Immunotherapy in Breast Cancer

Alberto J. Montero, MD, MBA
Clinical Director, Breast Cancer Medical Oncology Program

Diana Hyland Chair for Breast Cancer
University Hospitals Seidman Cancer Center

Case Comprehensive Cancer Center
Professor of Medicine
Case Western Reserve University

Overview

- Rationale for immunotherapy (IO) in TNBC and combination with chemotherapy
- Metastatic TNBC: Current state of IO & PD-L1 as biomarker
- Early TNBC
- Conclusions and future directions

Rationale for IO in TNBC and Combination with Chemotherapy

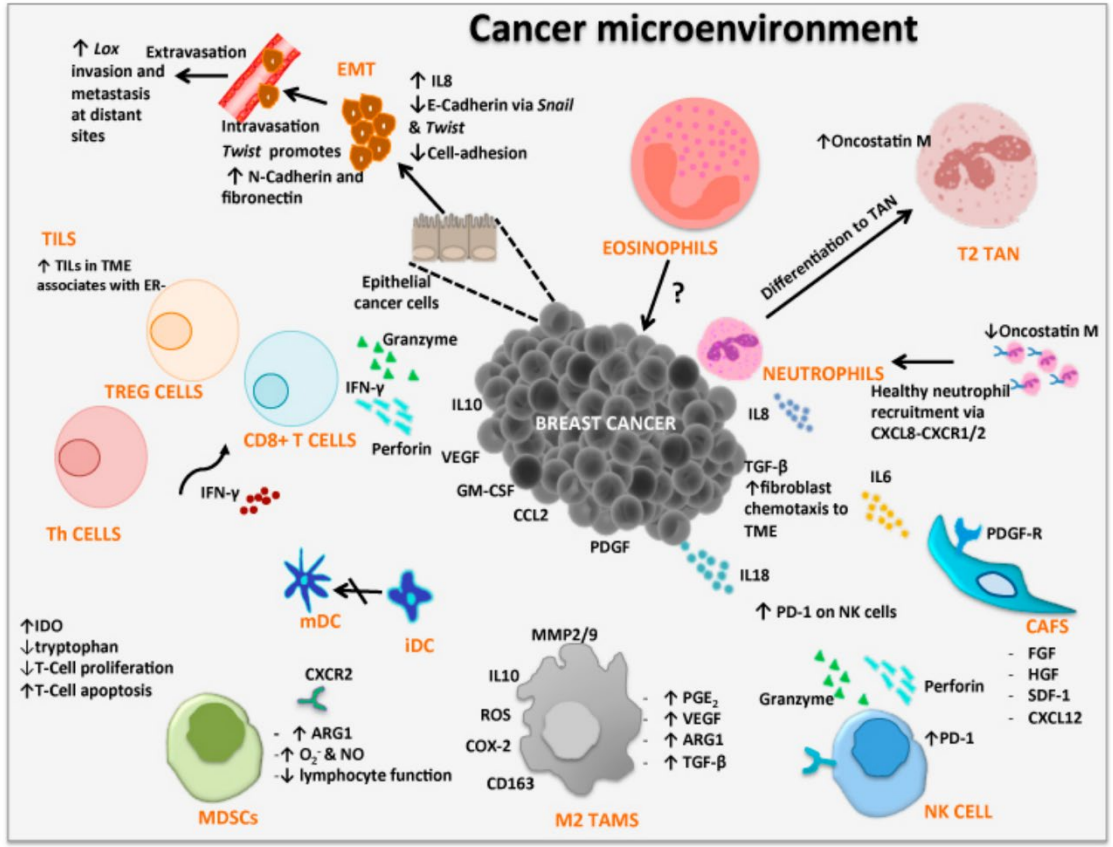
Immune checkpoints in breast cancer

- Expression associated with tumor-infiltrating lymphocytes (TILs)
- TILs are evidence of anti-tumor immune response; highest in TNBC
- **PD-L1** expressed mainly in infiltrating immune cells in BC
- **PD-1** on T-cells down-regulates immune response, blocking PD-1/PD-L1 can augment T-cell response

Anti- PD-1/PD-L1 antibodies have shown single agent activity in TNBC including durable responses (1L > 2L+)

Combination of IO with cytotoxics

- Chemotherapy is SOC in TNBC and can have several immunogenic effects, TIL-rich tumors have highest pCR rates
- Combination with chemotherapy may be synergistic by targeting different steps in the cancer immunity cycle



Barriga V. et al. *Cancers* 2019, *11*(8), 1205

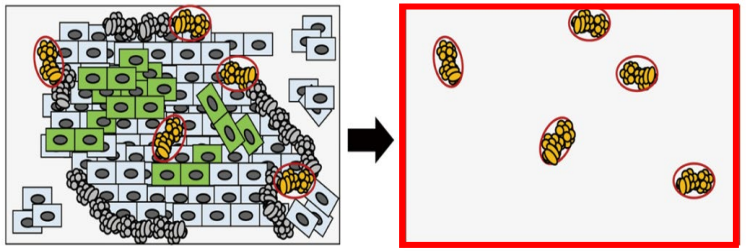
Luen et al, Breast 2016, Stanton et al, Jama Onc 2016, Nanda et al, JCO 2016, Adams et al Ann Oncol 2019, Cortes et al, ESMO 2019, Emens et al, JAMA Onc 2019, Gatti-Mays et al, Nature Breast Cancer 2019, Loi et al, JCO 2019, Adams et al, JAMA Onc 2019, Denkert et al, Lancet Oncol 2018, Page et al, Nature Breast Cancer 2019, Galluzzi et al, Nat Rev Clin Oncol 2020, Chen/Mellman Immunity 2013

Metastatic

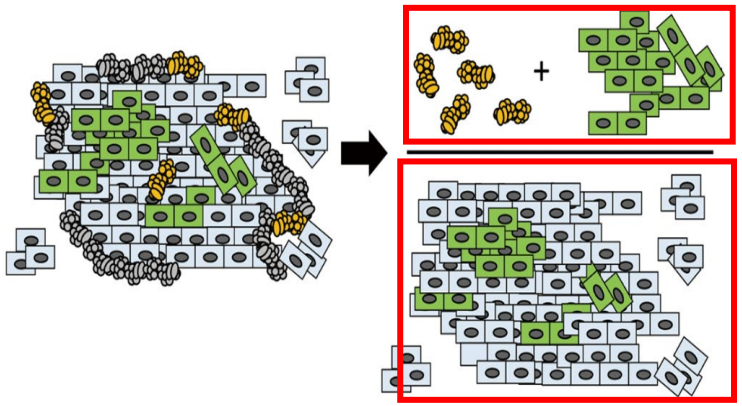
- Keynote 355

PD-L1 as Biomarker (in metastatic setting)

Two different PD-L1 companion diagnostics approved in US



Score	IHC Assay	Grading	
Immune cell score (IC)	Ventana SP142	% of tumor area covered by area of PD-L1+ immune cells	Ate… 4… IMpassion…



Score	IHC Assay	Grading	
Combined positive score (CPS)	Dako 22c3	Total number of PD-L1–positive cells (tumor cells, lymphocytes, and macrophages) divided by the total number of tumor cells x 100	Pembrolizumab **(CPS ≥ 10)** 37% in KEYNOTE-355

Retrospective comparison of SP142 and 22c3 assays in IMpassion130 (biomarker evaluable = 614 pts):
Rates of PD-L1 positivity vary by assay and threshold, analytic and clinical concordance suboptimal, clinical dilemma (see commentary Salgado et al, Lancet Oncol 2020)

Rugo et al ESMO 2019, Rugo et al SABCS 2019
Figure modified from Eckstein et al, Ann Transl Med 2019

[redacted] Withdraws Atezolizumab PD-L1–Positive Metastatic TNBC Indication in the United States

August 30, 2021
Kristi Rosa

[redacted] has made the voluntary decision to withdraw the indication for the use of atezolizumab plus chemotherapy in the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer whose tumors express PD-L1.

Phase 3 IO chemo combination 1L advanced TNBC trials

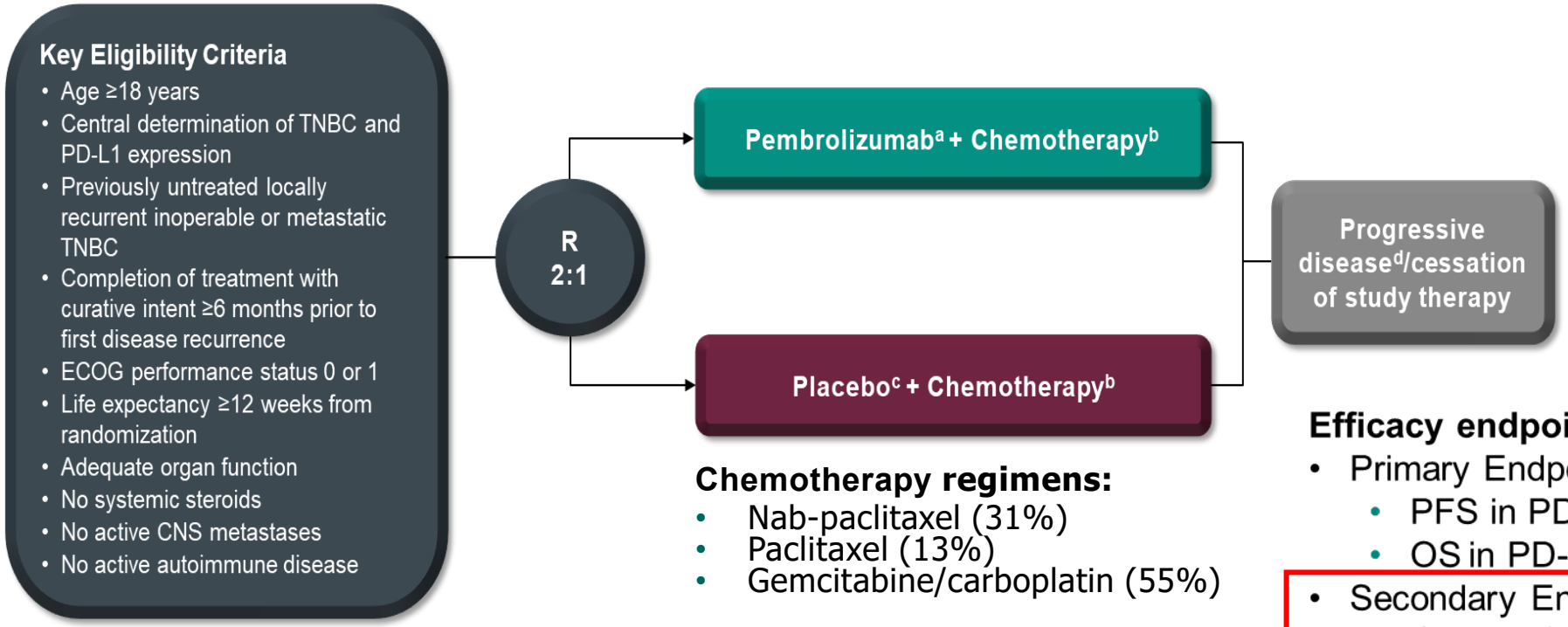
Trial	Target	Chemo	N	Open (Estimated Completion)	PD-L1+	Primary endpoints (Hierarchical testing)	Secondary endpoints	De novo, DFI (mos)
IMpassion130 (NCT02425891) FDA approval 3/2019; Withdrawal 8/2021	**PD-L1**	**Nab-Paclitaxel**	900	June 2015 (April 2020)	IC≥1 41%	PFS ITT **7.2 vs 5.5 mos** PFS PD-L1+ **7.5 vs 5 mos** OS ITT 21 vs 18.7 mos n.s.* OS PD-L1+ 25.4 vs 17.9 mos n.t.*	ITT | PD-L1+ **ORR (%):** 56 vs 46% | 59 vs 43% **DOR (mos)**: 7.4 vs 5.6 | 8.5 vs 5.5 **PRO** (no detriment to HRQoL with added IO)	37%, ≥ 12
IMpassion131 (NCT03125902) FDA warning	**PD-L1**	**Paclitaxel**	651	Aug 2017 (June 2021)	IC≥1 45%	PFS PD-L1+ 6 vs 5.7 mos n.s. PFS ITT 5.7 vs 5.6 mos n.t.*	PD-L1+ | ITT **OS (mos):** 22.1 vs 28.3 | 19.2 vs 22.8 ORR, PFS by IRC and PRO (pending)	30%, ≥ 12
IMpassion132 (NCT03371017)	**PD-L1**	**Gem/carbo** Or **capecitabine**	350	Jan 2018 (Jan 2023)	IC≥1 n/a	OS in PD-L1+ (pending) OS in ITT (pending)	12-mos OS, 18-mos OS, PFS, RR, DOR, CBR, PRO (pending)	0, ≤ 12
KEYNOTE-355 (NCT02819518) FDA approval 11/2020	**PD-1**	**Nab-Paclitaxel** Or **paclitaxel** Or **gem/carbo**	847	July 2016 (Dec 2019)	CPS≥10 37% CPS≥1 75%	PFS CPS≥10 **9.7 vs 5.6 mos** PFS CPS≥1 7.6 vs 5.6 n.s.* PFS ITT 7.5 vs 5.6 n.t.* OS in PD-L1+ (pending) OS ITT (pending)	CPS≥10 | CPS≥1 | ITT **ORR (%):** 53 vs 40 | 45 vs 38 | 41 vs 36 **DCR (%):** 65 vs 54 | 59 vs 54 | 56 vs 52 **DOR (mos):** 19 vs 7 | 10 vs 7 | 10 vs 6 Consistency of efficacy per chemo regimen^ **PFS HR nab-Pac:** 0.57 | 0.66 | 0.69 **PFS HR Pac:** 0.33 | 0.46 | 0.57 **PFS HR Gem/Carbo:** 0.77 | 0.86 | 0.93	29%, ≥ 6

IMpassion130: Atezolizumab 840/PLA q2w + Nab-Paclitaxel 100 D1, 8, 15 of 28 days
IMpassion131: Atezolizumab 840/PLA q2w + Paclitaxel 90 D1, 8, 15 of 28 days, 8–10 mg dexamethasone x at least 2 infusions. Stratifier prior taxane, PD-L1 status, liver mets, geographic location. 49% prior taxane, 50% prior anthracycline
IMpassion132: Atezolizumab 1200/PLA d1 q 3w + chemo (Gemcitabine 1000/carboplatin AUC 2 d 1, 8 of 21 days or Capecitabine 1000 mg/m2, BID d1 to 14 q21d)
KN-355: Pembro 200/PLA q3w + Chemo (Nab-Pac 100 D1, 8, 15 of 28 days Or Pac 90 D1, 8, 15 of 28 days Or Gem/ Carbo D1, 8 of 21 days). Stratified by taxane (45%) vs not (55%), PD-L1, prior expos to chemo class (same 22%).

* By hierarchical testing (n.s. not significant, n.t. not tested)
^ exploratory, not powered

Schmid et al, NEJM 2018, Adams et al, Ann Oncol 2020, Miles et al, ESMO 2020, Cortes et al, ASCO 2020, Rugo et al, SABCS 2020

Phase 3 IO chemo combination 1L advanced TNBC-KN-355



Chemotherapy regimens:

- Nab-paclitaxel (31%)
- Paclitaxel (13%)
- Gemcitabine/carboplatin (55%)

Stratification Factors:

- Chemotherapy on study (taxane vs gemcitabine-carboplatin)
- PD-L1 tumor expression (CPS ≥1 vs CPS <1)[e]
- Prior treatment with same class chemotherapy in the neoadjuvant or adjuvant setting (yes vs no)

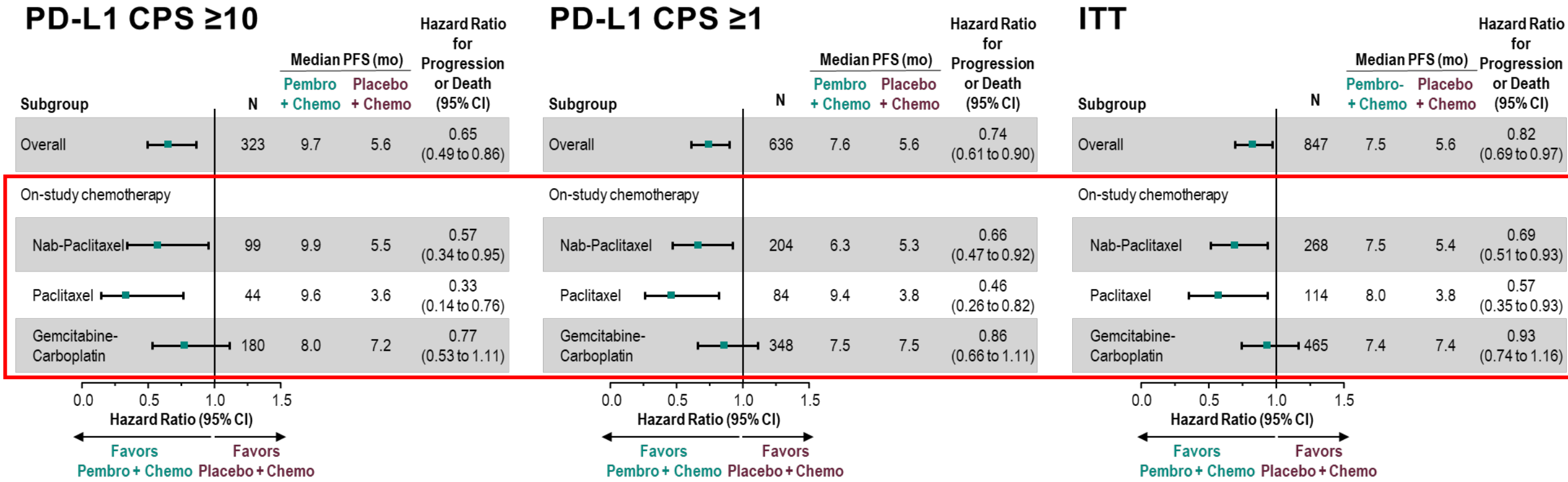
Efficacy endpoints

- Primary Endpoints
  - PFS in PD-L1+ (CPS ≥10 and CPS ≥1) and ITT
  - OS in PD-L1+ (CPS ≥10 and CPS ≥1) and ITT
- Secondary Endpoints
  - ORR, DCR, DOR
- Exploratory Endpoint
  - Consistency of treatment effect in all patients and PD-L1+ (CPS ≥10 and CPS ≥1) according to on-study chemotherapy partner

Cortes et al, ASCO 2020, Rugo et al, SABCS 2020

Phase 3 IO chemo combination 1L advanced TNBC-KN-355

Consistency of efficacy per chemo regimen^



^ exploratory, not powered

Cortes et al, ASCO 2020, Rugo et al, SABCS 2020

Phase 3 IO chemo combination 1L advanced TNBC-KN-355

Secondary endpoints

Trial	Target	Chemo	N	Open (Estimated Completion)	PD-L1+	Primary endpoints (Hierarchical testing)	Secondary endpoints	De novo, DFI (mos)
KEYNOTE-355 (NCT02819518) FDA approval 11/2020	**PD-1**	**Nab-Paclitaxel** Or **paclitaxel** Or **gem/carbo**	847	July 2016 (Dec 2019)	CPS≥10 37% CPS≥1 75%	PFS CPS≥10 **9.7 vs 5.6 mos** PFS CPS≥1 7.6 vs 5.6 n.s.* PFS ITT 7.5 vs 5.6 n.t.* OS in PD-L1+ (pending) OS ITT (pending)	CPS≥10 | CPS≥1 | ITT **ORR (%):** 53 vs 40 | 45 vs 38 | 41 vs 36 **DCR (%):** 65 vs 54 | 59 vs 54 | 56 vs 52 **DOR (mos):** 19 vs 7 | 10 vs 7 | 10 vs 6	29%, ≥ 6

* By hierarchical testing (n.s. not significant, n.t. not tested)
^ exploratory, not powered

Cortes et al, ASCO 2020, Rugo et al, SABCS 2020

Safety of IO in metastatic TNBC

Organ-specific Immune-related Adverse Events in metastatic TNBC trials (n>1000 patients)

irAE		All grades (%)	Grade 3-4 (%)	Grade 5 (%)
Dermatologic	Pruritis, Rash	18	0.5	0
Endocrine	Hypothyroidism	12	0	0
	Hyperthyroidism	5	0.1	0
Gastro-intestinal	Hepatitis; elevated transaminases	10	3	0.2
	Colitis, diarrhea	2.5	0.45	0
Hematologic	Prespecified autoimmune anemia, lymphopenia, thrombocytopenia and clotting abnormalities	4	1	0.2
Respiratory	Pneumonitis	3	0.5	0.1
Other (<1%)	Adrenal insufficiency, type 1 diabetes, ocular, myositis, neurological/myositis, nephritis/elevated creatinine	<1	<0.5	0

irAE incidence in mTNBC (any grade)

- Single agent: 18.5%
- Higher in combination trials:
  - 57% atezolizumab+nab-pac
  - 42% nab-pac monotherapy

Management guidelines ASCO/NCCN

(Brahmer et al, J Clin Oncol 2018)

D'Abreo and Adams. Nat Rev Clin Oncol 2019

Summary IO in advanced TNBC

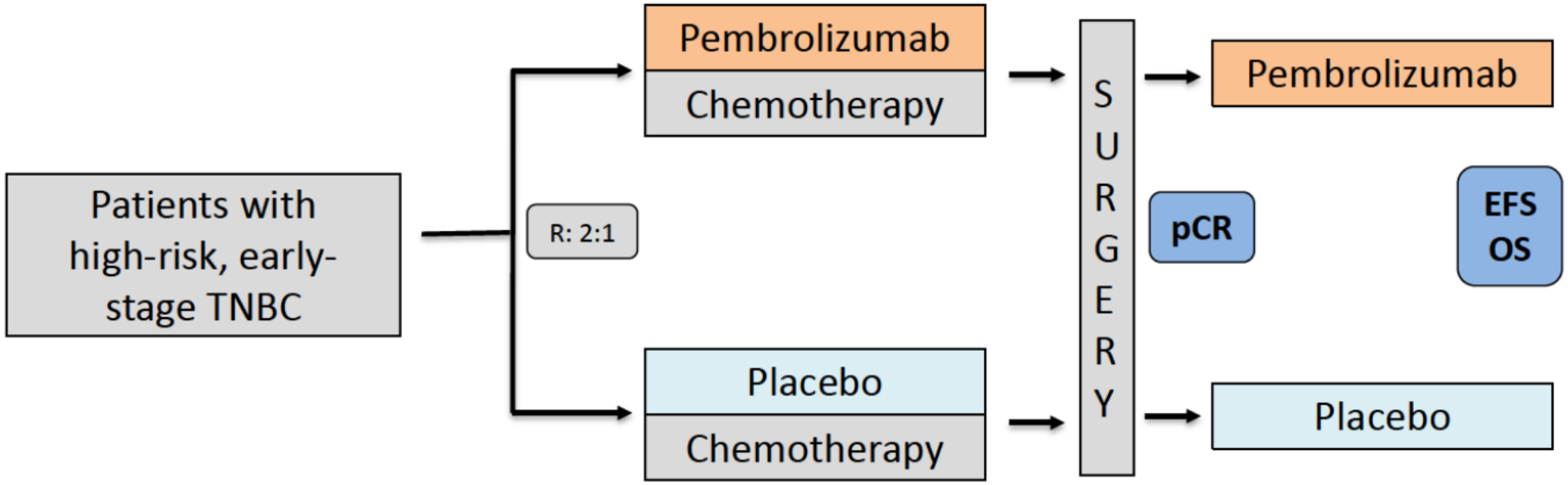
- Combining immune checkpoint inhibitors with chemotherapy has been demonstrated in two RPh3 trials to improve PFS. FDA approval only for pembrolizumab in PD-L1+ mTNBC.
- OS data appear promising.
- PD-L1 is an imperfect biomarker although the best to date. Degree of positivity associated with IO efficacy.
- Dilemma of different companion diagnostics and thresholds. Required hierarchical testing in trials and complicates clinical decision-making.

<u>Unmet needs & unanswered questions</u>

- De-escalation: Does every patient need chemotherapy? Who will do as well with IO monotherapy? Predictive markers?
- Effective therapies for PD-L1- mTNBC sorely needed
- Despite progress for PD-L1+ mTNBC, OS still too low
    - Other alternatives to augment durable immune response are needed

Neoadjuvant

Keynote 522 study schema



Co-primary endpoints: pCR rate and EFS

Key secondary endpoint: OS

Chemo= paclitaxel/carbo→AC Q3 wks x 4
Pembro continued Q3wks adjuvantly x 9 cycles

Keynote 522: pCR

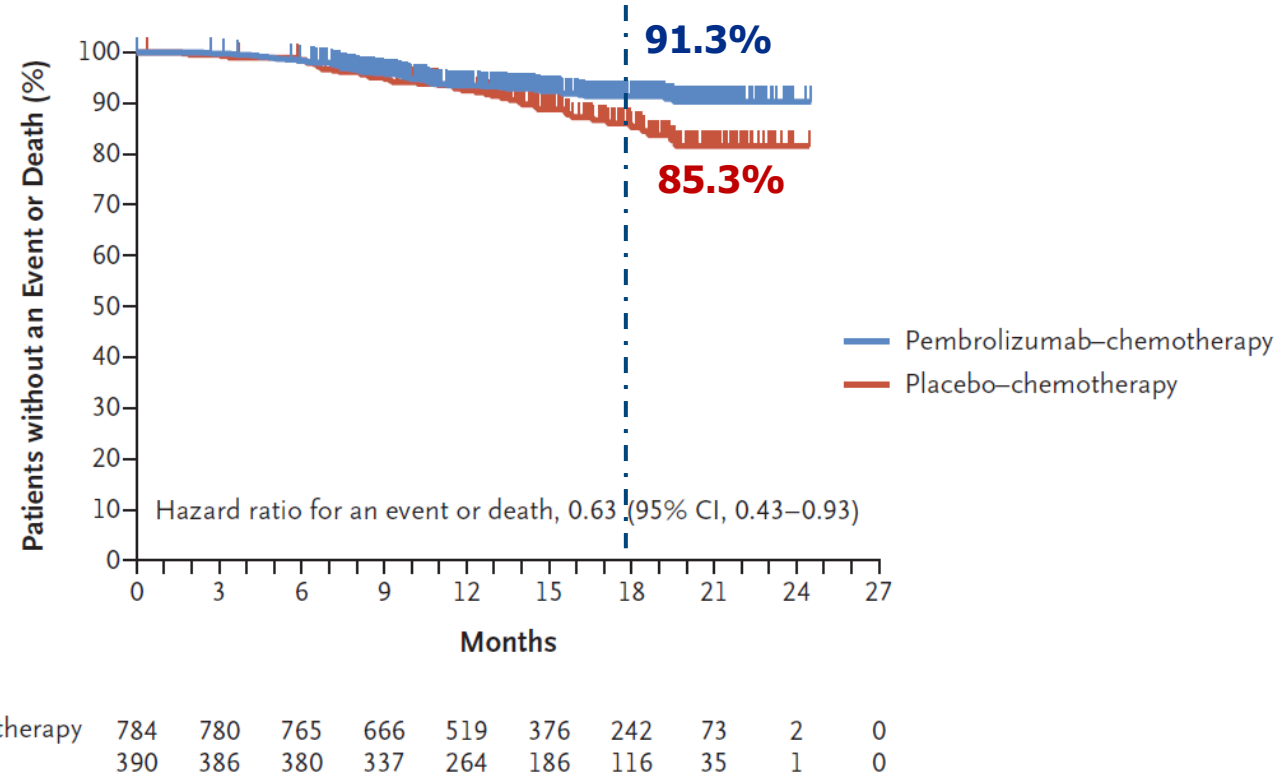
Table 2. Pathological Complete Response, According to Pathological Stage.*

Variable	Pembrolizumab–Chemotherapy (N = 401)	Placebo–Chemotherapy (N = 201)	Estimated Treatment Difference¨	P Value
			percentage points (95% CI)	
Pathological stage ypT0/Tis ypN0				
No. of patients	260	103		
Percentage of patients with response (95% CI)	64.8 (59.9–69.5)	51.2 (44.1–58.3)	13.6 (5.4–21.8)	P<0.001
Pathological stage ypT0 ypN0				
No. of patients	240	91		
Percentage of patients with response (95% CI)	59.9 (54.9–64.7)	45.3 (38.3–52.4)	14.5 (6.2–22.7)	
Pathological stage ypT0/Tis				
No. of patients	275	108		
Percentage of patients with response (95% CI)	68.6 (63.8–73.1)	53.7 (46.6–60.8)	14.8 (6.8–23.0)	

P Schmid et al *N Engl J Med* 2020;382:810-21.

Keynote 522: Event Free Survival (EVS)

EVS: “Progression of disease that precludes surgery, local or distant recurrence, second primary malignancy (breast or other cancers) or death due to any cause.”



No. at Risk										
Pembrolizumab–chemotherapy	784	780	765	666	519	376	242	73	2	0
Placebo–chemotherapy	390	386	380	337	264	186	116	35	1	0

P Schmid et al *N Engl J Med* 2020;382:810-21.

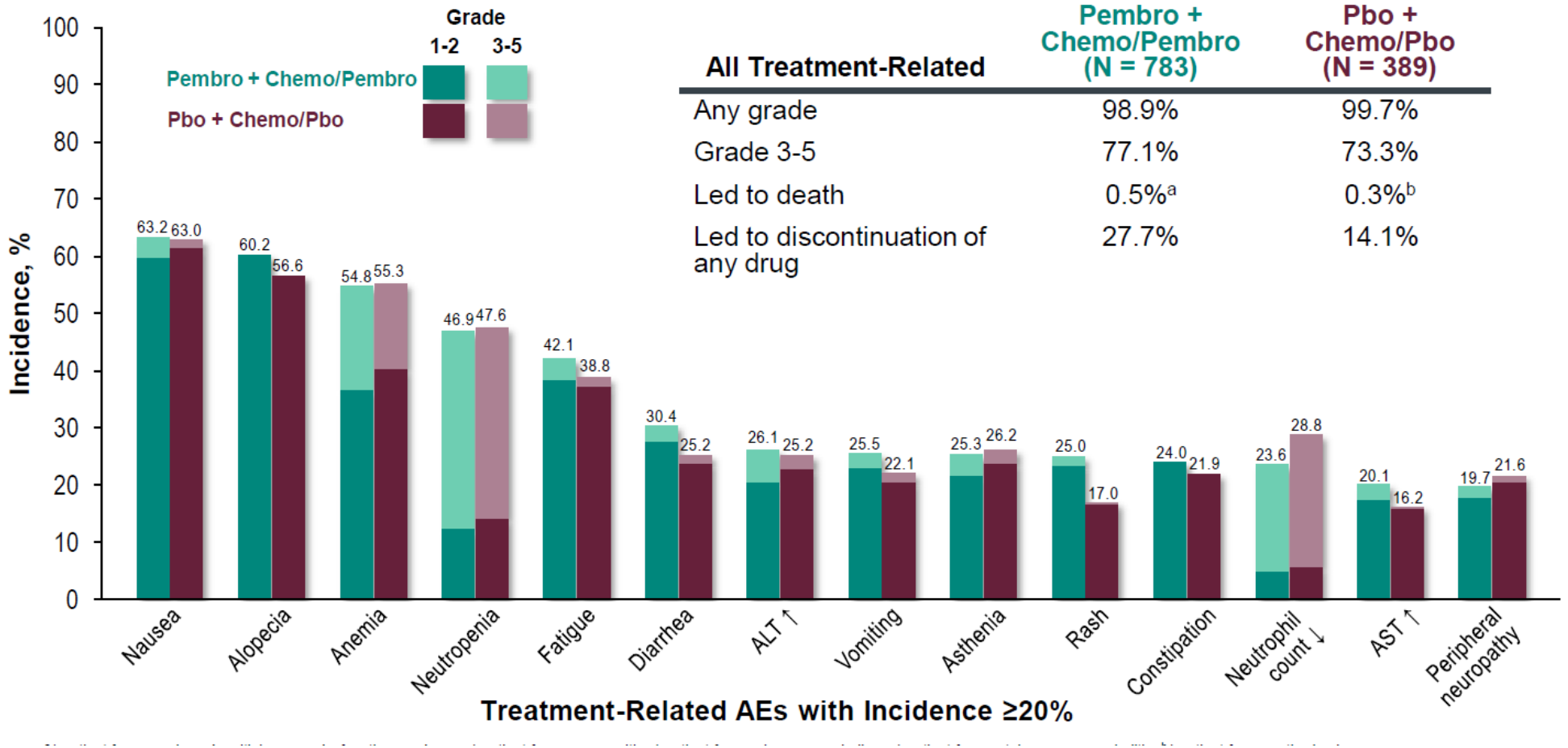
Keynote-522: Toxicity Profile

Event	Pembrolizumab–Chemotherapy (N=781)		Placebo–Chemotherapy (N=389)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any adverse event	777 (99.5)	633 (81.0)	389 (100.0)	295 (75.8)
Treatment-related adverse event†	773 (99.0)	600 (76.8)	388 (99.7)	281 (72.2)
Nausea	490 (62.7)	26 (3.3)	246 (63.2)	5 (1.3)
Alopecia	471 (60.3)	14 (1.8)	220 (56.6)	8 (2.1)
Anemia	430 (55.1)	142 (18.2)	215 (55.3)	58 (14.9)
Neutropenia	365 (46.7)	270 (34.6)	183 (47.0)	129 (33.2)
Fatigue	321 (41.1)	27 (3.5)	147 (37.8)	6 (1.5)
Diarrhea	230 (29.4)	17 (2.2)	92 (23.7)	5 (1.3)
Elevated alanine aminotransferase level	199 (25.5)	41 (5.2)	96 (24.7)	9 (2.3)
Vomiting	199 (25.5)	18 (2.3)	85 (21.9)	6 (1.5)
Asthenia	191 (24.5)	25 (3.2)	99 (25.4)	9 (2.3)
Constipation	185 (23.7)	0	82 (21.1)	0
Decreased neutrophil count	185 (23.7)	146 (18.7)	112 (28.8)	90 (23.1)
Rash	170 (21.8)	7 (0.9)	59 (15.2)	1 (0.3)
Peripheral neuropathy	154 (19.7)	15 (1.9)	82 (21.1)	4 (1.0)
Adverse event of interest‡	304 (38.9)	101 (12.9)	71 (18.3)	7 (1.8)
Infusion reaction	132 (16.9)	20 (2.6)	43 (11.1)	4 (1.0)
Hypothyroidism	107 (13.7)	3 (0.4)	13 (3.3)	0
Hyperthyroidism	36 (4.6)	2 (0.3)	4 (1.0)	0
Severe skin reaction	34 (4.4)	30 (3.8)	4 (1.0)	1 (0.3)
Adrenal insufficiency	18 (2.3)	10 (1.3)	0	0

~ Δ 5%

P Schmid et al *N Engl J Med* 2020;382:810-21.

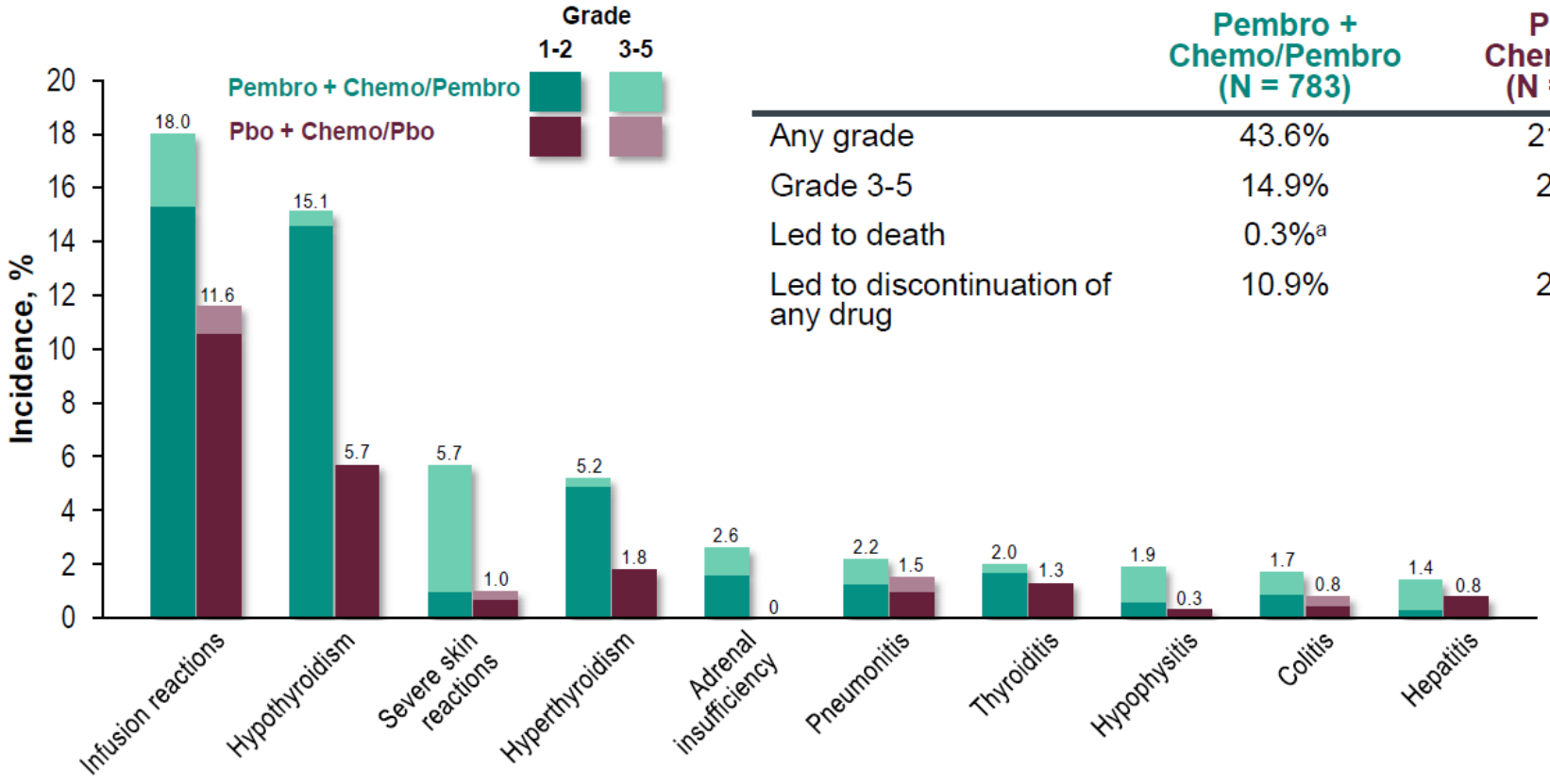
Keynote 522: AE's in combined phases



All Treatment-Related	Pembro + Chemo/Pembro (N = 783)	Pbo + Chemo/Pbo (N = 389)
Any grade	98.9%	99.7%
Grade 3-5	77.1%	73.3%
Led to death	0.5%[a]	0.3%[b]
Led to discontinuation of any drug	27.7%	14.1%

P Schmid et al *Ann Onc* 2021;32:VP7-2021.

Keynote 522- iRAEs in combined phase



	Pembro + Chemo/Pembro (N = 783)	Pbo + Chemo/Pbo (N = 389)
Any grade	43.6%	21.9%
Grade 3-5	14.9%	2.1%
Led to death	0.3%[a]	0
Led to discontinuation of any drug	10.9%	2.6%

Immune-Mediated AEs and Infusion Reactions with Incidence ≥10 Patients

P Schmid et al *Ann Onc* 2021;32:VP7-2021.

Safety of IO in early TNBC

- Commonly reported AEs similar between arms and mostly driven by chemotherapy
- Increased toxicity (Δ to chemotherapy arm)
  - Treatment-related G3/4 AE (3% in IMpassion031, 5% in KN-522, 7% in NeoTRIP)
  - Treatment-related G5 AE (0 in IMpassion031, 0.4% in KN-522, 0.7% in NeoTRIP)
  - IrAEs (10% in IMpassion031, 20% in KN-522)

- serious irAEs (such as adrenal insufficiency) similar to other studies w/PD-1 mAB. Patient education and early intervention is key.
- Patients should be informed that endocrinopathies can result in life-long requirement for monitoring and supplementation.

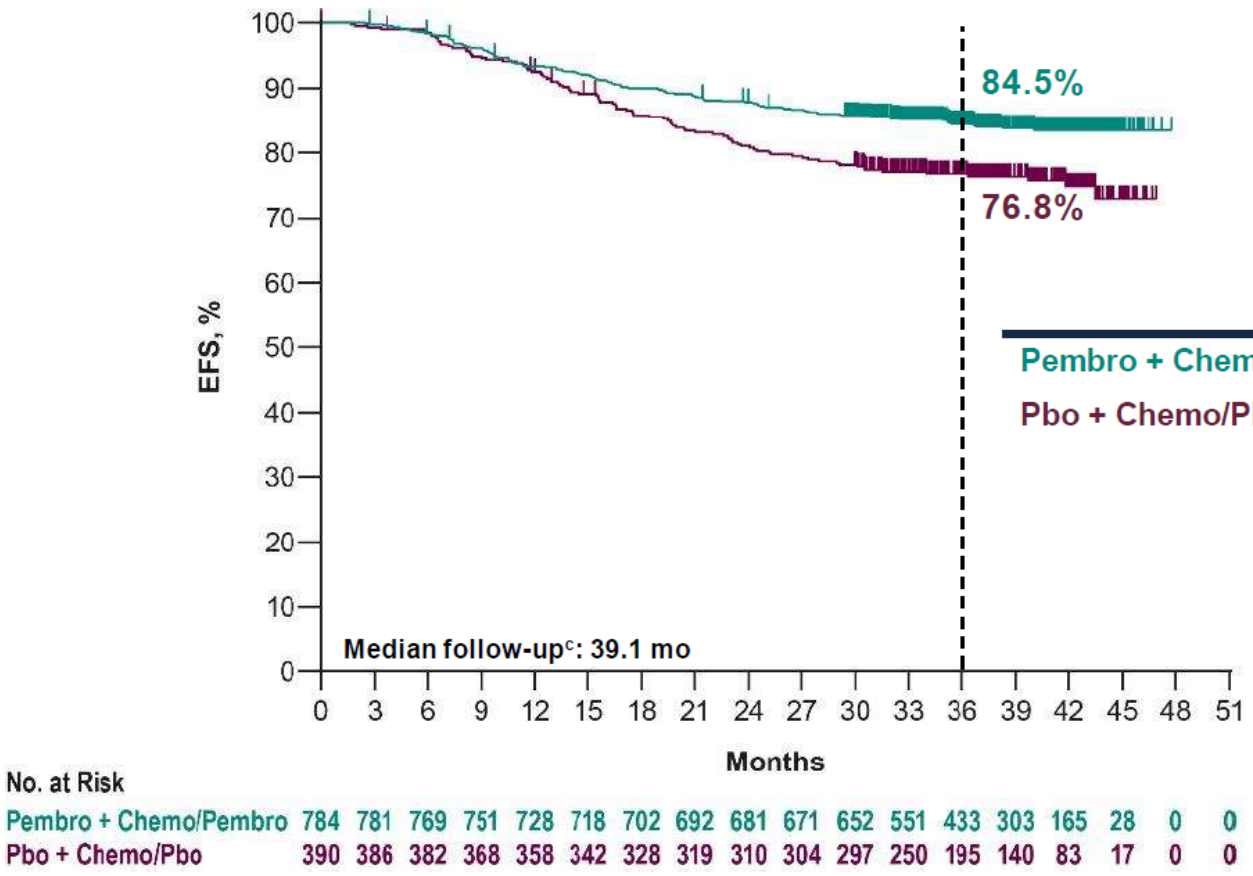
ESMO VIRTUAL PLENARY

KEYNOTE-522: Phase 3 Study of Neoadjuvant Pembrolizumab + Chemotherapy versus Placebo + Chemotherapy, Followed by Adjuvant Pembrolizumab versus Placebo for Early-Stage Triple-Negative Breast Cancer

Peter Schmid[1], Javier Cortes[2], Rebecca Dent[3], Lajos Pusztai[4], Heather McArthur[5], Sherko Kümmel[6], Jonas Bergh[7], Carsten Denkert[8], Yeon Hee Park[9], Rina Hui[10], Nadia Harbeck[11], Masato Takahashi[12], Michael Untch[13], Peter A. Fasching[14], Fatima Cardoso[15], Yu Ding[16], Konstantinos Tryfonidis[17], Gursel Aktan[17], Vassiliki Karantza[17], Joyce O'Shaughnessy[18]

1. Centre for Experimental Cancer Medicine, Barts Cancer Institute, Queen Mary University London, London, UK; 2. International Breast Cancer Center, Quirón Group, Madrid and Barcelona, Spain and Vall d'Hebron Institute of Oncology, Barcelona, Spain; 3. National Cancer Center Singapore, Duke–National University of Singapore Medical School, Singapore; 4. Yale School of Medicine, Yale Cancer Center, New Haven, CT, USA; 5. Breast Oncology, Cedars-Sinai Medical Center, Los Angeles, CA, USA; 6. Breast Unit, Kliniken Essen-Mitte, Essen, Germany; 7. Department of Oncology-Pathology, Karolinska Institutet and Breast Cancer Centre, Cancer theme, Karolinska University Hospital, Solna, Sweden; 8. Institute of Pathology, Philipps-University Marburg and University Hospital Marburg (UKGM), Marburg, Germany; 9. Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; 10. Westmead Breast Cancer Institute, Westmead Hospital and the University of Sydney, Sydney, NSW, Australia; 11. Breast Center, LMU University Hospital, Munich, Germany; 12. Department of Breast Surgery, Hokkaido Cancer Center, Sapporo, Japan; 13. Breast Cancer Center, Helios Klinikum Berlin-Buch, Berlin, Germany; 14. University Hospital Erlangen, Comprehensive Cancer Center Erlangen-EMN, Erlangen, Germany; 15. Breast Unit, Champalimaud Clinical Center/Champalimaud Foundation, Lisbon, Portugal; 16. Biostatistics, Merck & Co., Inc., Kenilworth, NJ, USA; 17. Merck Research Laboratories, Merck & Co., Inc., Kenilworth, NJ, USA; 18. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, TX, USA

Keynote-522: EFS, interim analysis #4



	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	15.7%	0.63[a] (0.48-0.82)	0.00031[b]
Pbo + Chemo/Pbo	23.8%		

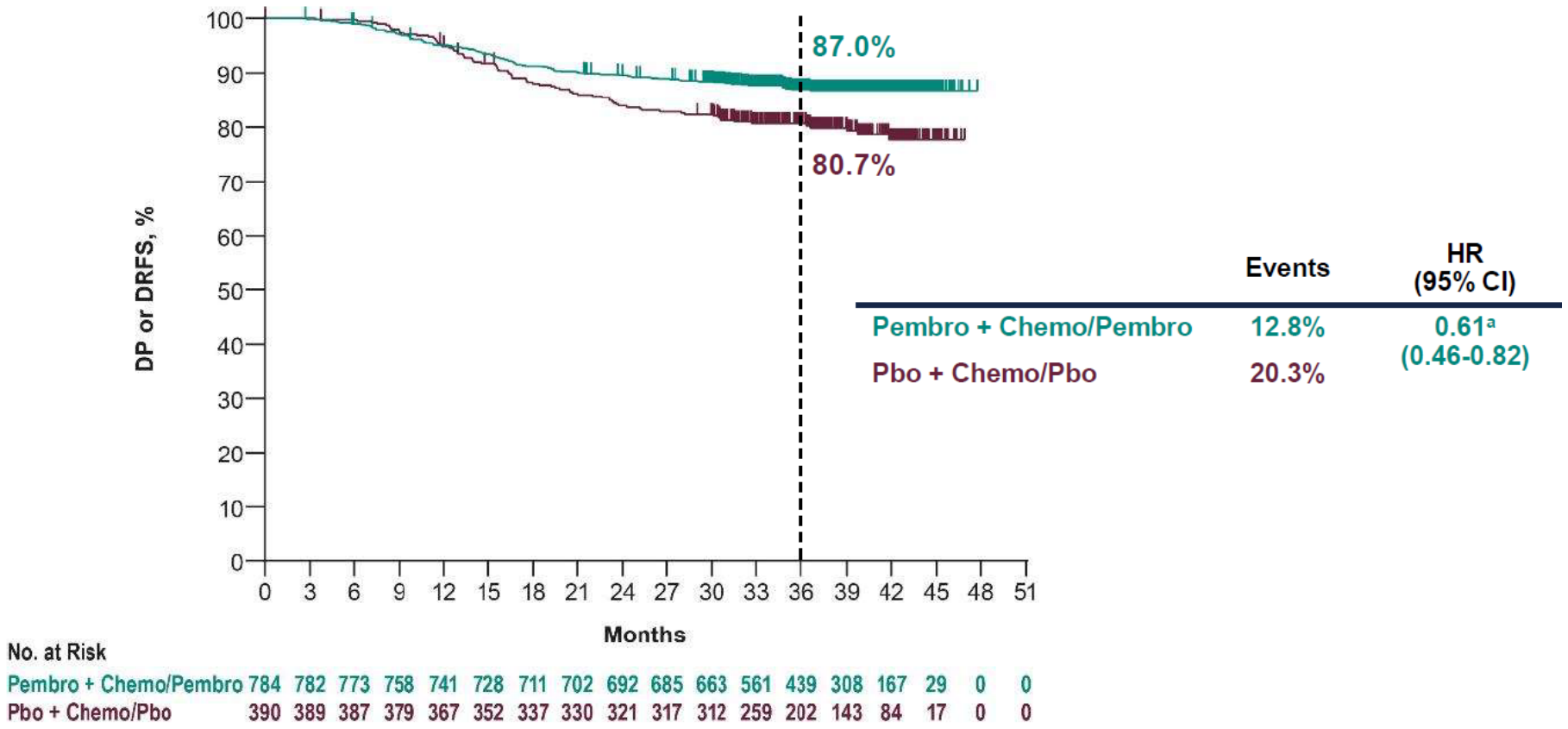
P Schmid et al *Ann Onc* 2021;32:VP7-2021.

Keynote 522: EFS by Category

Event	All Subjects, N = 1174	
	Pembro + Chemo/Pembro N = 784	Pbo + Chemo/Pbo N = 390
Any EFS event	123 (15.7%)	93 (23.8%)
Progression of disease that precludes definitive surgery	14 (1.8%)	15 (3.8%)
Local recurrence[a]	28 (3.6%)	17 (4.4%)
Distant recurrence	60 (7.7%)	51 (13.1%)
Secondary primary malignancy[b]	6 (0.8%)	4 (1.0%)
Death	15 (1.9%)	6 (1.5%)

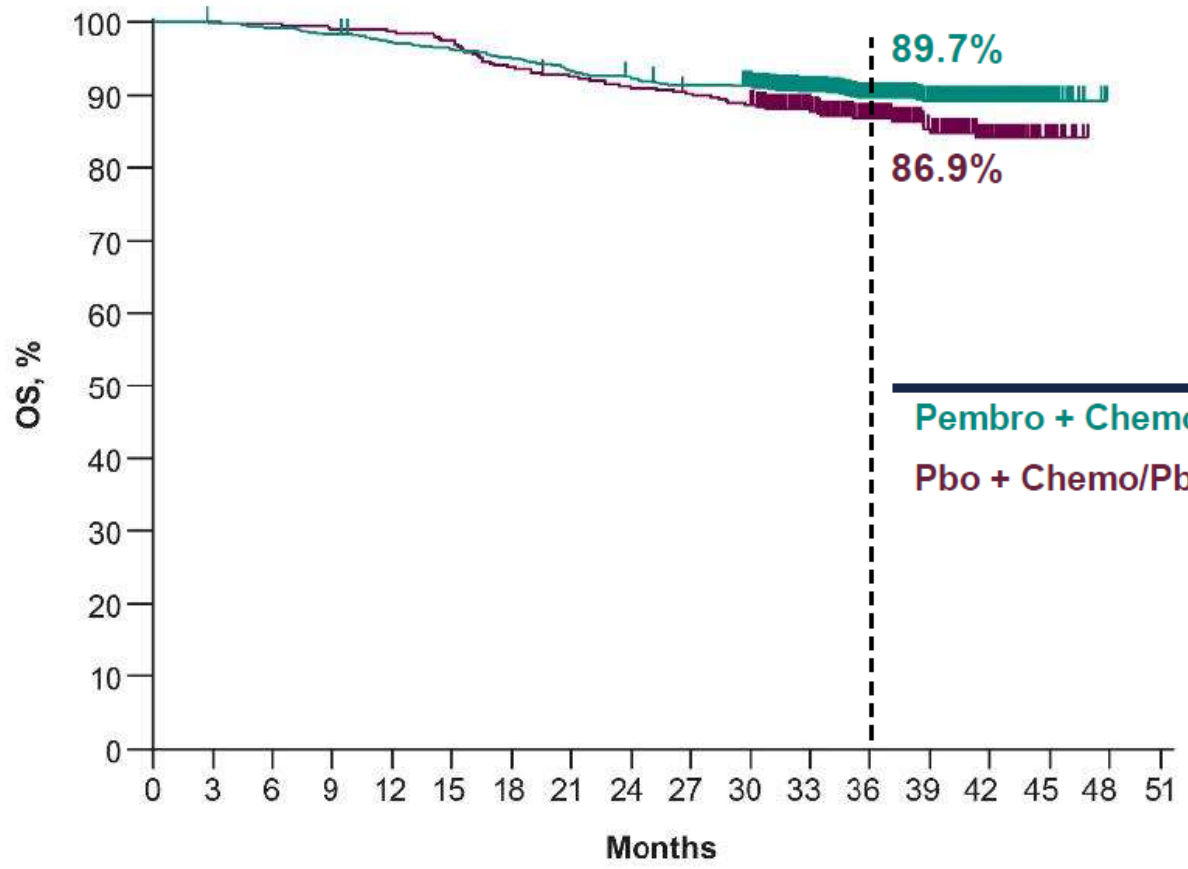
P Schmid et al *Ann Onc* 2021;32:VP7-2021.

Keynote-522: Distant RFS



P Schmid et al *Ann Onc* 2021;32:VP7-2021.

Keynote-522: 36 month OS

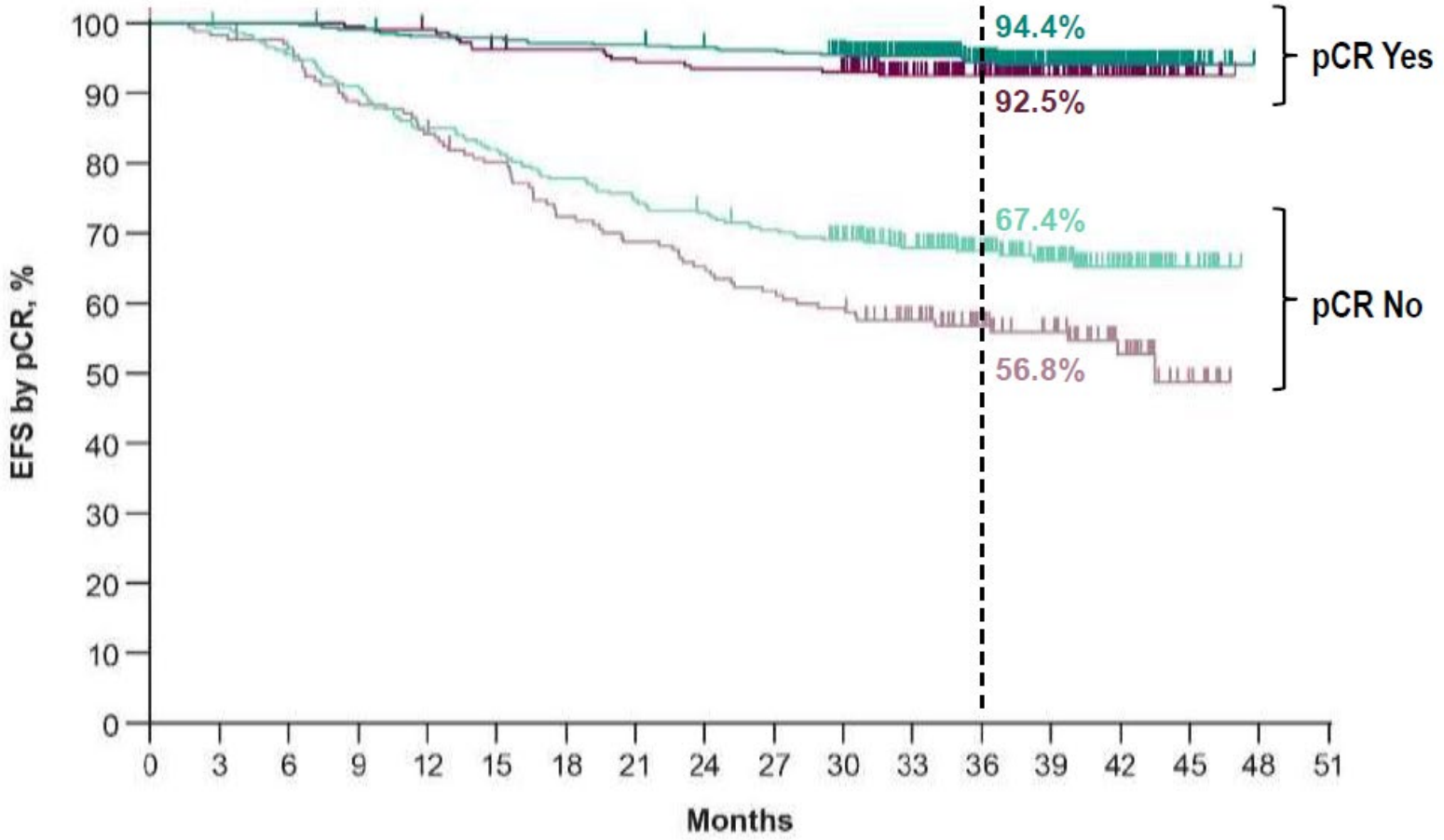


	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	10.2%	0.72[a] (0.51-1.02)	0.03214[b]
Pbo + Chemo/Pbo	14.1%		

k

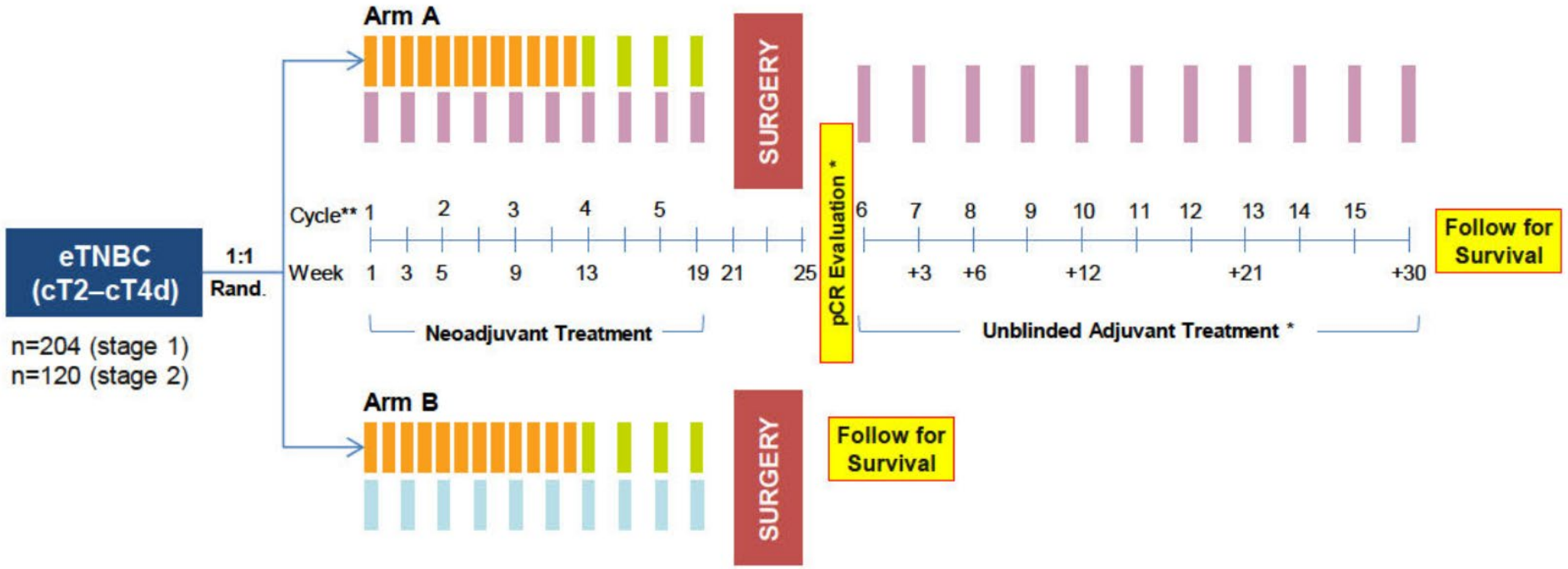
P Schmid et al *Ann Onc* 2021;32:VP7-2021.

EFS by pCR (ypT0/ypN0)



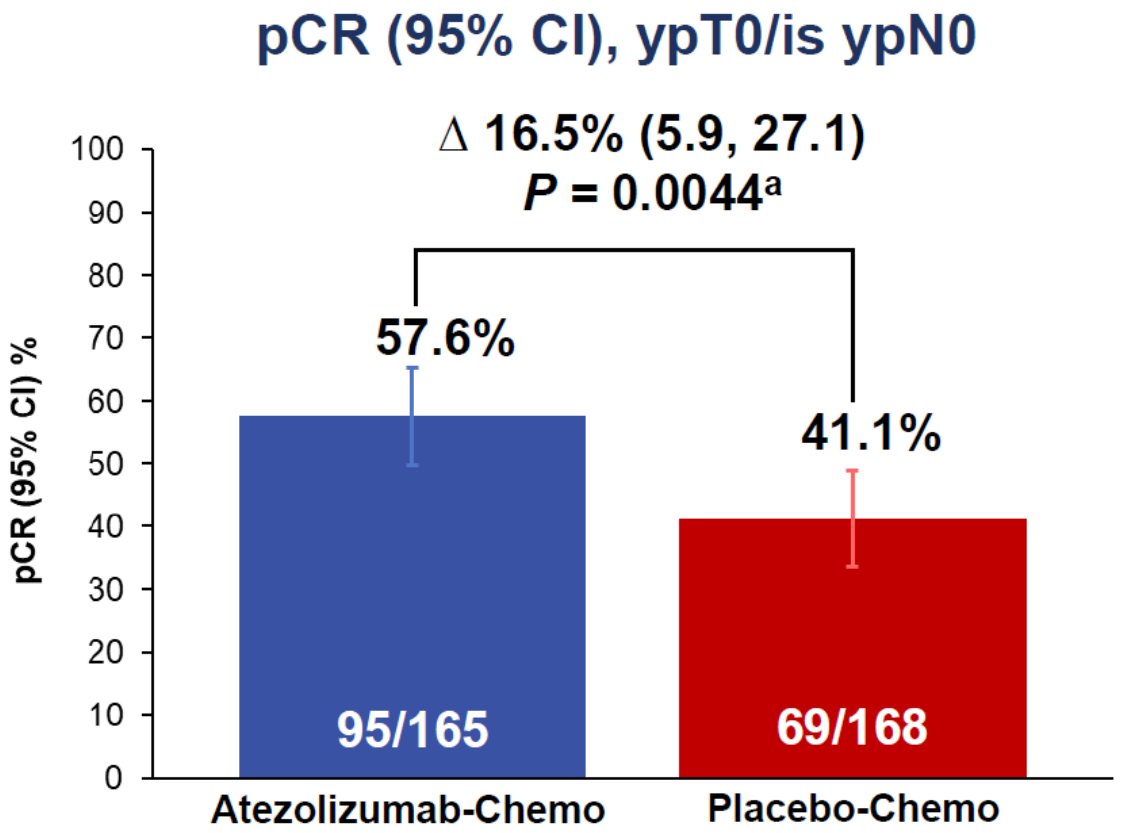
P Schmid et al *Ann Onc* 2021;32:VP7-2021.

Impassion 031



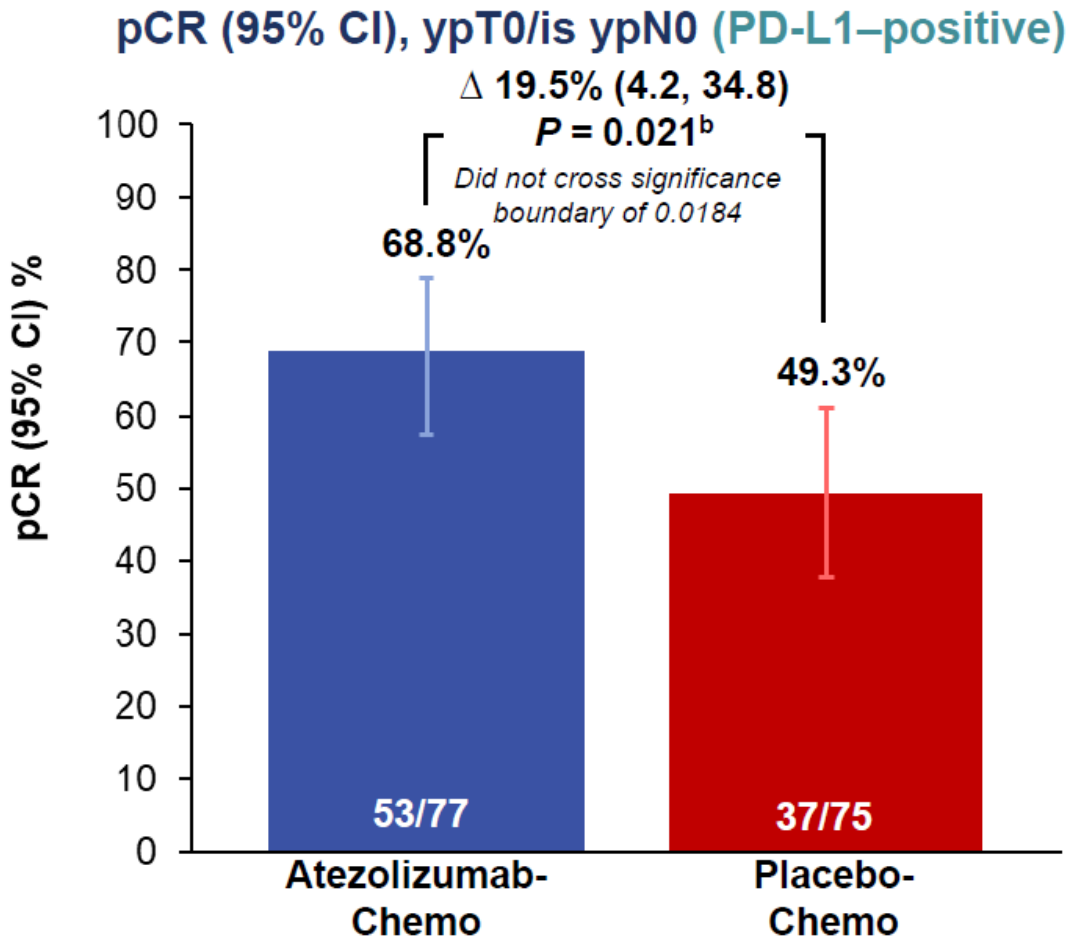
Mittendorf EA et al. *Lancet*. 2020 Oct 10;396(10257):1090-1100.

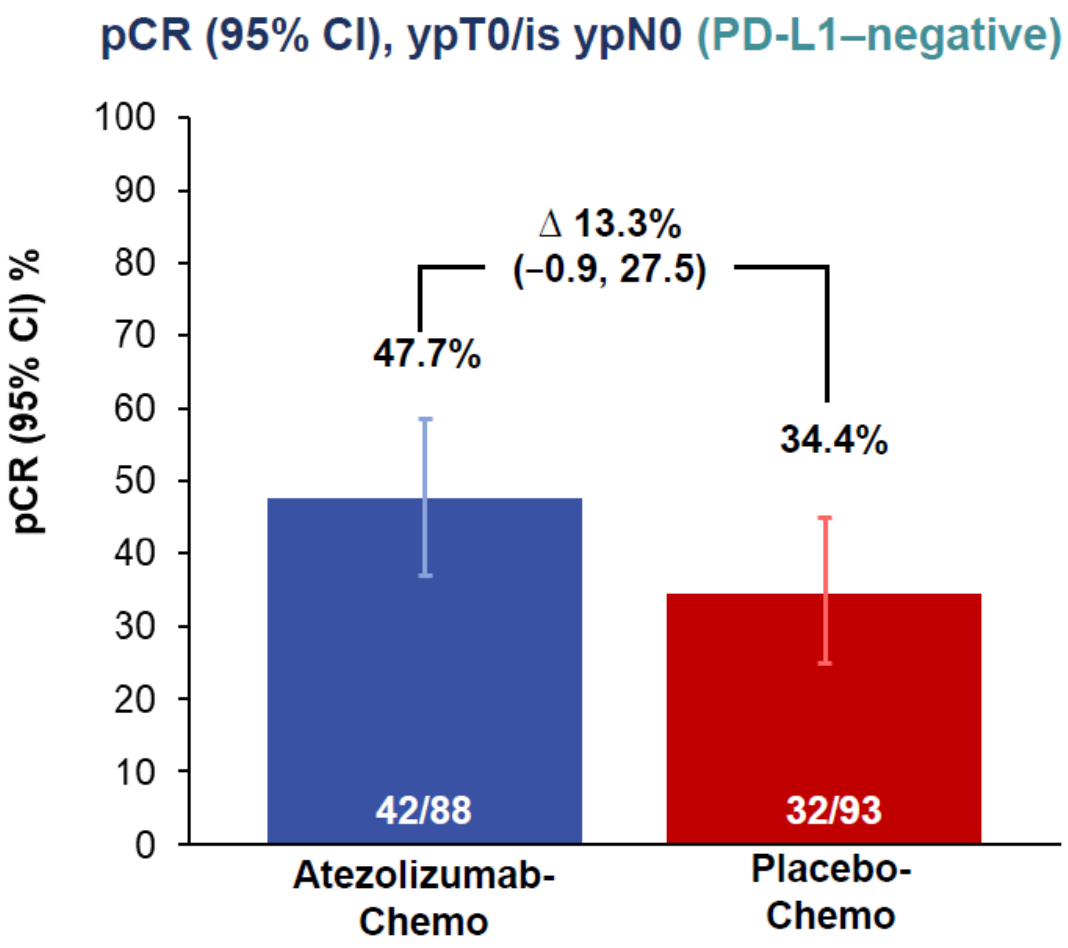
Impassion031: Co-primary endpoint pCR ITT



Mittendorf EA et al. *Lancet*. 2020 Oct 10;396(10257):1090-1100.

Impassion031: Co-primary endpoint pCR in PDL1+ tumors





Mittendorf EA et al. *Lancet*. 2020 Oct 10;396(10257):1090-1100.

Phase 3 IO + chemo neoadjuvant TNBC trials

Trial	Target	Chemotherapy	N	Open (Estimated Completion)	Primary endpoint(s)	Secondary endpoints	Eligibility	LN positive
IMpassion031 (NCT03197935)	PD-L1	Nab-paclitaxel, ddAC	333	July 2017 (Sept 2021)	**pCR ITT 58 vs 41%** pCR PD-L1+ 69 vs 49%$^{n.s.*}$	EFS, DFS, OS (all +trend), safety, PRO	T1N1-3 T2-4N0-3	36%
KEYNOTE-522 (NCT03036488)	PD-1	Paclitaxel + carbo, AC/EC	1150 (602)	March 2017 (March 2025)	**pCR ITT 65 vs 51%** EFS ITT (+ trend)	pCR PD-L1+ 69 vs 55%, EFS PD-L1+, OS	T1cN1-2 T2-4N0-2	51%
NeoTRIPaPDL1 (NCT02620280)	PD-L1	Nab-paclitaxel + carbo, postop AC/EC/FEC	280	April 2016 (October 2022)	5 yr-EFS (pending)	pCR ITT 44 vs 41%$^{n.s.}$, safety	T1cN1 T2N1 T3-4N0-3	87%
NSABP B-59 (NCT03281954)	PD-L1	Paclitaxel+ Carboplatin, AC/EC	1520	December 2017 (June 2024)	pCR (pending) EFS (pending)	OS, RFI, dDFS (all pending)	T1cN1-3 T2-3N0-3	n/a

IMpassion031: Atezolizumab 840/PLA q2w + nab-paclitaxel 125 q1w x 12 – Atezolizumab/PLA q2w + ddAC x 4 - surgery – atezolizumab 1200/PLA q3w to 1 year. Stratification stage II/III, PD-L1+/-.
KEYNOTE-522: Pembrolizumab 200/PLA q3w + weekly paclitaxel 80 + carboAUC1.5 qw or AUC 5 q3w x 4 cycles – pembrolizumab 200/PLA q3w + AC q3w x 4 - surgery – pembrolizumab 200/PLA q3w x 9 cycles. Stratification LN+/-, T1-2/3-4, Carbo qw/q3w.
NeoTRIP: open label Atezolizumab 1200/PLA q3w + Carboplatin AUC2 D1, 8 of 21 days + Nab-paclitaxel 125 D1, 8 of 21 days x 8 – surgery - AC/EC/FEC q3w (without adjuvant Atezolizumab/PLA). Stratification n/a.
NSABP B-59/GeparDouze: Weekly Paclitaxel 80 x 12 + Carboplatin AUC 5 q3w x 4 + Atezolizumab 1200 q3w x 4 - AC (or EC) q2-3w x 4 - surgery – Atezolizumab 1200 q3w until 1 year

* By hierarchical testing

Schmid et al, NEJM 2020, Mittendorf et al, Lancet 2020, Gianni et al SABCS 2019, Mittendorf et al, SABCS 2020

PD-L1 as biomarker (in neoadj setting)

- ✓PD-L1 positivity predicts higher likelihood of pCR but not who benefits from added IO

	IMpassion031	KEYNOTE-522	NeoTRIP
Assay (cutoff)	SP142 (IC 1%)	22C3 (CPS 1%)	SP142 (IC 1%)
PD-L1+ prevalence	46%	83%	54%
pCR (%): PD-L1+ | ITT | PD-L1-	**69 | 58 | 48**	**69 | 65 | 45**	**52 | 43 | 31**
pCR Δ: PD-L1+ | ITT | PD-L1-	**20 | 17 | 13**	**14 | 14 | 15**	**4 | 3 | 0**

Summary IO in early TNBC

- Combining immune checkpoint inhibitors with neoadjuvant chemotherapy has been demonstrated in two RPh3 trials to improve pCR rates.
- Significant improvement in EFS and OS at 36 months (Keynote-522).
- Toxicity is manageable.
- Adjuvant capecitabine becomes increasingly unnecessary in patients who receive keynote-522 regien

<u>Unmet needs & unanswered questions</u>

- De-escalation: Does every patient need chemotherapy? and immunotherapy?
- Lack of predictive biomarkers
- Will longer term f/u show significant advantage to continuation of pembro after pCR?

- Optimization of chemotherapy backbone: Carboplatin? Anthracyclines? Sequencing?
- Results of adjuvant IO trials
    - A-Brave (NCT02926196, estimated completion date June 2023)
    - IMpassion030 (NCT03498716, estimated completion date December 2024)
    - SWOG S1418/BR006 (NCT02954874, estimated completion date May 2026)

Thank You!