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KEYTRUDA® for Patients With Advanced Gastric Cancer

Nageatte Ibrahim, MD

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Merck & Co., Inc.

KEYTRUDA® Has Demonstrated Clinical Benefit Across Multiple Indications and Tumor Types

19 Traditional approvals

13 Original traditional approvals in 9 different tumor types

- Melanoma, 2 in non-small cell lung cancer (NSCLC), 2 in Head and neck squamous cell carcinoma (HNSCC), classical Hodgkin lymphoma (cHL), 2 in urothelial carcinoma, MSI-H colorectal cancer, 2 in esophageal and gastroesophageal junction (GEJ) carcinoma, renal cell carcinoma, cutaneous squamous cell carcinoma

6 Original accelerated approvals converted upon verification of benefit

- Melanoma, 1L and 2L NSCLC, HNSCC, 3L+ cHL, primary mediastinal large B-cell lymphoma

10 Accelerated Approvals

6 Ongoing confirmatory studies

- MSI-H (tumor agnostic), TMB-H (tumor agnostic), cervical cancer, Merkel cell carcinoma, endometrial carcinoma, triple-negative breast cancer

4 Confirmatory studies did not meet primary endpoints

- **Gastric cancer**, hepatocellular carcinoma, urothelial carcinoma, small cell lung cancer[a]

MSI-H=microsatellite instability high; TMB-H=tumor mutational burden high.

[a] Indication withdrawn after consultation with FDA.

Regulatory Approvals for KEYTRUDA® Relevant for Today's Discussion

Gastric and gastroesophageal junction (GEJ) cancer

June 2015: Orphan Drug Designation in gastric cancer (KEYNOTE-012)

Sep 2017: 3L+ gastric cancer, accelerated approval (KEYNOTE-059)

Mar 2021: 1L esophageal and GEJ cancer, traditional approval (KEYNOTE-590)

May 2017: MSI-H/dMMR accelerated approval

MSI-H or MMR deficient solid tumors (2L+)

June 2020: TMB-H accelerated approval

TMB-H (≥ 10 mut/Mb) solid tumors (2L+)

Tumor agnostic

Mb=megabase; MMR=mismatch repair; mut=mutation; MSI-H=microsatellite instability high; TMB-H=tumor mutational burden high.

Current Indication for KEYTRUDA® in 3L+ Gastric Carcinoma CPS ≥1

KEYNOTE-059, Accelerated Approval

- **Accelerated Approval September 22, 2017**

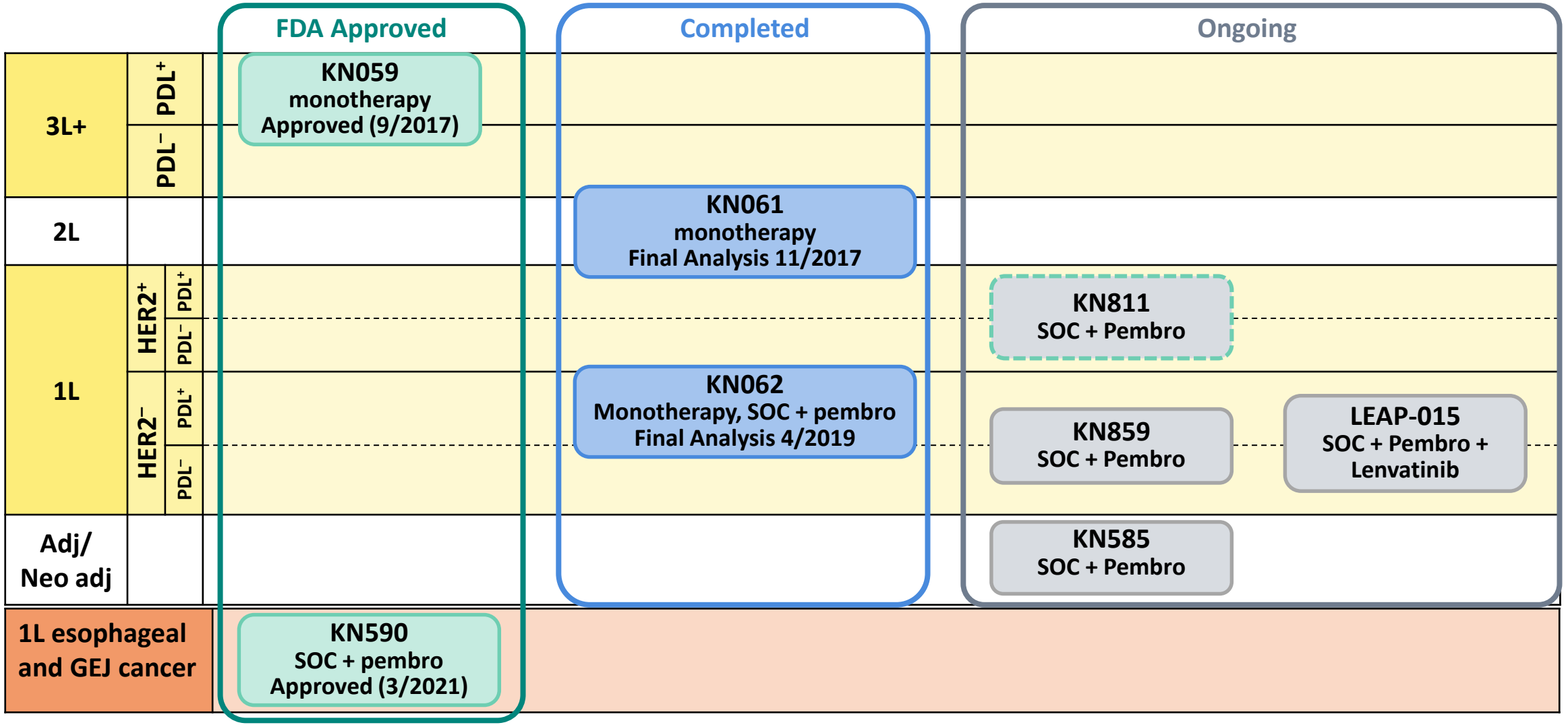
  Keytruda is indicated for the treatment of recurrent locally advanced or metastatic gastric or GEJ adenocarcinoma whose tumors express PD-L1 (CPS ≥1) with disease progression on or after 2 or more prior lines of therapy, including fluoropyrimidine- and platinum-containing chemotherapy, and if appropriate, HER2/neu targeted therapy.

- **Post-Marketing Requirement (PMR)**

  Conduct and submit the results of one or more randomized trials to verify and describe the clinical benefit of pembrolizumab over standard therapy based on a clinically meaningful improvement in overall survival in patients with PD-L1 positive, microsatellite stable/mismatch repair (MMR)-proficient metastatic gastric or GEJ adenocarcinoma.

HER2=human epidermal growth factor receptor-2; PD-L1=programmed death ligand-1.

Pembrolizumab Gastric Cancer Development Program



What You Will Hear Today

Unmet Medical Need	• Patients with metastatic gastric cancer in 3L+ have poor prognosis and limited treatment options
Efficacy and Safety	• In KEYNOTE-059, pembrolizumab provided an ORR of 13.3% with durable responses in 3L+ gastric cancer • The safety profile was manageable and consistent with known safety profile
Confirmatory Studies	• KEYNOTE-061 and -062 did not meet endpoints of superiority versus chemotherapy • Four ongoing, randomized, Phase 3 trials have potential to confirm clinical benefit of pembrolizumab in gastric cancer within 1-3 years
Benefit-Risk	• Pembrolizumab provides durable responses and has a manageable safety profile that is different from chemotherapy

Agenda

Introduction	**Nageatte Ibrahim, MD** Vice President, Oncology Clinical Research Merck & Co., Inc.
Disease Background & Unmet Need in Gastric Cancer	**Peter Enzinger, MD** Dana-Farber Cancer Institute Harvard University
Efficacy, Safety and Proposed Confirmatory Studies of Pembrolizumab in Gastric Cancer	**Pooja Bhagia, MD** Clinical Development Lead – GI Cancers Oncology Clinical Research Merck & Co., Inc.
Concluding Remarks	**Nageatte Ibrahim, MD**

Consultants

Ronan Kelly, MD, MBA
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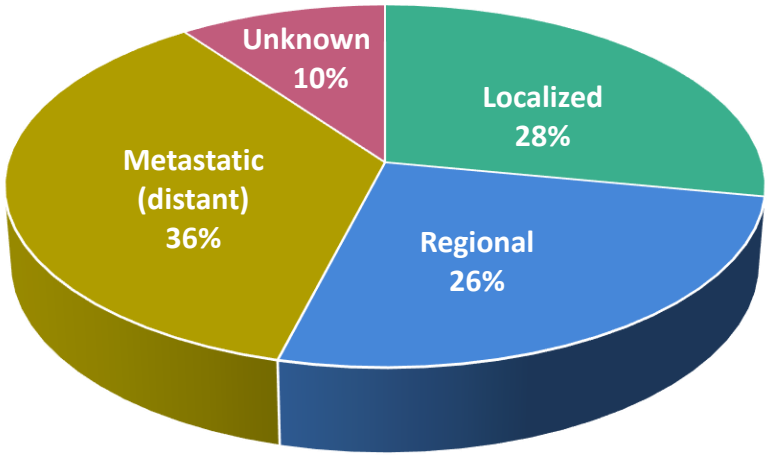
Disease Background and Unmet Need in Gastric Cancer

Peter Enzinger, MD

Dana-Farber Cancer Institute
Harvard University

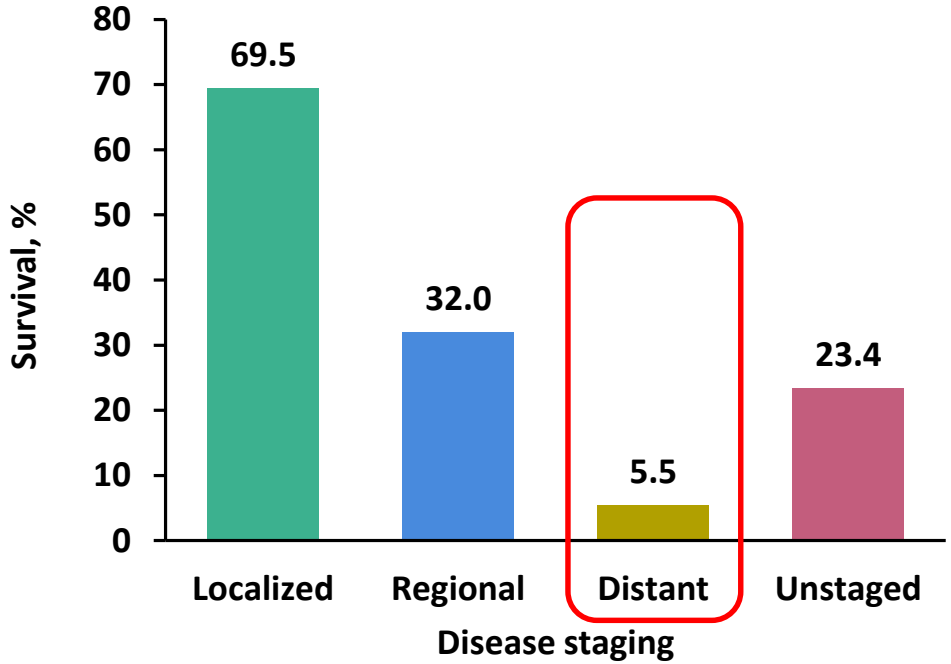
Gastric Cancer in the United States

Percentage of cases by stage at diagnosis



27,600 estimated new cases diagnosed and 11,010 deaths in 2020

5-year survival by stage



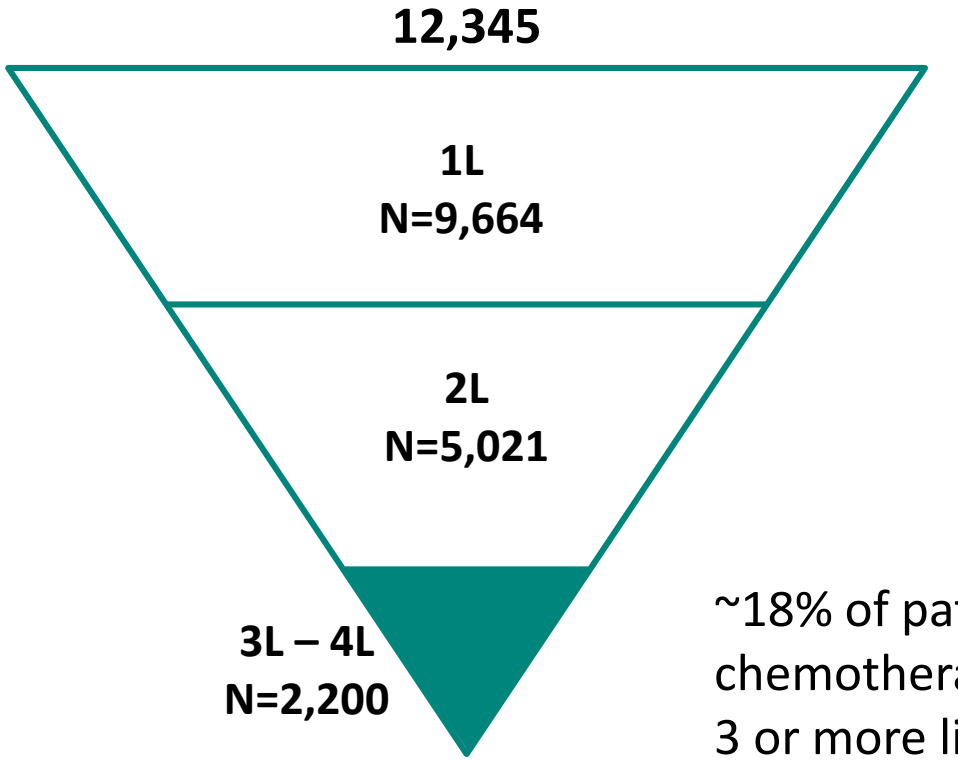
SEER=Surveillance, Epidemiology, and End Results.

SEER Cancer Stat Facts: Stomach Cancer. National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/statfacts/html/stomach.html (https://seer.cancer.gov/statfacts/html/stomach.html).

Gastric Cancer Treatment Patterns

Estimated Number of Patients Treated per Year in the United States

Stage IV treatment by line of therapy[1]



~18% of patients who received first-line chemotherapy for gastric cancer receive 3 or more lines of therapy[2-4]

1. Kantar Health CancerMPact, 2020; 2. Hess LM, et al. *Gastric Cancer.* 2016;19(2):607-615; 3. Barzi A, et al. *Cancer Control*. 2019;26(1): 1073274819847642.; 4. Le DT, et al. *Clin Colorectal Cancer*. 2020;19(1):32-38.e3.

Clinical Biomarkers Important for KEYTRUDA® in Gastric Cancer

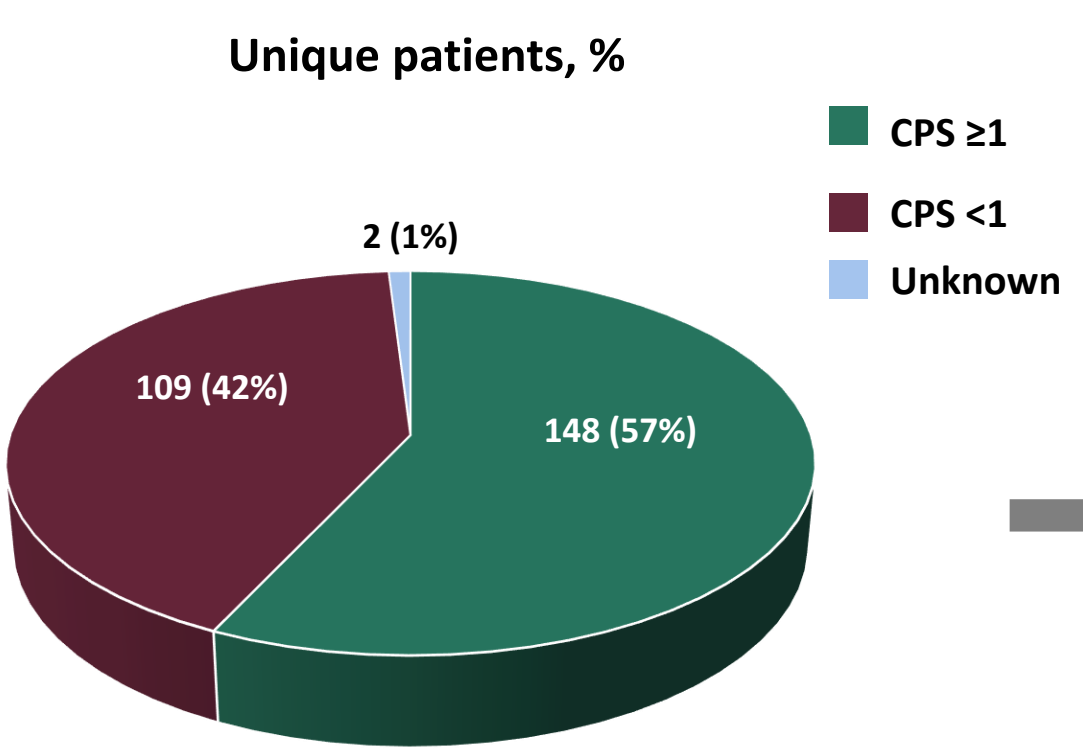
- **Combined positive score (CPS)** measures PD-L1 expression on tumor cells, lymphocytes, and macrophages
  - In KEYNOTE-059, CPS ≥1 enriched for increased likelihood of response to pembrolizumab
- **Tumor mutational burden (TMB)** is the number of mutations per tumor genome
  - ≥10 mut/Mb by F1CDx is classified as **TMB-H** (comparable to 175 mut/exome by WES)
- **Microsatellite instability (MSI)** refers to a high number of mutations in regions of repetitive DNA (microsatellites) as a result of deficiencies in mismatch-repair (dMMR) pathways
  - Tumors that are MSI-H are typically also TMB-H

F1CDx=Foundation medicine companion diagnostic; WES=whole exome sequencing.

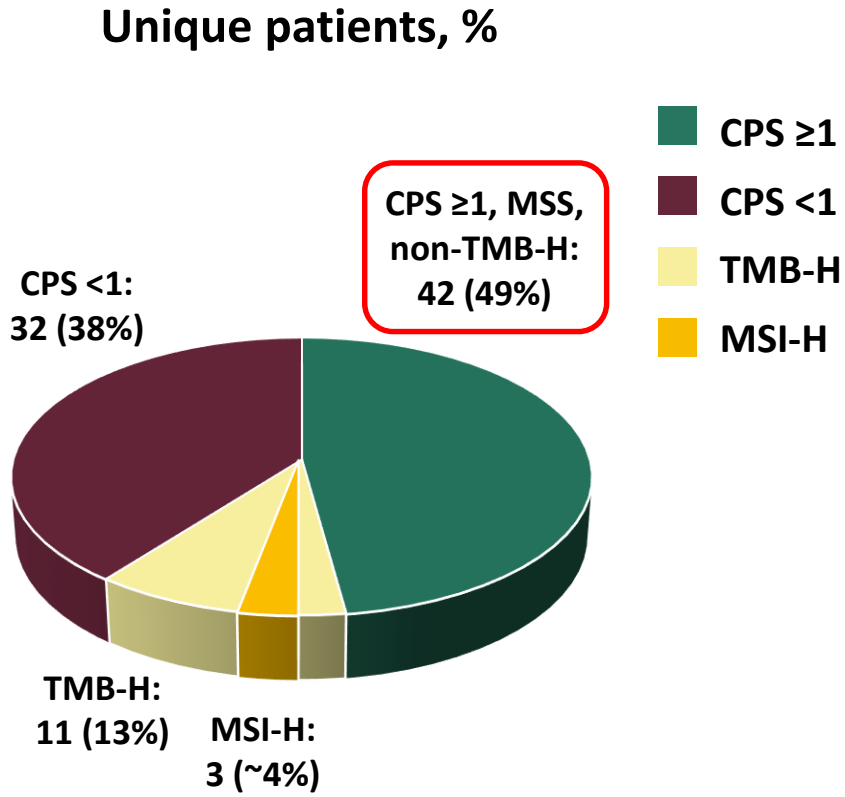
Gastric Cancer Biomarker Distribution in 3L+ From KEYNOTE-059

KEYNOTE-059 Cohort 1

Total Enrolled (N=259)



WES TMB-Evaluable Patients (n=85)

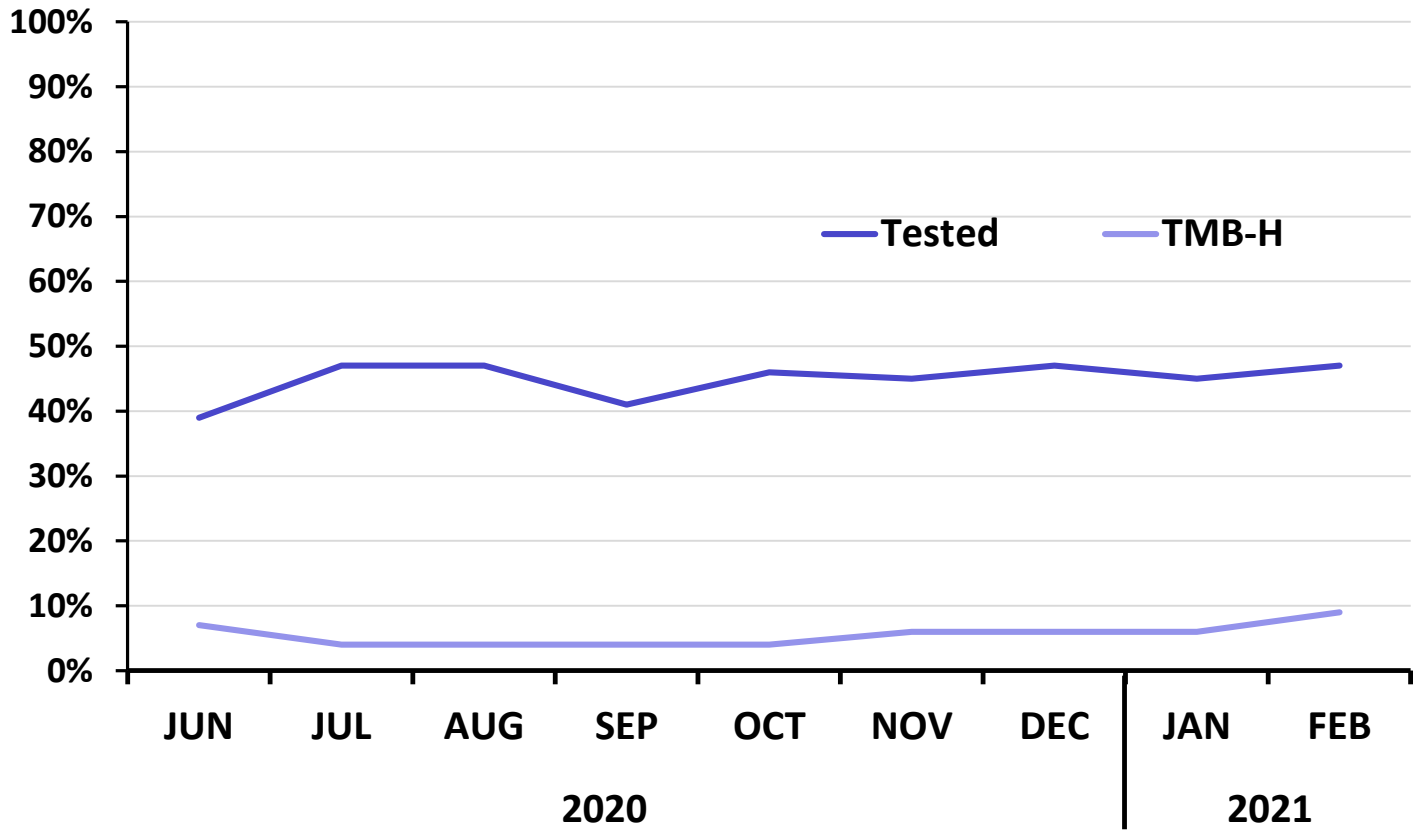


MSS=microsatellite stable.

Less than 10% of Patients With Gastric Cancer Are Being Identified as TMB-H in Clinical Practice

- <50% of patients are being tested for TMB status
- The proportion of patients identified as TMB-high is between 4%-9%
- Data from KEYNOTE-059 indicate that ~13% of patients with 3L+ gastric cancer have TMB-H cancer

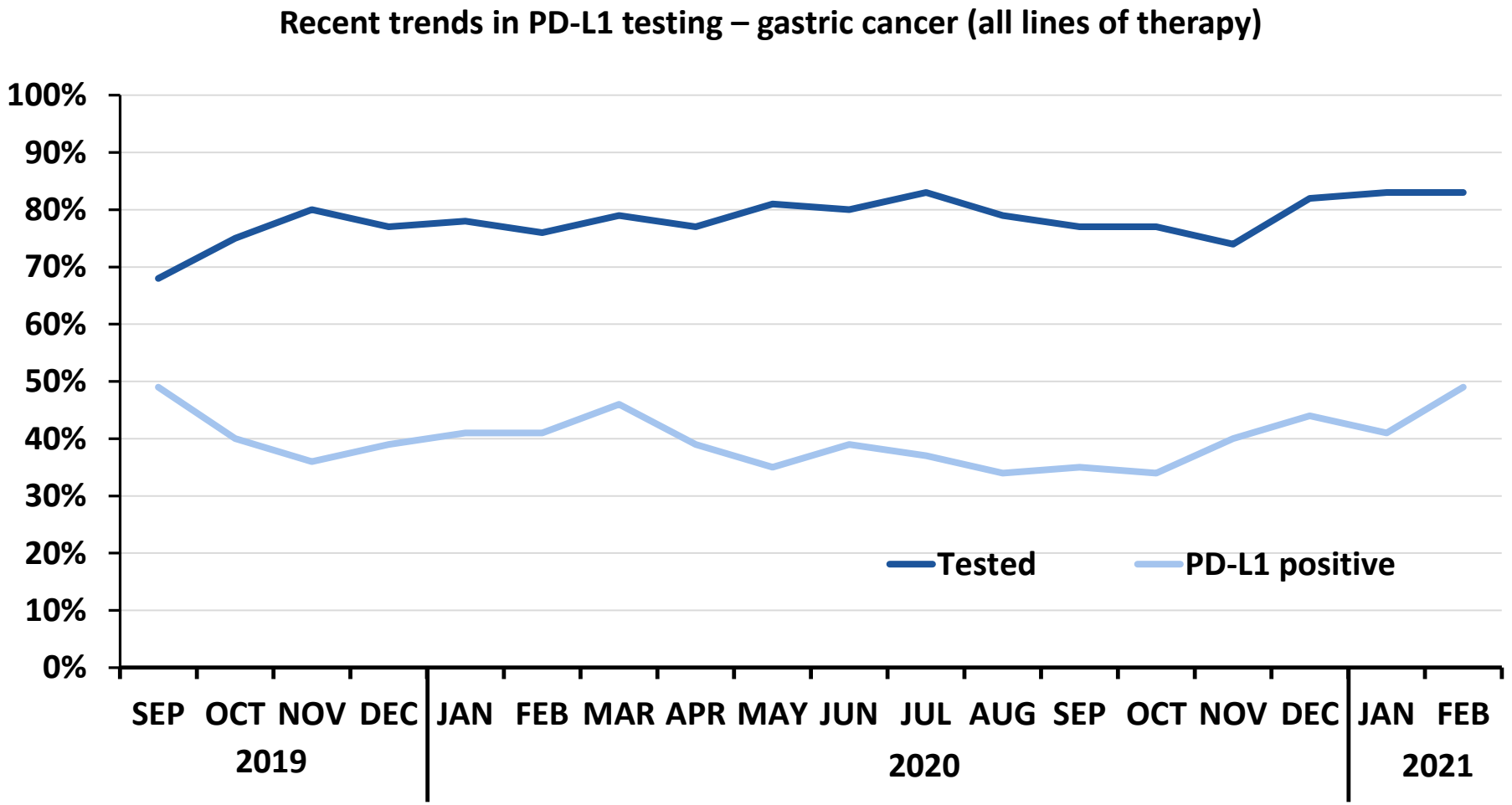
Recent trends in TMB testing – Gastric cancer (all lines of therapy)



IQVIA BrandImpact Survey, Feb 2021.

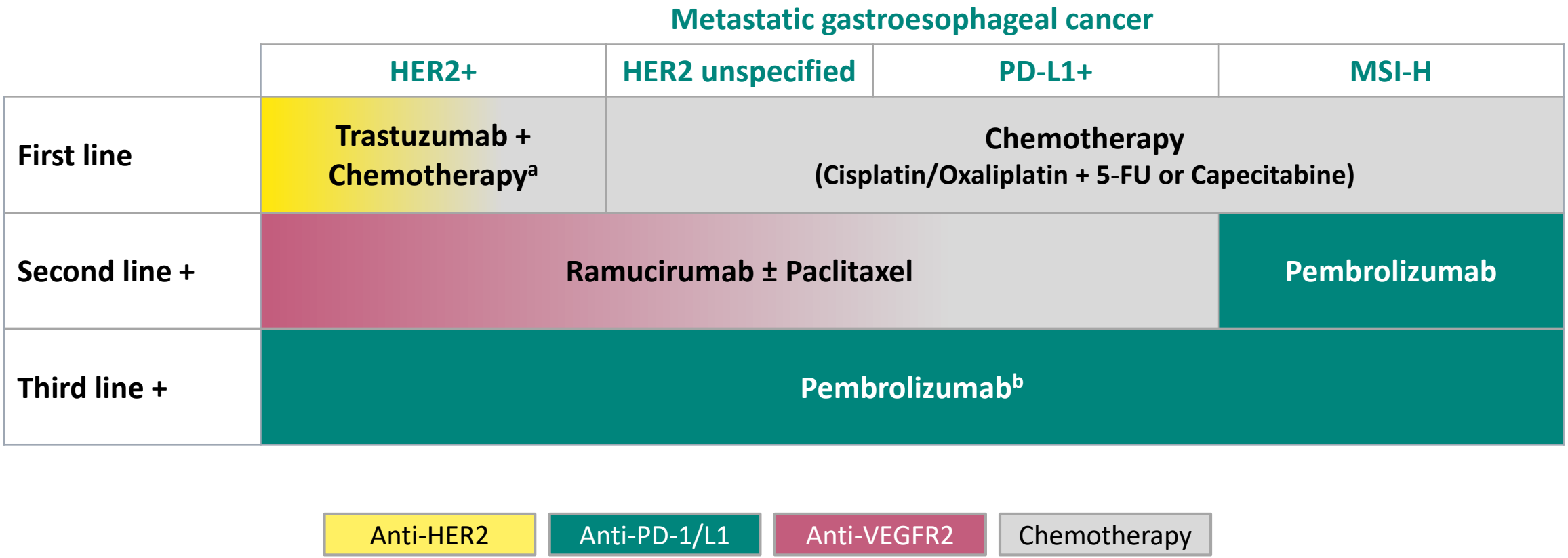
Most Gastric Cancer Patients Are Tested for PD-L1 in Clinical Practice and About Half Are PD-L1 Positive

- ~80% of patients are tested for PD-L1 status
- ~40%-50% of patients are identified as PD-L1 positive, similar to what was observed in KEYNOTE-059



IQVIA BrandImpact Survey, Feb 2021.

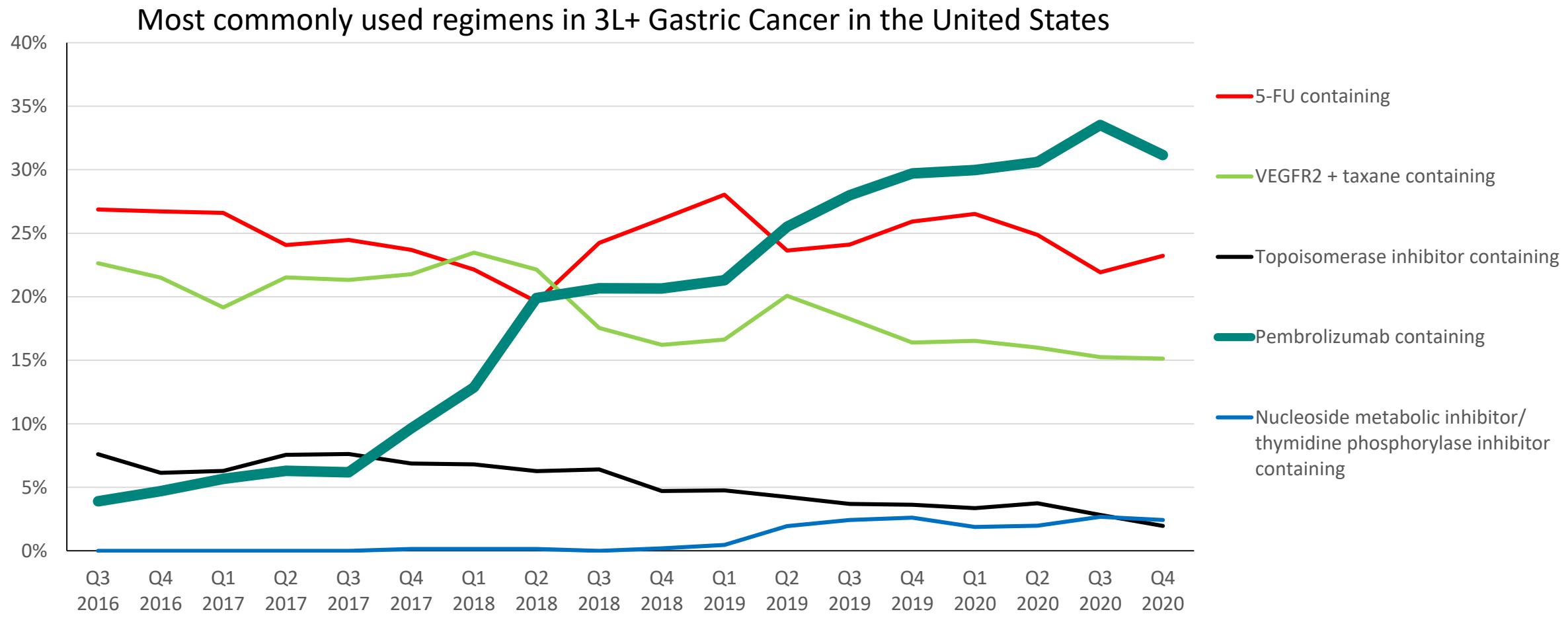
Standard of Care in Gastric/GEJ Cancer Upon Approval of Pembrolizumab in 2017 (Approved Indications)



[a] Cisplatin + Capecitabine or 5-FU.
[b] CPS ≥1 for those with HER2+ or HER2 unspecified.
NCCN Guidelines Gastric Cancer, v2.2018; Smyth EC, et al. *Ann Oncol*. 2016;27(5):v38-v49.

Increased Use Indicates That Pembrolizumab Addresses Unmet Need

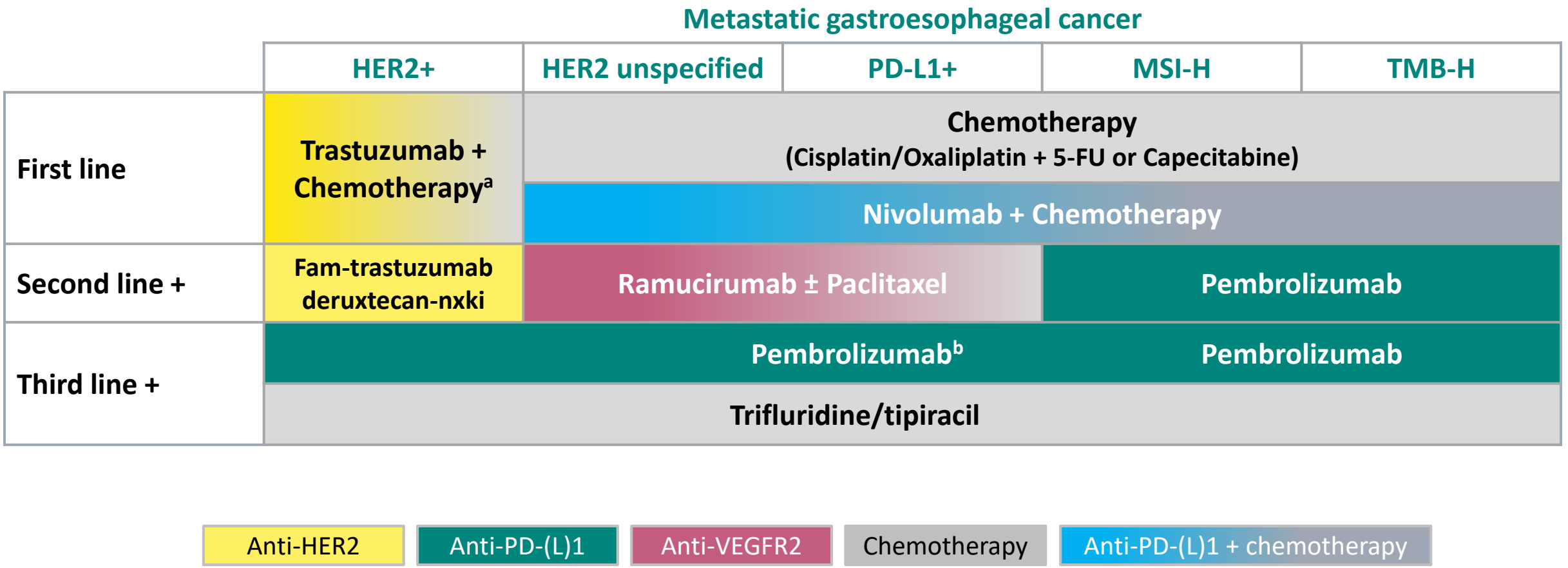
3-Quarter Moving Average



Data based on a projected ~500-700 patients per quarter with metastatic disease initiating third or higher line of therapy

Projection based on IQVIA claims data, Feb 2021.

Evolution of Therapeutic Landscape Since 2017



[a] Cisplatin + Capecitabine or 5-FU.
[b] CPS ≥1 for those with HER2+ or HER2 unspecified.
NCCN Guidelines Gastric Cancer, v4.2020; Smyth EC, et al. *Ann Oncol*. 2016;27(5):v38-v49; eUpdate 04Nov2019.

Recently Conducted RCTs in 3L+ Gastric Cancer With Approved Agents Compared to Pembrolizumab From KEYNOTE-059

Study	Experimental	N	ORR, %	Median OS, mo
Approved in United States				
TAGS[1]	Trifluridine/tipiracil + BSC	337	4	5.7
	Placebo + BSC	170	2	3.6
KEYNOTE-059[b]	Pembrolizumab	143	13	5.8
Approved outside United States				
Single inst.[2]	Apatinib (850 mg)	47	6	4.8
	Apatinib (425 mg)	46	13	4.3
	Placebo	48	0	2.5
Single inst.[3]	Apatinib	176	3[a]	6.5
	Placebo	91	0	4.7
ATTRACTION-2[4]	Nivolumab	268	11	5.3
	Placebo	131	0	4.1

RCT=randomized controlled trial; BSC=best supportive care.

[a] Determined by investigator; [b] Data is not from a randomized controlled study; no comparative data for OS is available.

1. Shitara K, et al. *Lancet Oncol*. 2018;19(11):1437-1448; 2. Li J, et al. *J Clin Oncol*. 2013;31(26):3219-3225; 3. Li J, et al. *J Clin Oncol*. 2016;34(13):1448-1454; 4. Kang YK, et al. *Lancet*. 2017;390:2461-2471.

Unmet Need in Patients With PD-L1 Positive Gastric Cancer in the Third-line Setting

- Patients who reach third line have
  - Poor prognosis (median OS <6 months)
  - Limited treatment options, particularly chemotherapy-free options
- Cytotoxic chemotherapy beyond 2L
  - Provides low response rates
  - Associated with considerable toxicities and potential impact on quality of life[1]
  - Limited evidence that chemotherapy confers a meaningful survival advantage[1,2]
- Treatment landscape for 3L+ gastric cancer patients has not changed substantially since approval of pembrolizumab
  - Trifluridine/tipiracil approved in 2019 for 3L gastric cancer
  - Pembrolizumab changed treatment landscape in 3L+ gastric cancer, producing durable responses

1. Zheng Y, et al. *Medicine*. 2017;96(24):e6884; 2. Kim SM, Park SH. *World J Gastroenterol*. 2015;21(29):8811-8816.

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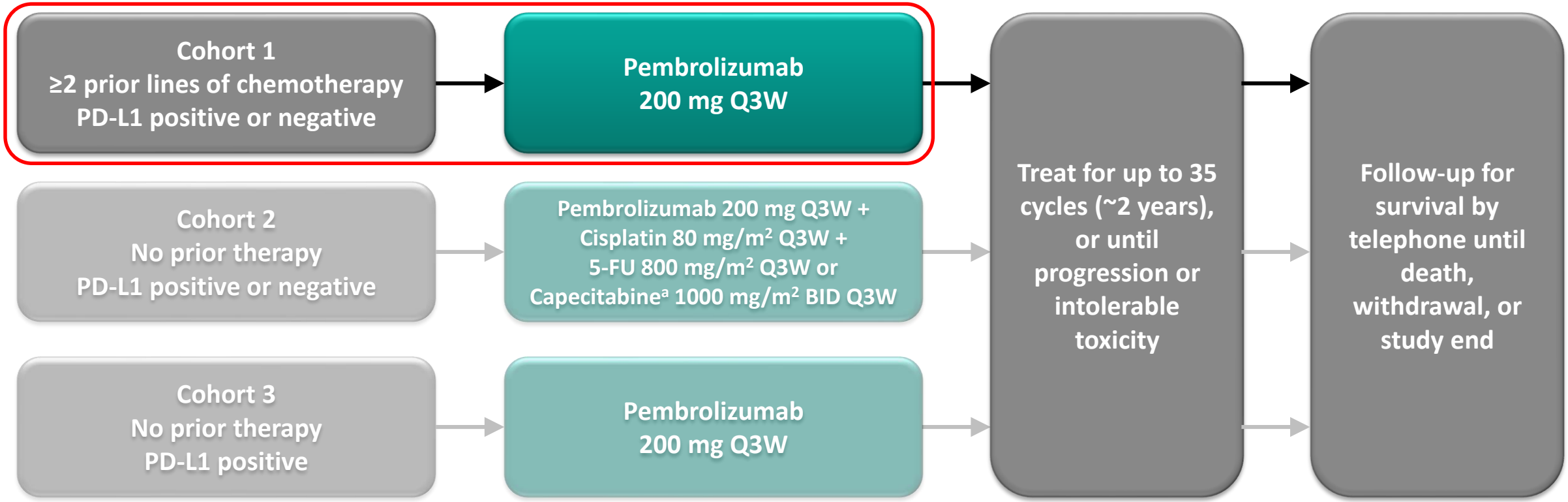
Efficacy, Safety, and Proposed Confirmatory Studies of Pembrolizumab in Gastric Cancer

Pooja Bhagia, MD

Clinical Development Lead – GI Cancers
Oncology Clinical Research
Merck & Co., Inc.

Study Design

KEYNOTE-059 Cohort 1 (3L+)



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

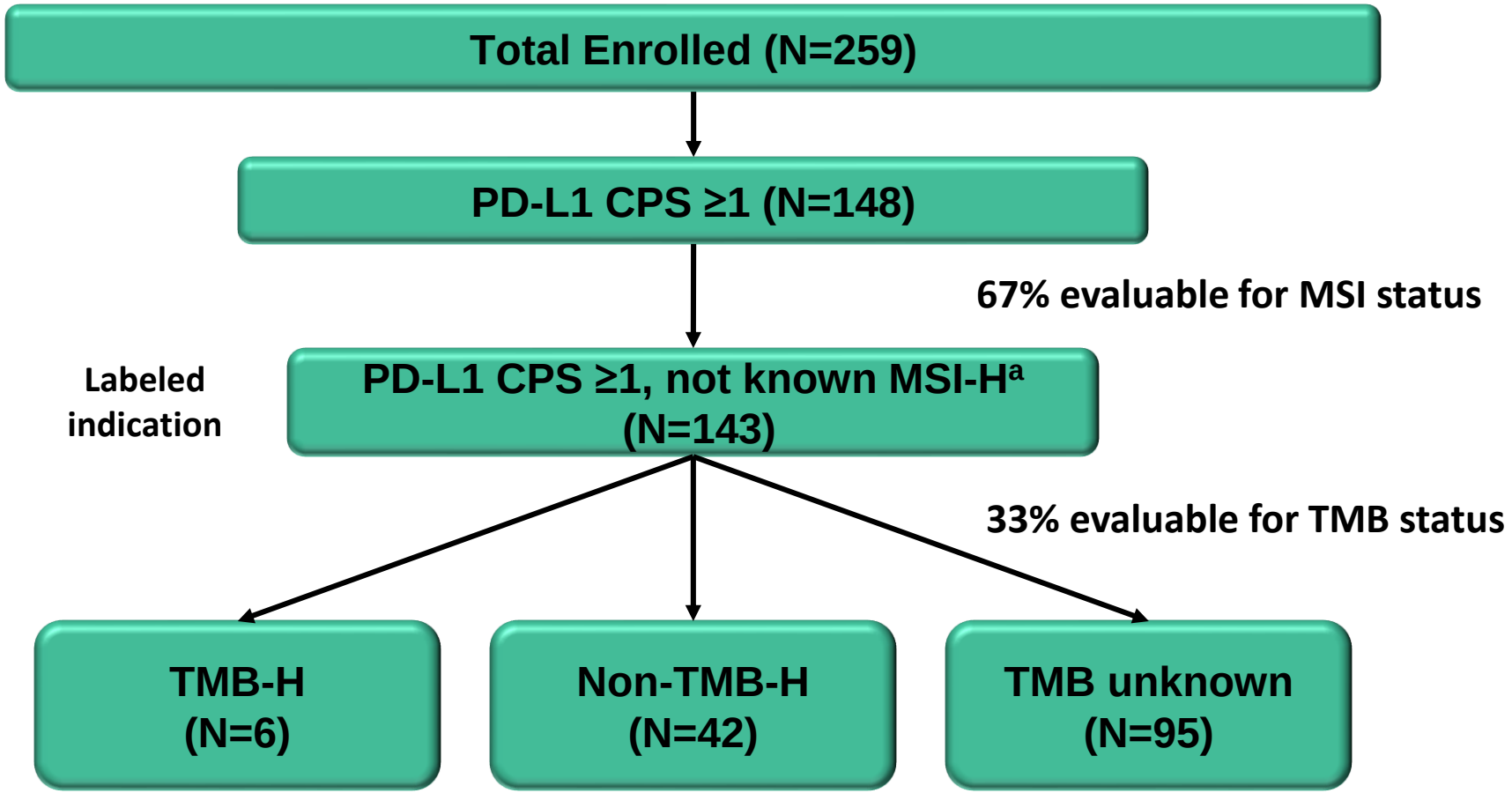
Primary efficacy endpoint - ORR

[a] Capecitabine was administered only in Japan.

Wainberg, ESMO, Sept 2017.

Cohort 1 Patient Breakdown

KEYNOTE-059



[a] Microsatellite stable (MSS) or undetermined MSI/MMR status.

Response Rate and Duration of Response

KEYNOTE-059 Cohort 1

Response	Labeled indication[a] CPS ≥1, not known MSI-H N=143	Additional 48-mo follow-up[b] CPS ≥1, not known MSI-H N=143	CPS ≥1, MSS N=100[b]
ORR, n (%)	**19 (13.3)**	**19 (13.3)**	**11 (11.0)**
CR	2 (1.4)	4 (2.8)	2 (2.0)
PR	17 (11.9)	15 (10.5)	9 (9.0)
DCR, n (%)	**45 (31.5)**	**45 (31.5)**	**16 (26.0)**
Median DoR, months (range)	**9.9 (2.8+ - 19.4+)**	**9.9 (2.8+ - 50.4)**	**15.4 (2.8+ - 47.1+)**
DoR ≥6 months, n (%)	11 (58)	12 (70.6)	8 (73)
DoR ≥12 months, n (%)	5 (26)	8 (42)	5 (45)

[a] Data cutoff: 16-JAN-2017 for ORR and 21-APR-2017 for DoR used in current US label.
[b] Data cutoff: 22-JAN-2021.

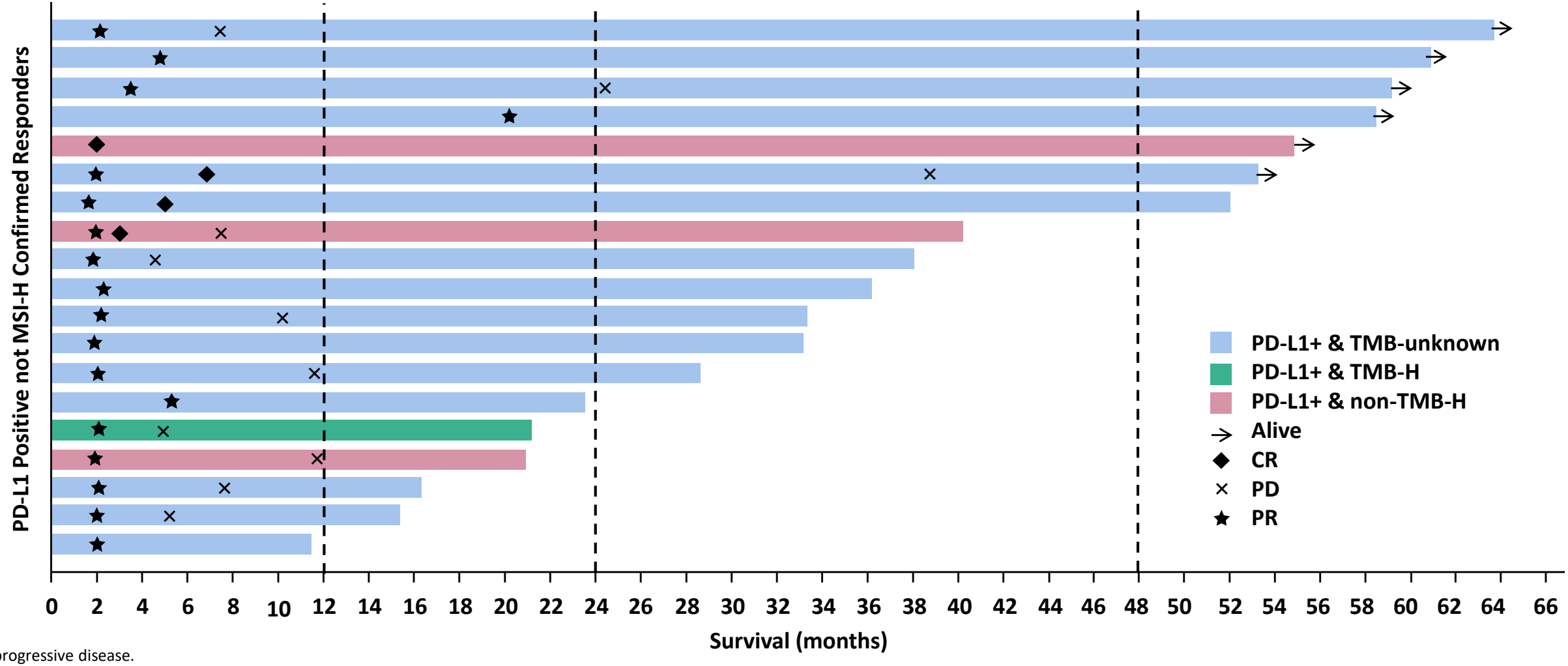
Post hoc Analysis of KEYNOTE-059 by TMB Status in the Not Known MSI-H, CPS ≥1 Population

Response	TMB unknown N=95	Non TMB-H[a] N=42	TMB-H N=6
ORR, n (%) [95% CI]	15 (15.8) [9.1 – 24.7]	3 (7.1) [1.5 – 19.5]	1 (16.7) [0.4 – 64.1]
CR	2 (2.1)	2 (4.8)	0
PR	13 (13.7)	1 (2.4)	1 (16.7)
DCR, n (%) [95% CI]	32 (33.7) [24.3 – 44.1]	10 (23.8) [12.1 – 39.5]	3 (50.0) [11.8 – 88.2]
DoR for responders, months	Median 15.7 (range 2.8 – 50.4)	5.5, 9.9, 47.1+	2.9
OS for responders, months	Median 36.2 (range 11.5 – 63.8)	21.0, 40.3, 55.0+	21.2

[a] These patients are known to be MSS and non TMB-H.
Data cutoff date: 22-Jan-2021.

Survival Analysis Based on Biomarker Status Among the 19 Responders

KEYNOTE-059 Cohort 1



PD=progressive disease.
Data cutoff date: 22-Jan-2021.

Summary of Adverse Events
KEYNOTE-059

	Patients, n (%)	
	Pembrolizumab N=259	Reference Safety Dataset Pembrolizumab Monotherapy N=2799
Any AE	**248 (95.8)**	**2727 (97.4)**
Grade 3-5	163 (62.9)	1273 (45.5)
SAE	118 (45.6)	1042 (37.2)
Death due to AE	17 (6.6)	110 (3.9)
Discontinuation due to AE	17 (6.6)	334 (11.9)
Immune-mediated events and infusion reactions	**49 (18.9)**	**597 (21.3)**
Grade 3-5	12 (4.6)	154 (5.5)
SAE	9 (3.5)	161 (5.8)
Death due to AE	0	4 (0.1)
Discontinuation due to AE	2 (0.8)	83 (3.0)

Data cutoff date: 08-Aug-2018.

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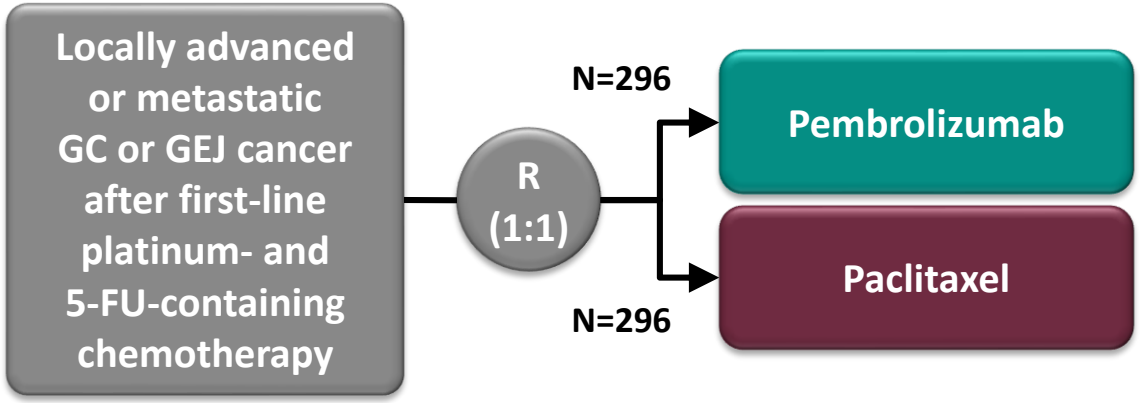
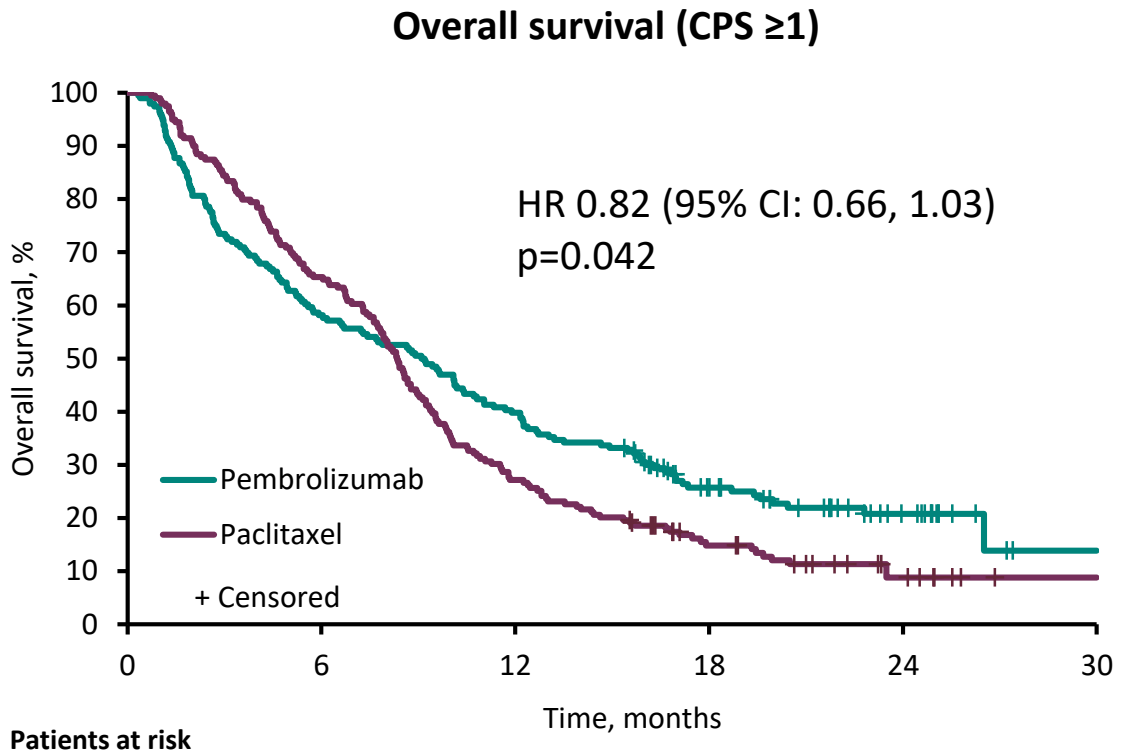
Original PMR Studies

KEYNOTE-061 and KEYNOTE-062

KEYNOTE-061 in Second-Line Gastric Cancer



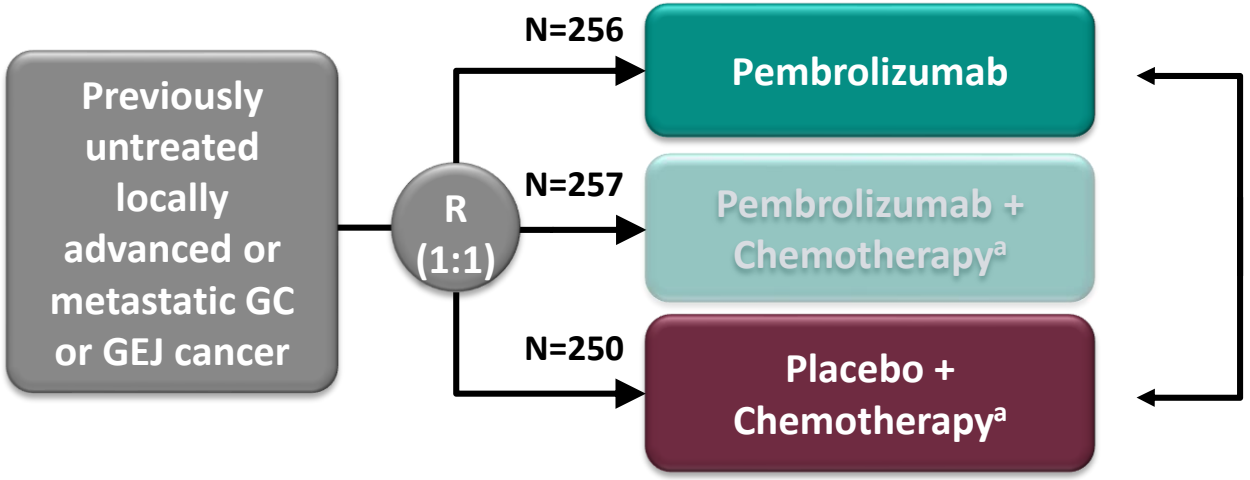
Primary endpoints OS and PFS



Patients at risk

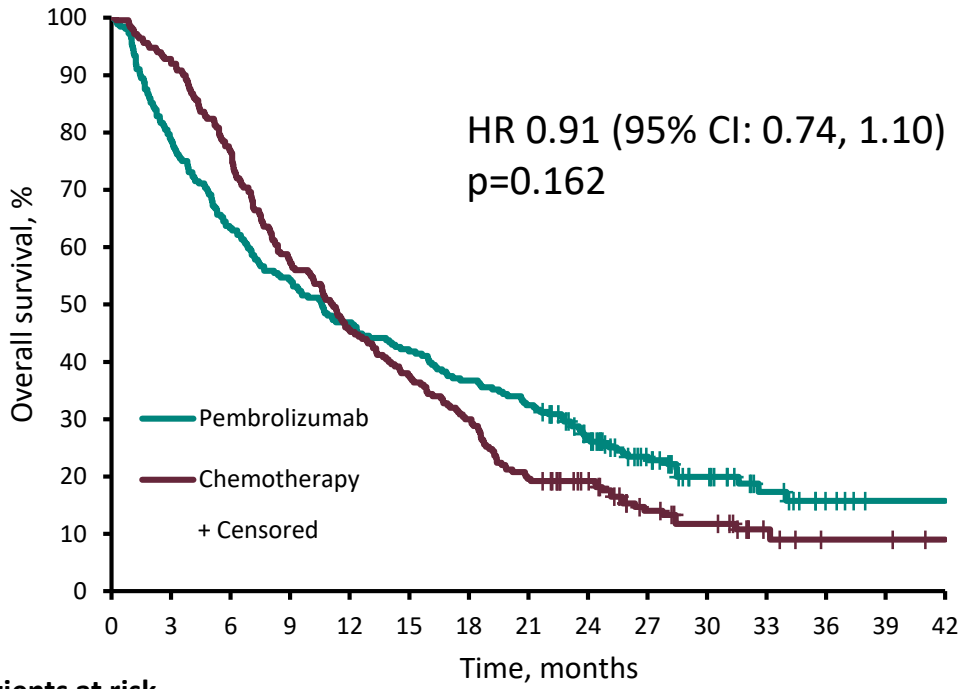
Pembrolizumab	196	114	78	39	14	0
Paclitaxel	199	130	54	23	7	0

KEYNOTE-062 in First-Line Gastric Cancer



Primary endpoints OS and PFS

Overall survival
pembrolizumab vs chemotherapy (CPS ≥1)

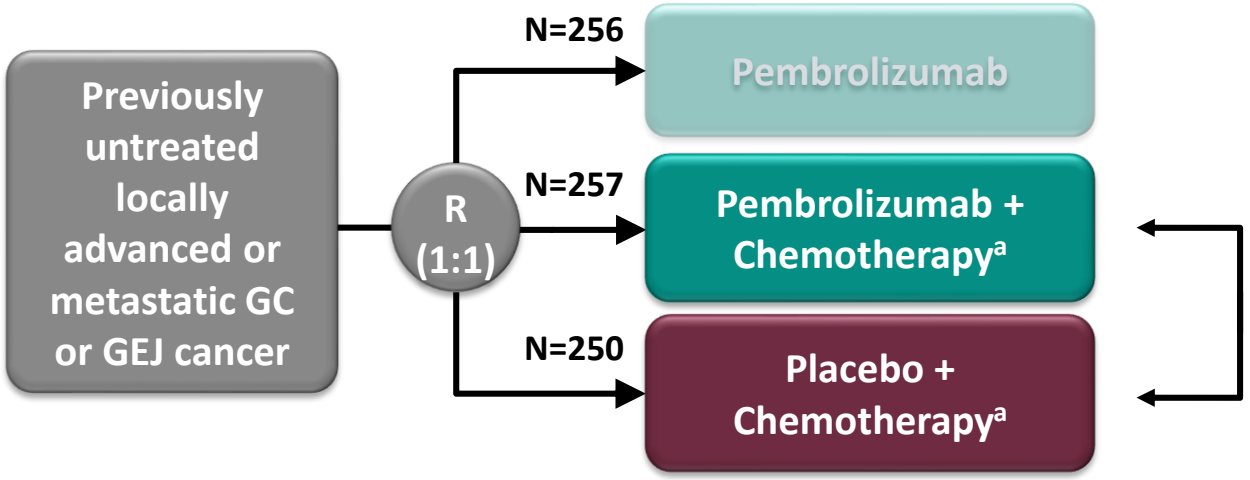


Patients at risk

Pembrolizumab n=	256	201	162	139	120	107	94	83	59	38	23	12	4	0	0
Chemotherapy n =	250	230	192	144	114	94	75	49	38	21	15	6	2	2	0

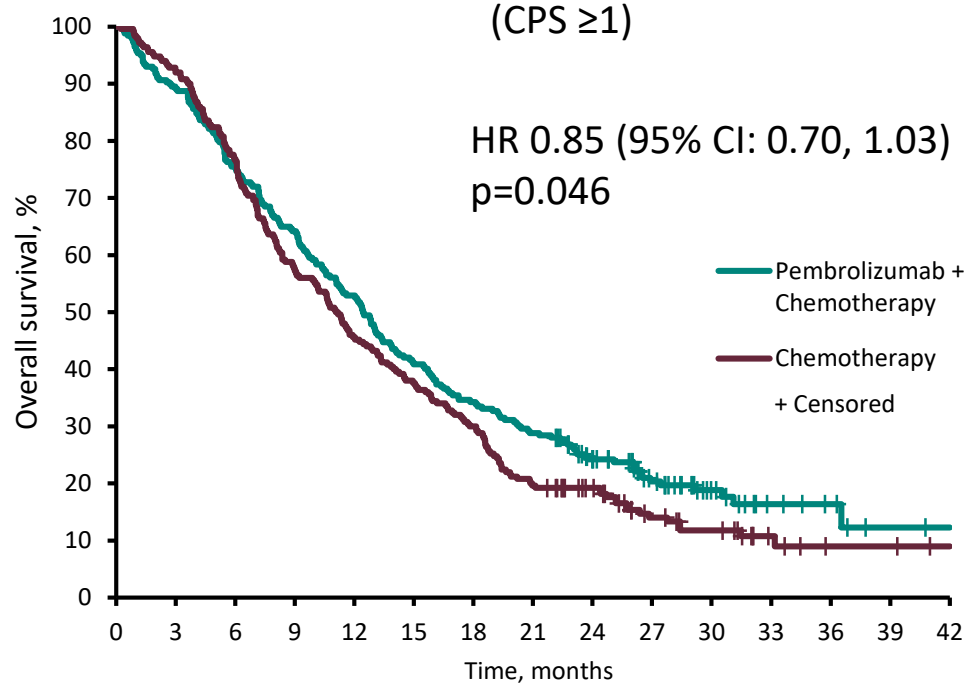
[a] Chemotherapy: Cisplatin 80 mg/m^2 Q3W + 5-FU 800 mg/m^2/d for 5 days Q3W or capecitabine BID d1-14 Q3W (Cisplatin may be capped at 6 cycles as per country guidelines).

KEYNOTE-062 in First-Line Gastric Cancer



Primary endpoints OS and PFS

Overall survival
pembrolizumab + chemotherapy vs chemotherapy
(CPS ≥1)



Patients at risk

Pembro + chemo n=	257	229	194	165	136	105	88	74	52	33	17	8	5	1	0
Chemotherapy n=	250	230	192	144	114	94	75	49	38	21	15	6	2	2	0

[a] Chemotherapy: Cisplatin 80 mg/m^2 Q3W + 5-FU 800 mg/m^2/d for 5 days Q3W or capecitabine BID d1-14 Q3W (Cisplatin may be capped at 6 cycles as per country guidelines).

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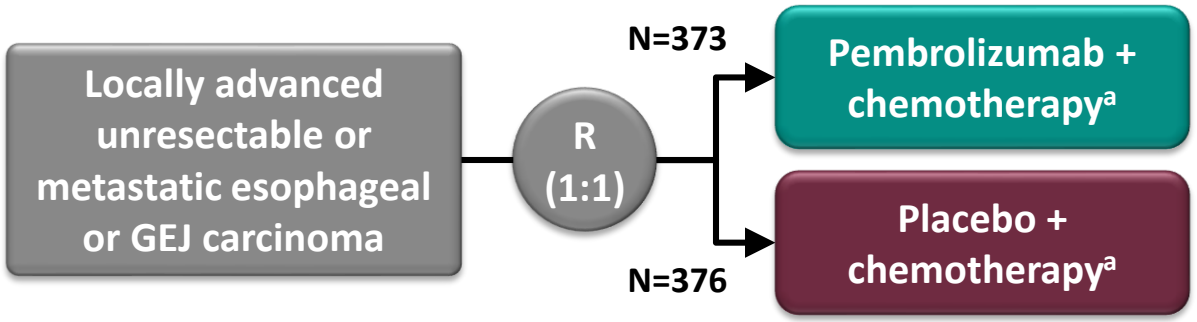
KEYNOTE-590

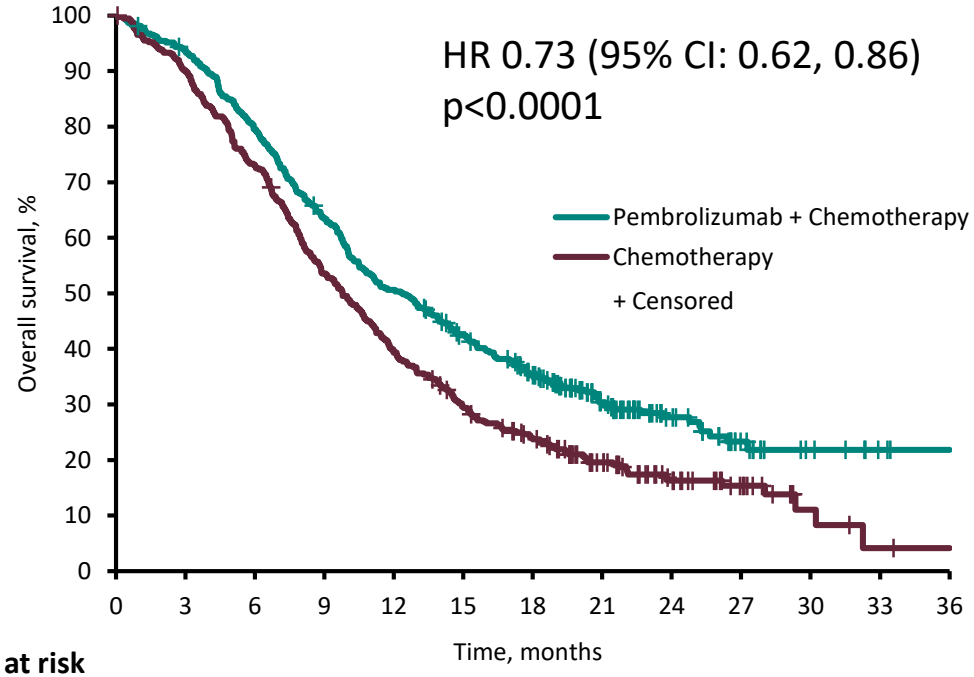
1L Esophageal and GEJ Cancer

KEYNOTE-590 in First-Line Esophageal and GEJ Carcinoma



Primary endpoints OS and PFS

Overall survival
pembrolizumab + chemotherapy vs chemotherapy

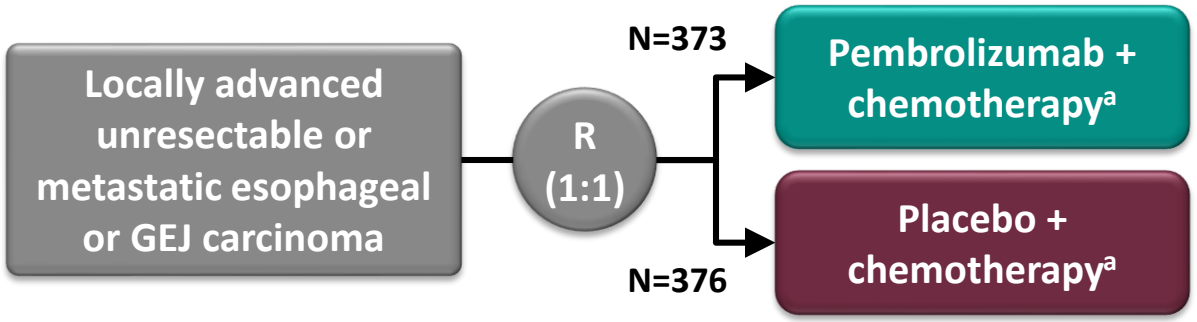


Patients at risk

Pembro + chemo n=	373	348	295	235	187	151	118	68	36	17	7	2	0
Chemotherapy n=	376	338	274	200	147	108	82	51	28	15	4	1	0

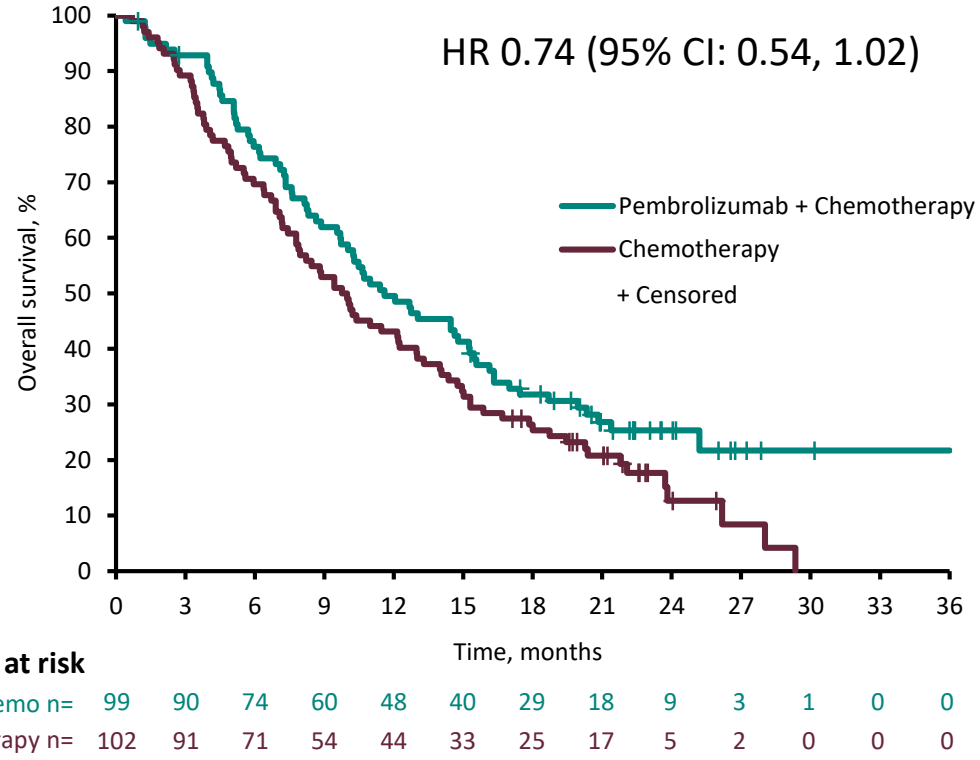
[a] Chemotherapy: 5-FU 800 mg/m^2 IV for days 1-5 Q3W for ≤35 cycles + Cisplatin 80 mg/m^2 IW Q3W for ≤6 cycles.

KEYNOTE-590 in First-Line Esophageal and GEJ Carcinoma



Primary endpoints OS and PFS

Adenocarcinoma (which includes GEJ)
(prespecified subgroup)



Patients at risk

Pembro + chemo n=	99	90	74	60	48	40	29	18	9	3	1	0	0
Chemotherapy n=	102	91	71	54	44	33	25	17	5	2	0	0	0

[a] Chemotherapy: 5-FU 800 mg/m^2 IV for days 1-5 Q3W for ≤35 cycles + Cisplatin 80 mg/m^2 IW Q3W for ≤6 cycles.

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Options and Timing for PMR Confirmatory Studies

Ongoing Phase 3 Pembrolizumab Studies in Gastric Cancer

	KEYNOTE-859 N=1542	KEYNOTE-811 N=692	LEAP-015 N=790	KEYNOTE-585 N=1000
Study intervention	Pembro + chemo vs placebo + chemo	Pembro + trastuzumab + chemo vs placebo + trastuzumab + chemo	Lenvatinib + pembro + chemo vs chemo	Pembro + perioperative chemo vs placebo + perioperative chemo
Patient population	Unresectable or metastatic gastric or GEJ adenocarcinoma	Unresectable or metastatic gastric or GEJ adenocarcinoma	Unresectable or metastatic gastric or GEJ adenocarcinoma	Resectable gastric or GEJ adenocarcinoma
PD-L1 (CPS) status	All	All	All	All
HER2 status	Negative	Positive	Negative[a]	Positive or negative
Line of therapy	1L	1L	1L	Neoadjuvant/adjuvant
Enrollment status	> 95% complete	> 90% complete	Safety run-in ongoing	Fully enrolled
Study completion	3Q2024	1Q2024	4Q2024	2Q2024
Interim analyses planned	1	3	2	3
Primary endpoints	OS	PFS, OS	PFS, OS	pCR, EFS, OS

[a] Not known HER2 positive.

Summary

- In KEYNOTE-059, pembrolizumab provided clinically meaningful and durable responses with a manageable safety profile in the CPS ≥1, 3L+ setting
  - Including durable responses in CPS ≥1, MSS, TMB unknown and non-TMB-H
- Four ongoing, randomized, phase 3 trials (KN-859, KN-811, LEAP-015, and KN-585) have the potential to confirm the clinical benefit of pembrolizumab in gastric cancer within the next 1-3 years

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Concluding Remarks

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Summary

Patients with 3L+ gastric cancer have a poor prognosis and limited treatment options

- Pembrolizumab provides durable responses and has a manageable safety profile that is different from chemotherapy
- Tumor-agnostic indications in 2L (MSI-H, TMB-H) cover a small subset of the population

Merck is committed to fulfilling the KEYNOTE-059 Accelerated Approval requirements

- In line with FDA guidance, our confirmatory trials are intended to show benefit in a different, but related, population

Current 3L indication should remain until additional confirmatory data are available

- Patients may not be eligible for combination chemo-immunotherapy in 1L
- Totality of data supports the biological activity of pembrolizumab in gastric cancer