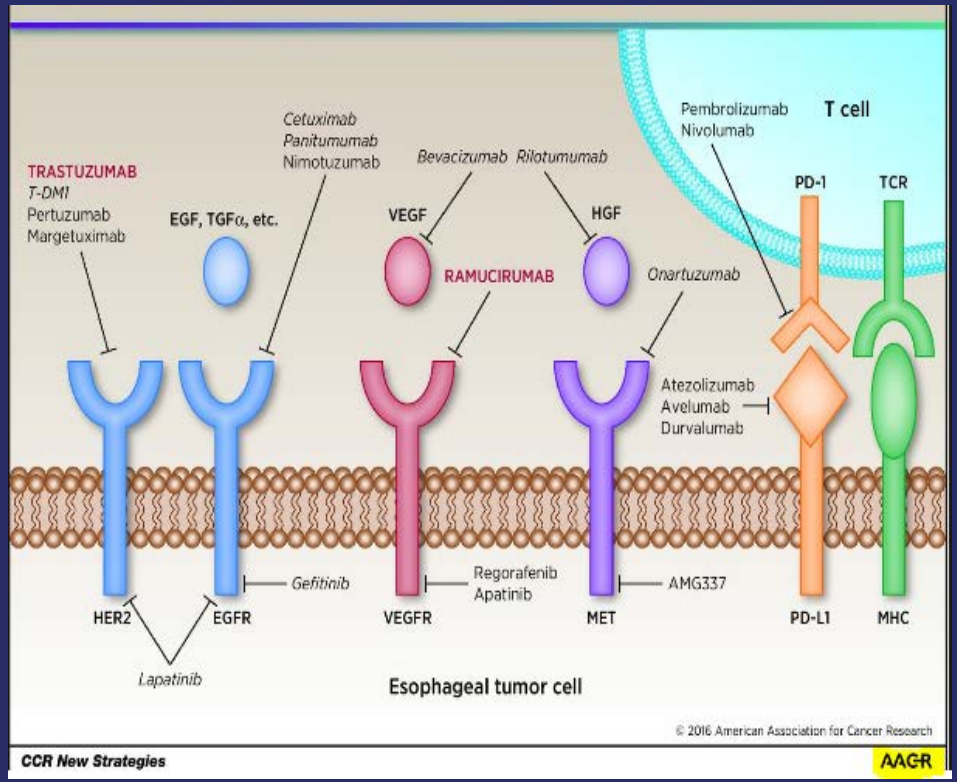
OS rate*	ECF/ECX	FLOT
2y		59%
		68%
3y		48%
		57%
5y		36%
		45%

*projected OS rates

Gastro-esophageal CA Current Status: Biomarkers/ Target Rx



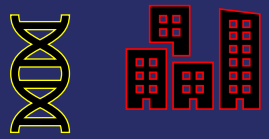
Gastro-esophageal CA Current Status: Biomarkers/ Combination Target Rx



- ERB/Heur-2 inhibition→ PDL-1 Inhibition →Optimize ImmunoRx
- VEGF→ may expert Immune supressive effect through tissue remodeling and fibrosis→ preventing immune infiltration Into tumors
- Epigenetic → DNA methylation and histone modification may lead regulation of immune checkpoints and tumor antigen expression

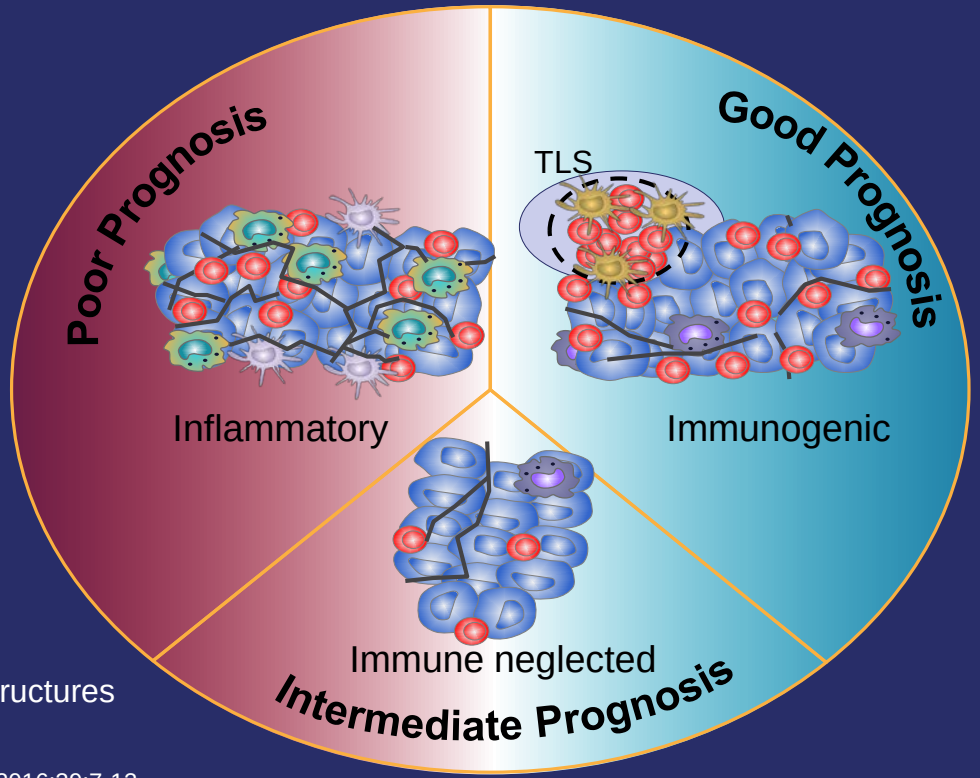
Wang et Al: Clin. Cancer research 2016

Immunotherapy in GE cancers : Challenges and Future



- Role of Biomarkers and What constitutes PD-L1 positive staining?
- Resistance : How does resistance develop, Can we overcome the process?
- Can Immunotherapy be combined with chemotherapy for GE cancers?
- Can immunotherapy be combined to improve the likelihood of response?

Immunological "Wheel" Depicting Three "Immune Contextures" in Tumors



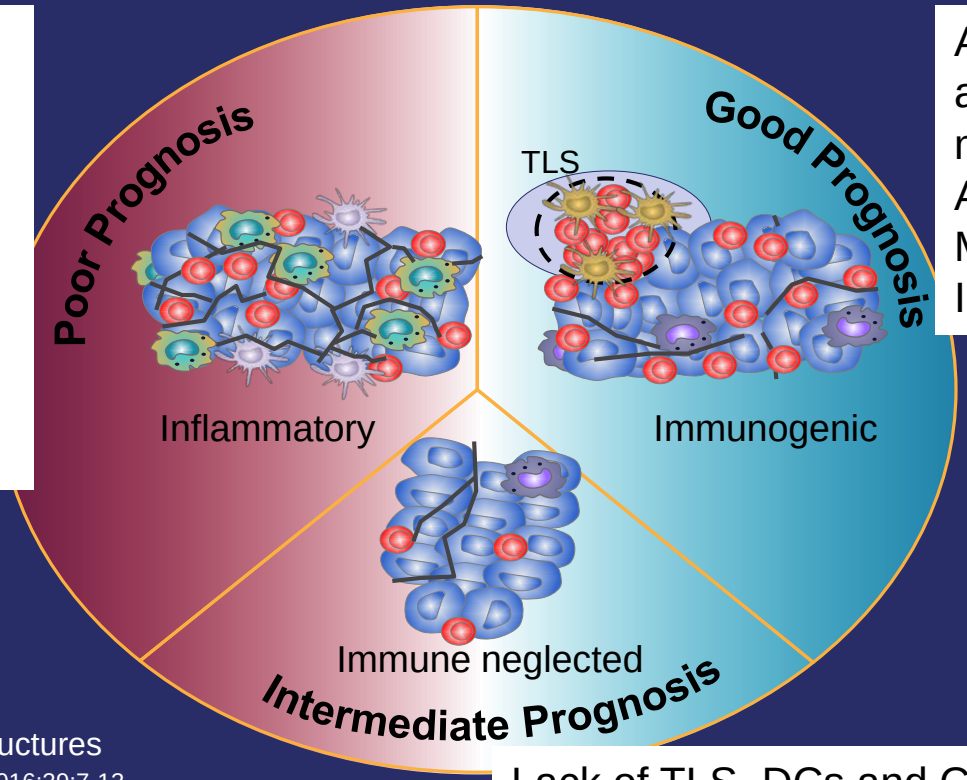
Immature DC
Mature DC
T cell
M1 MΦ
M2 MΦ

TLS - tertiary lymphoid structures

Becht E et al. *Curr Opin Immunol*. 2016;39:7-13.

Immunological "Wheel" Depicting Three "Immune Contextures" in Tumors

Lack of TLS
Abundant immature DCs and lymphocytes,
Abundant M2 Macrophages
IL-1, IL-6, TNF-a, PD-L1 and PD-L2 expression



Abundant TLS associated with mature DC
Abundant CTLs and M1 Macrophages
IFN-y and CXCL13

Immature DC
Mature DC
T cell
M1 MΦ
M2 MΦ

TLS - tertiary lymphoid structures

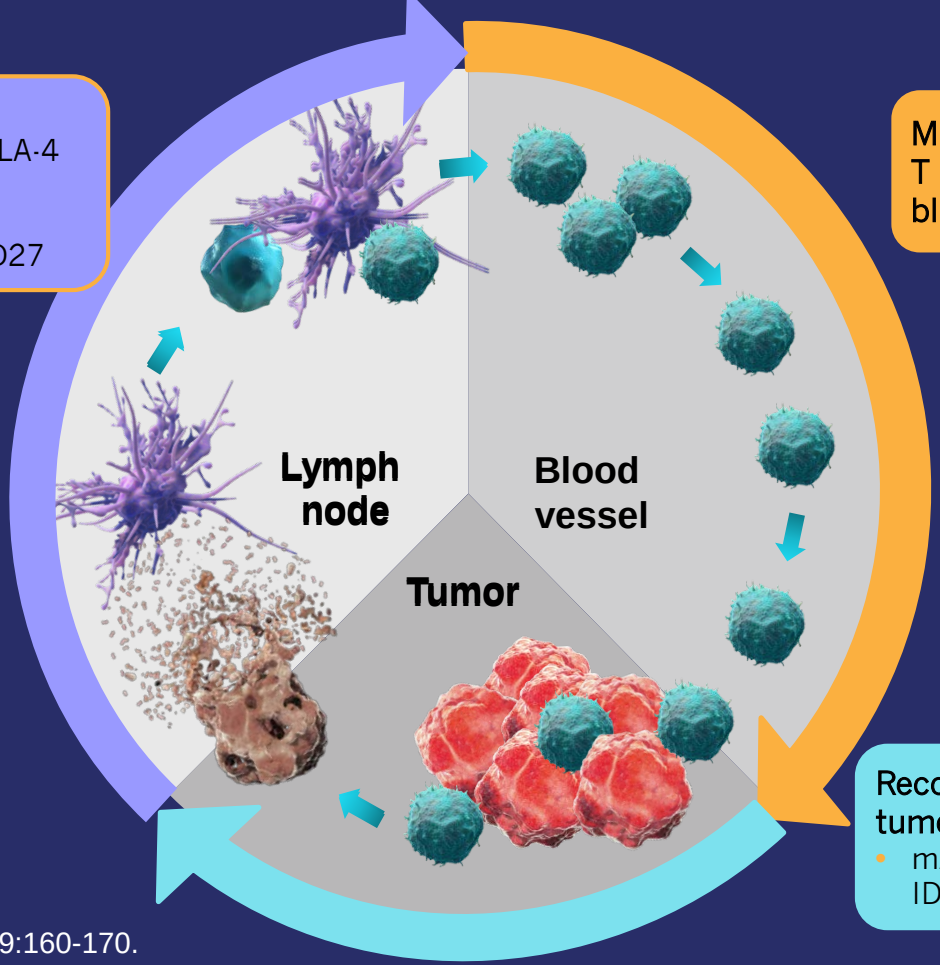
Lack of TLS, DCs and CTLs,
Lack of cytokines

Becht E et al. *Curr Opin Immunol*. 2016;39:7-13.

Activation/priming of T cells
- mAb against PD-1, PD-L1, CTLA-4
- IL-2
- IL-12
- Agonists for CD137, OX40, CD27

Presentation of tumor-associated antigens by APC
- Vaccines
- IFN-α
- GM-CSF

Release of tumor-associated antigens
- Chemotherapy
- Radiotherapy
- Targeted therapy



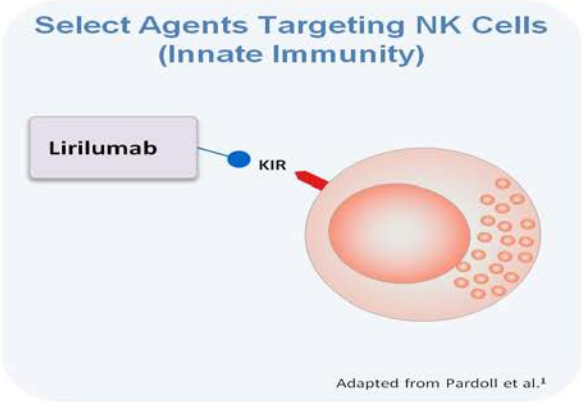
Migration of activated T cells to the tumor via blood vessels

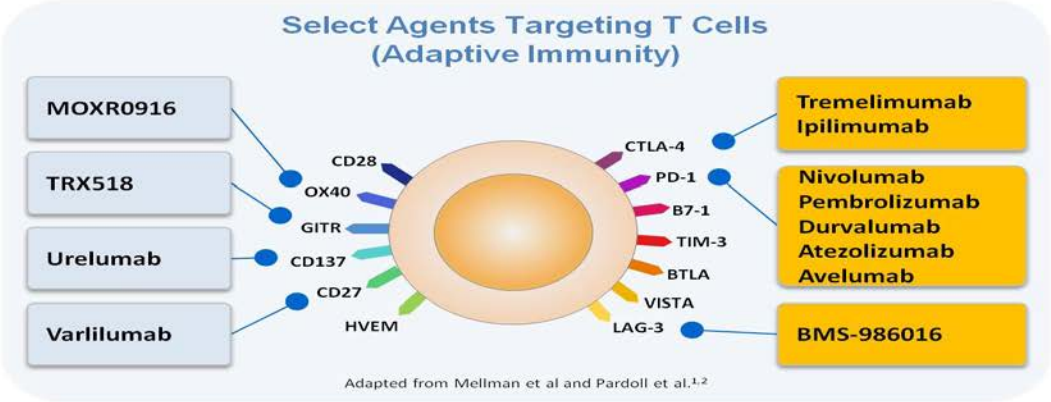
Infiltration of T cells into the tumor
- mAb against VEGF/VEGFR

Recognition and killing of tumor cells
- mAb against PD-1, PD-L1, IDO, LAG-3

Moehler M et al. *Eur J Cancer.* 2016;59:160-170.

Targeting Checkpoints as an Approach to Cancer Therapy





Blocking agents **Stimulating agents**

*
CTLA-4=cytotoxic T-lymphocyte antigen-4; GITR=glucocorticoid-induced TNFR family related gene; KIR=killer-cell immunoglobulin-like receptor; LAG-3=lymphocyte-activation gene-3; NK=natural killer; PD-1=programmed death-1; PD-L1=programmed death ligand-1.

1. Pardoll DM. *Nat Rev Cancer*. 2012;12(4):252-264. 2. Mellman I et al. *Nature*. 2011;480(7378):480-489. 3. Clinicaltrials.gov.

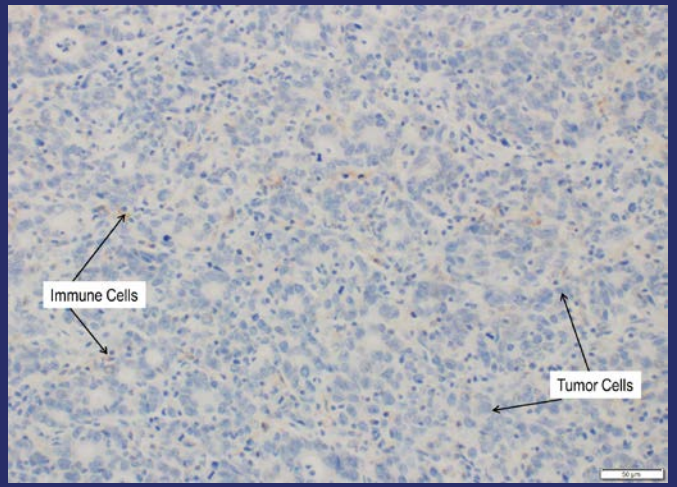
PD-L1 Expression IHC

- PD-L1 expression in gastric cancer is determined by combined positive score (CPS)

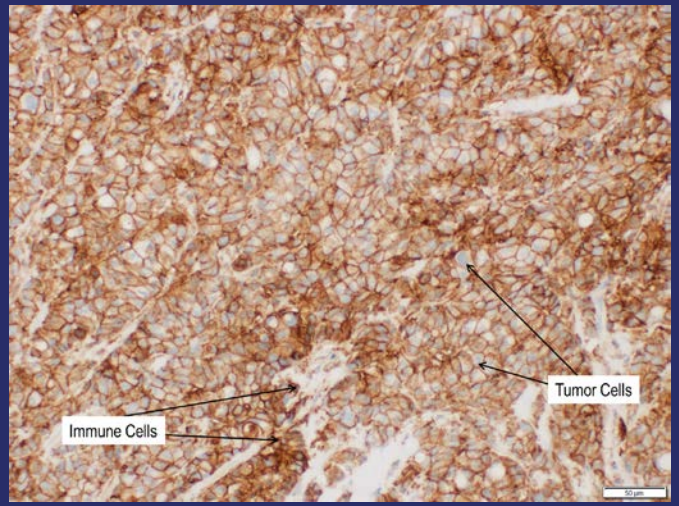
$$\text{CPS} = \frac{\text{No. of PD-L1 staining cells (tumor cells, lymphocytes, macrophages)}}{\text{Total No. viable tumor cells}} \times 100$$

- A specimen is considered to have positive PD-L1 expression if CPS ≥1

PD-L1–negative



PD-L1–positive



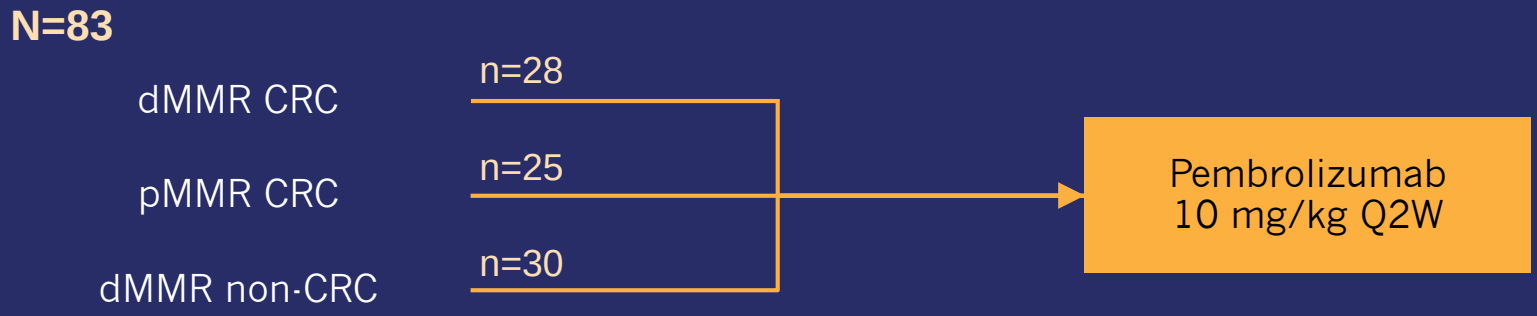
[a]22C3 pharmDx kit, Agilent Technologies, Carpinteria, CA

Biomarkers To Predict Response To Immunotherapy

Interferon-gamma expression signature?
Tumor Infiltrating Lymphocytes?
Qualification of Mutation/Neoantigen?

*Currently under FDA examinations.

Phase II multicenter, open-label trial of pembrolizumab as monotherapy in three different treatment-refractory patient populations

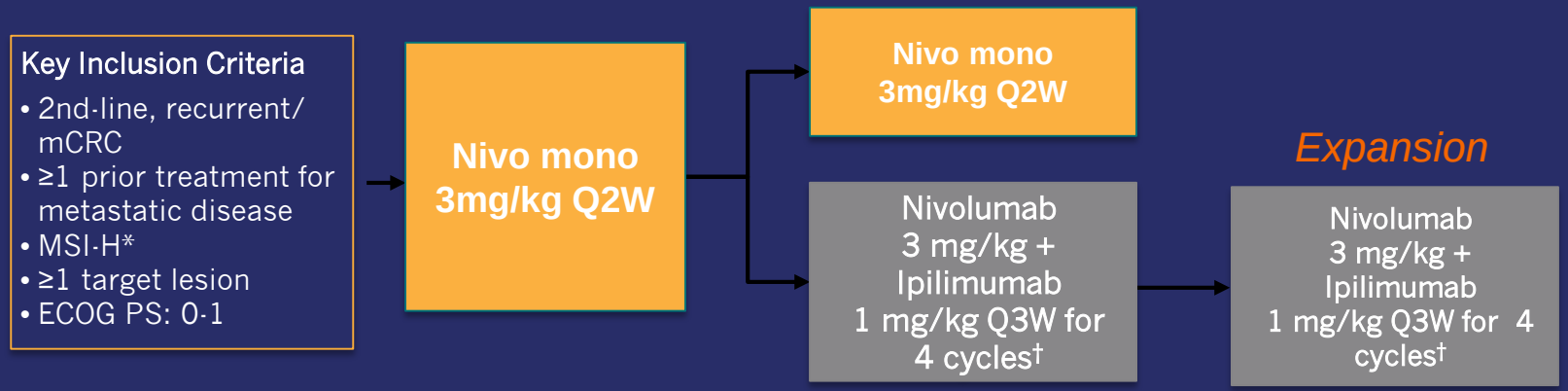


- **Primary Outcome Measures:** irPFS*†, irORR† (using irRC)
- **Secondary Outcome Measures:** OS, irPFS/PFS (using irRC and RECIST 1.1), ORR, IRAEs, MSI and treatment response, markers of MSI status

- dMMR and pMMR CRC groups had received a median of 3 and 4 prior treatment regimens, respectively

1. Clinicaltrials.gov. NCT01876511. 2. Le DT et al. Oral presentation at ASCO 2016. TPS3631.

Phase I/II open-label study of nivolumab and nivolumab plus ipilimumab in recurrent and metastatic colon cancer : MSI-H Metastatic Colorectal Cancer



- **Primary Outcome Measures:** Investigator-assessed ORR by RECIST 1.1 in MSI-H patients
- **Secondary Outcome Measure:** Independent radiology review committee-assessed ORR

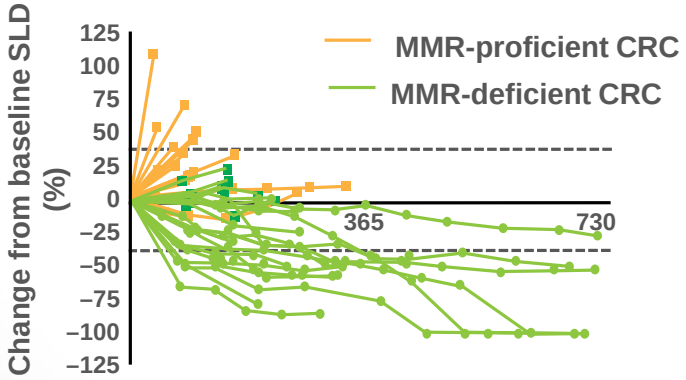
- 86% and 93% of patients in the Nivo mono and Nivo + Ipi groups had ≥2 prior therapy lines, respectively

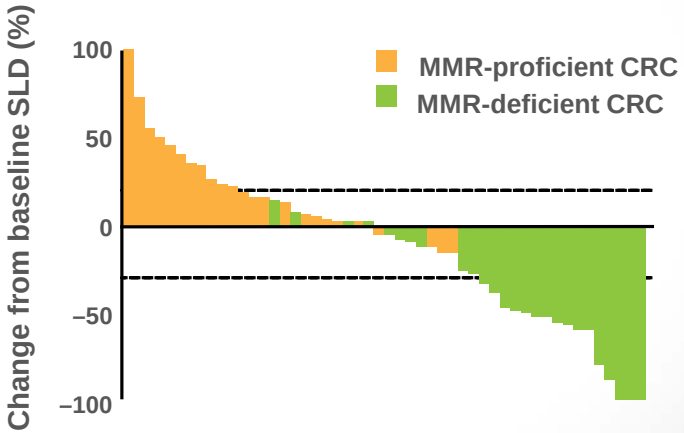
*Confirmed by ≥30% of marker with instability by PCR, or by loss of ≥1 marker by immunohistochemistry. †Followed by nivo 3 mg/kg Q2W thereafter.

1. Clinicaltrials.gov. NCT02060188. 2. Overman M et al. Oral presentation at ASCO 2016. 3501.

MSI-high tumours are responsive to PD-1 inhibitors

Pembrolizumab
(KEYNOTE 016, phase II)





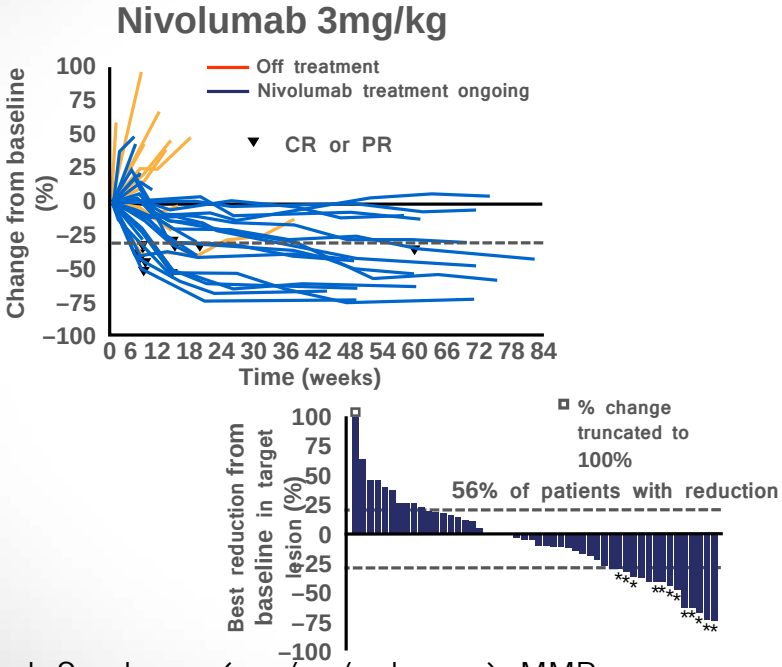
*Lynch Syndrome (yes/no/unknown): MMR-deficient CRC = 54/7/39; MMR-proficient CRC = 0/100/0

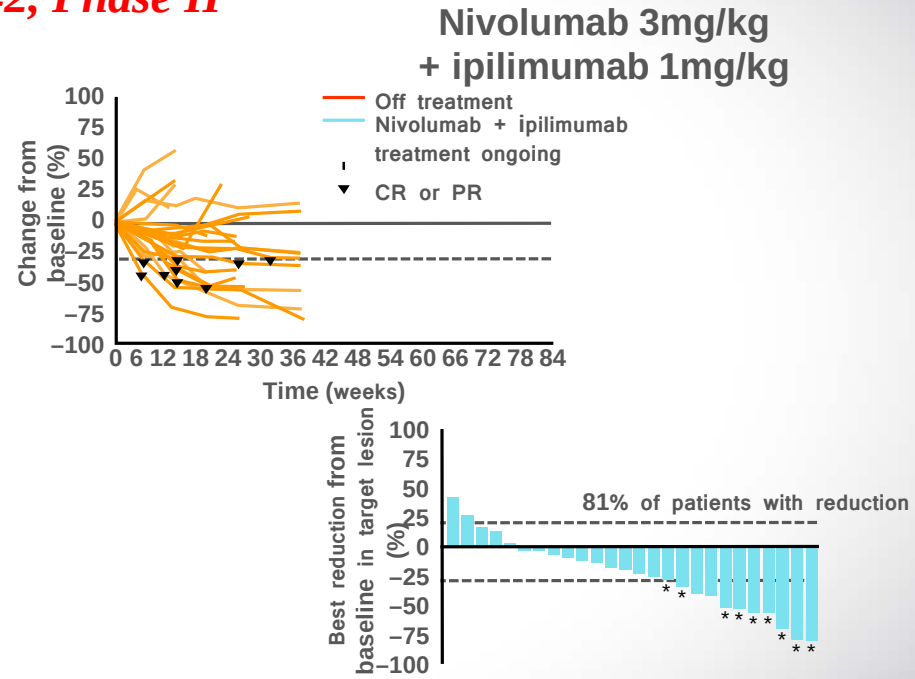
1. Le et al. ASCO 2016;

MSI-high tumours are responsive to PD-1 inhibitors

Nivolumab ± ipilimumab

CheckMate-142, Phase II





*Lynch Syndrome (yes/no/unknown): MMR-deficient CRC = 54/7/39; MMR-proficient CRC = 0/100/0

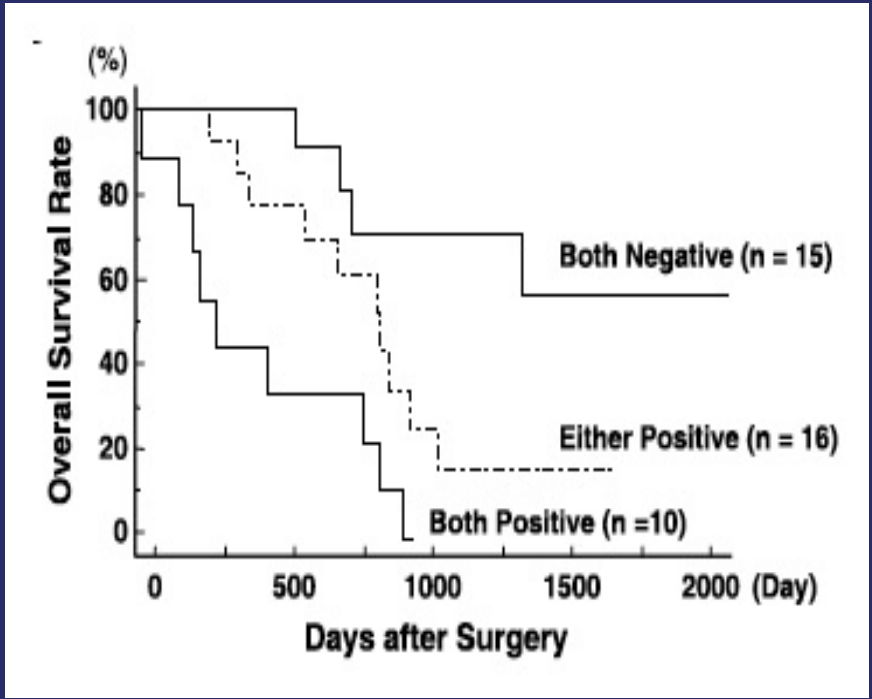
1.Overman et al. ASCO 2016

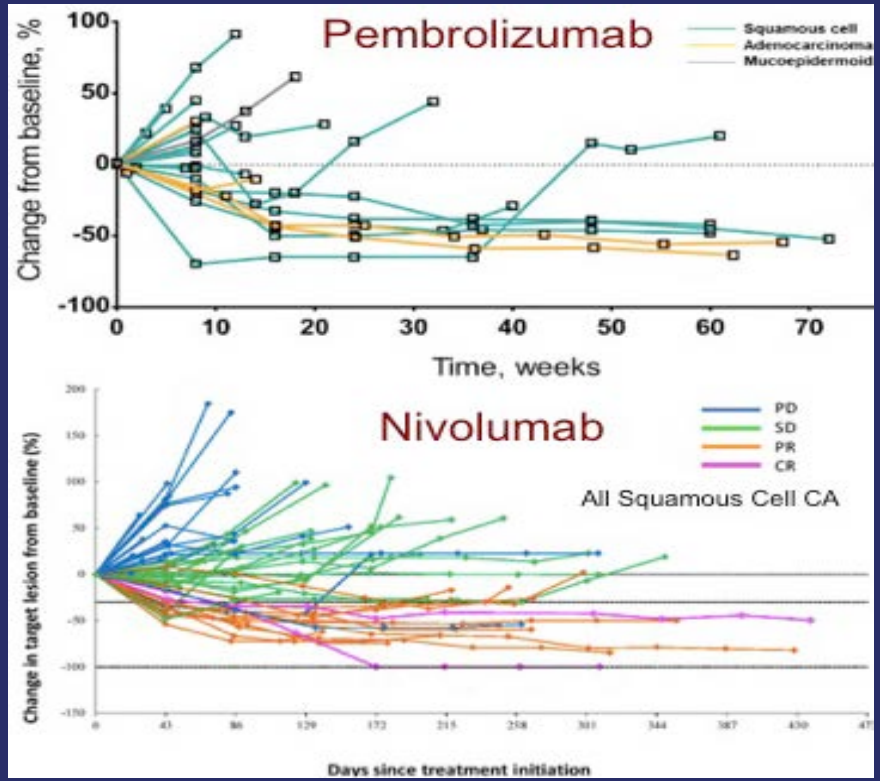
Immunotherapy in Gastric CA

Immunotherapy	Target	Phase	N	Author	Efficacy
Nivolumab	PD-1	3	493	Kang 2017	mOS: 5.3 (nivo) vs 4.1 mo (placebo) HR, 0.63; *P*<0.0001
Nivolumab + ipilimumab	PD-1 & CTLA-4	1/2	160	Janjigian 2016	mOS: 6.9 mo (nivo 1 mg/kg + ipi 3 mg/kg) 4.8 mo (nivo 3 mg/kg + ipi 1 mg/kg) 5.0 mo (nivo 3 mg/kg)
Tremelimumab	CTLA-4	2	18	Ralph 2010	1 PR >30 mo
Atezolizumab	PD-L1	Expansion	1	Tabernero 2013	1 pt had TTP of 9.8 mo
Durvalumab	PD-L1	Dose-expansion	28	Segal 2014	2 PRs and 12-week DCR of 25%
Pembrolizumab	PD-1	1b (KEYNOTE-012)	36	Muro 2016	ORR=22% 53% of pts had reduction in size of target lesions Median duration of response=40 wks

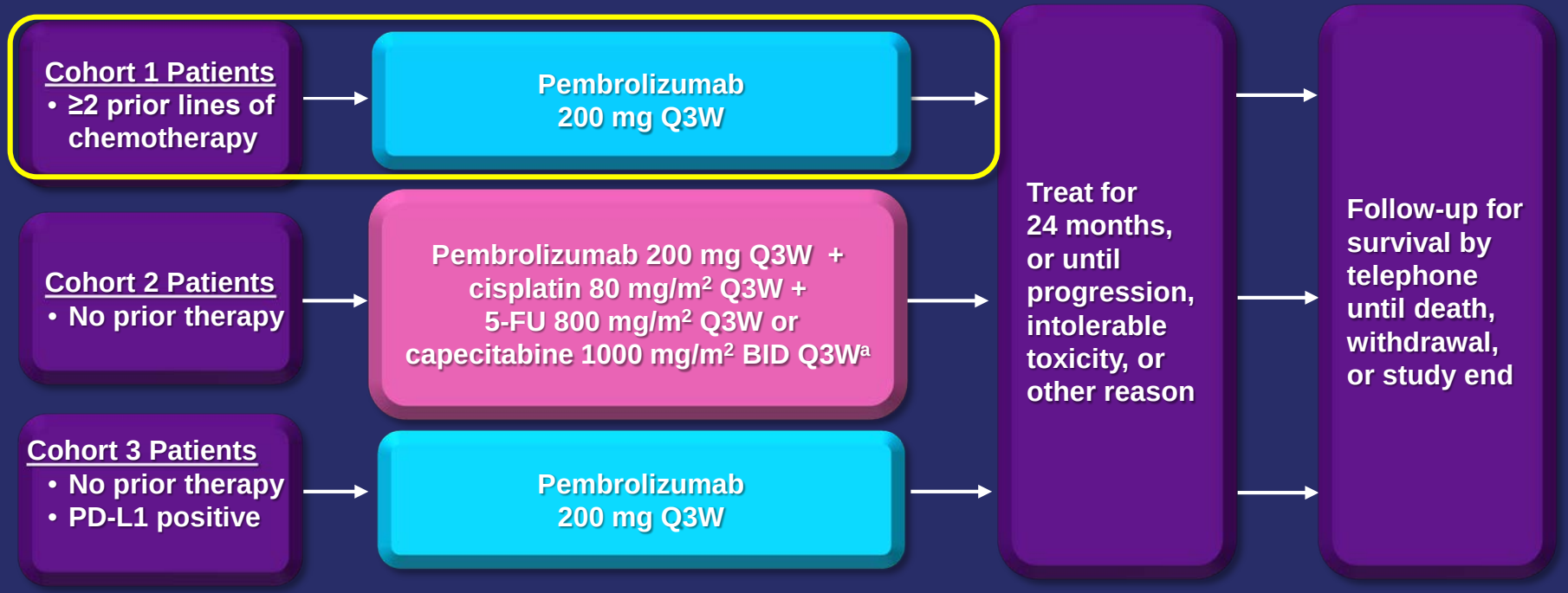
Immunotherapy in Esophagus CA

PD-L1 and PD-L2 staining is prognostic





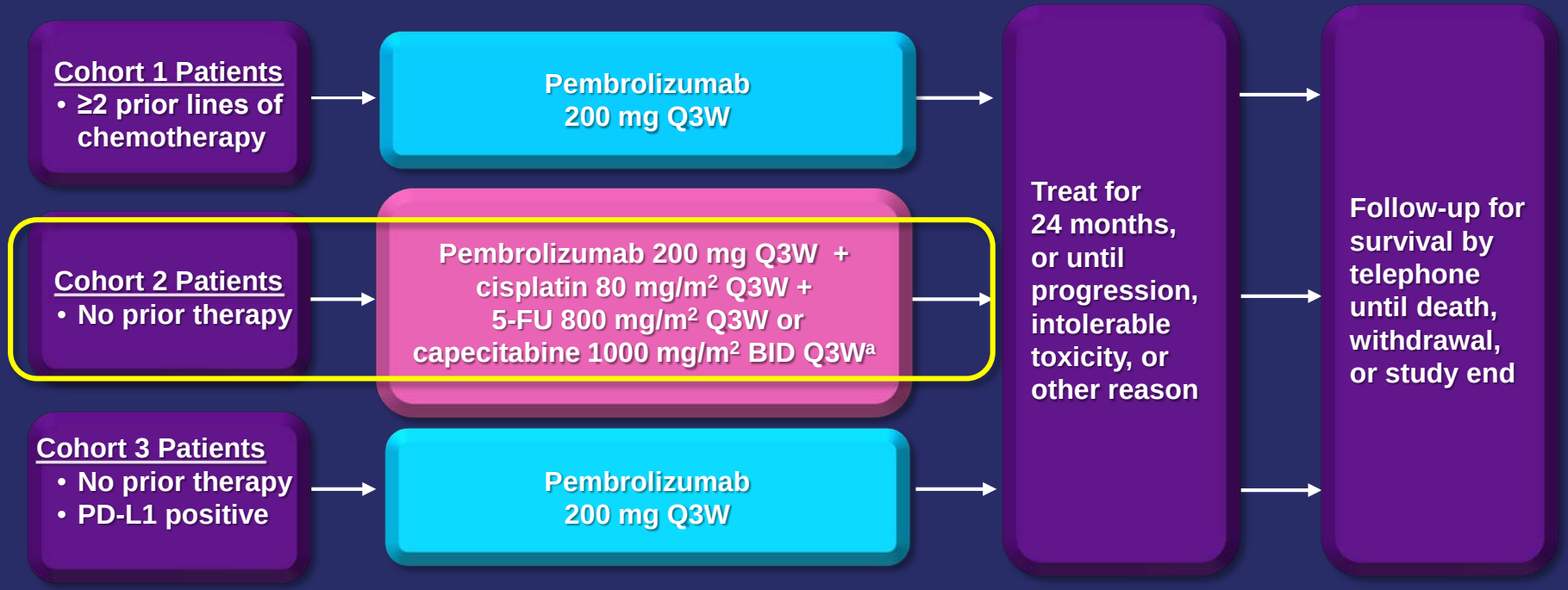
KEYNOTE-059 (NCT02335411): Phase 2 Multicohort Study of Pembrolizumab for G/GEJ Adenocarcinoma



Response assessment by RECIST v1.1: first scan at 9 weeks after cycle 1, every 6 weeks for 1st year, followed by every 9 weeks

[a]Capecitabine was administered *only in* Japan

KEYNOTE-059 (NCT02335411): Phase 2 Multicohort Study of Pembrolizumab for G/GEJ Adenocarcinoma



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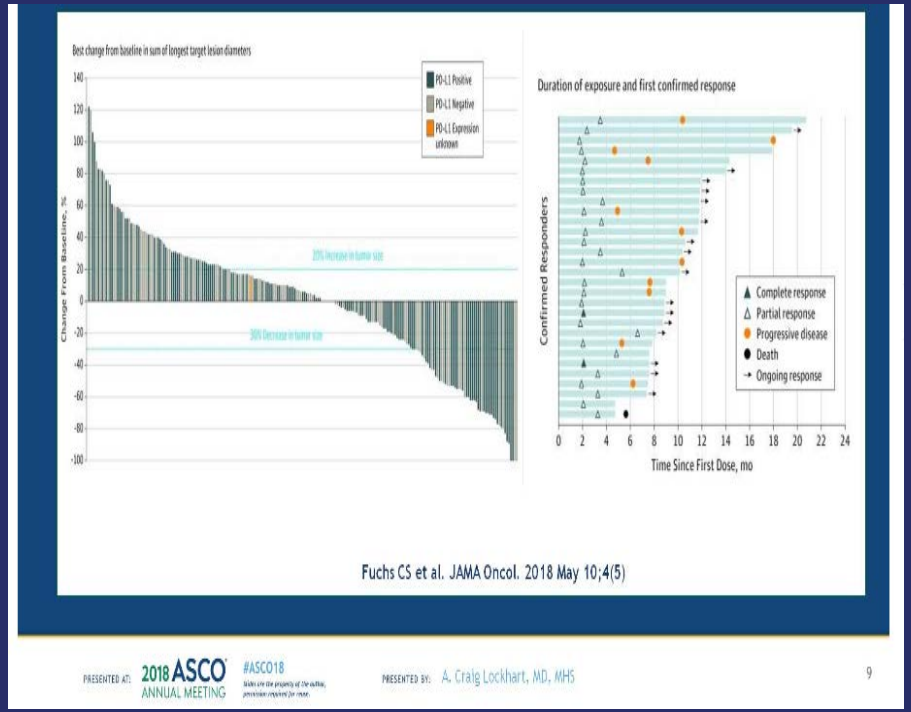


- *CONCLUSION*

- Pembrolizumab monotherapy showed encouraging efficacy and manageable safety after ≥2 prior lines of therapy
  - **Overall objective response rate (ORR) was 11.2% and 15.5% in 143 PD-L1-positive patients**
  - ORR was higher in patients with PD-L1–positive tumors, but responses were also observed in patients with PD-L1–negative tumors
- Pembrolizumab plus 5-FU & cisplatin showed manageable safety and encouraging antitumor activity as first-line therapy
- (**ORR was 60% and 68.8% in PD-L1-positive patients**)

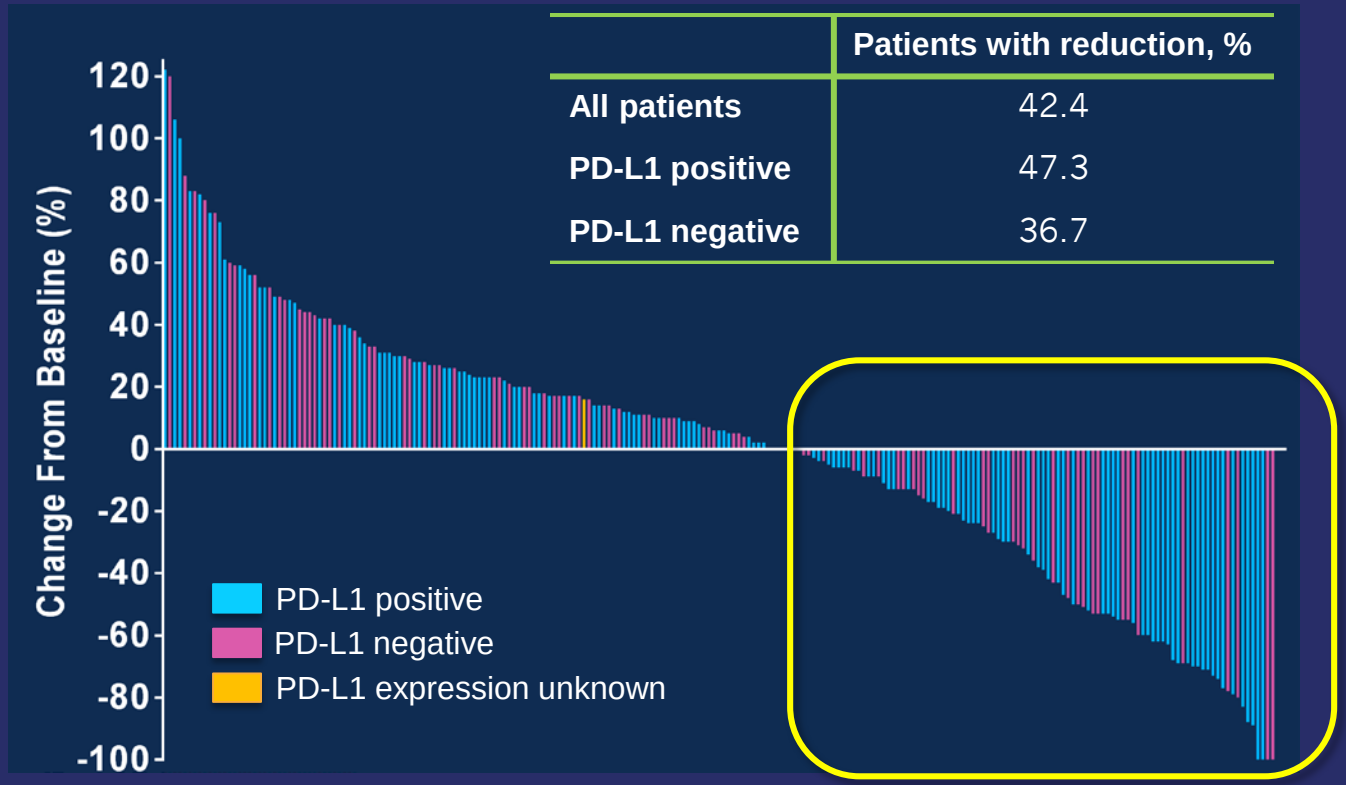
Response in All Patients and by PD-L1 Expression

	All Patients N = 25		PD-L1 Positive n = 16		PD-L1 Negative n = 8	
	n	% (95% CI[b])	n	% (95% CI[b])	n	% (95% CI[b])
ORR	15	60 (39-79)	11	69 (41-89)	3	38 (9-76)
DCR[c]	20	80 (59-93)	13	81 (54-96)	6	75 (35-9)
CR	1	4 (0-20)	0	0 (0-21)	1	13 (0-53)
PR	14	56 (35-76)	11	69 (41-89)	2	25 (3-65)

Data cutoff: Jan 16, 2017
[a]Only confirmed responses were included
[b]Based on binomial exact confidence interval method
[c]CR+PR+SD≥2 months

Maximum Percentage Change From Baseline in Target Lesion Size[a]

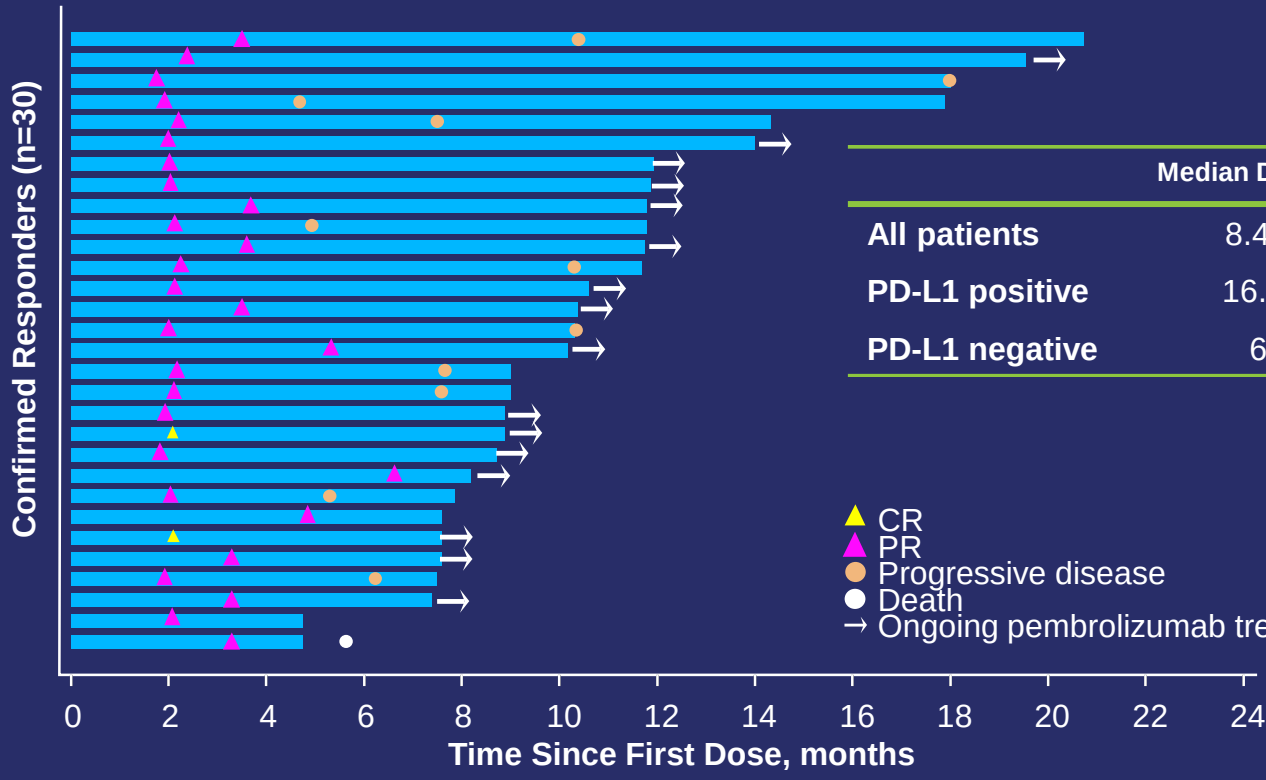
	Patients with reduction, %
All patients	42.4
PD-L1 positive	47.3
PD-L1 negative	36.7



Data cutoff: Jan 16, 2017

[a]Only patients with measurable disease per RECIST v1.1 by central review at baseline and at least 1 postbaseline tumor assessment were included (n = 223)

Treatment Exposure[a] and Duration of Response



	Median DOR (95% CI), months
All patients	8.4 (1.6+[b] to 17.3+)
PD-L1 positive	16.3 (1.6+ to 17.3+)
PD-L1 negative	6.9 (2.4 to 7.0+)

Data cutoff: Jan 16, 2017. [a]Patients with measurable disease per RECIST v1.1 by central review at baseline who had ≥1 postbaseline assessment (n = 30). Bar length indicates time to last imaging assessment. [b]no progressive disease at last disease assessment.

Response by Line of Therapy

Response[a]	Third Line (n = 134)		Fourth+ Line (n = 125)	
	%	95% CI	%	95% CI
ORR	16.4	10.6-23.8	6.4	2.8-12.2
DCR[b]	31.3	23.6-39.9	22.4	15.4-30.7
CR	3·0	0·8-7·5	1.6	0.2-5.7
PR	13.4	8.2-20.4	4.8	1.8-10.2

Data cutoff: Jan 16, 2017
[a]Only confirmed responses were included
[b]CR+PR+SD≥2 months

CHECKMATE 032 : Nivolumab +/- Ipilimumab in advanced refractory G-E cancers ASCO 2017

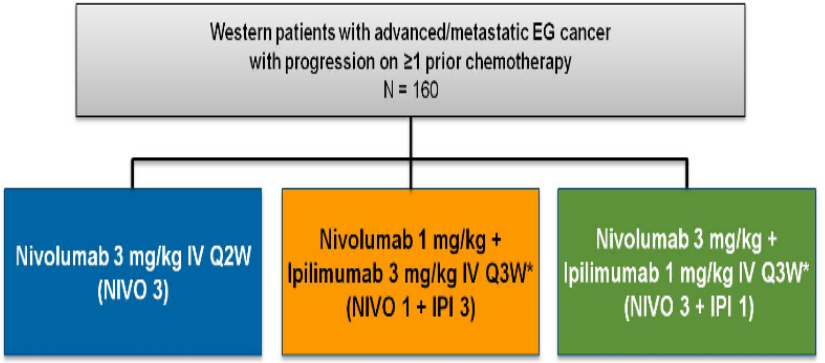
Nivolumab ± Ipilimumab in Patients With Advanced/Metastatic Chemotherapy-Refractory Gastric, Esophageal, or Gastroesophageal Junction Cancer: CheckMate 032 Study

Yelena Y. Janjigian,[1] Patrick A. Ott,[2] Emiliano Calvo,[3] Joseph W. Kim,[4] Paolo A. Ascierto,[5] Padmanee Sharma,[6] Katriina Peltola,[7] Dirk Jaeger,[8] Jeffrey Evans,[9] Filippo de Braud,[10] Ian Chau,[11] Marina Tschaika,[12] Christopher T. Harbison,[12] Weiguo Cai,[12] Johanna Bendell,[13] Dung T. Le[14]

[1]Gastrointestinal Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; [2]Dana-Farber Cancer Institute, Boston, MA; [3]START Madrid, Centro Integral Oncológico Clara Campal, Madrid, Spain; [4]Yale Cancer Center, New Haven, CT; [5]Istituto Nazionale Tumori IRCCS, Naples, Italy; [6]The University of Texas MD Anderson Cancer Center, Houston, TX; [7]Comprehensive Cancer Center, Helsinki University Hospital, Helsinki, Finland; [8]National Center for Tumor Diseases, University Hospitals Heidelberg, Heidelberg, Germany; [9]Beatson West of Scotland Cancer Centre, University of Glasgow, Glasgow, UK; [10]Fondazione IRCCS Istituto Tumori Milano, University of Milan, Milan, Italy; [11]Royal Marsden Hospital, London and Surrey, UK; [12]Bristol-Myers Squibb, Princeton, NJ; [13]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; [14]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD

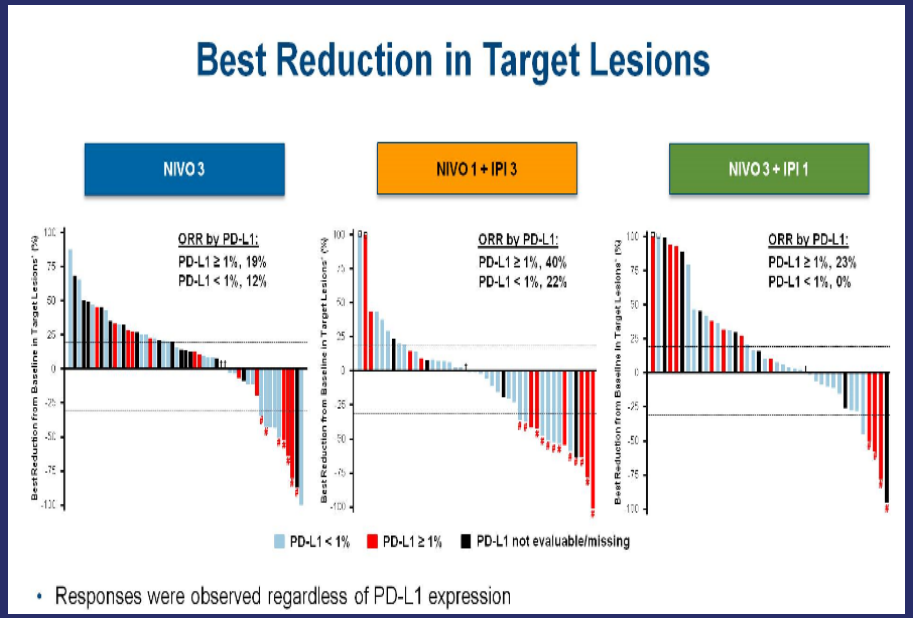
PRESENTED AT: ASCO ANNUAL MEETING '17 #ASCO17

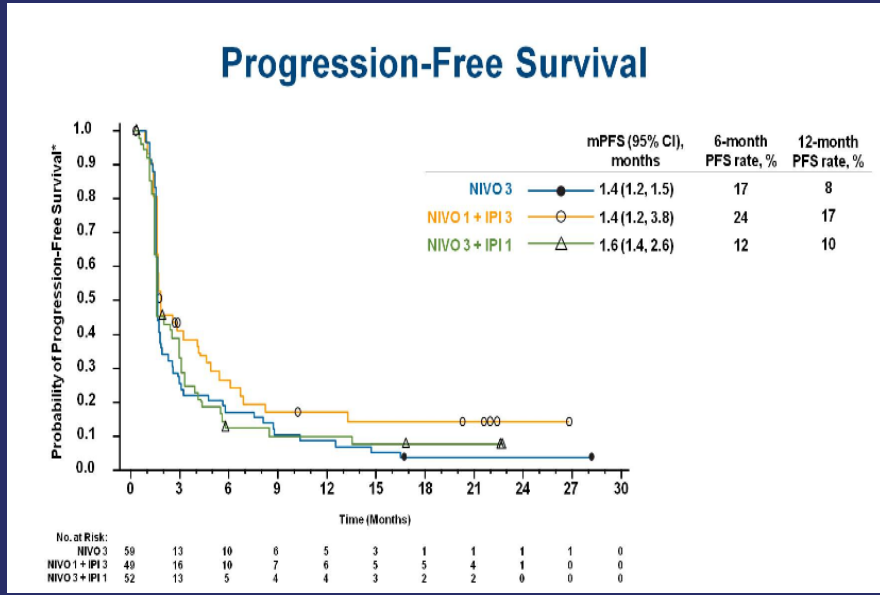
Checkmate 032 EG Cohort



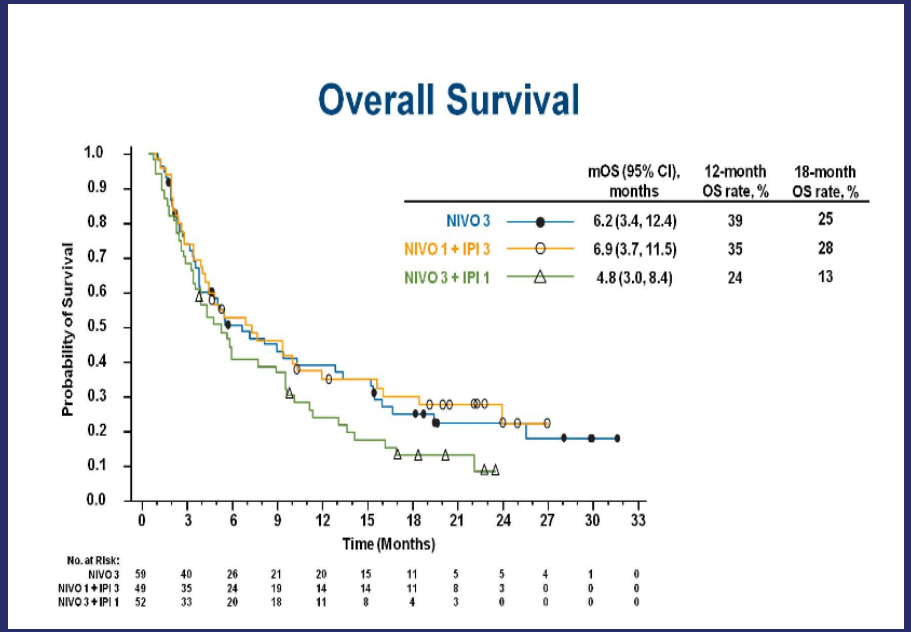
Primary endpoint:	Secondary endpoints:	Exploratory endpoint:
• ORR per RECIST v1.1	• OS, PFS, TTR, DOR • Safety	• PD-L1 tumor expression (Dako 28-8 pharmDx assay)

CHECKMATE 032 : Nivolumab +/- Ipilimumab in advanced refractory G-E cancers
ASCO 2017





CHECKMATE 032 : Nivolumab +/- Ipilimumab in advanced refractory G-E cancers ASCO 2017



CONCLUSION

- Nivolumab tested in heavily pretreated patients with both PD-L1-positive and negative advanced gastric or GEJ cancer, having an ORR of 14% accompanied with an acceptable safety profile
- PD-L1 positivity (PD-L1 expression above 1%) was associated with improved responses

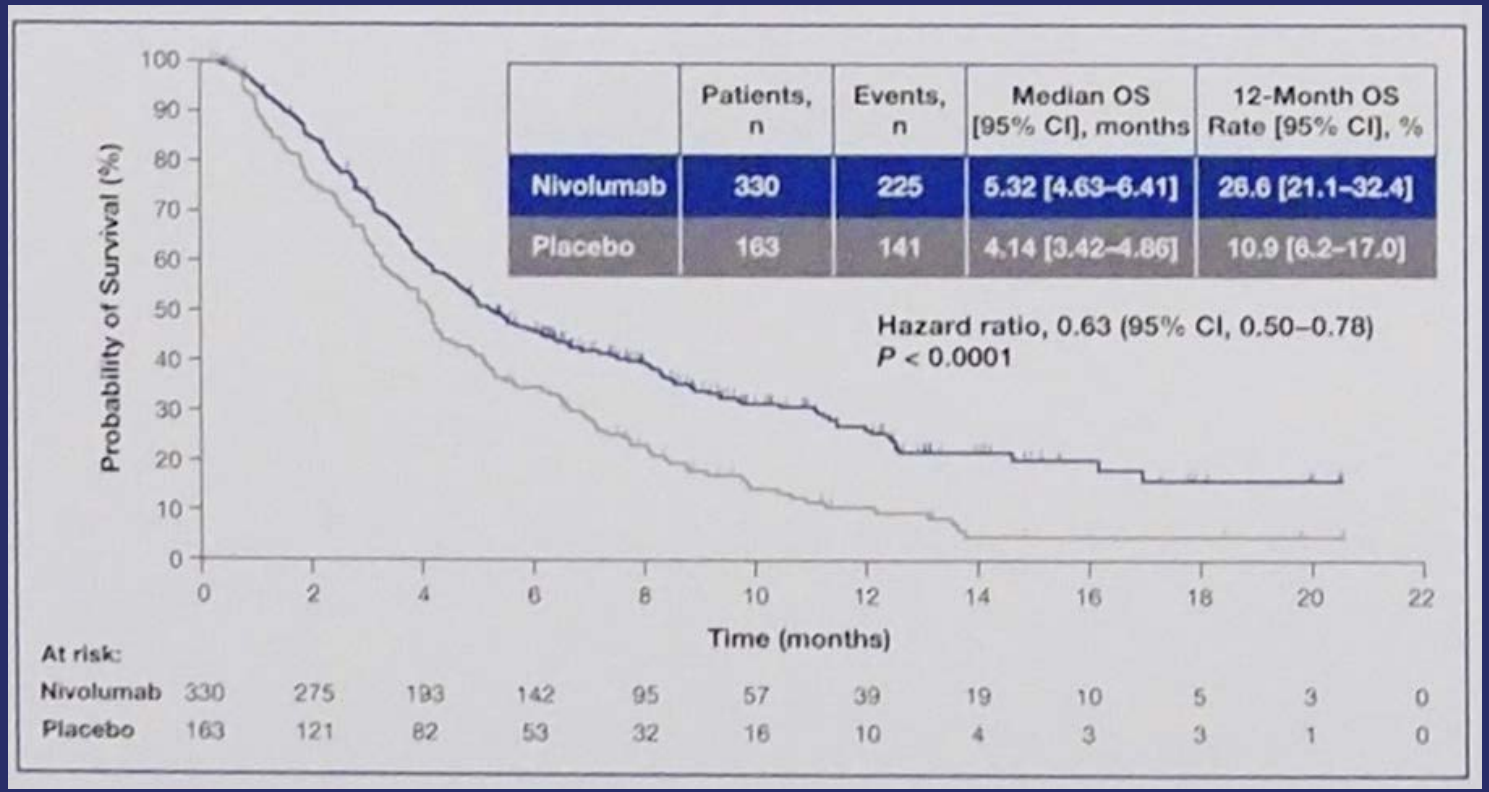
Major phase 3 trials involving targeted immunotherapeutic agents in the advanced/metastatic gastric cancer setting

Trials	No. of patients	Treatment arms	HR for death (*P* value)	Primary endpoint comparison (in months)
Advanced gastric cancer – first line				
Bang et al. 26 (ToGA)[a]	584	CX/CF + Trastuzumab versus CX/CF	0.74 (0.0046)	OS: 13.8 versus 11.1
Advanced gastric cancer – Second line				
Fuchs et al. 32 (REGARD)	355	Ramucirumab + BSC versus BSC	0.776 (0.0473)	OS: 5.2 versus 3.8
Wilke et al. 33 (RAINBOW)	665	Paclitaxel + Ramucirumab versus Paclitaxel	0.81 (0.017)	OS: 9.6 versus 7.4
Advanced gastric cancer – third line				
Li et al. 34 (Apatinib)	271	Apatinib + BSC versus BSC	0.71 (0.0149)	OS: 6.5 versus 4.7PFS: 2.6 versus 1.8
Kang et al. 46 (ONO-4538-12, ATTRACTION-2)	493	Nivolumab versus Placebo	0.63 (<0.0001)	OS: 5.26 versus 4.14

Future Status of Immunotherapy

- Immunotherapy Beyond 3rd Line RC
- Combination with Cytotoxic Agents
- Combination with Targeted Therapy : Anti-VEGF, TKI
- Immunotherapy and Radiation
- Role of Immunotherapy in Adjuvant Setting ?
- Combo : Nivo + Ipilimubab

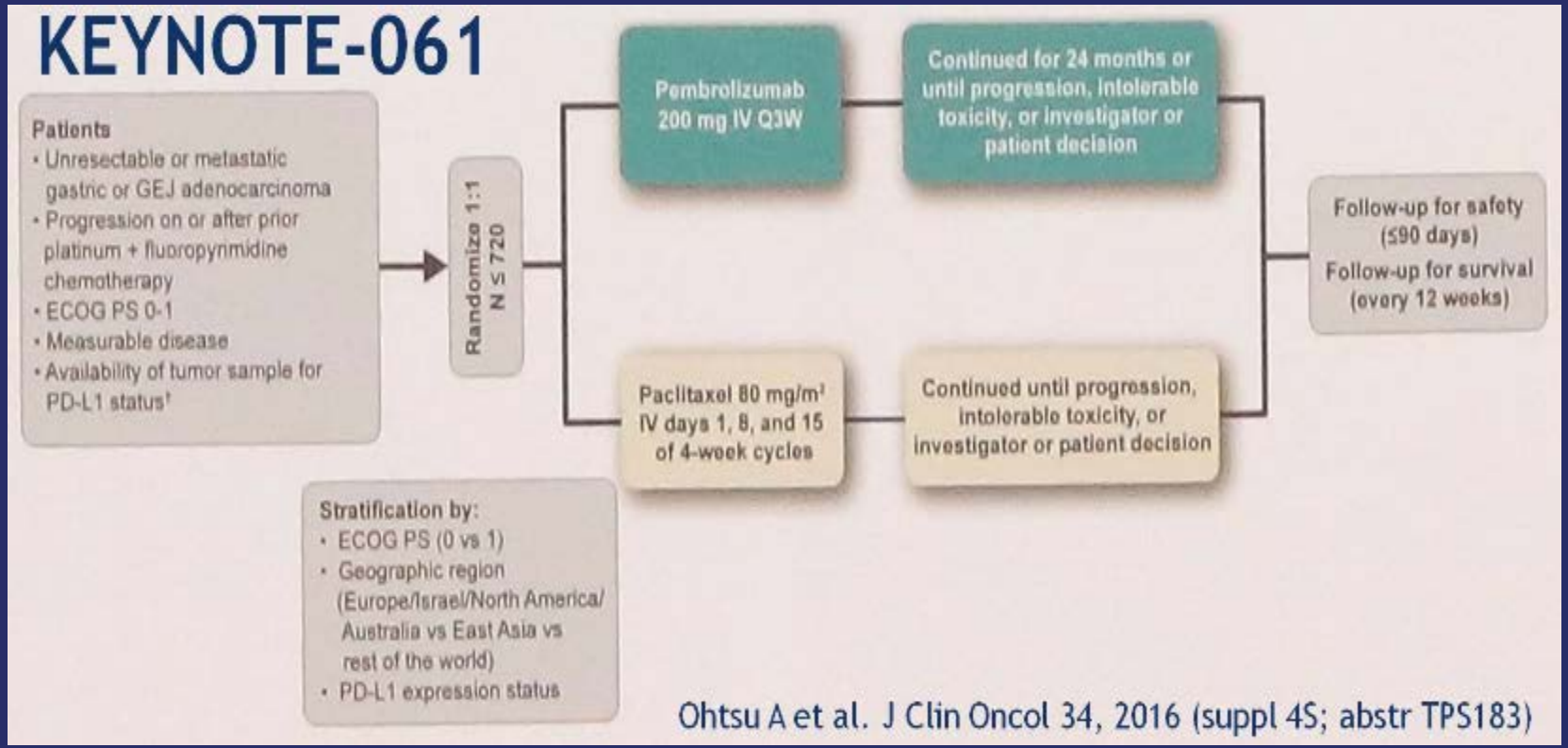
Efficacy of Nivolumab in ≥ 3rd line AGC: Attraction-2



	Patients, n	Events, n	Median OS [95% CI], months	12-Month OS Rate [95% CI], %
Nivolumab	330	225	5.32 [4.63–6.41]	26.6 [21.1–32.4]
Placebo	163	141	4.14 [3.42–4.86]	10.9 [6.2–17.0]

Presented by: Yoon Koo Kang, ASCO GI Jan 2017

Pembrolizumab vs paclitaxel for previously treated advanced gastric or gastroesophageal junction (G/GEJ) cancer: Phase III <u>KEYNOTE-061 Trial.</u>

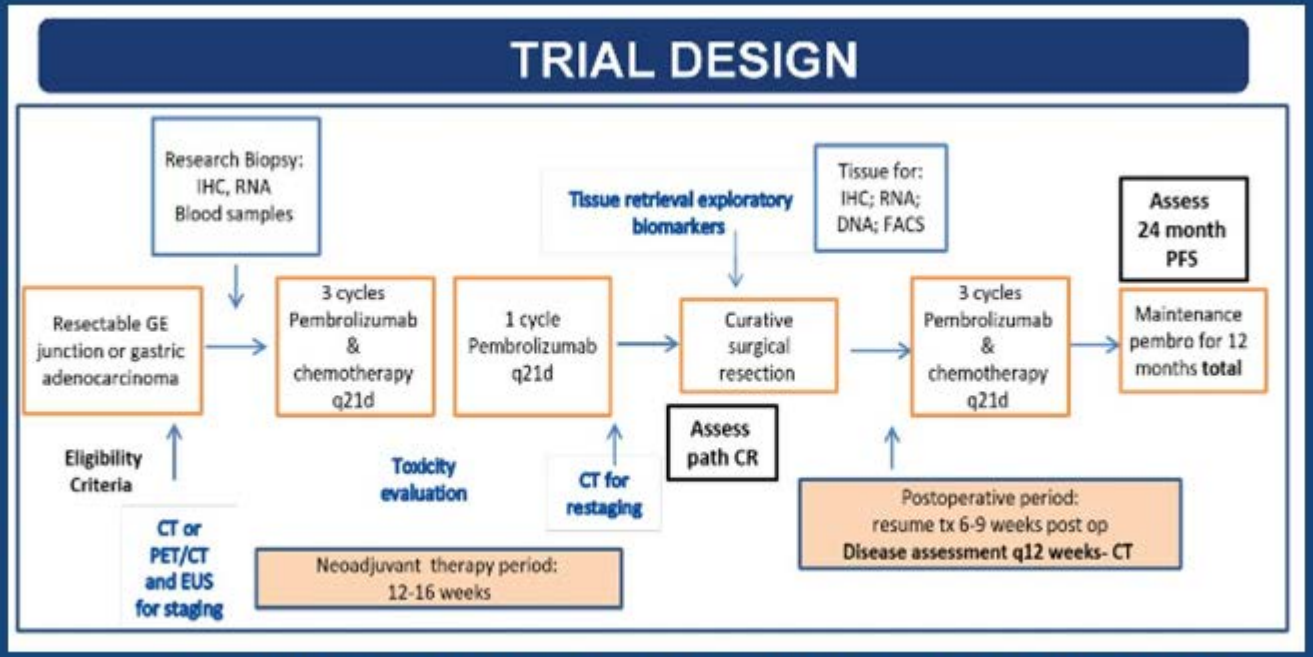


Pembrolizumab vs paclitaxel for previously treated advanced gastric or gastroesophageal junction (G/GEJ) cancer: Phase III ***KEYNOTE-061 Trial.***

- Open-label, phase 3 study : Eligible patients were randomized (1:1) to receive
  - Pembrolizumab 200 mg Q3 wks for up to 2 years or standard-dose paclitaxel.
  - Primary endpoints →OS and PFS in patients with (PD-L1) combined positive score (CPS) of 1 or >. Safety was assessed in all patients, irrespective of CPS.
- 592 patients were enrolled. Of the 395 patients who had a PD-L1 CPS of 1 or higher
  - 196 patients were assigned tp Pembrolizumab Vs 199 patients were assigned to receive paclitaxel.
  - Median OS was 9·1 months (95% CI 6·2–10·7) with pembrolizumab Vs 8·3 months with paclitaxel
  - (hazard ratio 0·82, one-sided p=0·0421).
  - Median progression-free survival was 1·5 months (95% CI 1·4–2·0) with pembrolizumab and 4·1 months (3·1–4·2) with paclitaxel (HR 1·27, 95% CI 1·03–1·57).
- Conclusion :
  - Pembrolizumab did not significantly improve overall survival compared with paclitaxel as second-line therapy for advanced gastric or Gastro-Esophageal junction cancer with PD-L1 CPS of 1 or higher.
  - Pembrolizumab had a better safety profile than paclitaxel

Presented at World of GI cancer Barcelona June 2018

ASCO 2018



Oberstein PE et al. J Clin Oncol 36, 2018 (suppl 4S; abstr TPS197)

Phase III Trial : CheckMate 649 Abstract 2018

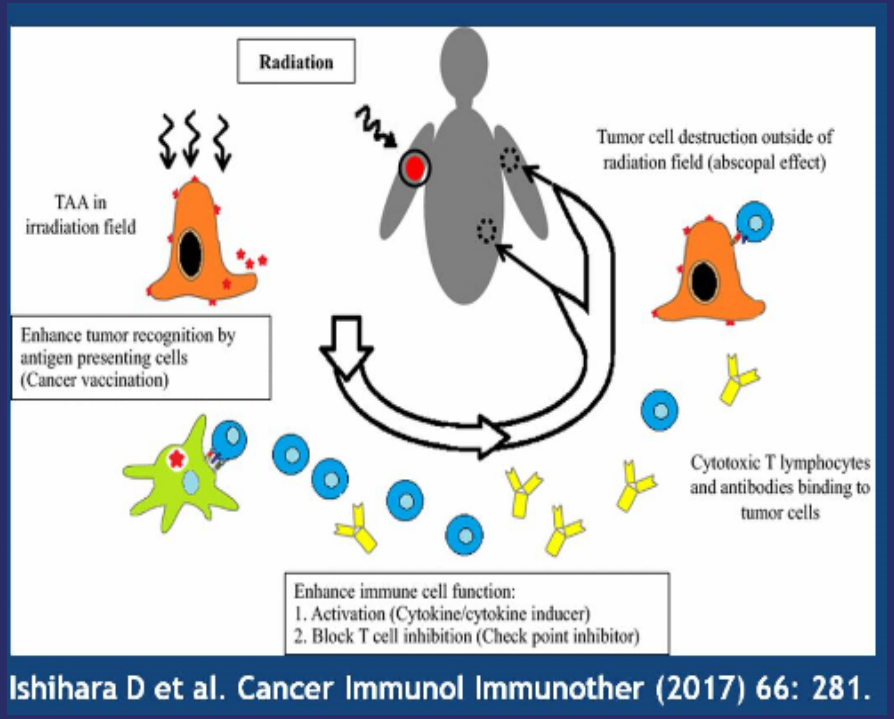
- A Phase III Randomized Multicenter, open-Label in Pts with Advanced Gastric or GE Junction
- 870 pts aged ≥ 18 years with untreated advanced or metastatic G/GEJ cancer with or without PD-L1 expression will be randomized :
  - Nivo + Ipi (4 doses; followed by Nivo monotherapy) or
  - Investigator's choice of capecitabine/oxaliplatin (XELOX) or FU /leucovorin/oxaliplatin (FOLFOX).
- Tumor tissue for determination of PD-L1 status must be provided from ≤ 6 months before study treatment.
- Pts receiving chemotherapy or radiotherapy for G/GEJ cancer within the last 6 months or pts with suspected autoimmune disease, uncontrolled medical disorder, or active infection are excluded.

- Primary endpoint is OS in pts with PD-L1+ tumors.
- Secondary endpoints is OS in all pts and progression-free survival and time to symptom deterioration in all pts and pts with PD-L1+ tumors.

-
- Moehler M. H., Janjigian Y. Y., Adenis A., Aucoin J. S., Boku N., Chau I., et al. ASCO 2018

Radiation and Immunotherapy

- Radiation therapy interacts with the tumor and immune system through a variety of mechanisms.
  - It promotes the release of tumor neoantigens during cancer cell death,
  - Generates tumor-specific T cells with local as well as potentially distant, systemic effects.
  - key molecular signals generated by radiation-induced cell death that promote uptake of dying cancer cells by dendritic
    - Antigen cross-presentation and activation of the inflammasome collectively constitute immunogenic cell death.
    - Complex effects on the tumor microenvironment → enhanced infiltration of activated T cells
    - Trials in solid tumors are investigating the strategy of combining immunostimulatory signals with radiation,



Ishihara D et al. Cancer Immunol Immunother (2017) 66: 281.

ASTRO
TARGETING CANCER CARE

News Release

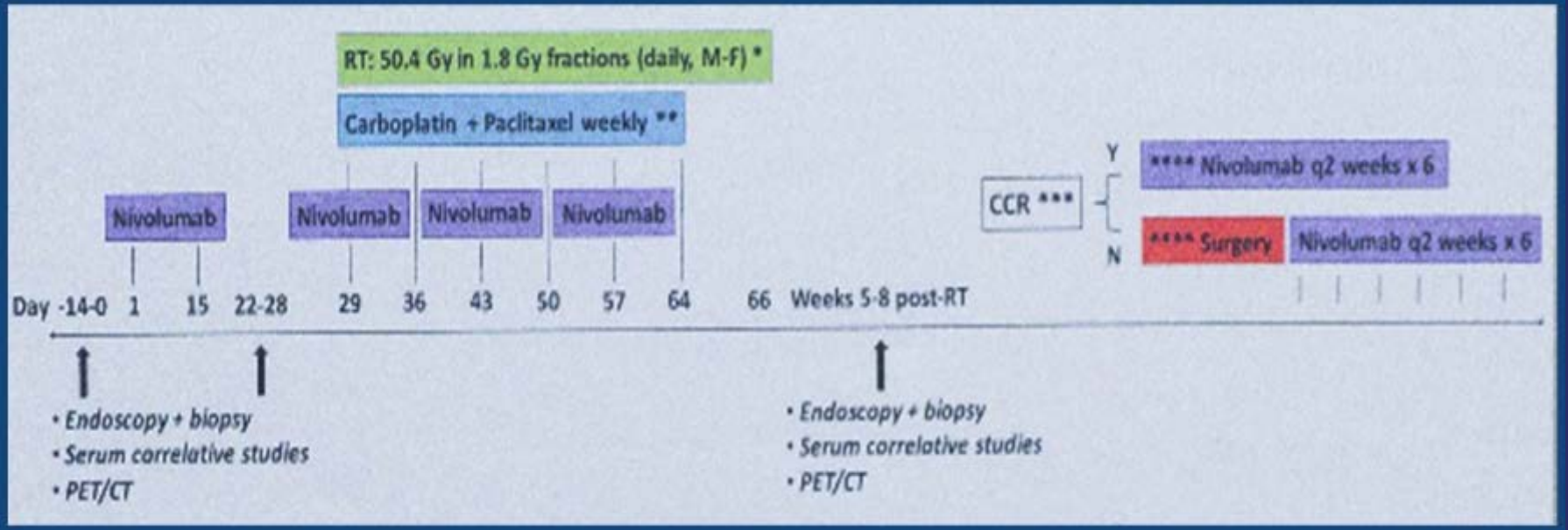
leah.fogarty@astro.org

Radiation-immunotherapy combination can slow tumor growth for some patients with metastatic late-stage cancer

Phase II trial finds at least 30 percent of patients experienced favorable response after treatment

SAN DIEGO, September 24, 2017 – A new study involving patients with stage IV cancer finds that treatment with radiation therapy and immunotherapy can halt the growth of tumors by stimulating the body's immune system to attack the cancer. In the phase II trial, patients with end-stage cancer that had spread to the lungs or liver demonstrated a favorable response to the combined treatment. Between 30 and 60 percent of the patients, depending on the treatment arm, found that their cancer stopped spreading. Findings will be presented today at the 59th Annual Meeting of the American Society for Radiation Oncology (ASTRO).

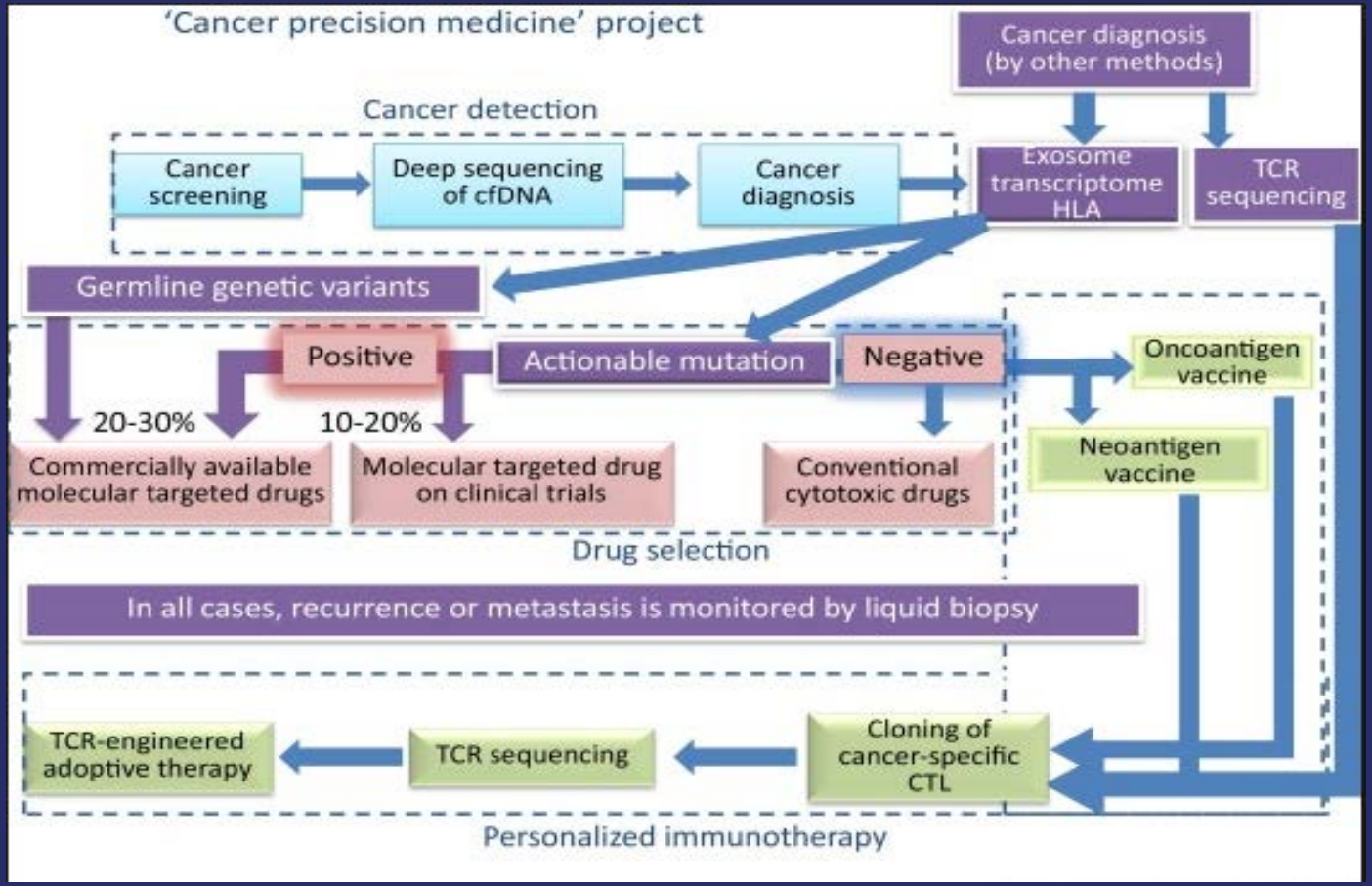
Esophageal Adeno/GE junction: Chemo-ImmunoRx with XRT



Giuroiu I et al. J Clin Oncol 36, 2018 (suppl 4S; abstr TPS199)

Gastro Esophageal CA and ImmunoRx Conclusions

- Management of AGC and GE cancers is an evolving process and shifting the Paradigm
- PD-1 and PD-L1 inhibition has modest activity in GI malignancies
- Hence, Combination Therapy is a reasonable future step
- Patients who respond seem to have durable responses (significantly longer than typically seen with chemotherapy in the advanced setting)
- Incorporating PD-1 Inhibition in early Stages (Peop & Post Op) of Gastric/ GE junction cancers may be a crucial step in enhancing Cure rate in addition to Surgery
- Ongoing Clinical Trials will be the answer to all Our questions


'Cancer precision medicine' project
Cancer diagnosis (by other methods)
Cancer detection
Cancer screening
Deep sequencing of cfDNA
Cancer diagnosis
Exosome transcriptome HLA
TCR sequencing
Germline genetic variants
Positive
Actionable mutation
Negative
Oncoantigen vaccine
20-30%
10-20%
Neoantigen vaccine
Commercially available molecular targeted drugs
Molecular targeted drug on clinical trials
Conventional cytotoxic drugs
Drug selection
In all cases, recurrence or metastasis is monitored by liquid biopsy
TCR-engineered adoptive therapy
TCR sequencing
Cloning of cancer-specific CTL
Personalized immunotherapy