MERCK
INVENTING FOR LIFE

KEYTRUDA® (pembrolizumab)
KEYNOTE-522

U.S. Food & Drug Administration

Oncologic Drugs Advisory Committee

February 9, 2021

MERCK
INVENTING FOR LIFE

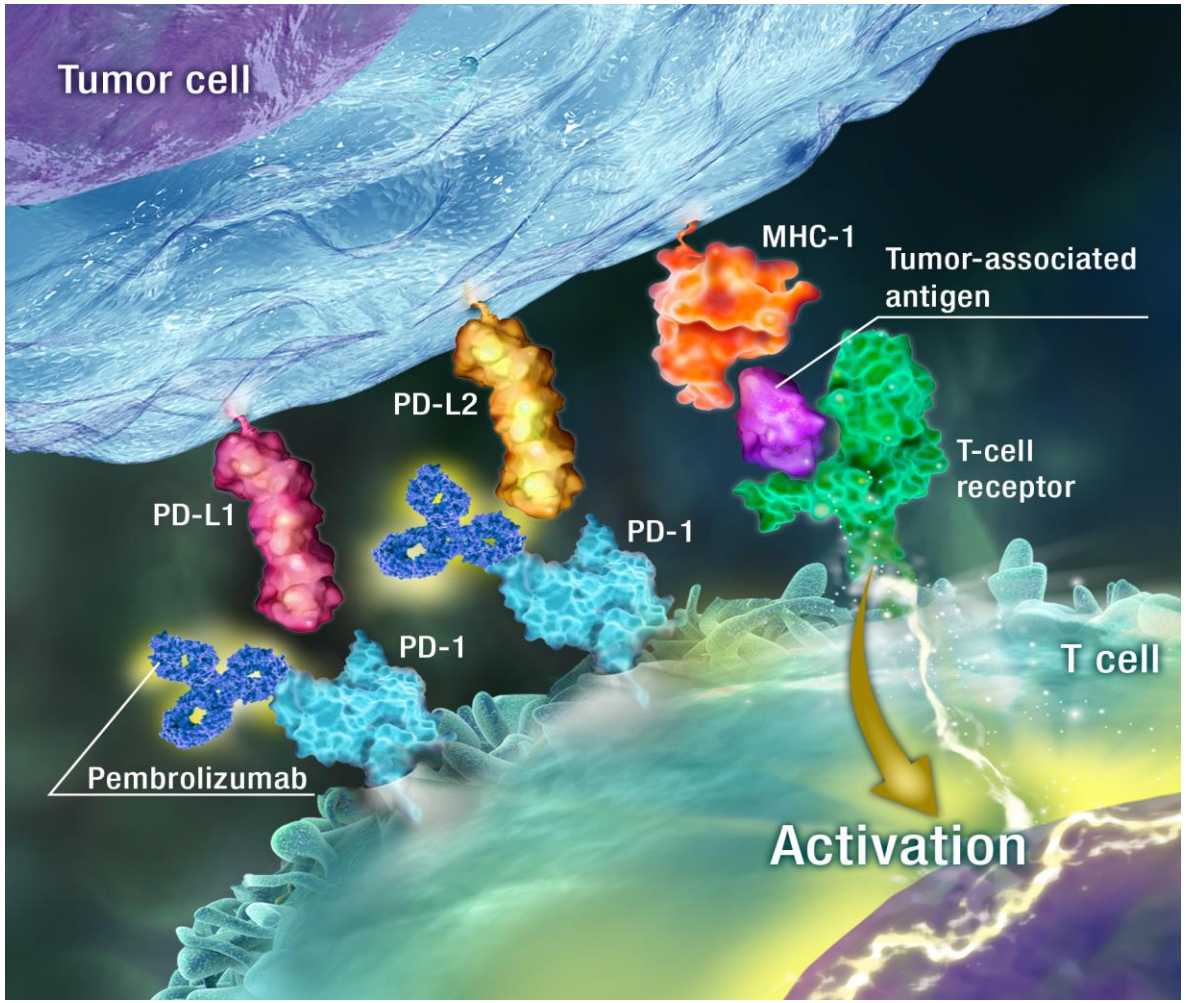
Introduction

Sunita Zalani, PhD

Vice President
Global Regulatory Affairs and Clinical Safety
Merck & Co., Inc

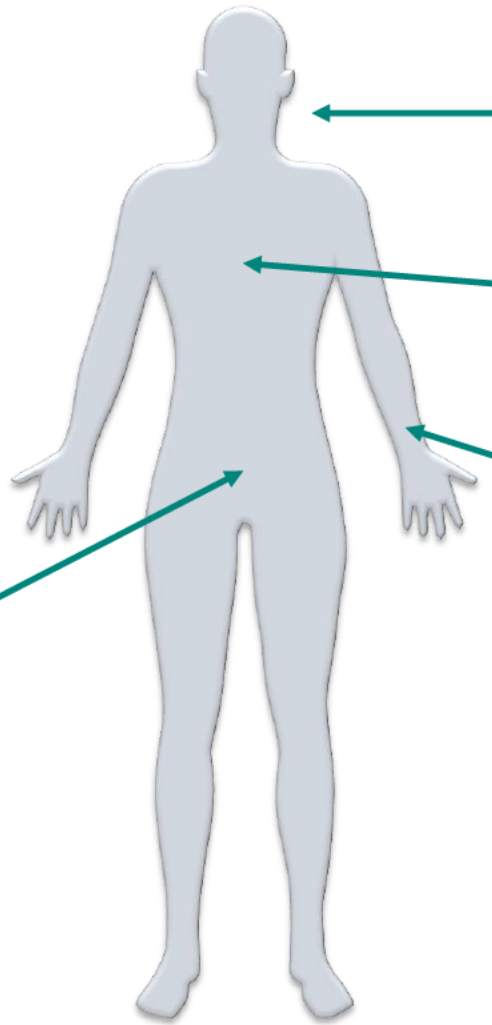
KEYTRUDA® (pembrolizumab)

- Humanized monoclonal antibody
- Blocks interaction between PD-1 and its ligands (PD-L1 and PD-L2)
- Approved in more than 90 countries



Iwai Y, et al. *Proc Natl Acad Sci U S A*. 2002;99(19):12293-12297.

KEYTRUDA® (pembrolizumab): FDA-Approved Cancer Types



- ✓ Urothelial carcinoma
- ✓ BCG-unresponsive non-muscle invasive bladder cancer
- ✓ Gastric cancer
- ✓ Hepatocellular carcinoma
- ✓ Cervical cancer
- ✓ Endometrial carcinoma
- ✓ Renal cell carcinoma

- ✓ **Head and neck squamous cell cancer**
- ✓ Esophageal cancer

- ✓ **Metastatic triple-negative breast cancer**
- ✓ **SQ Non-small cell lung cancer**
- ✓ **NSQ Non-small cell lung cancer**
- ✓ Small cell lung cancer

- ✓ Melanoma
- ✓ Merkel cell carcinoma
- ✓ Cutaneous squamous cell carcinoma

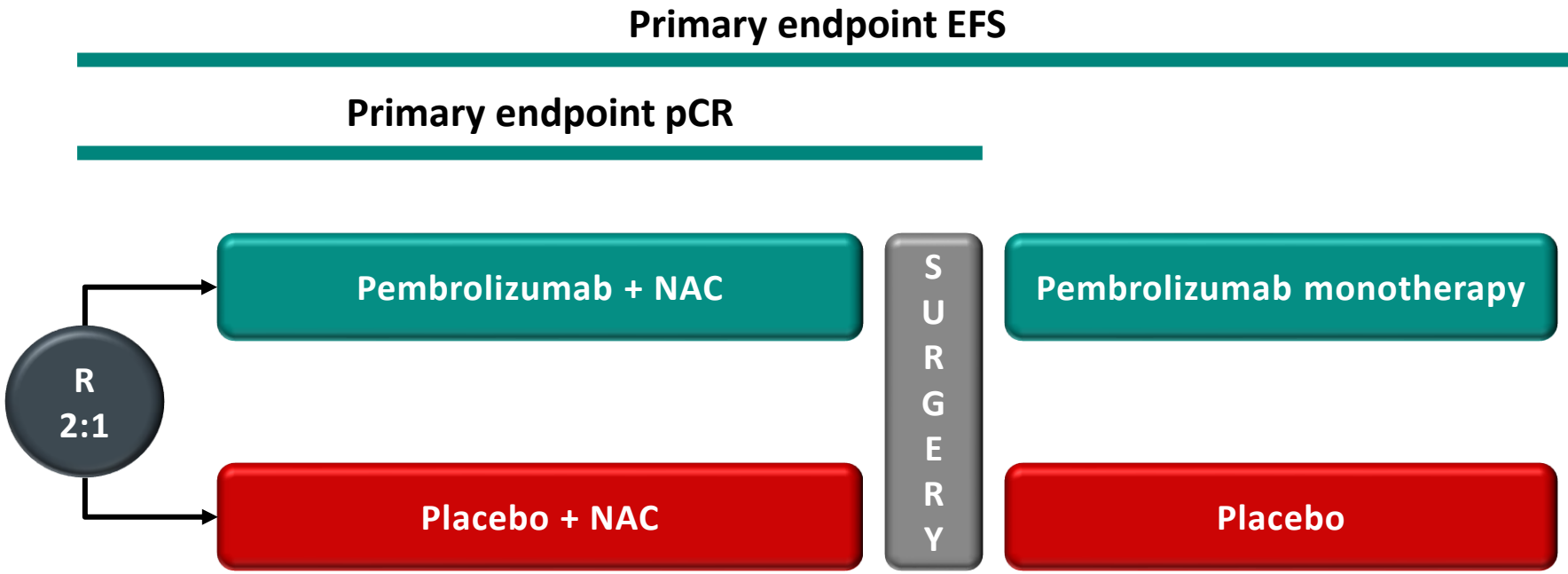
Other:

- ✓ Classic Hodgkin lymphoma
- ✓ Primary mediastinal large B-cell lymphoma
- ✓ Microsatellite instability-high cancers
- ✓ Tumor mutational burden (TMB)-high cancers

Keytruda USPI as of June 2020.

Rationale for Single-Study Approach

- KEYNOTE-522 has a single-study design (with 1 year of pembrolizumab as add-on to SOC before and after surgery)
- Short-term pathologic complete response (pCR) and long-term event-free survival (EFS) benefit evaluated in the same patient population



NAC=neoadjuvant chemotherapy.

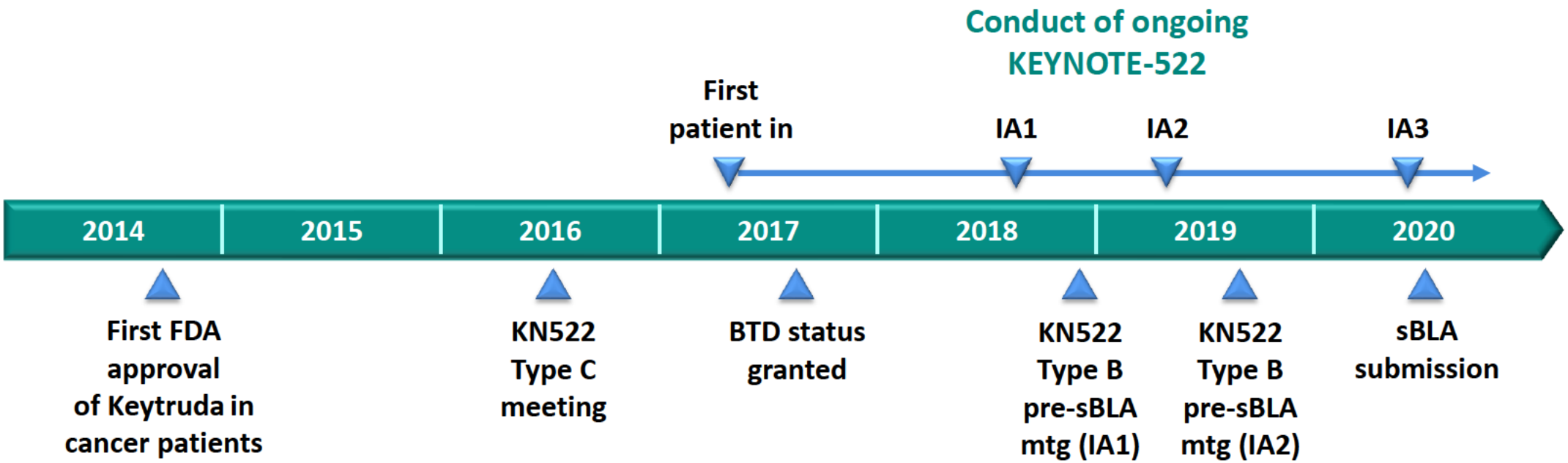
Proposed Indication

Proposed Indication

- *KEYTRUDA is indicated for the treatment of patients with high-risk early-stage triple-negative breast cancer (TNBC), in combination with chemotherapy as neoadjuvant treatment, then as a single agent as adjuvant treatment after surgery.*

- Request for Accelerated Approval

Regulatory Timeline for KEYNOTE-522



What You Will Hear Today

Unmet Medical Need	• TNBC has poor prognosis compared with other breast cancer subtypes • Patients who do not achieve a pCR following NAC have a particularly poor prognosis
Efficacy	• KN522 met the primary pCR endpoint, demonstrating a statistically significant improvement in pCR compared with NAC • Promising and stable effect on EFS observed at IA3
Safety	• Pembrolizumab plus NAC has a manageable safety profile • No new safety signals were identified
Benefit-Risk	• The data from KEYNOTE-522 support a favorable benefit/risk profile for the addition of pembrolizumab to NAC followed by continued pembrolizumab monotherapy as adjuvant treatment for high-risk, early-stage TNBC

Agenda

Introduction	**Sunita Zalani, PhD** Merck & Co., Inc.
Treatment Landscape and Unmet Need in TNBC	**Joyce O'Shaughnessy, MD** Baylor University Medical Center
Efficacy and Safety	**Vassiliki Karantza, MD, PhD** Merck & Co., Inc.
Clinical Perspective	**Hope S. Rugo, MD** University of California San Francisco
Moderator (Q&A)	**Vicki Goodman, MD** Merck & Co., Inc.

Consultants

Aditya Bardia, MD, MPH
Massachusetts General Hospital
Dana-Farber/Harvard Cancer Center

Don Berry, PhD
Professor, Department of Biostatistics
The University of Texas M.D. Anderson Cancer Center

Treatment Landscape and Unmet Need in TNBC

Joyce O'Shaughnessy, MD

Celebrating Women Chair in Breast Cancer Research
Baylor University Medical Center
Chair, Breast Cancer Program
Texas Oncology
US Oncology Research

Triple-Negative Breast Cancer (TNBC) Is a Virulent Subtype Associated With Early Onset and Increased Risk of Early Recurrence

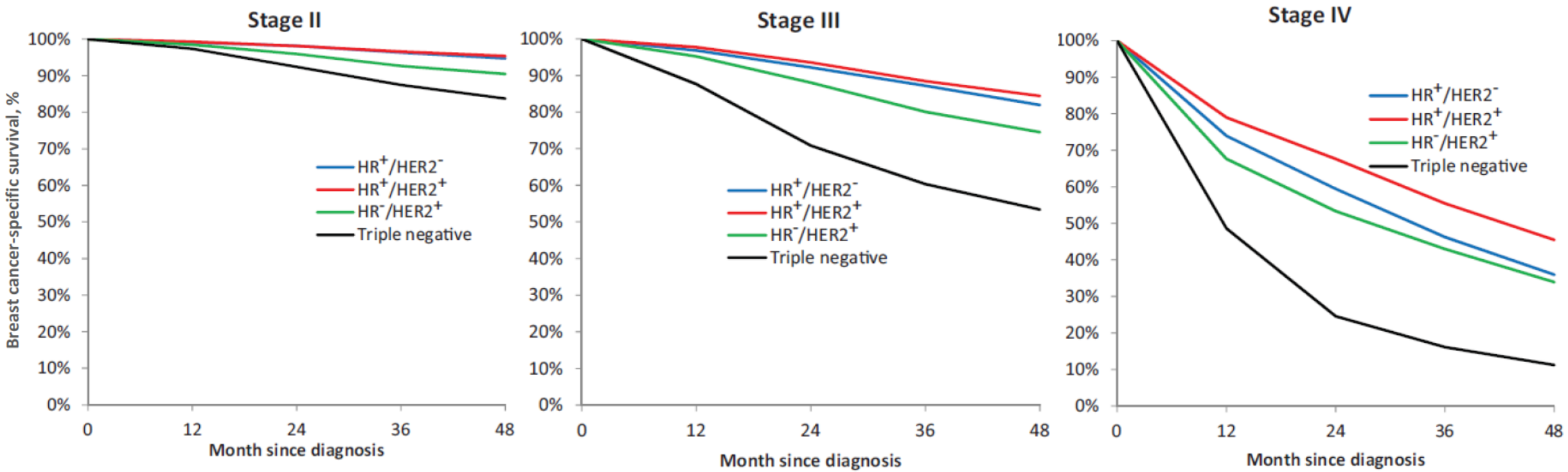
- TNBC accounts for 15% to 20% of breast cancers[a,b]

Region	New cases	Deaths
Worldwide[c]	~420,000	~150,000
United States[d]	~56,000	~10,000

- Higher risk in premenopausal and African-American women[e,f,g]
- At diagnosis
  - Majority of tumors (~70%) are histologically grade 3 and highly proliferative[h]
  - Majority diagnosed at stage II (43%) or stage III (19%)
- Recurs 1 to 3 years following diagnosis in lungs, liver, and brain

[a] Arnedos M, et al. *Ther Adv Med Oncol*. 2012;4(4):195-210; [b] Bauer KR, et al. *Cancer*. 2007;109(9):1721-8; [c] Bray F, et al. *CA Cancer J Clin*. 2018;68:394-424; [d] Siegel RL, et al. *CA Cancer J Clin*. 2020;70:7-30; [e] Sajid MT, et al. *J Coll Physicians Surg Pak*. 2014;24(6):400-403; [f] Jitariu AA, et al. *Oncotarget*. 2017;8(28):46652-46662; [g] Dietze EC, et al. *Nat Rev Cancer*. 2015;15(4):248-254; [h] Urru SAM, et al. *BMC Cancer*. 2018;18(1):56.

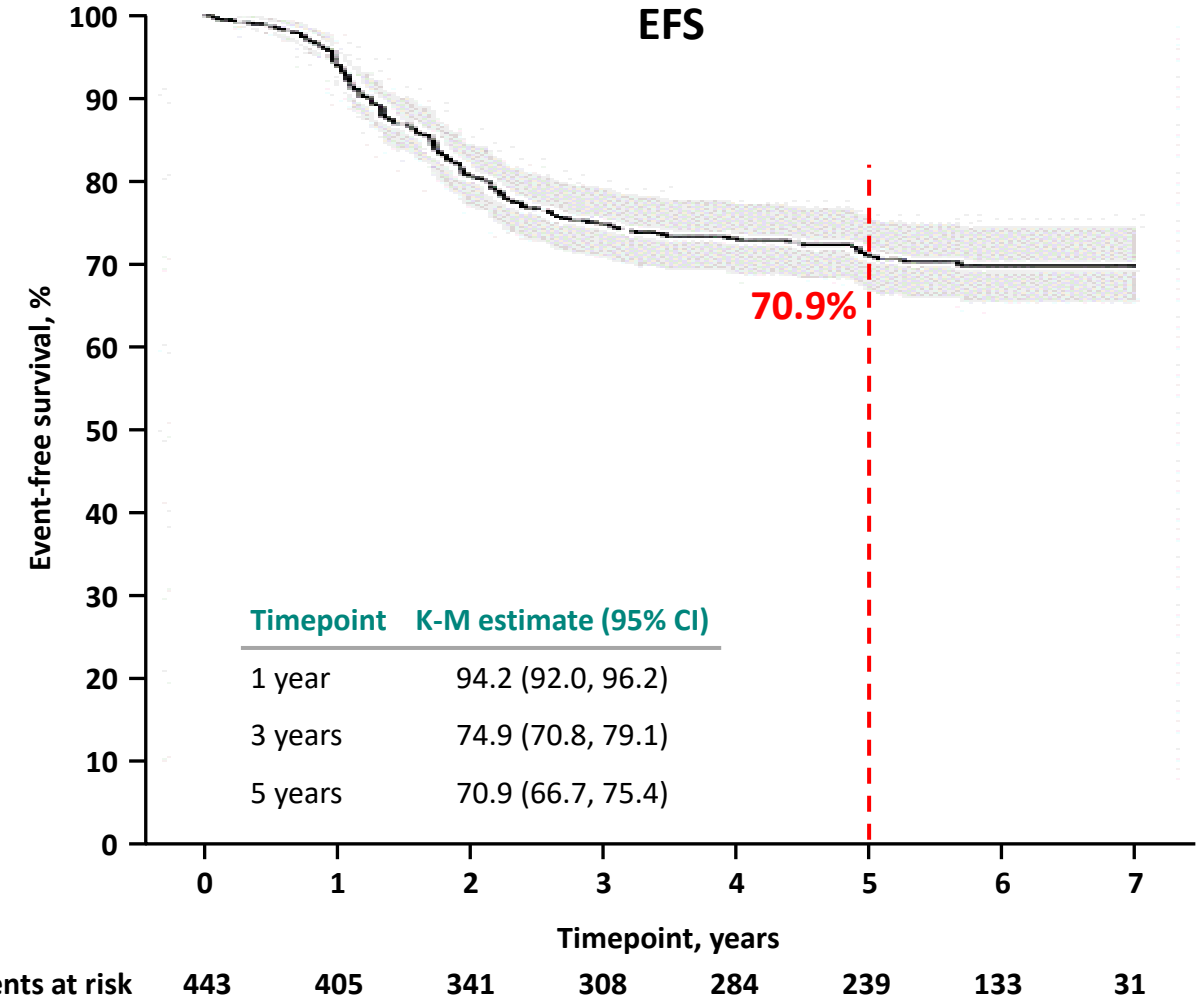
TNBC Is Associated With Shorter Overall Survival Compared With Other Subtypes Despite Anthracycline and Taxane Systemic Therapy

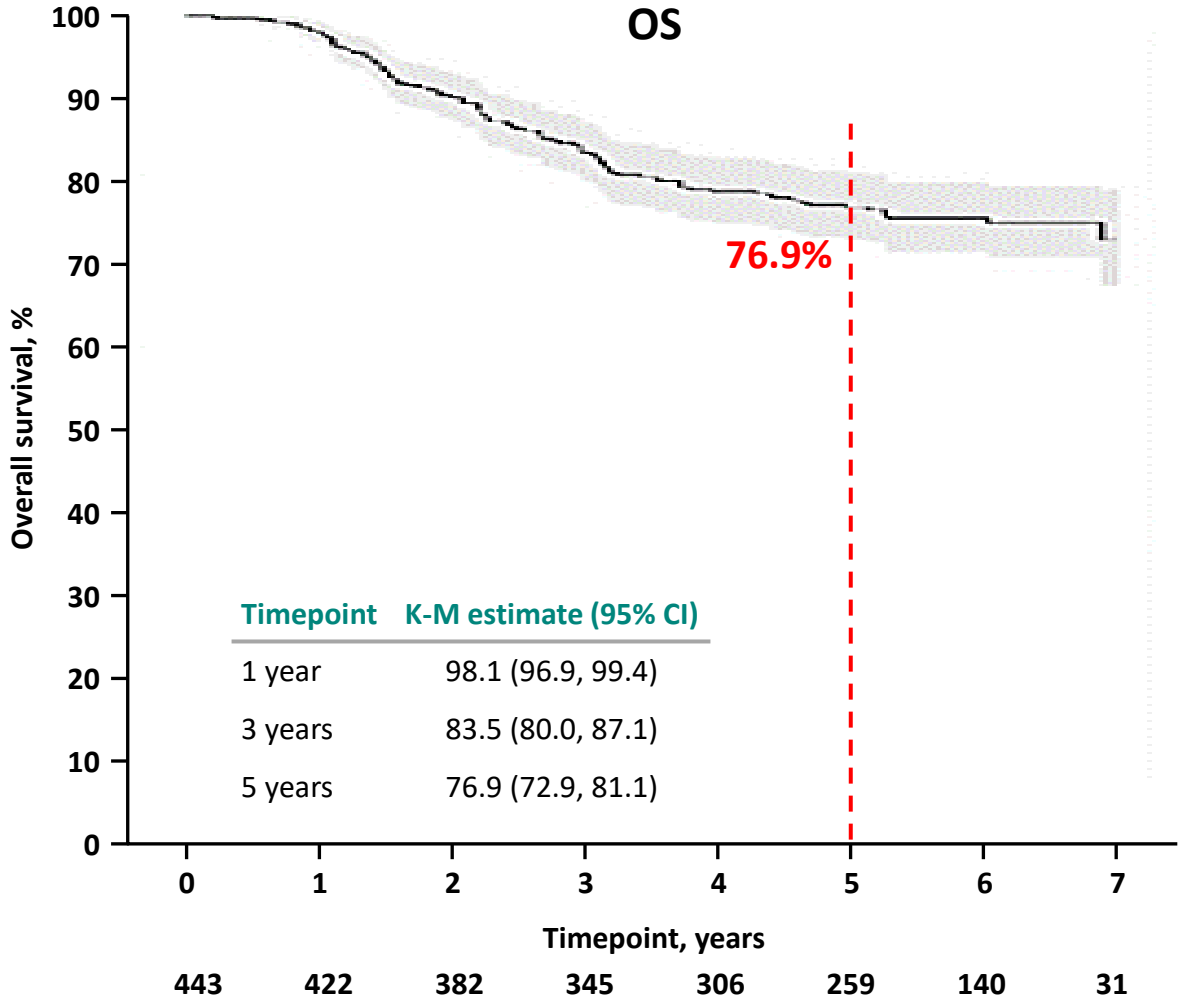


Howlader N, et al. *Cancer Epidemiol Biomarkers Prev*. 2018;27(6):1-8; Bauer KR, et al. *Cancer*. 2007;109(9):1721-1728.

High-Risk TNBC Associated With 71% Event-Free Survival at 5 Years

CALGB 40603





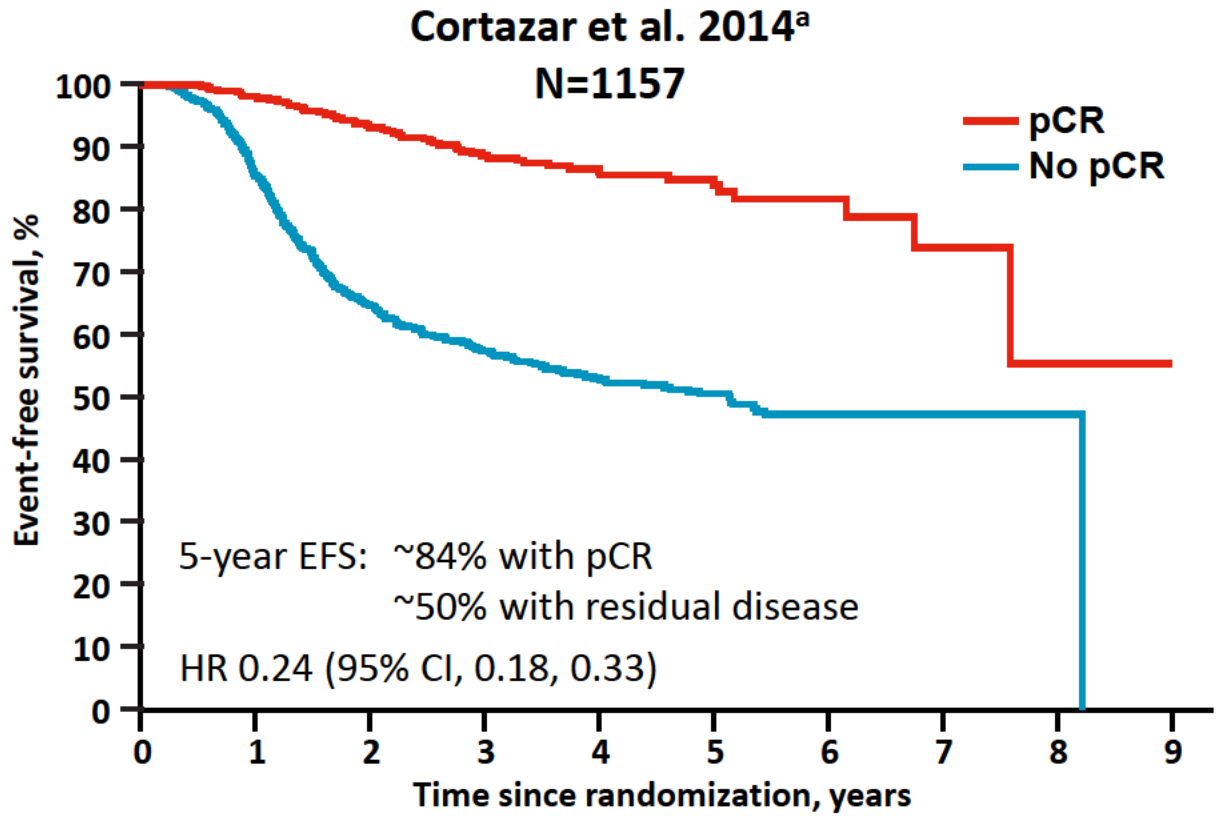
Sikov WM, et al. Presented at ASCO 2019; abstract 591.

NCCN and ESMO Guidelines Recommend Use of Standard Cytotoxic Chemotherapy for High-Risk, Early-Stage TNBC

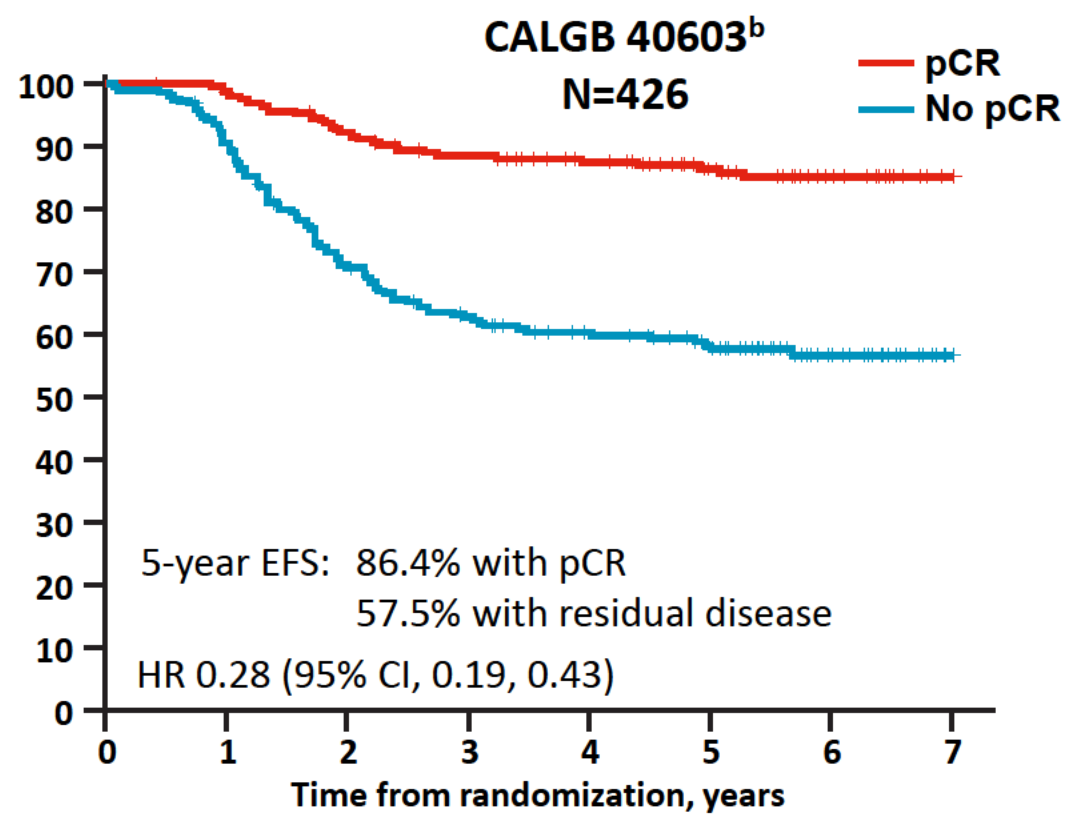
- Chemotherapy is mainstay of curative therapy recommended by guidelines[a,b,e]
- Preferred neoadjuvant regimens[b,e]
  - Doxorubicin/cyclophosphamide followed by a taxane
  - Docetaxel and cyclophosphamide
- Commonly used anthracycline/taxane-based regimens yield **30%-40%** pCR rates[c,d,f,g]
- Adding carboplatin to anthracycline/taxane regimen increases pCR rate to **~50%**[h-j]

[a] Cardoso F, et al. *Ann Oncol*. 2019;30(8):1194-1220; [b] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Breast Cancer. Version 3.2020. March 6, 2020;
[c] Santonja A, et al. *Oncotarget*. 2018;9(41):26406-26416; [d] Cortazar P, et al. *Lancet*. 2014;384(9938):164-172; [e] Cardoso F, et al. *Ann Oncol*. 2018;29(8):1634-1657;
[f] Schilling J, et al. *Curr Med Res Opin*. 2019;35(8):1405-1414; [g] Rhodes WC, et al. Poster presented at: San Antonio Breast Cancer Symposium 2019; December 10-14, 2019; San Antonio, TX;
[h] Loibl S, et al. *Lancet Oncol*. 2018;19(4):497-509; [i] Sikov W, et al. *J Clin Oncol*. 2015;33(1):13-21; [j] von Minckwitz G, et al. *Lancet Oncol*. 2014;15(7):747-756.

Poor Prognosis in High-Risk, Early-Stage TNBC With Residual Disease After Neoadjuvant Chemotherapy



Number at risk									
pCR	389	349	310	250	166	88	29	11	1
No pCR	768	604	429	317	198	125	50	13	1



Number at risk								
pCR	205	201	185	174	164	139	78	17
No pCR	221	199	153	132	117	38	54	14

[a] Cortazar P, et al. *Lancet*. 2014;384:164-172; [b] Sikov WM, et al. Presented at ASCO 2019 Abstract 591.

Association Between pCR and EFS in Breast Cancer

	EFS hazard ratio (95% CI) for pCR vs no pCR			
Population	**I-SPY2[a]**	**Meta analysis[b]**	**CALGB 40603[c]**	**Meta analysis[d]**
Overall	0.19 (0.12, 0.31)	0.48 (0.43, 0.54)		
HR positive, HER2 negative	0.14 (0.03, 0.55)	0.49 (0.33, 0.71)		
HER2 positive	0.14 (0.05, 0.41)[e]	0.39 (0.31, 0.50)		
Triple negative	**0.18 (0.09, 0.34)**	**0.24 (0.18, 0.33)**	**0.28 (0.19, 0.43)**	**0.26 (0.22, 0.30)**

Regulatory guidance supports the use of pCR as an endpoint for accelerated approval of neoadjuvant therapy in high-risk, early-stage breast cancer, including TNBC[f,g]

[a] I-SPY2 Trial Consortium. *JAMA Oncol*. 2020;6(9):1355-1362; [b] Cortazar P, et al. *Lancet*. 2014;384:164-172; [c] Sikov WM, et al. Presented at ASCO 2019, Abstract 591;
[d] Huang M, et al. *Cancer Res.* 2020. Epub ahead of print; [e] HR-negative, HER2-positive; [f] US FDA Guidance for industry: Pathologic Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval. July 2020; [g] European Medicines Agency. Committee for Medicinal Products for Human Use. The Role of the Pathological Complete Response as an Endpoint in Neoadjuvant Breast Cancer Studies. London, UK. 2014. publication 151853/2014.

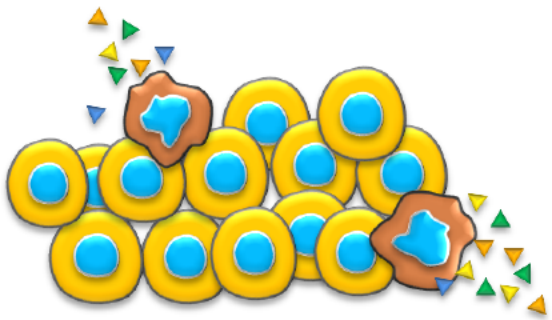
Rationale for Immunotherapy in TNBC

- Higher PD-L1 expression
  - ~50% in TNBC vs ~20%-30% in other BC subtypes[a,b]
  - ~85% in early-stage, high-risk TNBC[c,d]
- Increased tumor-infiltrating lymphocytes (TILs)
  - 70%-77% in TNBC vs 25%-44% in other BC subtypes[b,e,f]
- Immune cell infiltrates associated with pCR in pembrolizumab arm of I-SPY2[d]

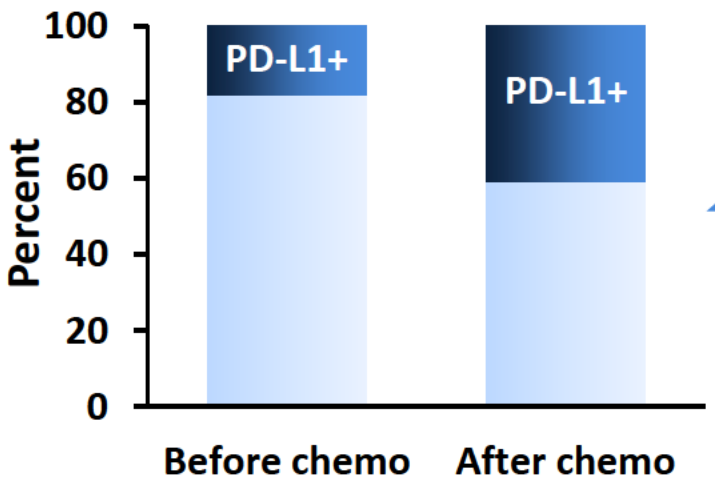
[a] Basu GD, et al. *J Clin Oncol*. 2014;32(15 suppl):1001; [b] Gatalica Z, et al. *Cancer Epidemiol Biomarkers Prev*. 2014;23(12):2965-2970; [c] Schmid P, et al. *N Engl J Med*. 2020;382:810-821;
[d] Campbell MJ, et al. Presented at: American Association for Cancer Research (AACR) Annual Meeting 2019; March 29-April 3, 2019; Atlanta, GA. Abstract CT003;
[e] Muenst S, et al. *Breast Cancer Res Treat*. 2013;139(3):667-676; [f] Loi, S, et al. *J Clin Oncol*. 2019;37:559-569.

Rationale for Combining Pembrolizumab With Chemotherapy

- Chemotherapy results in:

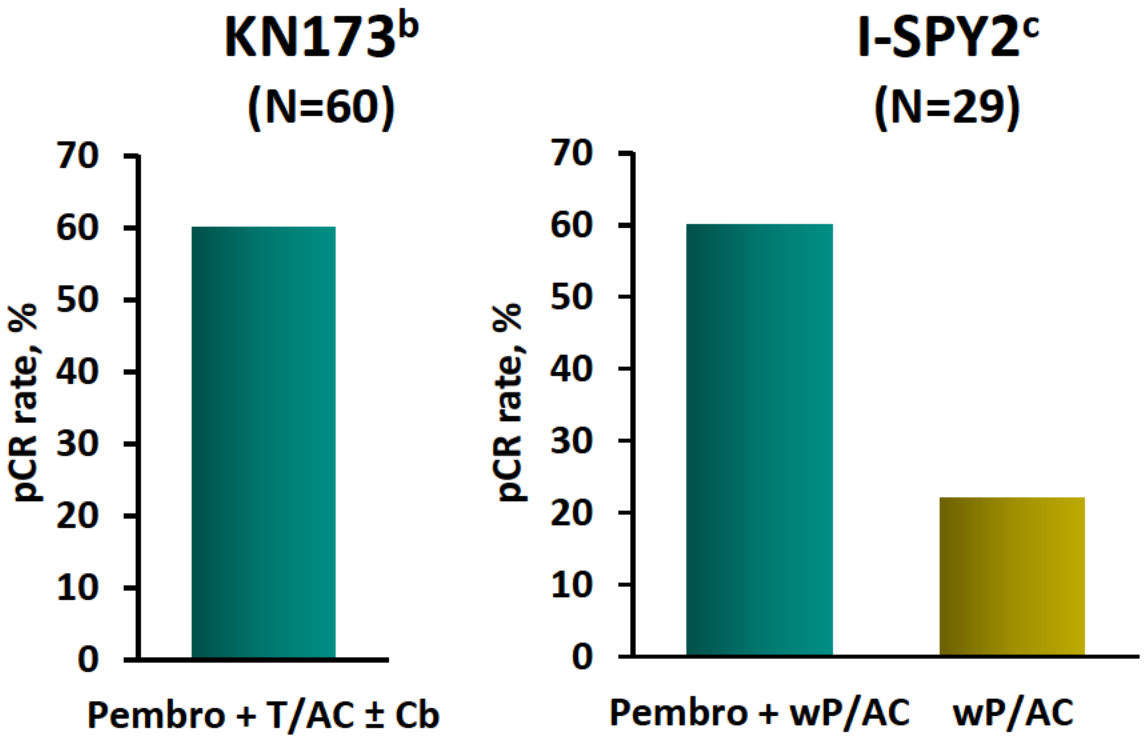


Tumor lysis and antigen shedding[a]



PD-L1 expression[d]

- Pembrolizumab plus standard neoadjuvant chemotherapy in TNBC



pCR=pathologic complete response as defined as ypT0/Tis ypN0; TNBC=triple-negative breast cancer; PAC=paclitaxel, doxorubicin, cyclophosphamide.

[a] Economopoulou P, et al. *Ann Oncol*. 2016;27:1675-1685; [b] Schmid P, et al. *Ann Oncol*. 2020;31:569-581; [c] Nanda R, et al. *JAMA Oncol*. 2020;6(5):1-9. Epub ahead of print; [d] Bailly C, et al. *NAR Cancer*. March 2020;2(1).

Summary

- Patients with high-risk, early-stage TNBC have a worse prognosis and treatment options are limited to chemotherapy
  - Platinum-containing neoadjuvant regimens associated with highest pCR rates (~50%)
- Short-term goal of neoadjuvant therapy is pCR, which is associated with improved EFS and OS
- Long-term goal of neoadjuvant + adjuvant therapy in TNBC is improved EFS and OS
- High unmet need for novel therapies that can augment effectiveness of chemotherapy
- Strong rationale for combination of immunotherapy and chemotherapy in TNBC
- Clinical trials have shown that pembrolizumab substantially improves pCR rates when combined with standard neoadjuvant chemotherapy

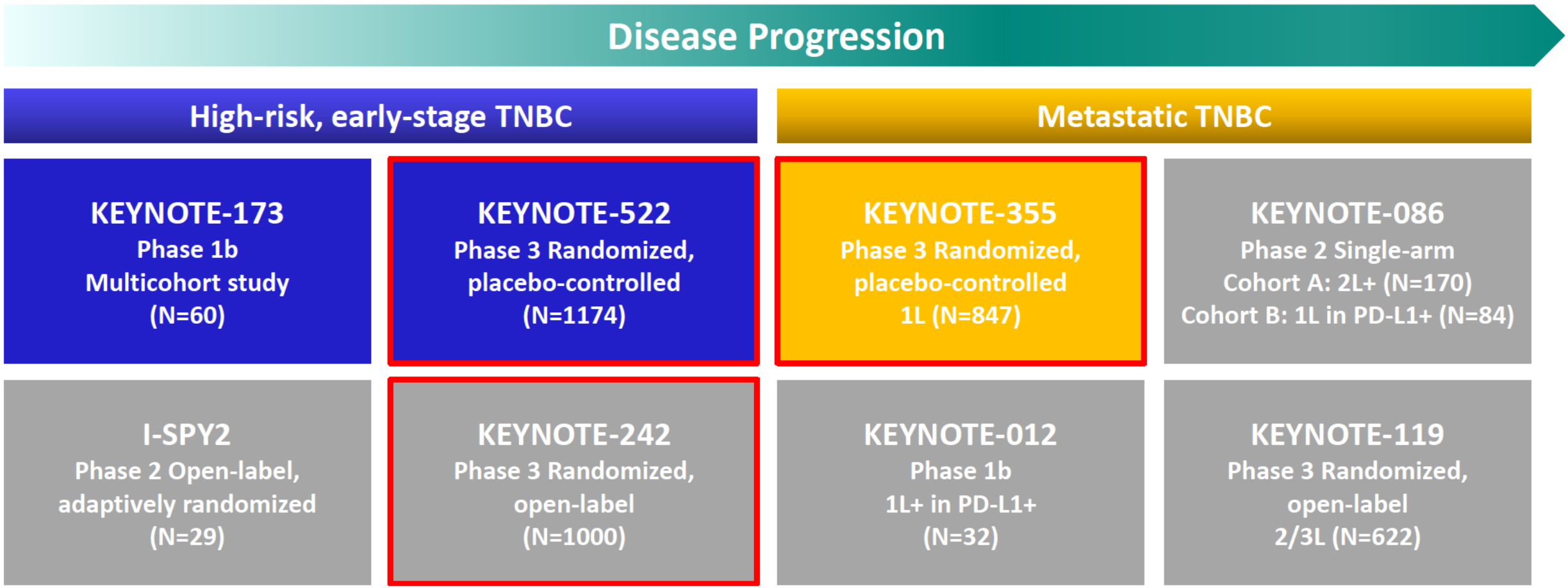
MERCK
INVENTING FOR LIFE

Efficacy and Safety

Vassiliki Karantza, MD, PhD

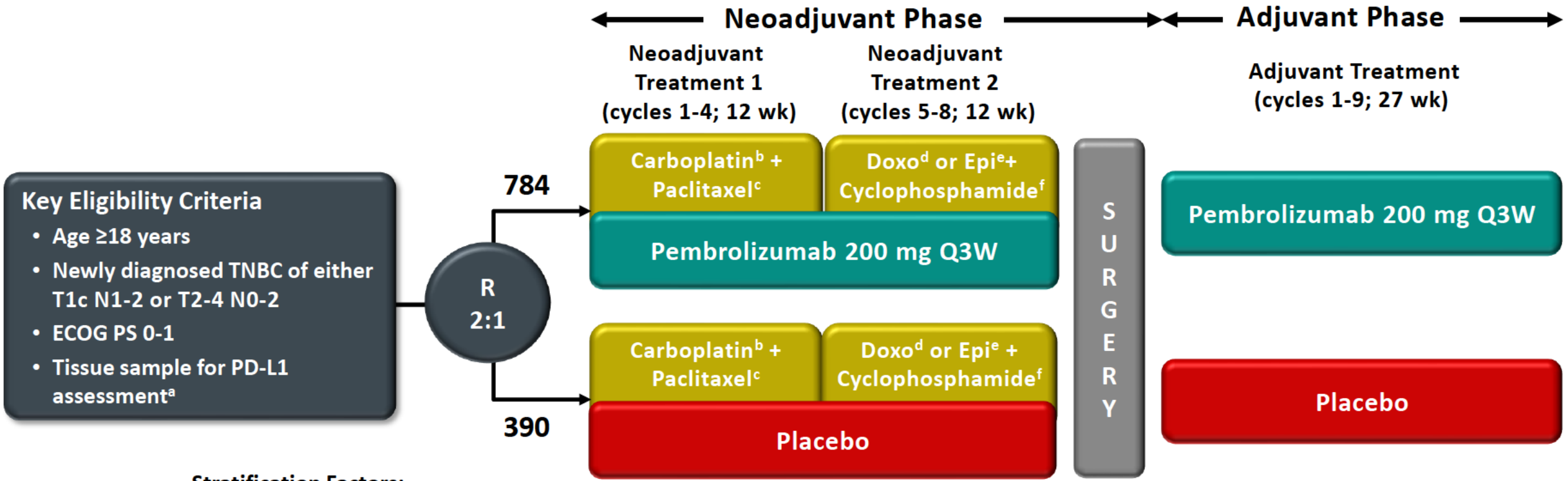
Women's Cancers – Sub-Section Head for Breast Cancer
Associate Vice President – Global Clinical Development
Merck & Co., Inc.

Clinical Development Program in TNBC



Study Design: One Year of Pembrolizumab Add-on to Standard of Care Treatment Before and After Surgery

KEYNOTE-522



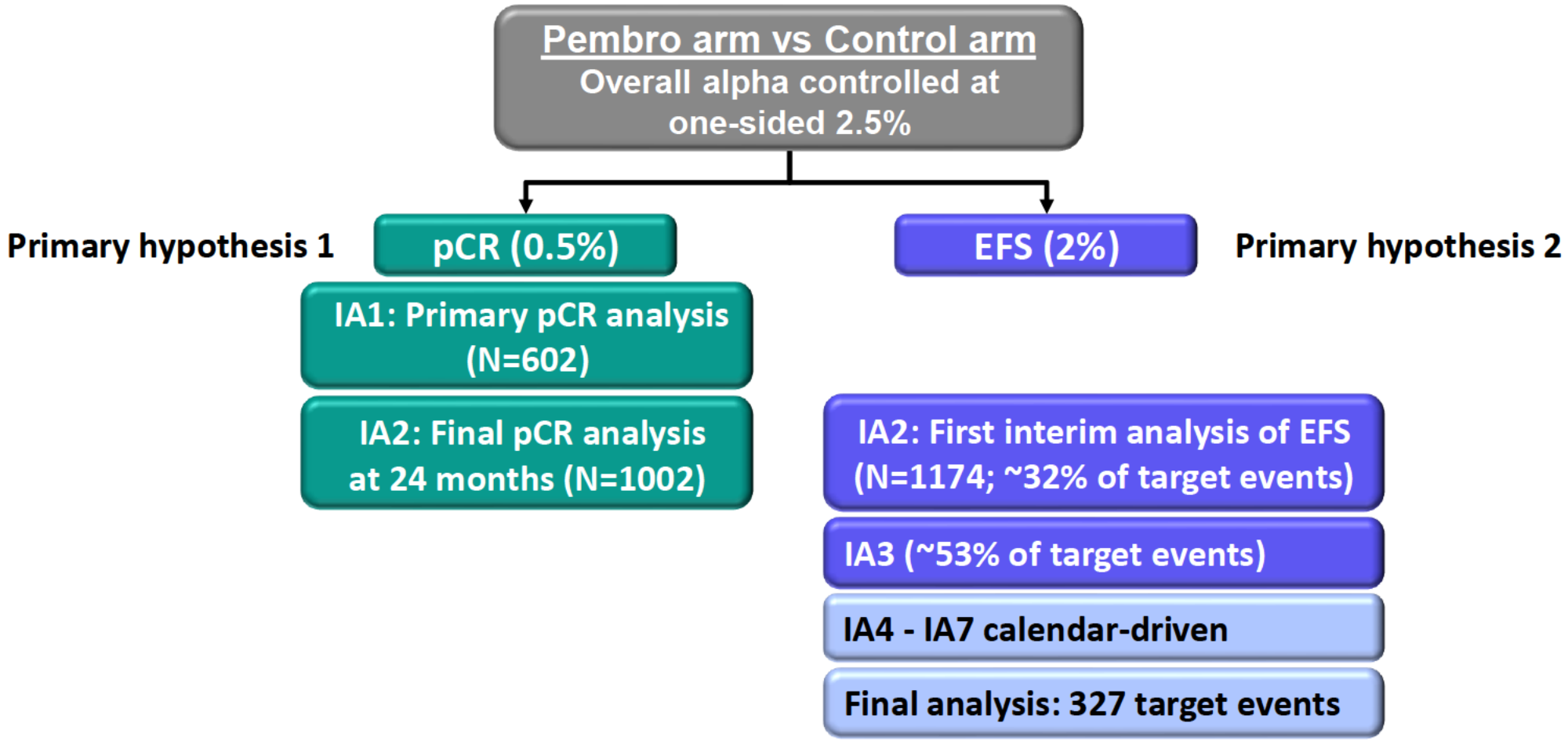
Stratification Factors:
- Nodal status (+ vs –)
- Tumor size (T1/T2 vs T3/T4)
- Carboplatin schedule (QW vs Q3W)

Dual Primary Endpoints
- Pathological Complete Response (pCR) (ypT0/Tis ypN0) assessed by blinded local pathologist
- Event-Free Survival (EFS) assessed by investigator

[a] Must consist of at least 2 separate tumor cores from the primary tumor; [b] Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW;
[c] Paclitaxel dose was 80 mg/m² QW; [d] Doxorubicin dose was 60 mg/m² Q3W; [e] Epirubicin dose was 90 mg/m² Q3W; [f] Cyclophosphamide dose was 600 mg/m² Q3W.

Prespecified Statistical Analysis Plan and Hypothesis Testing

KEYNOTE-522



The timings for IAs in EFS are calendar-driven and final analysis of EFS is event-driven; IA1-IA3 have occurred.

Baseline Characteristics

KEYNOTE-522 ITT Population

Characteristic, n (%)		Patients, n (%) Pembro + Chemo/Pembro N=784	Patients, n (%) Placebo + Chemo/Placebo N=390
Median age, yr (range)		49 (22-80)	48 (24-79)
ECOG PS 1		106 (13.5)	49 (12.6)
PD-L1 (CPS ≥1)[a]		656 (83.7)	317 (81.3)
PD-L1 (CPS ≥10)[a]		393 (50.1)	177 (45.4)
Carboplatin schedule	QW	449 (57.3)	223 (57.2)
	Q3W	335 (42.7)	167 (42.8)
Tumor size	T1/T2	580 (74.0)	290 (74.4)
	T3/T4	204 (26.0)	100 (25.6)
Nodal involvement	Positive	405 (51.7)	200 (51.3)
	Negative	379 (48.3)	190 (48.7)
Overall stage	II	590 (75.3)	291 (74.6)
	III	194 (24.7)	98 (25.1)

[a] PD-L1 assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay and measured using the combined positive score (CPS; number of PD-L1–positive tumor cells, lymphocytes, and macrophages divided by total number of viable tumor cells × 100). Data cutoff date: March 23, 2020.

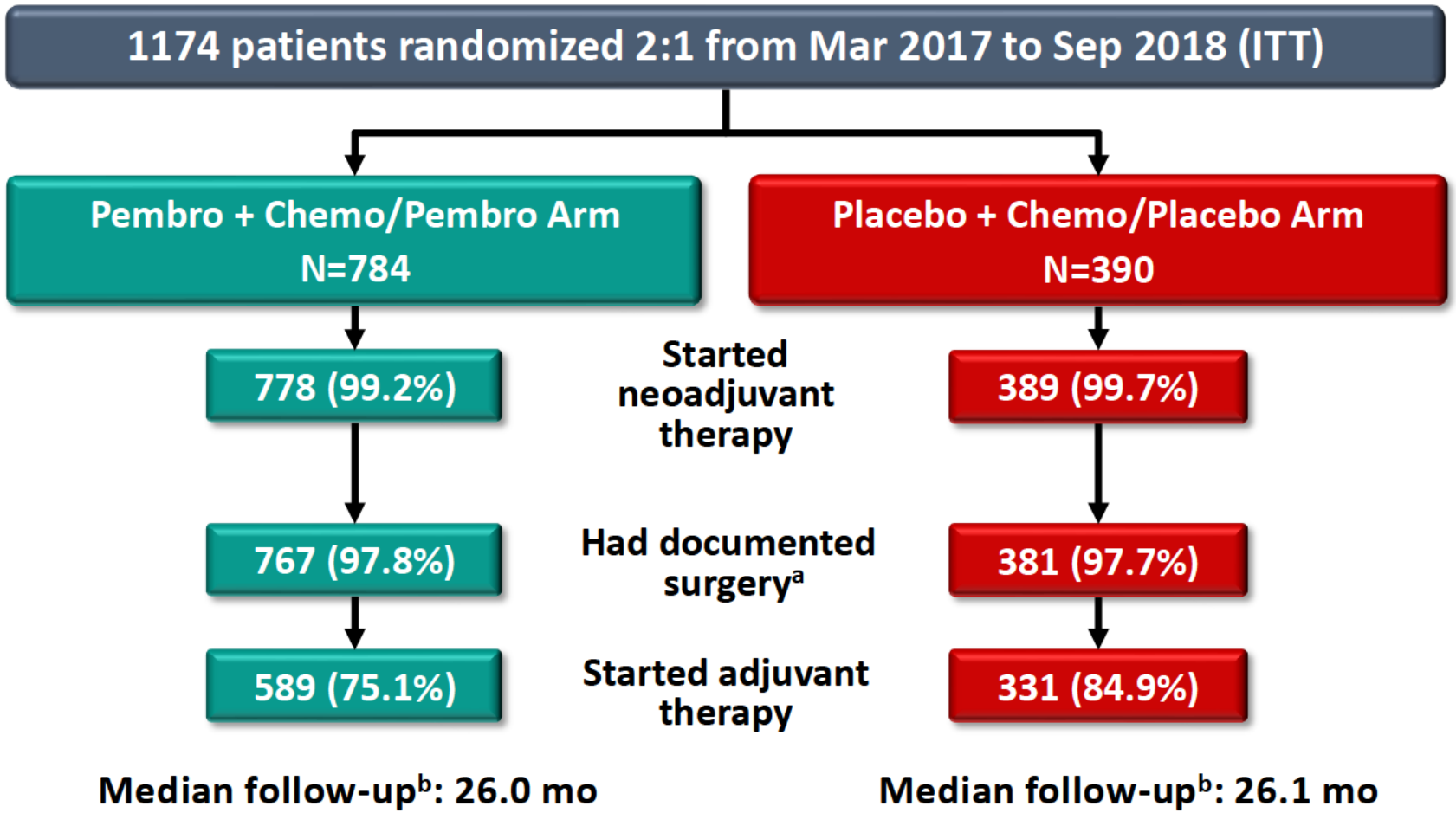
Baseline Demographics

KEYNOTE-522 ITT Population

Characteristic, n (%)	Patients, n (%)	
	Pembro + Chemo/Pembro N=784	Placebo + Chemo/Placebo N=390
Race		
American Indian or Alaska Native	14 (1.8)	7 (1.8)
Asian	149 (19.0)	89 (22.8)
Black or African American	38 (4.8)	15 (3.8)
Multiple	13 (1.7)	6 (1.5)
Native Hawaiian/Pacific Islander	1 (0.1)	0
White	504 (64.3)	242 (62.1)
Missing	65 (8.3)	31 (7.9)
Geographic region		
Asia	166 (21.2)	91 (23.3)
Europe	388 (49.5)	180 (46.2)
Australia	23 (2.9)	16 (4.1)
North America	166 (21.2)	78 (20.0)
Rest of the World	41 (5.2)	25 (6.4)

Summary of Study Treatment and Analysis Populations: IA3

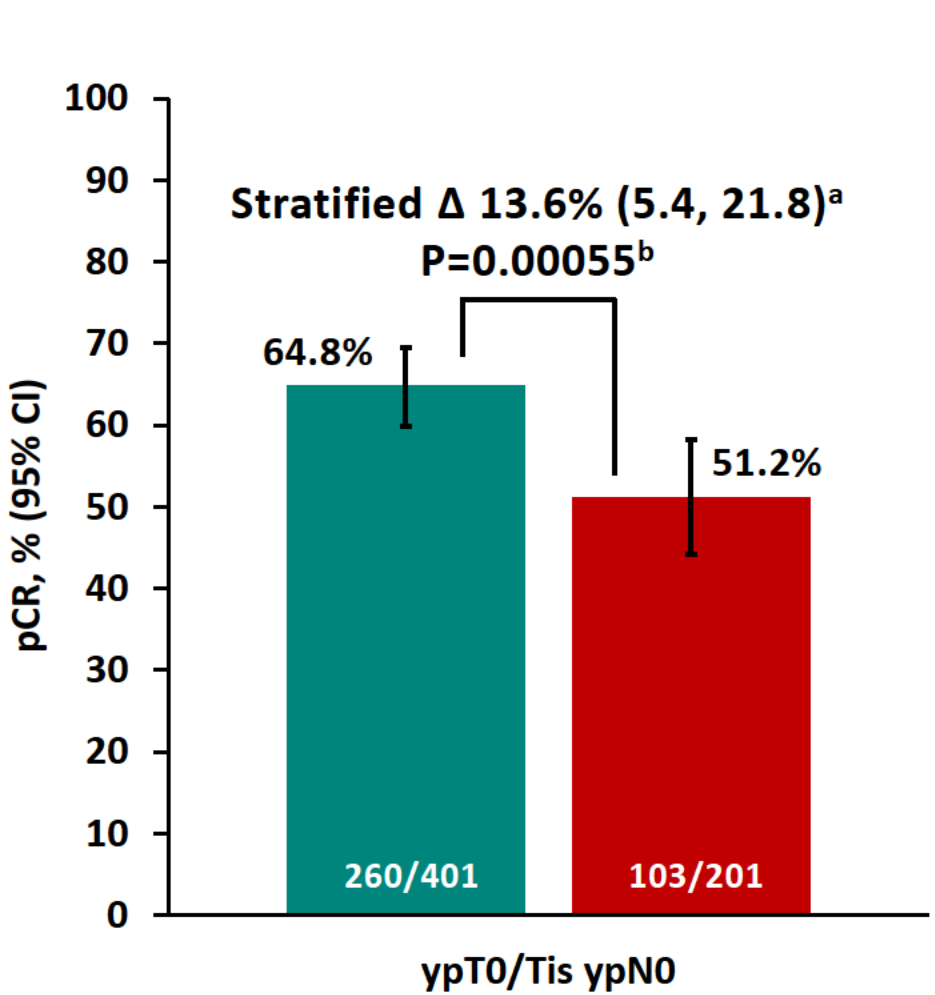
KEYNOTE-522

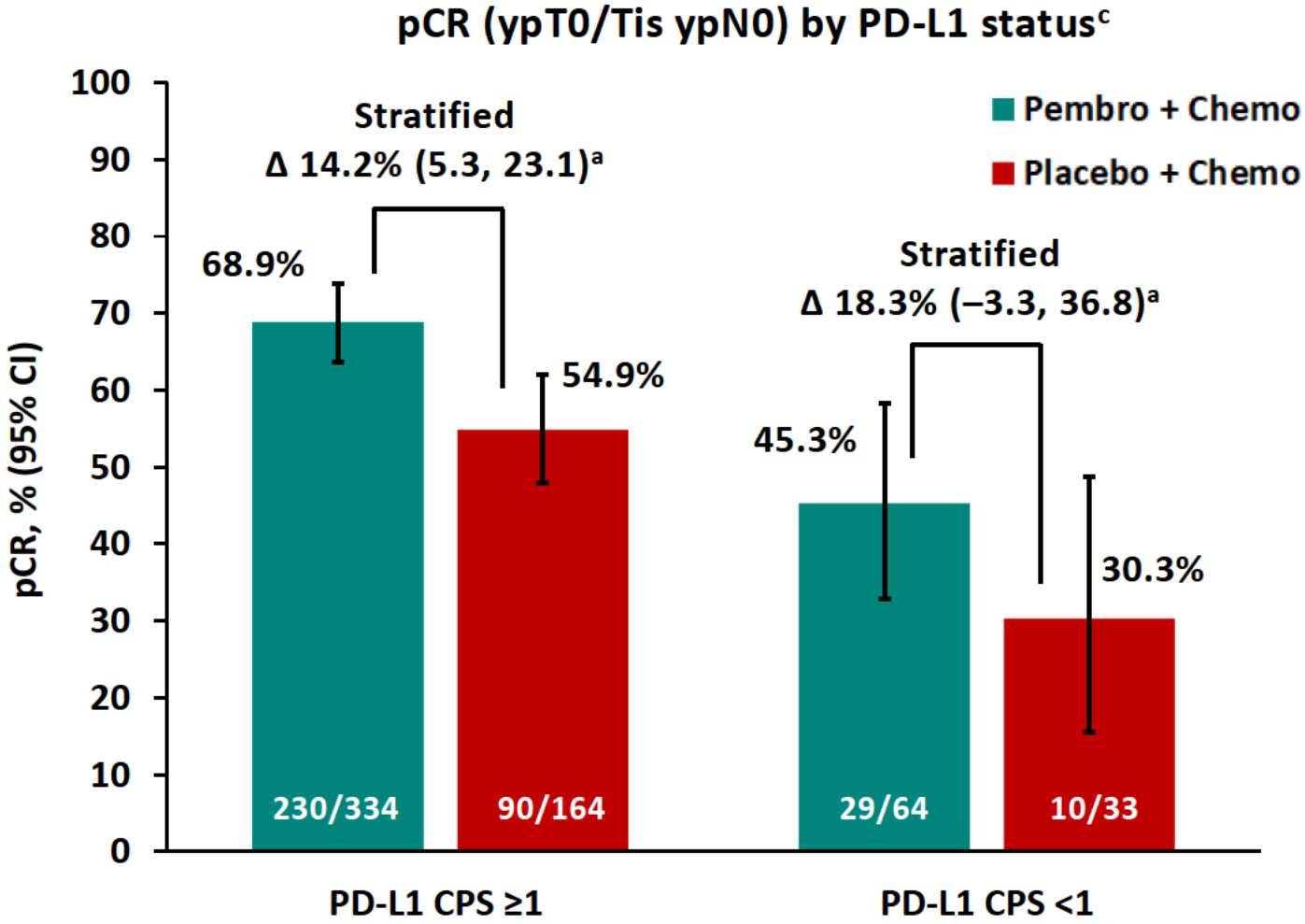


[a] Patients did not have to complete all neoadjuvant therapy to undergo surgery; 4 patients did not start neoadjuvant therapy but had documented surgery.
[b] Defined as the time from randomization to the date of death or database cutoff date of March 23, 2020, if the patient was alive.

Primary Endpoint of pCR at IA1 → Primary Analysis for pCR (N=602)

KEYNOTE-522



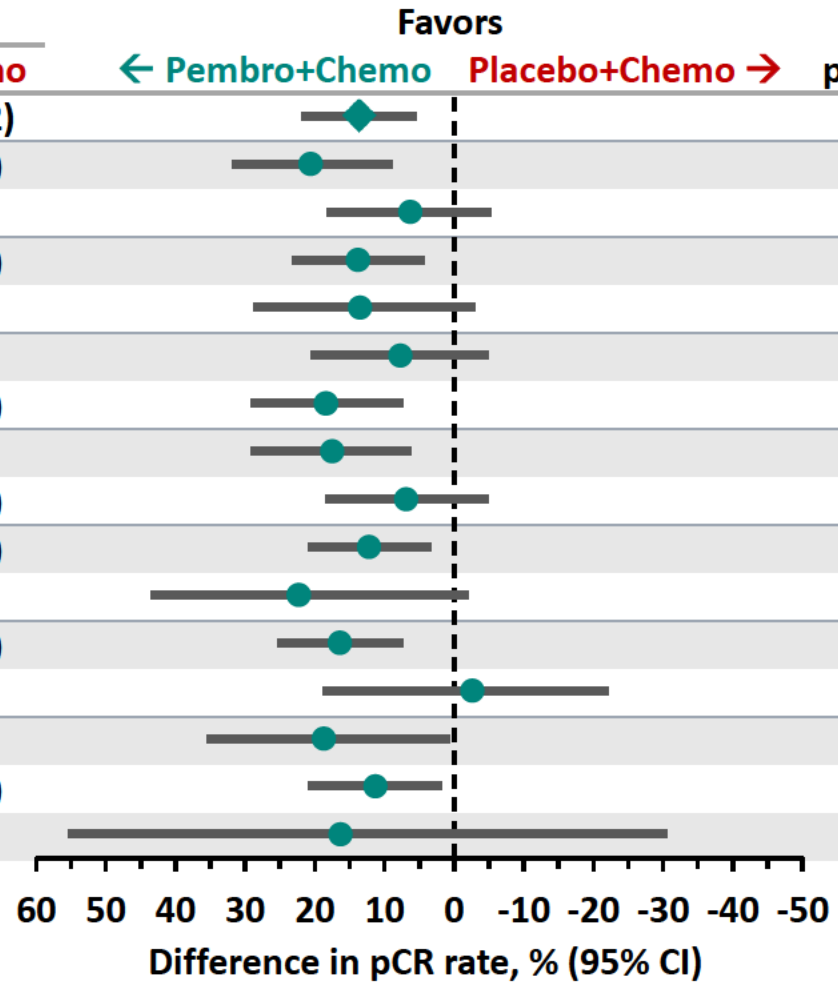


[a] Estimated treatment difference based on Miettinen & Nurminen method stratified by randomization stratification factors; [b] Pre-calculated P value boundary for significance of 0.003.
[c] Seven subjects with unknown PD-L1 status were not included. Data cutoff date: September 24, 2018.

Pathological Complete Response at IA1 by Subgroup

KEYNOTE-522

Subgroup		With pCR, n/participants (%) Pembro+Chemo	With pCR, n/participants (%) Placebo+Chemo	Difference in pCR rate, % (95% CI)
Overall		**260/401 (64.8)**	**103/201 (51.2)**	**13.6 (5.4, 21.8)**
Nodal status	Positive	136/210 (64.8)	45/102 (44.1)	20.6 (8.9, 31.9)
	Negative	124/191 (64.9)	58/99 (58.6)	6.3 (-5.3, 18.2)
Tumor size	T1/T2	207/295 (70.2)	84/149 (56.4)	13.8 (4.3, 23.3)
	T3/T4	53/106 (50.0)	19/52 (36.5)	13.5 (-3.1, 28.8)
Carboplatin schedule	Every 3 weeks	105/165 (63.6)	47/84 (56.0)	7.7 (-5.0, 20.6)
	Weekly	154/231 (66.7)	56/116 (48.3)	18.4 (7.4, 29.1)
PD-L1 CPS cutoff	≥10	162/208 (77.9)	55/92 (59.8)	17.5 (6.2, 29.1)
	<10	97/190 (51.1)	45/105 (42.9)	6.9 (-4.9, 18.5)
Age category	<65 years	235/355 (66.2)	95/176 (54.0)	12.2 (3.4, 21.0)
	≥65 years	25/46 (54.3)	8/25 (32.0)	22.3 (-2.1, 43.5)
ECOG PS	0	215/328 (65.5)	85/173 (49.1)	16.4 (7.3, 25.4)
	1	45/73 (61.6)	18/28 (64.3)	-2.6 (-22.1, 18.9)
Geographic region	Asia	44/75 (58.7)	20/50 (40.0)	18.7 (0.7, 35.4)
	EU/Israel/N Am/Australia	207/310 (66.8)	81/146 (55.5)	11.3 (1.8, 20.9)
	Rest of world	9/16 (56.3)	2/5 (40.0)	16.3 (-30.5, 55.4)



For the overall population and PD-L1 subgroup, analysis was based on Miettinen and Nurminen method stratified by randomization stratification factors.
For other subgroups, analysis was based on unstratified Miettinen and Nurminen method. Data cutoff date: September 24, 2018.

Analysis of pCR at IA2 (N=1002) and IA3 (N=1174)

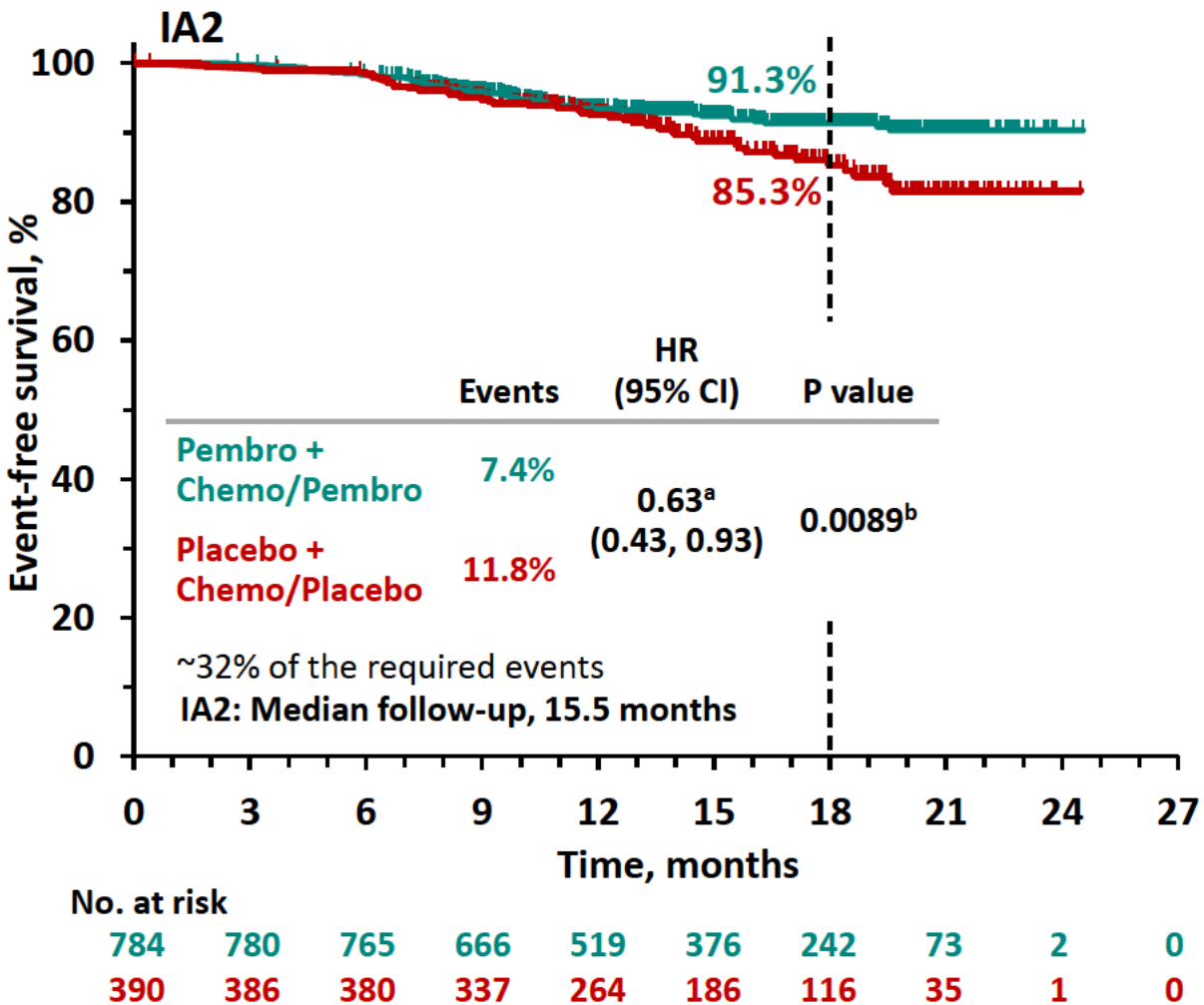
KEYNOTE-522

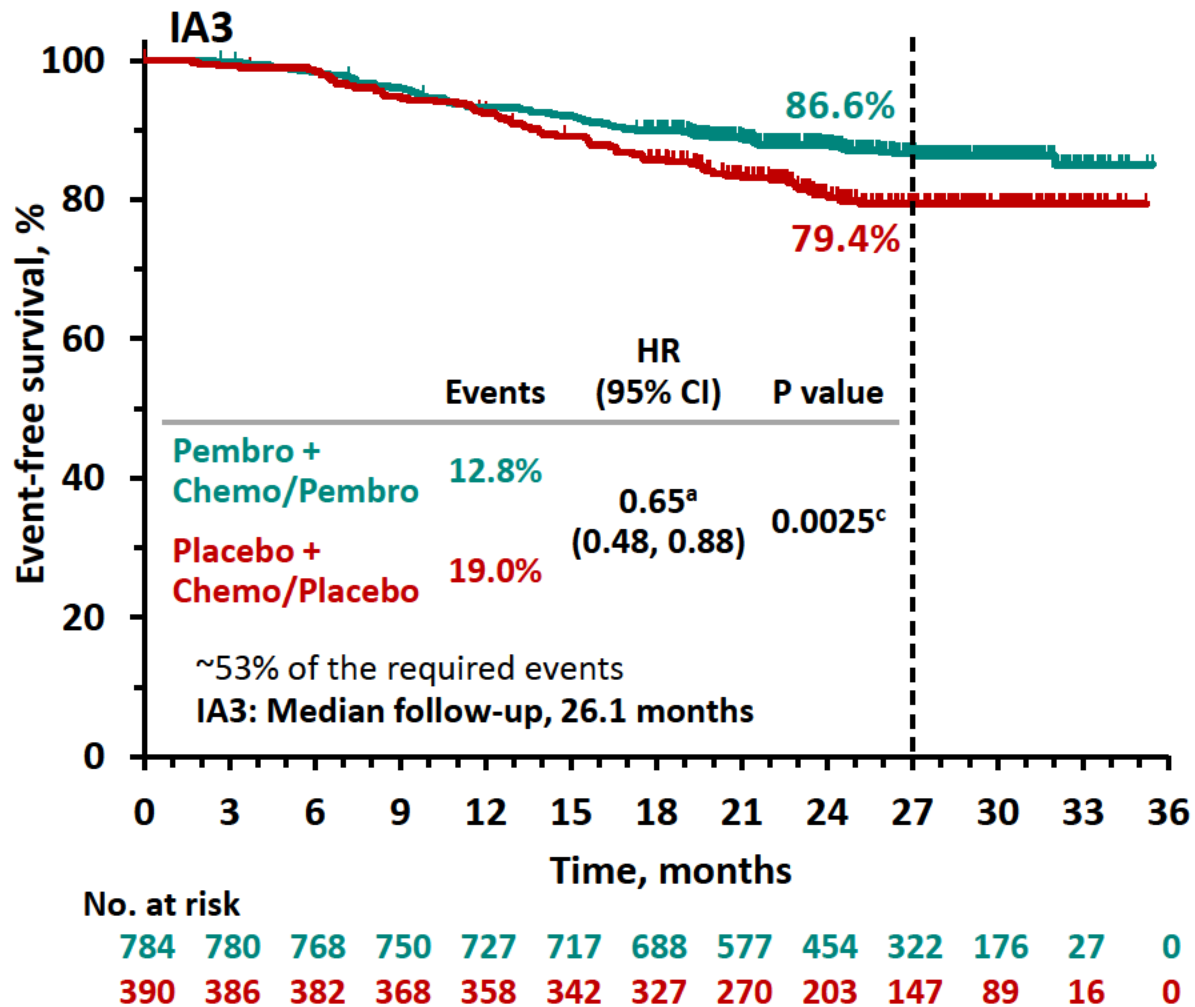
	Pembro + Chemo		Placebo + Chemo		P value
	n/N	% (95% CI)	n/N	% (95% CI)	
Supportive analysis at IA2[a]					
Patients with pCR	428/669	64.0 (60.2, 67.6)	182/333	54.7 (49.1, 60.1)	
Stratified delta[b], % (95% CI)		9.2 (2.8, 15.6)			0.00221[c]
Descriptive analysis at IA3[d]					
Patients with pCR	494/784	63.0 (59.5, 66.4)	217/390	55.6 (50.6, 60.6)	
Stratified delta[b], % (95% CI)		7.5 (1.6, 13.4)			

[a] IA2 data cut-off data: April 24, 2019.
[b] Estimated treatment difference based on Miettinen & Nurminen method stratified by randomization stratification factors.
[c] Pre-calculated P value boundary for significance of 0.0028.
[d] IA3 Data cutoff date: March 23, 2020.

Interim Analyses at IA2 and IA3 (N=1174) Showed Reduction in Risk of Disease Progression/Recurrence or Death

KEYNOTE-522





[a] Hazard ratio (CI) analyzed based on a Cox regression model with treatment as covariate stratified by the randomization stratification factors. [b] Pre-calculated P value boundary for significance of 0.000051; [c] Pre-specified P value boundary for significance of 0.0021. IA2 Data cutoff date: April 24, 2019; IA3 Data cutoff date: March 23, 2020.

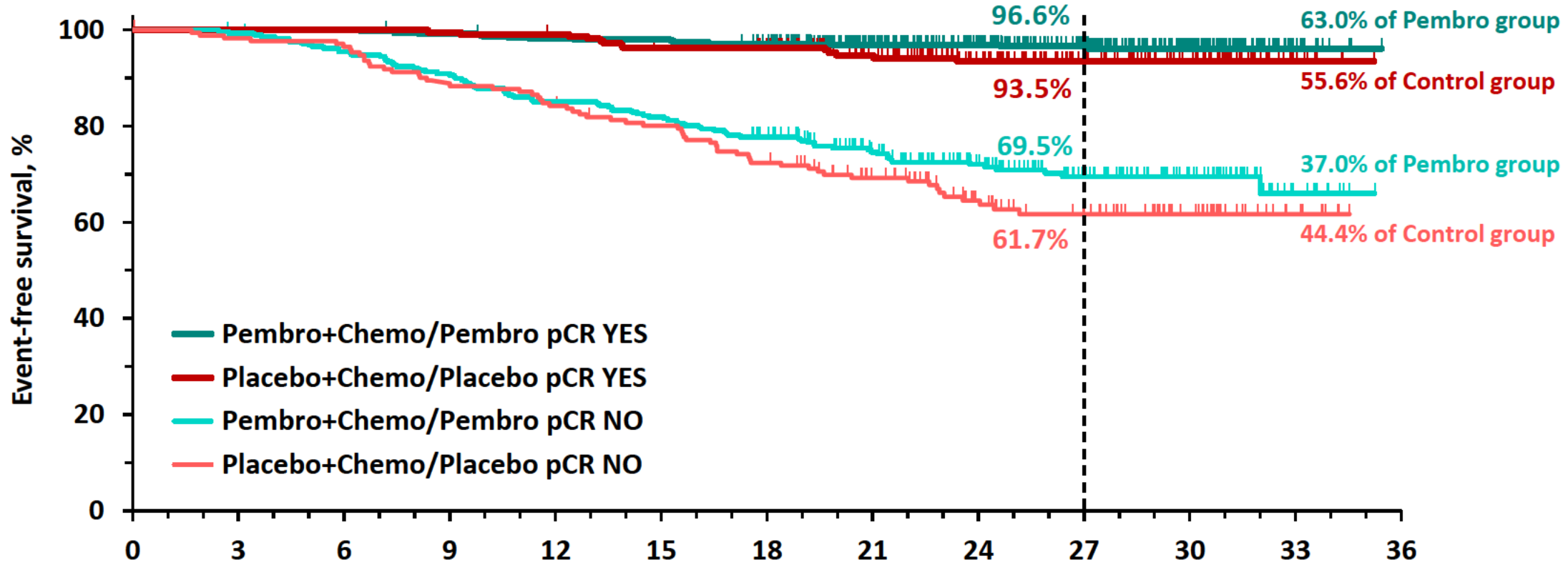
Bayesian Predictive Power of Achieving a Significant EFS Based on IA3 Observation

KEYNOTE-522

Analysis	Range Based on Different Model Assumptions
Interim Analysis 4	~73% to ~80%
Entire trial (IA4 to final analysis)	~90% to >95%

EFS by pCR Status (Yes vs No) and Treatment Group at IA3 (N=1174)

KEYNOTE-522



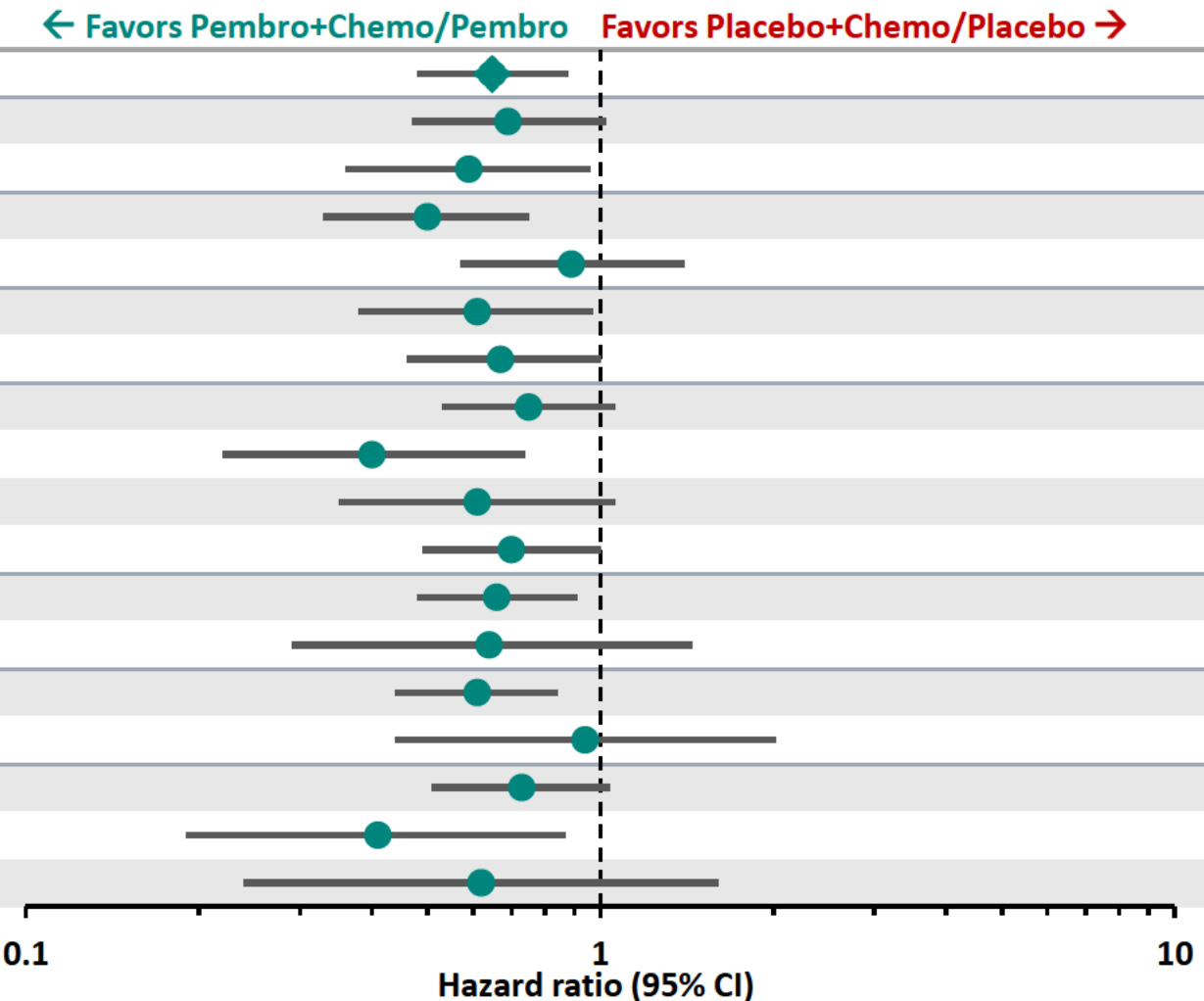
At risk, n													
Pembro pCR YES	494	494	494	489	483	482	471	396	317	229	126	17	0
Placebo pCR YES	217	217	217	216	214	207	205	169	130	89	58	8	0
Pembro pCR NO	290	286	274	261	244	235	217	181	137	93	50	10	0
Placebo pCR NO	173	169	165	152	144	135	122	101	73	58	31	8	0

Data cutoff date: March 23, 2020.

Event-Free Survival by Subgroup (IA3)

KEYNOTE-522 ITT Population

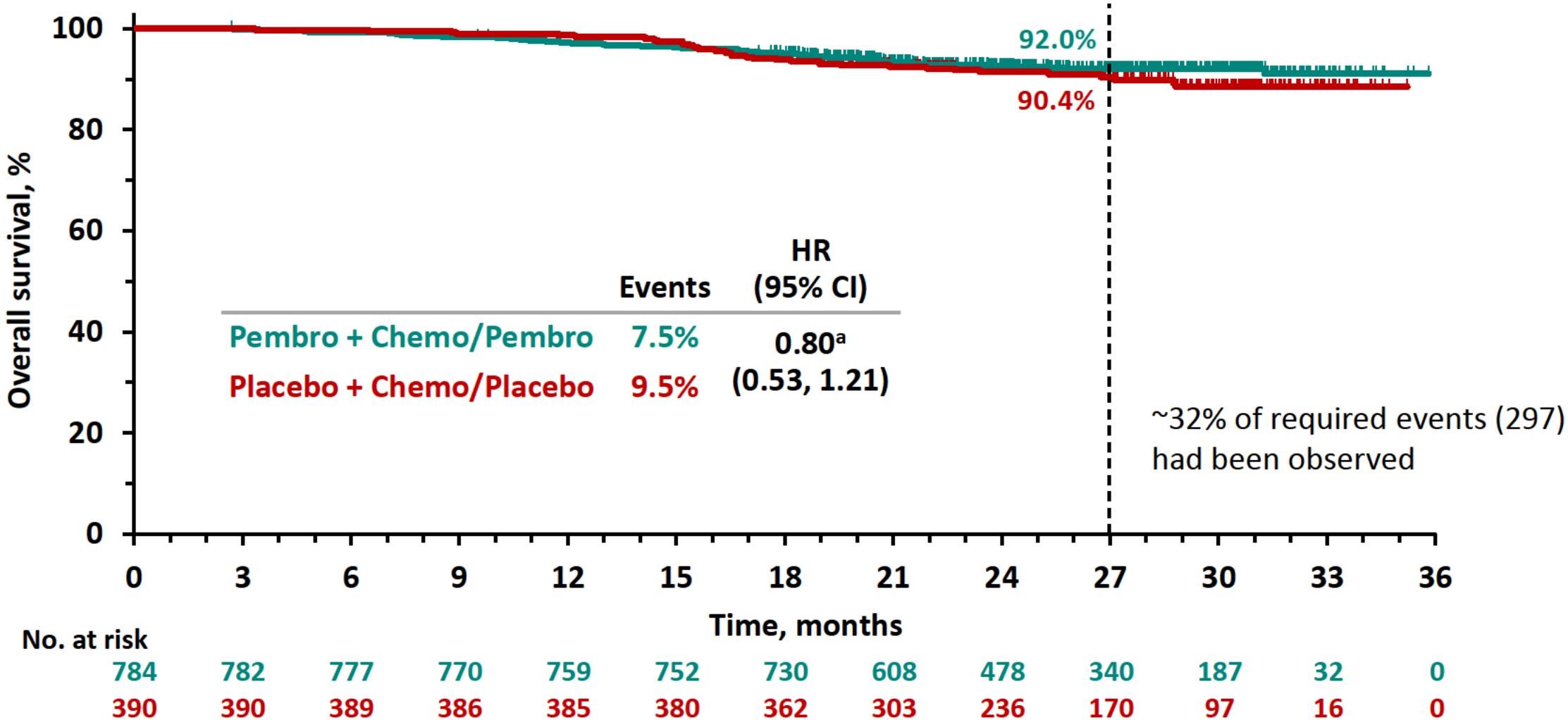
Subgroup		#Event/N	Hazard ratio (95% CI)
Overall		**174/1174**	**0.65 (0.48, 0.88)**
Nodal status	Positive	108/604	0.69 (0.47, 1.02)
	Negative	66/570	0.59 (0.36, 0.96)
Tumor size	T1/T2	92/871	0.50 (0.33, 0.75)
	T3/T4	82/303	0.89 (0.57, 1.40)
Carboplatin schedule	Every 3 weeks	70/501	0.61 (0.38, 0.97)
	Weekly	103/664	0.67 (0.46, 1.00)
PD-L1 CPS cutoff	≥1	131/973	0.75 (0.53, 1.06)
	<1	43/197	0.40 (0.22, 0.74)
	≥10	53/570	0.61 (0.35, 1.06)
	<10	121/600	0.70 (0.49, 1.00)
Age category	<65 years	150/1042	0.66 (0.48, 0.91)
	≥65 years	24/132	0.64 (0.29, 1.44)
ECOG PS	0	145/1019	0.61 (0.44, 0.84)
	1	29/155	0.94 (0.44, 2.02)
Geographic region	EU/Israel/N Am/Australia	129/892	0.73 (0.51, 1.04)
	Asia	28/216	0.41 (0.19, 0.87)
	Rest of world	17/66	0.62 (0.24, 1.60)



For the overall population and PD-L1 subgroup, analysis (HR and 95% CI) was based on Cox regression model with treatment covariate stratified by randomization stratification factors; For other subgroups, analysis was based on the unstratified Cox model. Data cutoff date: March 23, 2020.

Overall Survival at IA3

KEYNOTE-522



[a] Hazard ratio (CI) analyzed based on a Cox regression model with treatment as covariate stratified by the randomization stratification factors. Data cutoff date: March 23, 2020.

MERCK
INVENTING FOR LIFE

Safety

Pembrolizumab Safety Profile Is Well Characterized and Established

- The safety profile of pembrolizumab is well characterized based on an extensive clinical trial program and postmarketing experience
  - **>42,000** patients received pembrolizumab in the clinical development program
  - **>370,000 patient-years** of exposure with pembrolizumab in post-marketing setting

- The Reference Safety Dataset (**N=2799**) represents the established safety profile for pembrolizumab monotherapy and comprises of
  - **1567** patients with advanced melanoma
  - **1232** patients with advanced non-small cell lung cancer

Summary of Drug Exposure

KEYNOTE-522 (Neoadjuvant and Adjuvant Phases)

	Neoadjuvant Phase		Adjuvant Phase[a]		Reference safety dataset for Pembro mono N=2799
	Pembro + Chemo N=782	Placebo + Chemo N=389	Pembro mono N=589	Placebo N=331	
Duration of therapy, mo					
Mean (SD)	4.9 (1.1)	5.0 (0.9)	5.3 (1.4)	5.3 (1.2)	6.5 (5.93)
Median (range)	5.1 (0.0-7.9)	5.1 (0.0-7.2)	5.6 (0.0-8.7)	5.6 (0.0-9.1)	4.17 (0.03-30.39)

[a] Patients who had post-surgery radiation therapy, but did not yet have adjuvant pembro/placebo, were included in Adjuvant Phase ASaT population.

Overall Summary of Adverse Events

KEYNOTE-522 (Neoadjuvant and Adjuvant Phases)

	Patients, n (%)			
	Neoadjuvant phase		Adjuvant phase	
Adverse event	Pembro + Chemo N=782	Placebo + Chemo N=389	Pembro mono N=589	Placebo N=331
≥1 adverse event	**777 (99.4)**	**389 (100)**	**542 (92.0)**	**294 (88.8)**
Grade 3-5 adverse event	627 (80.2)	295 (75.8)	88 (14.9)	38 (11.5)
Serious adverse event	315 (40.3)	101 (26.0)	41 (7.0)	14 (4.2)
Death due to AE	5 (0.6)[a]	1 (0.3)[b]	2 (0.3)[a]	0
Death due to drug-related AE	2 (0.3)[c]	1 (0.3)	2 (0.3)[c]	0
Discontinued any drug due to AE	205 (26.2)	53 (13.6)	32 (5.4)	8 (2.4)
Immune-mediated AEs/Infusion reaction	306 (39.1)	71 (18.3)	59 (10.0)	20 (6.0)
Grade 3-5 AEs	102 (13.0)	7 (1.8)	17 (2.9)	1 (0.3)
Serious AEs	71 (9.1)	4 (1.0)	12 (2.0)	1 (0.3)

[a] Death, Multiple organ dysfunction syndrome/Myocardial Infarction/Sepsis, Pneumonia, Pneumonitis, Pulmonary embolism, Shock, and Autoimmune encephalitis;
[b] Septic shock; [C] Per investigator, 3 cases related to pembrolizumab (Pneumonitis, Pulmonary embolism, and Autoimmune encephalitis) and 1 case, with 3 events, related to chemo (MODS/MI/Sepsis).

Most Common Grade 3-5 Adverse Events

KEYNOTE-522 (Neoadjuvant and Adjuvant Phases)

Neoadjuvant Phase

Events Occurring in ≥5% Patients

	Patients, n (%)	
	Pembro + Chemo N=782	Placebo + Chemo N=389
≥1 adverse event	**627 (80.2)**	**295 (75.8)**
Neutropenia	276 (35.3)	133 (34.2)
Anemia	152 (19.4)	61 (15.7)
Neutrophil count decreased	148 (18.9)	92 (23.7)
Febrile neutropenia	144 (18.4)	63 (16.2)
WBC count decreased	61 (7.8)	20 (5.1)
ALT increased	48 (6.1)	10 (2.6)

Adjuvant Phase

Events Occurring in ≥ 4 Patients

	Patients, n (%)	
	Pembro mono N=589	Placebo N=331
≥1 adverse event	**88 (14.9)**	**38 (11.5)**
Radiation skin injury	5 (0.8)	3 (0.9)
Lymphopenia	4 (0.7)	1 (0.3)
Rash	5 (0.8)	0 (0.0)
Neutropenia	4 (0.7)	3 (0.9)
Neutrophil count decreased	5 (0.8)	1 (0.3)
Pneumonitis	4 (0.7)	1 (0.3)

Serious Adverse Events

KEYNOTE-522 (Neoadjuvant and Adjuvant Phases)

Neoadjuvant phase

Events occurring in ≥1% patients

	Patients, n (%)	
	Pembro + Chemo N=782	Placebo + Chemo N=389
≥1 adverse event	**315 (40.3)**	**101 (26.0)**
Febrile neutropenia	118 (15.1)	47 (12.1)
Pyrexia	29 (3.7)	2 (0.5)
Anemia	20 (2.6)	9 (2.3)
Neutropenia	12 (1.5)	1 (0.3)
Pulmonary embolism	10 (1.3)	2 (0.5)
Pancytopenia	11 (1.4)	4 (1.0)
Sepsis	7 (0.9)	4 (1.0)
Adrenal insufficiency	8 (1.0)	0 (0.0)
Hypophysitis	8 (1.0)	0 (0.0)
Pneumonia	4 (0.5)	6 (1.5)
Postop wound infection	3 (0.4)	4 (1.0)

Adjuvant phase

Events occurring in ≥2 patients

	Patients, n (%)	
	Pembro mono N=589	Placebo N=331
≥1 adverse event	**41 (7.0)**	**14 (4.2)**
Pneumonia	3 (0.5)	2 (0.6)
Pneumonitis	4 (0.7)	1 (0.3)
Acute kidney injury	2 (0.3)	0
Atrial fibrillation	2 (0.3)	0
Device-related infection	2 (0.3)	0
Pulmonary embolism	2 (0.3)	0
Radiation skin injury	2 (0.3)	0
Sepsis	2 (0.3)	0

Summary of Immune-Mediated AEs and Infusion Reactions

KEYNOTE-522 (Neoadjuvant and Adjuvant Phases)

	Patients, n (%)				
	Neoadjuvant Phase		Adjuvant Phase		Reference safety dataset for Pembro mono N=2799
	Pembro + Chemo N=782	Placebo + Chemo N=389	Pembro mono N=589	Placebo N=331	
≥1 adverse event	**306 (39.1)**	**71 (18.3)**	**59 (10.0)**	**20 (6.0)**	**598 (21.4)**
Grade 3-5 adverse event	102 (13.0)	7 (1.8)	17 (2.9)	1 (0.3)	155 (5.5)
Serious adverse event	71 (9.1)	4 (1.0)	12 (2.0)	1 (0.3)	162 (5.8)
Death due to AE	1 (0.1)[a]	0	1 (0.2)[b]	0	4 (0.1)
Death due to drug-related AE	1 (0.1)[a]	0	1 (0.2)[b]	0	4 (0.1)
Discontinued any drug due to AE	77 (9.8)	9 (2.3)	8 (1.4)	1 (0.3)	84 (3.0)

[a] Pneumonitis
[b] Autoimmune encephalitis

Immune-Mediated AEs and Infusion Reactions (≥1%)

KEYNOTE-522 (Neoadjuvant and Adjuvant Phases)

	Patients, n (%)				
	Neoadjuvant Phase		Adjuvant Phase		Reference safety dataset for Pembro mono N=2799
	Pembro + Chemo N=782	Placebo + Chemo N=389	Pembro mono N=589	Placebo N=331	
≥1 adverse event	**306 (39.1)**	**71 (18.3)**	**59 (10.0)**	**20 (6.0)**	**598 (21.4)**
Infusion reactions	134 (17.1)	43 (11.1)	11 (1.9)	4 (1.2)	70 (2.5)
Hypothyroidism	104 (13.3)	10 (2.6)	16 (2.7)	12 (3.6)	237 (8.5)
Severe skin reactions	34 (4.3)	4 (1.0)	11 (1.9)	0 (0.0)	39 (1.4)
Hyperthyroidism	36 (4.6)	5 (1.3)	5 (0.8)	2 (0.6)	96 (3.4)
Adrenal insufficiency	17 (2.2)	0 (0.0)	3 (0.5)	0 (0.0)	22 (0.8)
Pneumonitis	10 (1.3)	5 (1.3)	7 (1.2)	2 (0.6)	94 (3.4)
Hypophysitis	15 (1.9)	1 (0.3)	0 (0.0)	0 (0.0)	17 (0.6)
Colitis	12 (1.5)	3 (0.8)	2 (0.3)	0 (0.0)	48 (1.7)
Thyroiditis	16 (2.0)	4 (1.0)	0 (0.0)	1 (0.3)	16 (0.6)
Hepatitis	11 (1.4)	3 (0.8)	0 (0.0)	0 (0.0)	19 (0.7)

MERCK
INVENTING FOR LIFE

Conclusions

Conclusions
KEYNOTE-522

- KEYNOTE-522 is the first trial to investigate the benefit of adding 1 year of immunotherapy before and after surgery to standard of care treatment for high-risk early-stage TNBC
  - Statistically significant pCR improvement compared with platinum-based chemotherapy
  - Highest absolute pCR rate
  - Promising and stable improvement in EFS at IA3 (HR=0.65)
- Manageable safety profile with no new safety concerns identified
- Role of pembrolizumab in the treatment of TNBC is further supported by significant PFS benefit observed in metastatic TNBC
- Given the favorable benefit/risk profile and unmet medical need in high-risk early-stage TNBC, this regimen should be made available to patients now

Clinical Perspective

Hope S. Rugo, MD

Professor of Medicine

University of California San Francisco Comprehensive Cancer Center

UCSF

University of California
San Francisco

KEYNOTE-522 Establishes a New Treatment Paradigm for TNBC

- Strong biological rationale for adding immunotherapy to neoadjuvant chemotherapy while primary tumor is still present[a]
- Adjuvant immunotherapy enhances antitumor immunity and prolongs DFS in other tumor types[a]
- Trastuzumab for early-stage HER2+ breast cancer provides precedent for use of targeted immunomodulatory drug pre- and postoperatively (total exposure of 1 year)[b]
- Risk of disease recurrence in early-stage TNBC is highest in first 1-3 years after diagnosis
  - The most effective therapy should be given in curative setting

[a] Liu J, et al. *Cancer Discov*. 2016;6:1382-1399; [b] Gianni L, et al. *Lancet*. 2010;375:377-384.

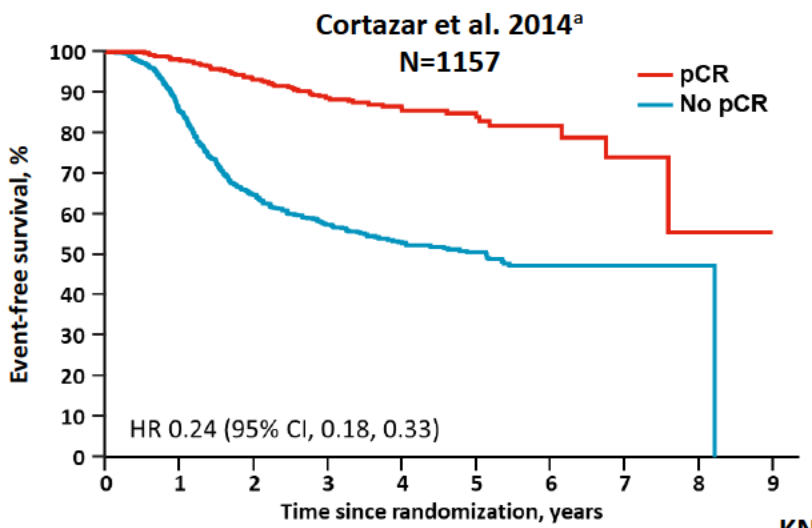
Immunotherapy Neoadjuvant Studies

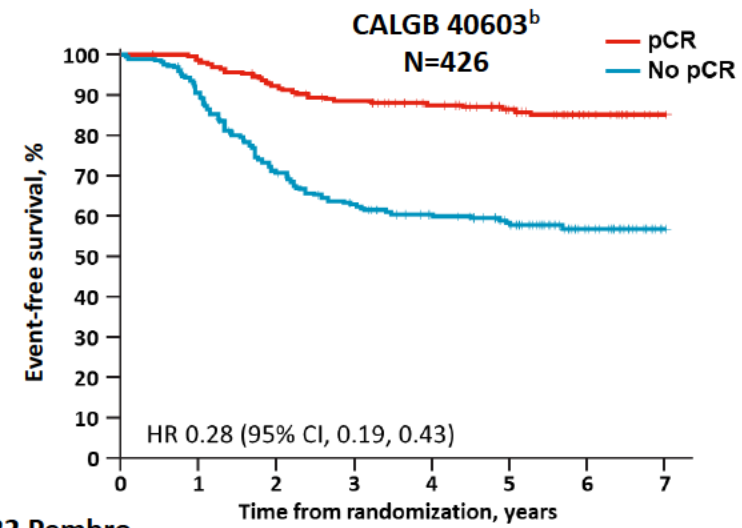
	KEYNOTE-522[a] Pembrolizumab	I-SPY2[b] Pembrolizumab	IMpassion 031[c] Atezolizumab	NEOTRIP[d] Atezolizumab	GEPARNUEVO[e] Durvalumab
Total patients	602/1174	69/181	333	280	174
Target	PD-1	PD-1	PD-L1	PD-L1	PD-L1
Stage	II/III	II/III	II/III	Included N3	35% stage I
Anthracyclines	Yes	Yes	Yes	No	Yes
Carboplatin	Yes	No	No	Yes	No
pCR rate	**65%** vs 51% (P=0.00055)	60% vs 22% (graduated)	58% vs 41% (P=0.0044)	44% vs 41% (P=0.66)	53% vs 44% (P=0.287)

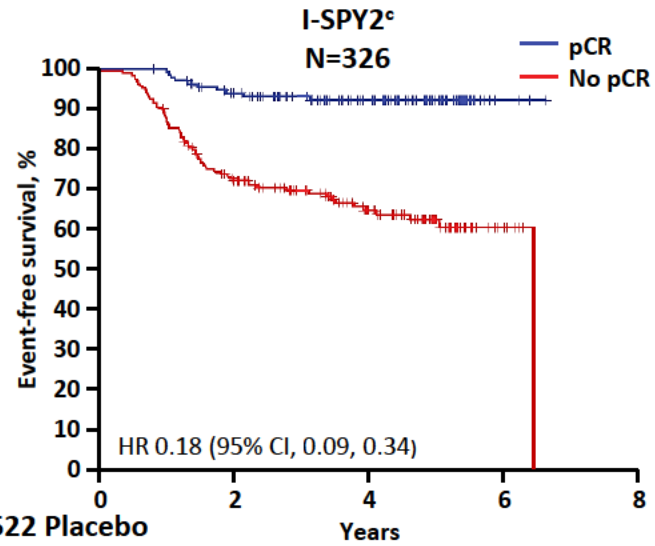
- Anthracyclines and stage are key factors determining benefit from neoadjuvant immunotherapy
- PD-L1 status is not predictive for response when the immune system is intact
- Other variables may play role, such as tumor-infiltrating lymphocytes

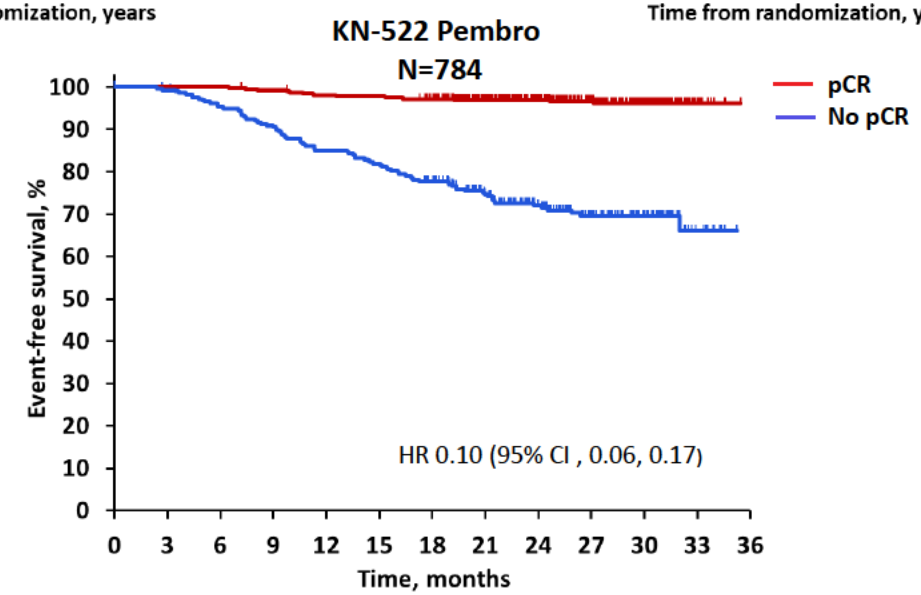
[a] Schmid P, et al. *N Engl J Med*. 2020;382:810-821; [b] Nanda R, et al. *JAMA Oncol*. 2020;6(5):1-9. Epub ahead of print; [c] Mittendorf EA, et al. *Lancet*. Sept 20, 2020. Epub ahead of print;
[d] Gianni L, et al. 2019 San Antonio Breast Cancer Symposium. Abstract GS3-04. Presented December 12, 2019. [e] Loibl S, et al. *Ann Oncol*. 2019;30(8):1279-1288.

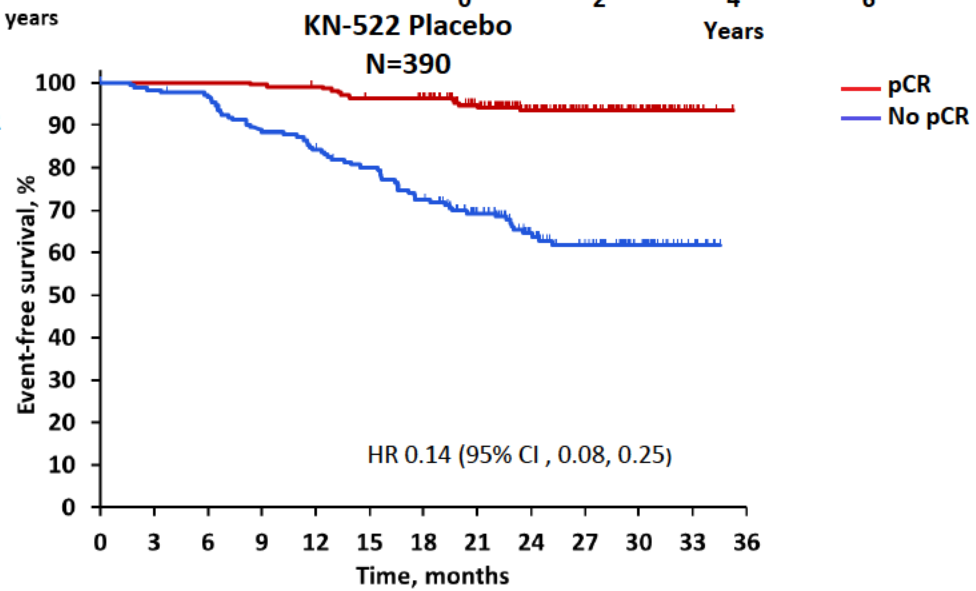
Strong Patient-level Association of pCR and EFS in TNBC





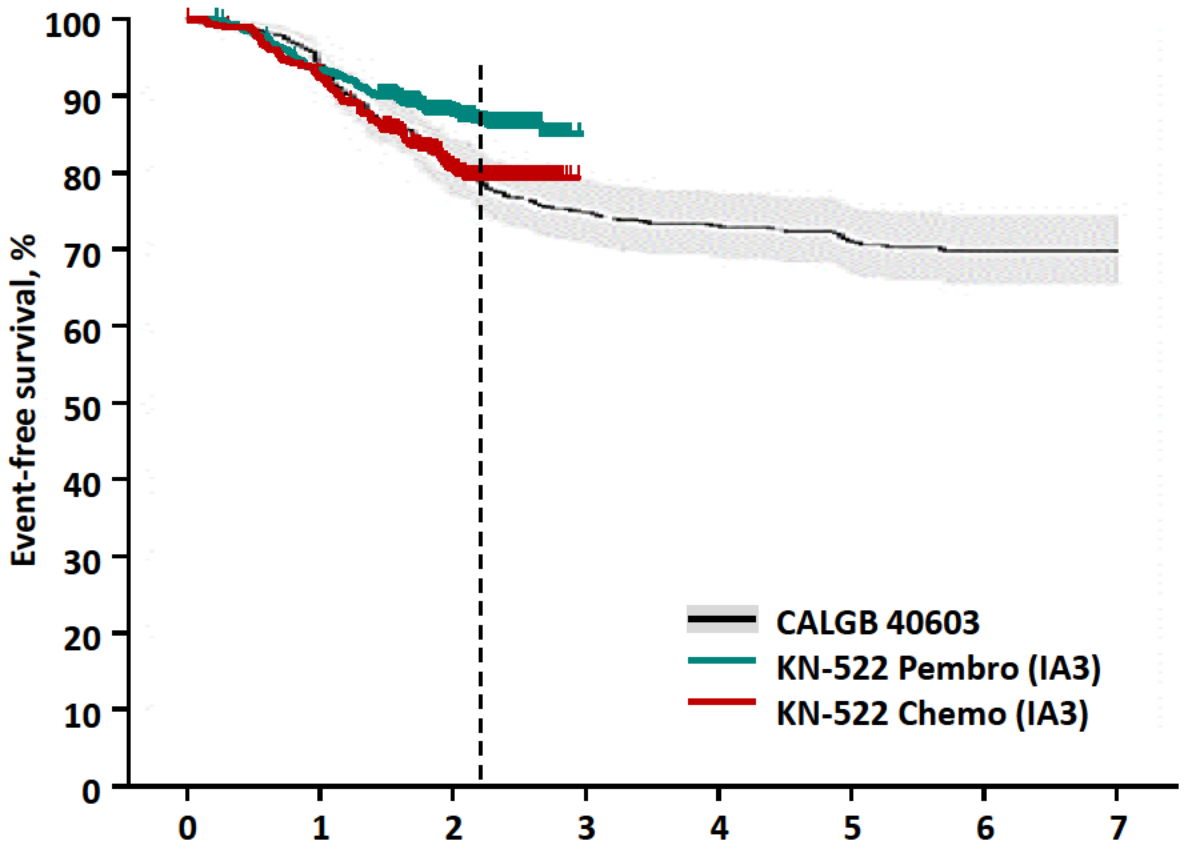






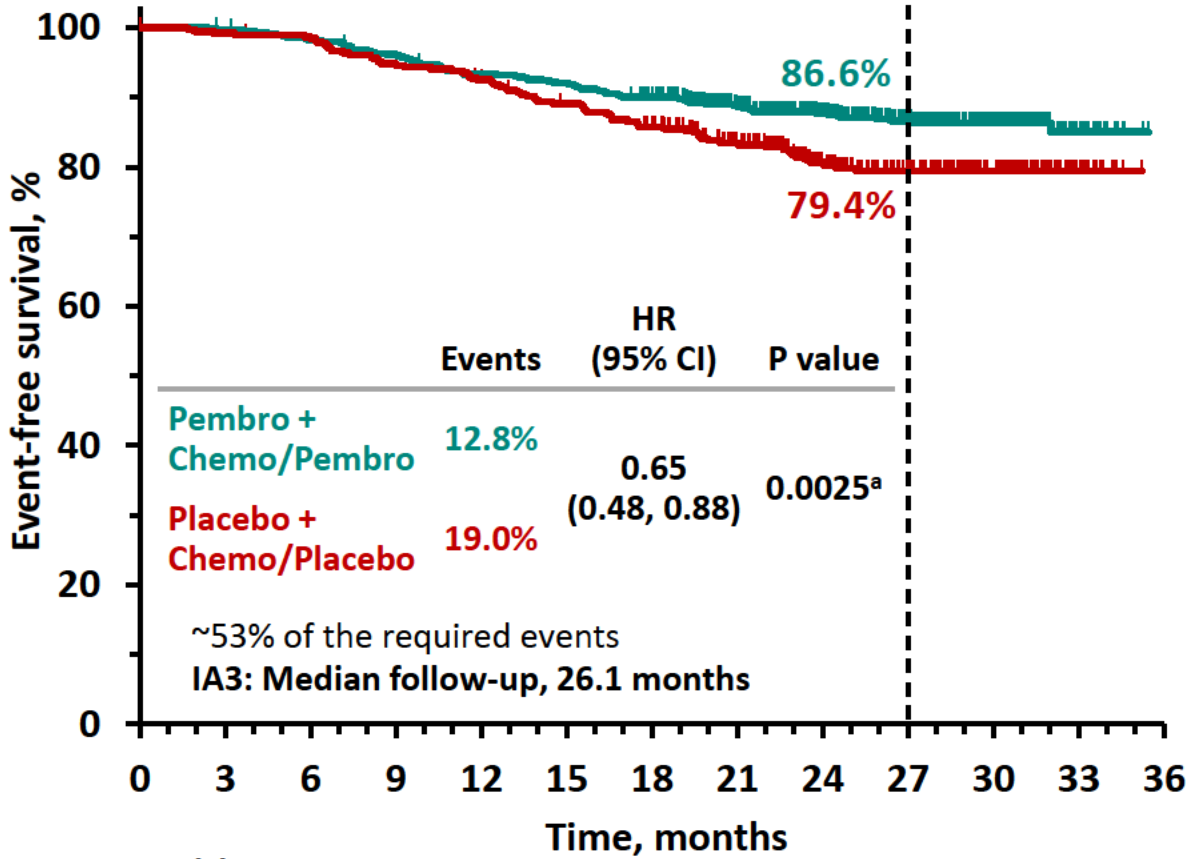
[a] Cortazar P, et al. *Lancet*. 2014;384:164-172;
[b] Sikov WM, et al. Presented at ASCO 2019 Abstract 591; [c] I-SPY2 Trial Consortium *JAMA Oncol*. 2020;6(9):1355-1362;

Putting KEYNOTE-522 EFS Data at IA3 Into Context



No. at risk								
CALGB 40603	443	405	341	308	284	239	133	31
Pembro	784	727	454	0				
Chemo	390	358	203	0				

Sikov WM, et al. Presented at ASCO 2019; abstract 591.



No. at risk													
	784	780	768	750	727	717	688	577	454	322	176	27	0
	390	386	382	368	358	342	327	270	203	147	89	16	0

[a] Pre-specified P value boundary for significance of 0.0021.

Immune-Mediated Adverse Events and Infusion Reactions (≥1%)

KEYNOTE-522 (Combined Phases)

	Patients, n (%)	
	Pembro + Chemo/Pembro N=782	Placebo + Chemo/Placebo N=389
≥1 adverse event	**339 (43.4)**	**85 (21.9)**
Infusion reactions	141 (18.0)	45 (11.6)
Hypothyroidism	117 (15.0)	22 (5.7)
Severe skin reactions	45 (5.8)	4 (1.0)
Hyperthyroidism	41 (5.2)	7 (1.8)
Adrenal insufficiency	20 (2.6)	0
Pneumonitis	17 (2.2)	6 (1.5)
Colitis	13 (1.7)	3 (0.8)
Hypophysitis	15 (1.9)	1 (0.3)
Thyroiditis	16 (2.0)	5 (1.3)
Hepatitis	11 (1.4)	3 (0.8)

Pembrolizumab Plus Chemotherapy in Metastatic Disease
KEYNOTE-355

- Ongoing, randomized, global, Phase 3 study for locally recurrent inoperable or metastatic TNBC not previously treated with chemotherapy[a]
- Pembrolizumab plus chemotherapy resulted in statistically significant and clinically meaningful improvement in PFS compared with chemotherapy alone in patients with tumors expressing PD-L1 (CPS ≥10)
  - Basis for accelerated approval in metastatic TNBC
- Early-stage TNBC is immunologically distinct from metastatic TNBC

[a] Cortes J, et al. ASCO 2020.

Why We Should Make This Regimen Available Now

- An additional 4% to 6%[a] of patients may be event free at Year 5 with Pembro + Chemo/Pembro (based on IA3)
- On average, 17 to 25 patients in early TNBC would need to receive Pembro + Chemo/Pembro (instead of Chemo alone) for one additional patient without EFS events at Year 5

Region	New cases yearly[b,c,d]	New cases within 5 years	New cases in stage II or stage III (62%) within 5 years	Additional patients without EFS events at Year 5
United States	~ 56,000	~280,000	~ 173,600	~ 6,900 to 10,400

- For patients with distant EFS events, the median overall survival is 18 to 24 months

[a] EFS rate in Control group (Chemo) estimated by weighted average using pCR rate in KN522 placebo arm in IA3 and EFS rates by pCR status in CALGB 40603; EFS rate in Pembro group estimated using a cure model with cure rates of 60% or 65% and assumed HR range of 0.63 to 0.71. These results are limited to the assumptions made. [b] Arnedos M, et al. *Ther Adv Med Oncol*. 2012;4(4):195-210; [c] Bauer KR, et al. *Cancer*. 2007;109(9):1721-8; [d] Siegel RL, et al. *CA Cancer J Clin*. 2020;70:7-30.

How I Would Use Pembrolizumab in Clinical Practice

- Neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab monotherapy should become a new standard of care for patients with early-stage TNBC with high-risk clinico-pathologic features
  - This represents an unmet need for patients with limited therapeutic options
- Immune-mediated AEs are manageable in clinical practice
  - Early recognition and intervention minimize toxicity
  - Provider and patient education is critical

Questions and Answers

Vicki Goodman, MD

Vice President, Clinical Research
Therapeutic Area Head, Late Stage Oncology
Merck Research Laboratories