Neoadjuvant Immunotherapy in Breast Cancer

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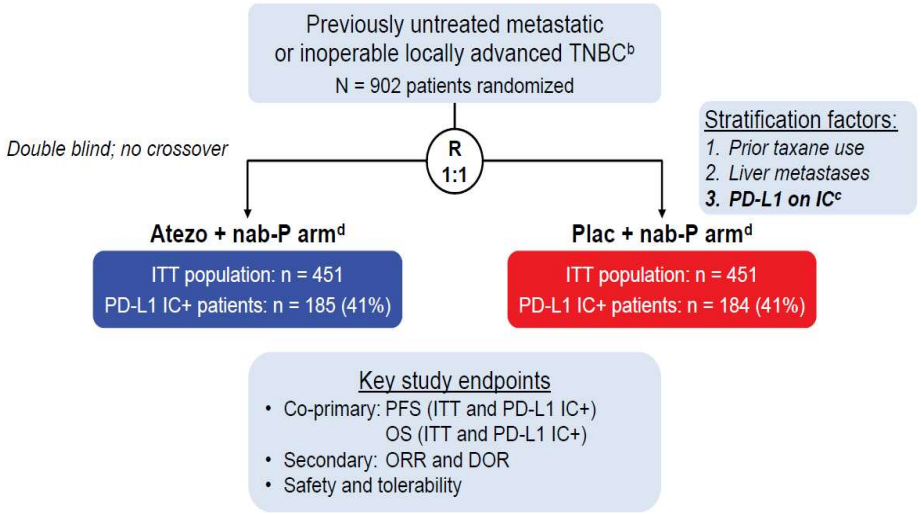
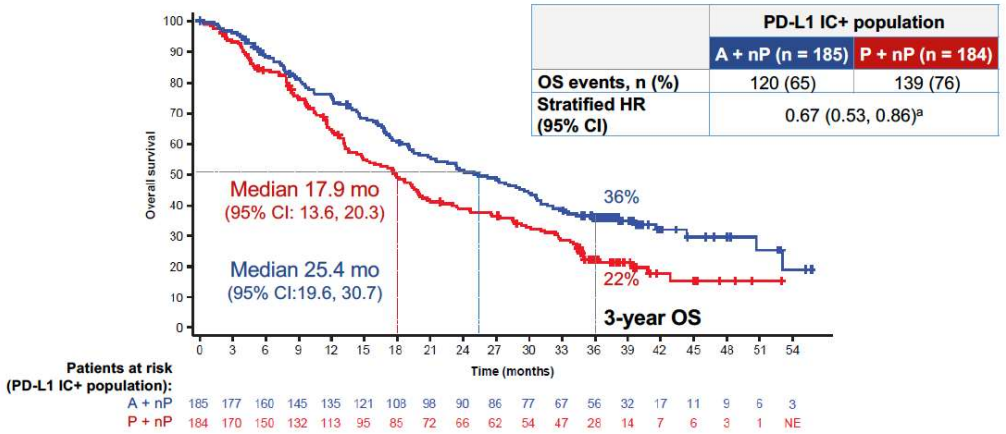
IMpassion 130



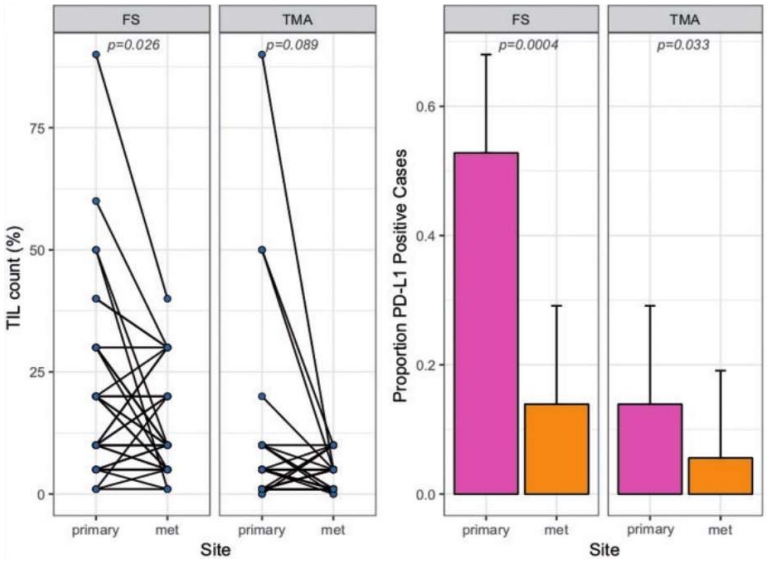


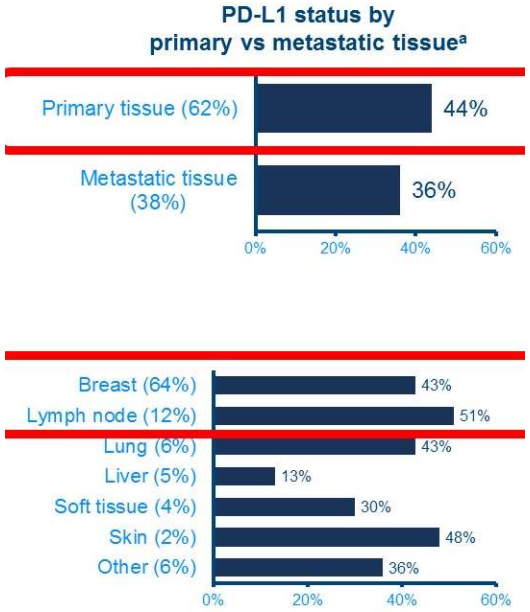
Schmid P, et al. *N Engl J Med* 2018;379:2108-2121
Emens L, et al. *ESMO* 2020

Questions

- Would the benefit of adding IO to chemotherapy be greater in an earlier disease setting?
- Will the addition of IO to chemotherapy ↑ pCR rates?
  - And if ↑ pCR rates, will this lead to improved survival?
- Is it safe to give IO before surgery?

Primary Tumors have more TILs and Higher PD-L1 Expression

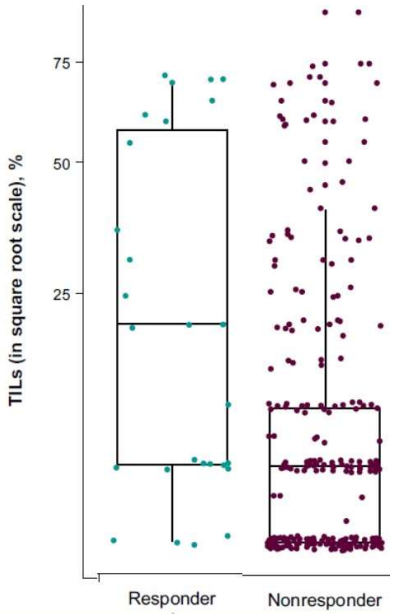




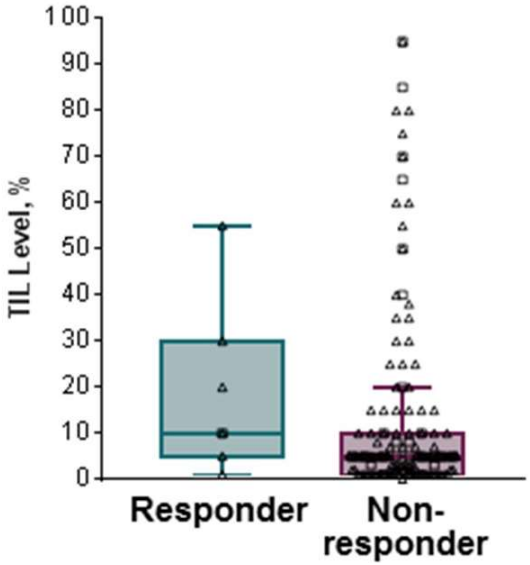
Szekely B, et al. *Ann Onc* 2018;29:2232-2239
Rugo H, et al. *ESMO* 2019

TILs are Predictive of Response to Pembrolizumab

KEYNOTE-119

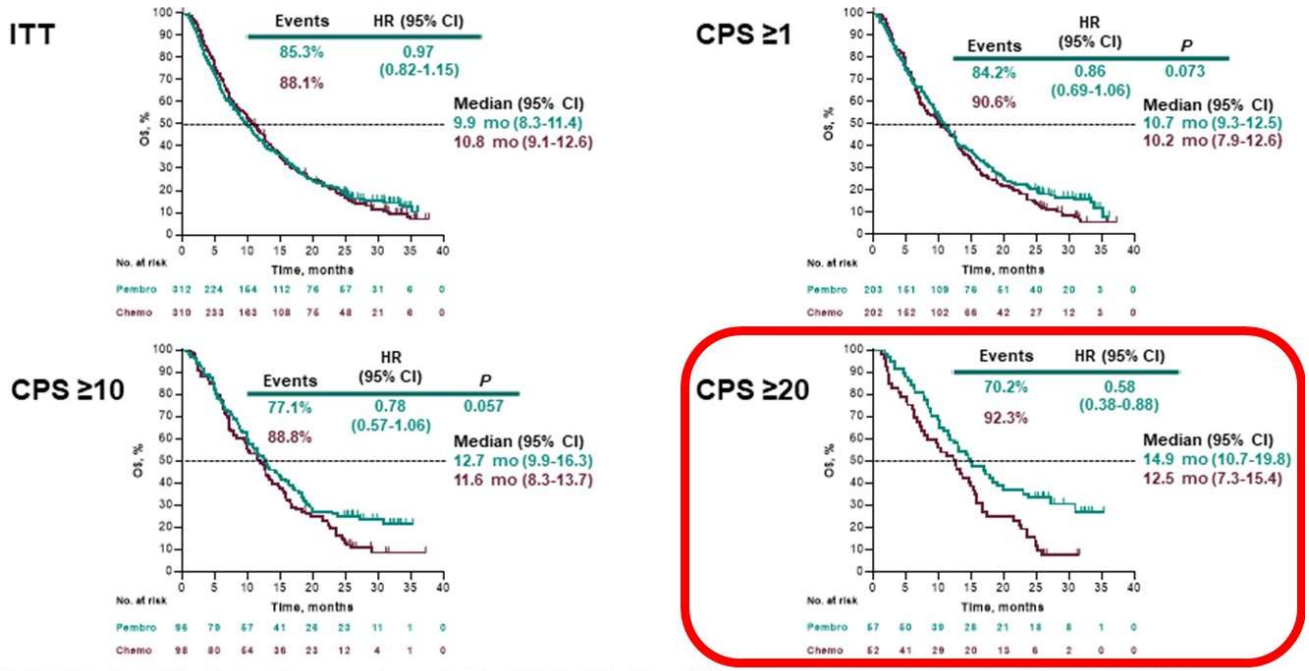


KEYNOTE-086



Loi S, et al. *SABCS* 2019

Benefit of Pembrolizumab ↑ with Greater PD-L1 Expression



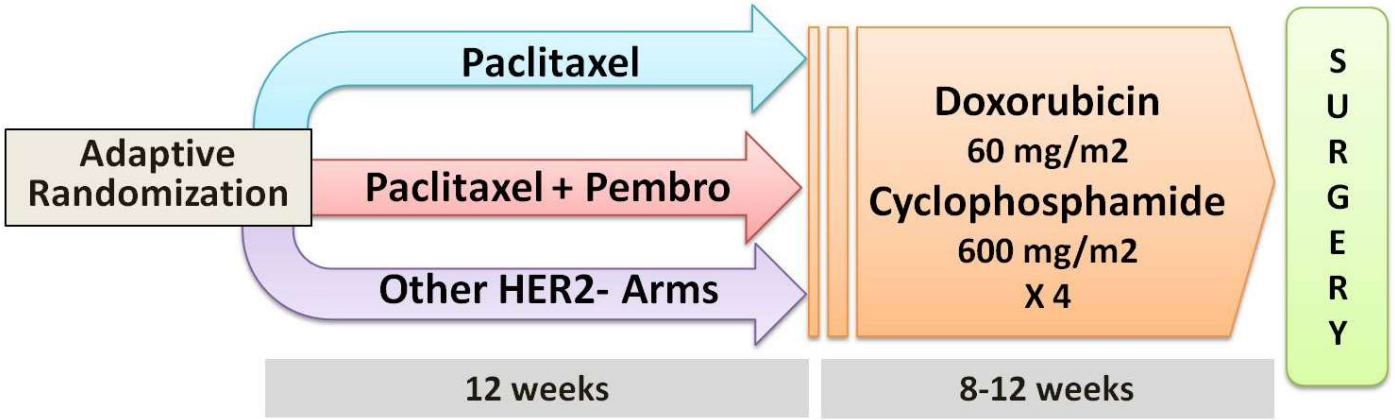
OS in the ITT, CPS ≥1 and CPS ≥10 populations were primary endpoints; OS in the CPS ≥20 population was an exploratory endpoint. Data cutoff date: April 11, 2019

Cortes J, et al. *ESMO* 2019

Neoadjuvant Trials

- I-SPY2
- Geparnuevo
- NeoTRIP
- KEYNOTE 522
- IMpassion 031

I-SPY2: Neoadjuvant Pembrolizumab



Control

Paclitaxel 80 mg/m2 every wk x 12

Experimental

Paclitaxel 80 mg/m2 every wk x 12

Pembro 200 mg every 3 wks x 4

pCR Rates

Subtype	Estimated pCR Rate (95% probability interval)		Probability, %	
	Pembro (n=69)	Control (n=181)	Probability Superior Control	Predictive Probability of Success in Phase 3 Trail
HER2-	44 (33-55)	17 (11-23)	>99.9	98.5
HR+/HER2-	30 (17-43)	13 (7-19)	>99.9	99.6
TNBC	60 (44-75)	22 (13-30)	99.6	83.4

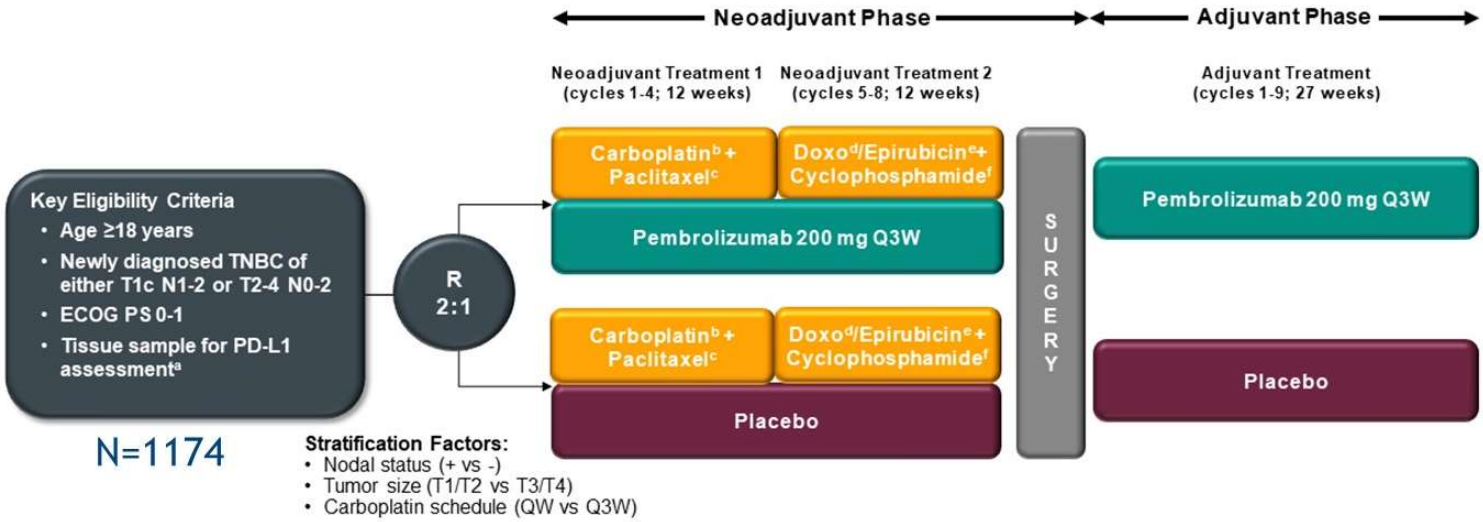
Nanda R, et al. *JAMA Oncol* 2020;6:1-9

irAEs

	Pembrolizumab (n=69) % (n)		Control (n=180) % (n)	
	All grades	Grade 3-5	All grades	Grade 3-5
Hypothyroidism	8.7 (6)	1.4 (1)	0.6 (1)	0 (0)
Hyperthyroidism	4.3 (3)	0 (0)	0 (0)	0 (0)
Adrenal Insufficiency	8.7 (6)	7.2 (5)	0 (0)	0 (0)
Hepatitis	2.9 (2)	2.9 (2)	0 (0)	0 (0)
Pneumonitis	2.9 (2)	0 (0)	1.1 (2)	0.6 (1)
Colitis	1.4 (1)	1.4 (1)	0.6 (1)	0.6 (1)
Pruritis	24.6 (17)	0 (0)	11.1 (20)	0.6 (1)

Nanda R, et al. *JAMA Oncol* 2020;6:1-9

KEYNOTE 522: Preoperative Pembro



Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

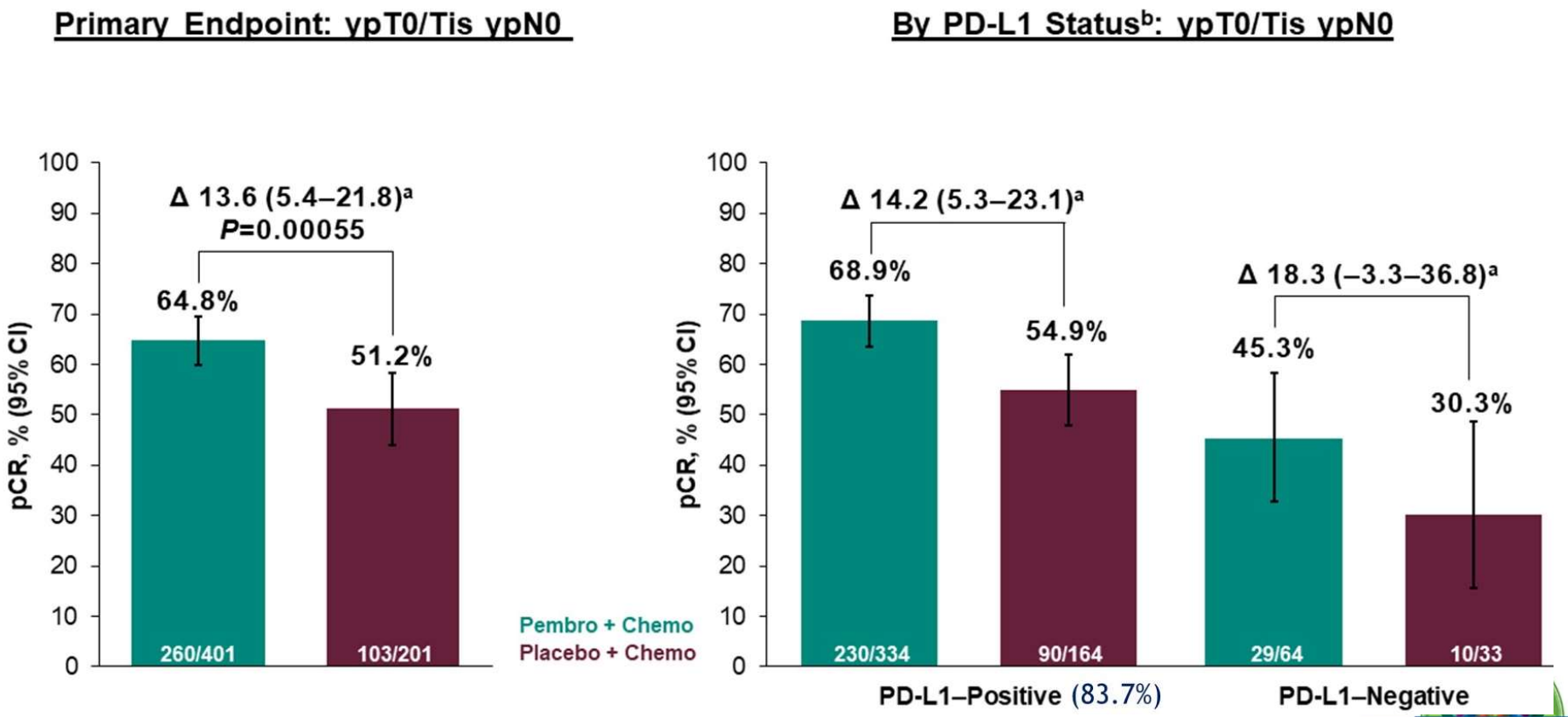
Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post treatment included)

[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.

Primary Endpoints:
pCR
EFS

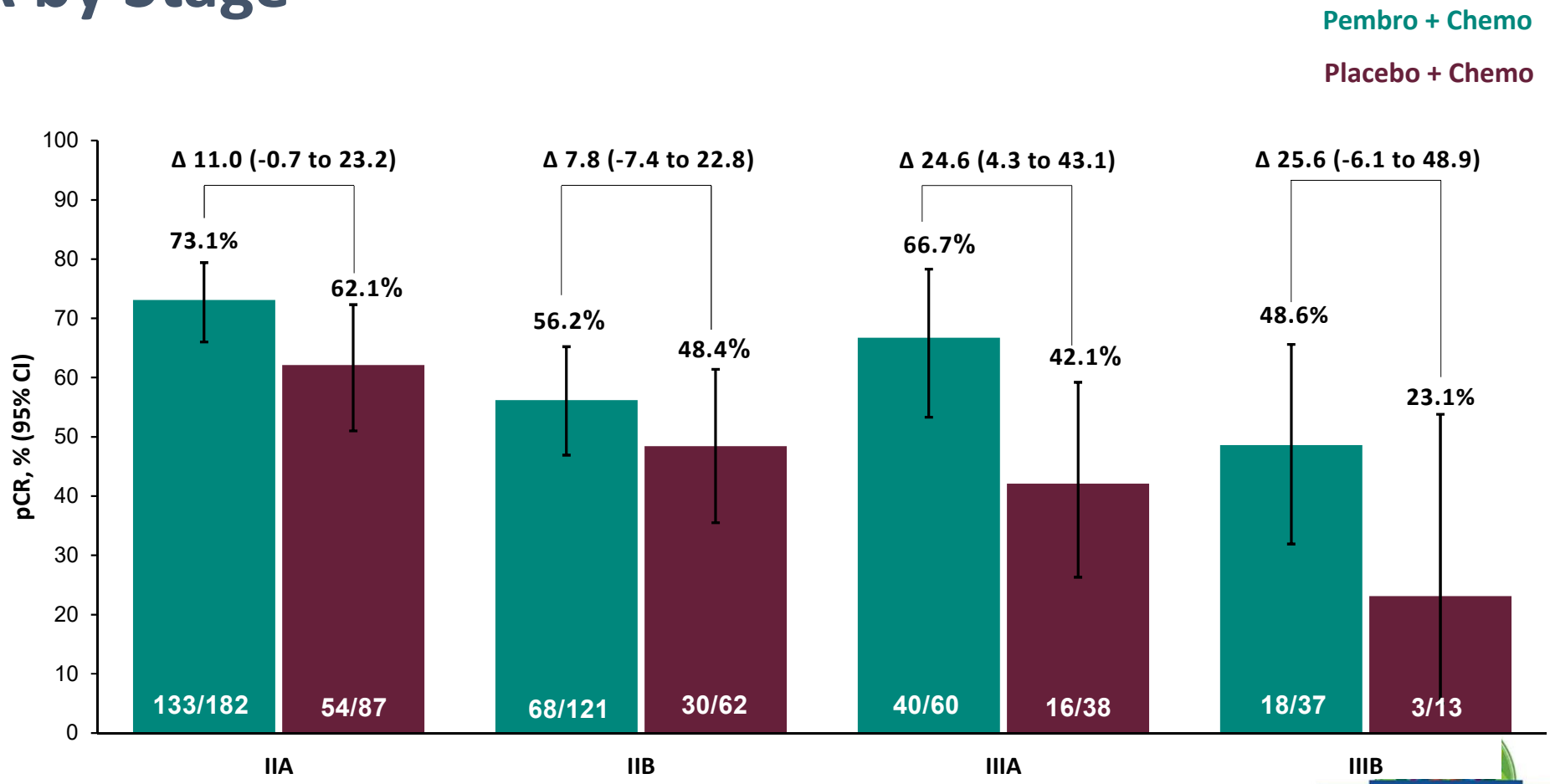
Schmid P, et al. *N Engl J Med* 2020;382:810-821

pCR



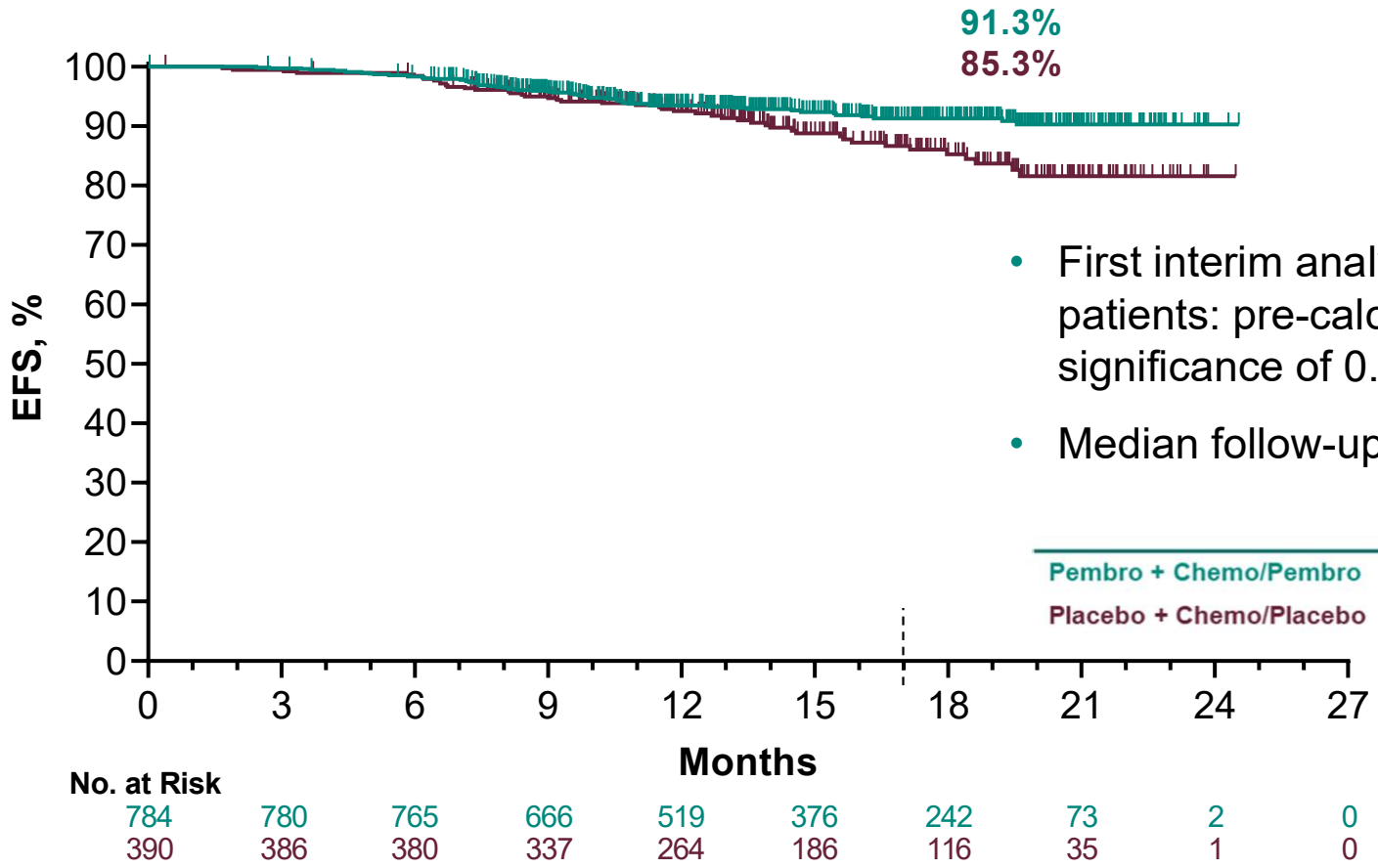
Schmid P, et al. *N Engl J Med* 2020;382:810-821

pCR by Stage



Schmid P, et al. *N Engl J Med* 2020;382:810-821

EFS – Interim Analysis



- First interim analysis of EFS based on 1174 patients: pre-calculated P value boundary for significance of 0.000051 (HR <0.4)
- Median follow-up, 15.5 months

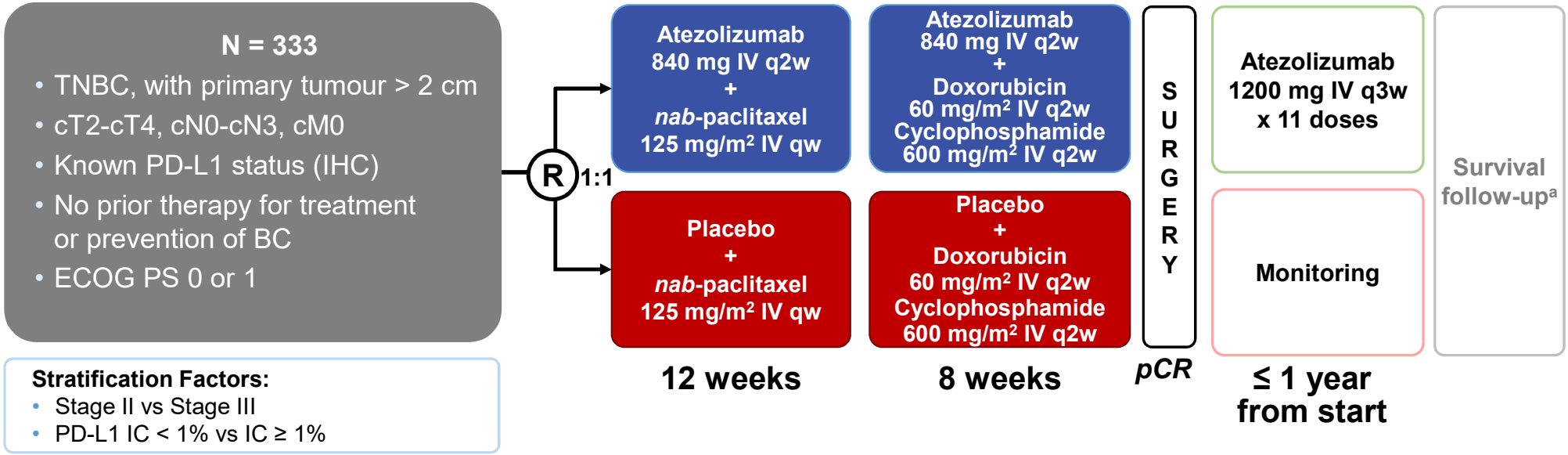
	Events	HR (95% CI)
Pembro + Chemo/Pembro	7.4%	0.63[a] (0.43-0.93)
Placebo + Chemo/Placebo	11.8%	

Schmid P, et al. *N Engl J Med* 2020;382:810-821

Treatment-Related AEs

- Generally similar rates of grade 3-5 tox during neoadjuvant phase
- Discontinuation rates
  - Neoadjuvant: 23.3% pembro vs 12.3% placebo
  - Adjuvant: 3.3% pembro vs 1.3% placebo
- Immune related: 10-15% can be permanent
  - Hypothyroidism 14.9%; hyperthyroidism 5.1%
  - Adrenal insufficiency 2.7%
  - Pneumonitis 1.9%
  - Colitis 1.8%
  - Hypophysitis 1.8%
  - Hepatitis 1.4%

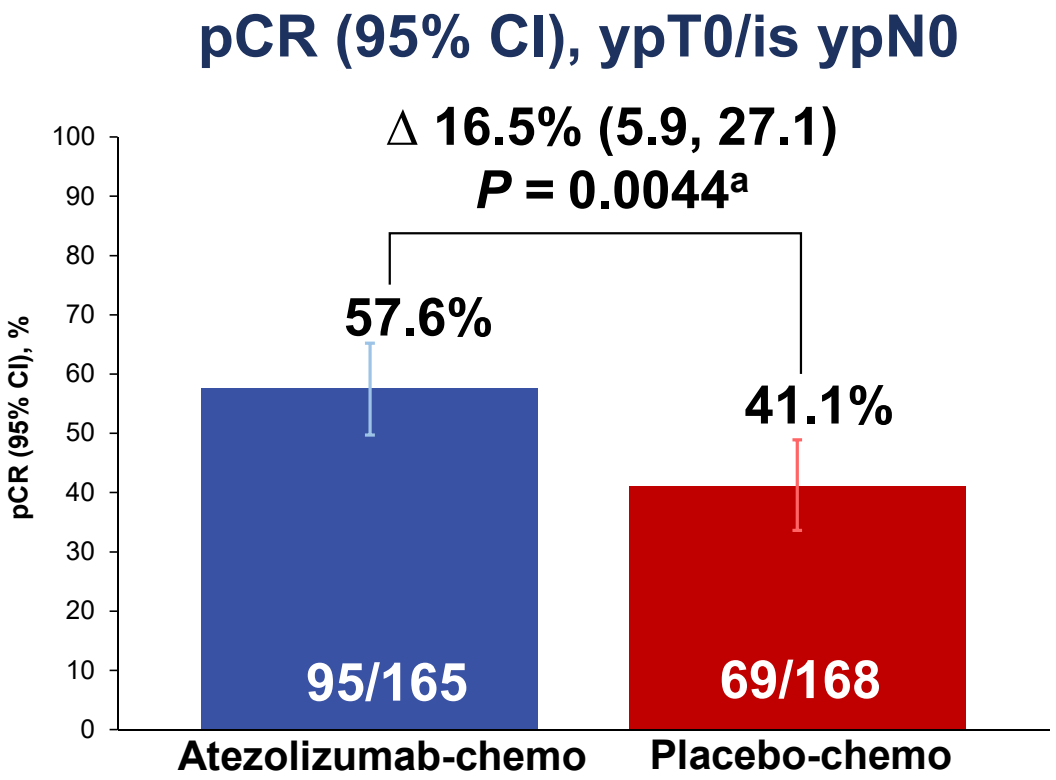
IMpassion031: Preoperative Atezolizumab



Primary Endpoints: pCR in ITT andPD-L1+ populations
Secondary Endpoints: EFS/DFS/OS in ITT and PD-L1+ populations, safety, PROs

Mittendorf EA, et al. *Lancet* 2020;396:1090-1100

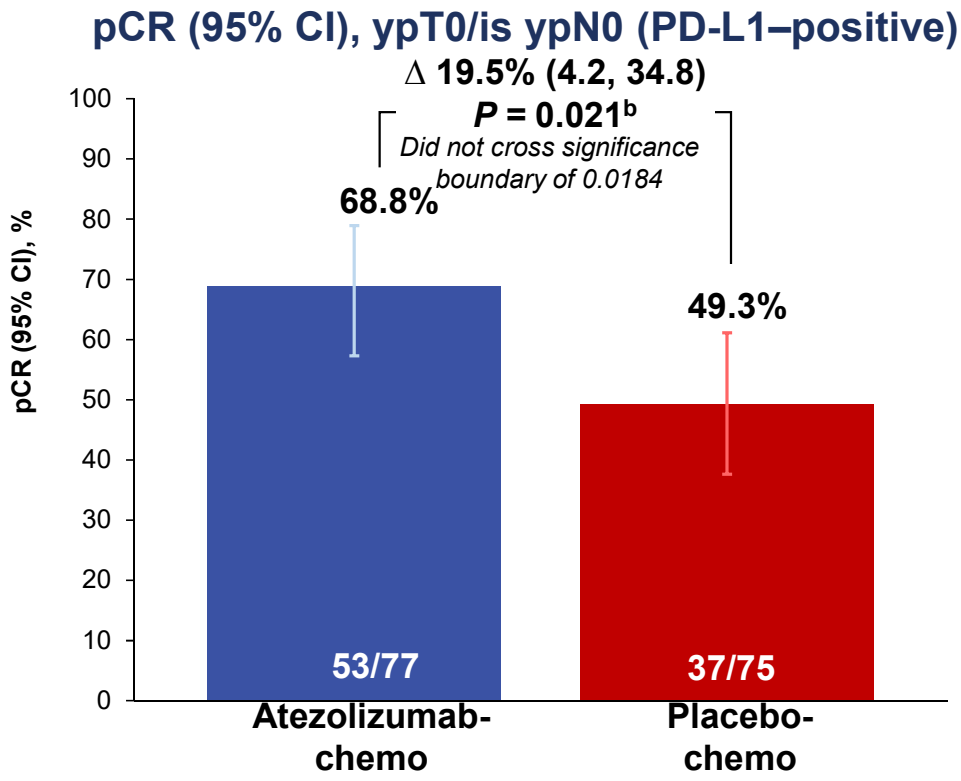
pCR

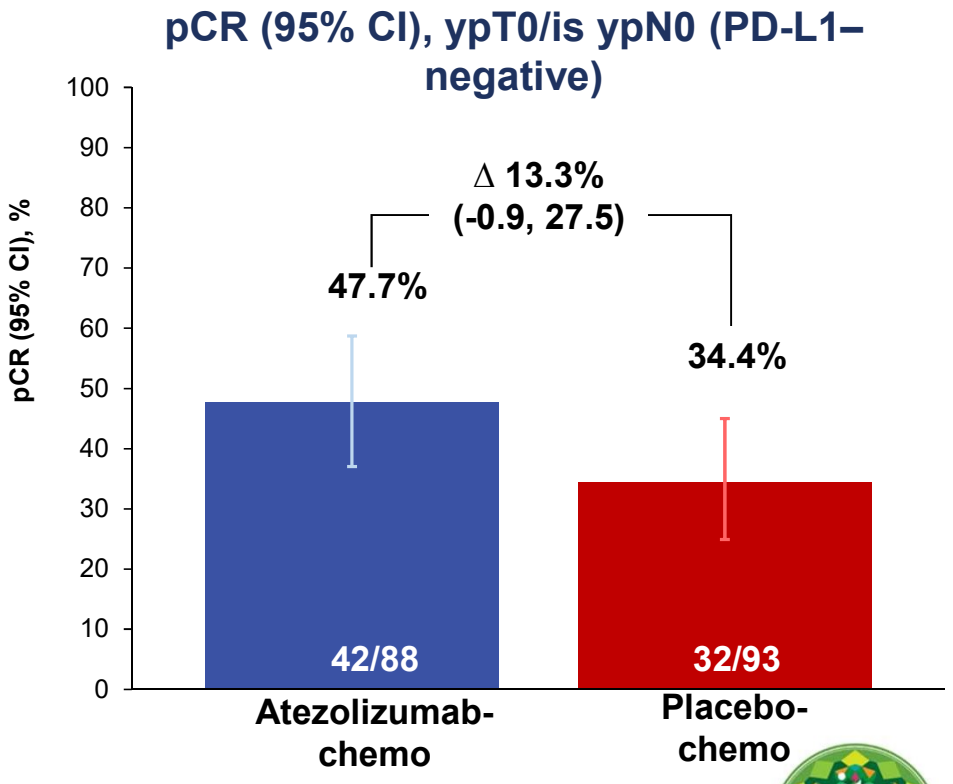


[a]One-sided significance boundary $P = 0.0184$ (accounting for the adaptive enrichment design). $P = 0.0085$ for the intersection hypothesis of pCR in the ITT and PD-L1-positive population.

Mittendorf EA, et al. *Lancet* 2020;396:1090-1100

pCR by PD-L1 Status





Mittendorf EA, et al. *Lancet* 2020;396:1090-1100

Adverse Events of Special Interest

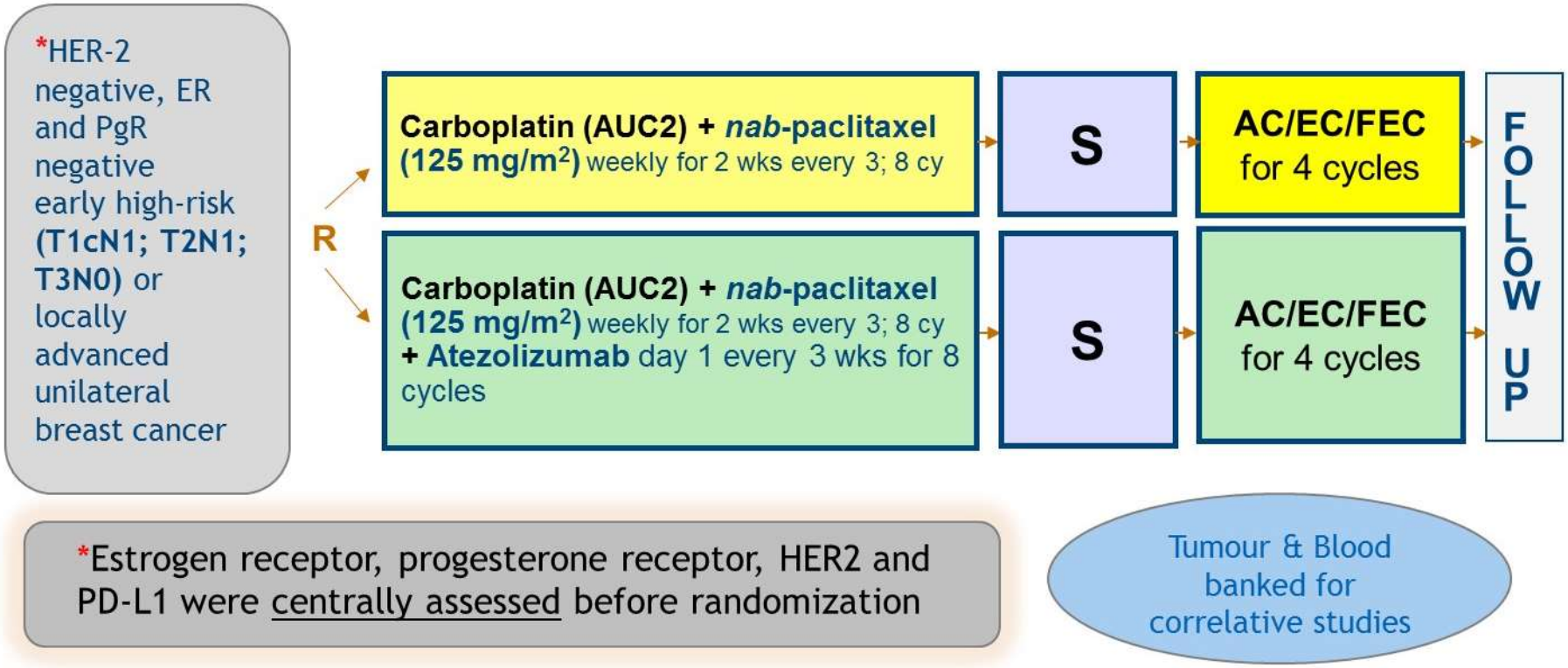
Summary, n (%)	Atezolizumab-Chemo (n = 164)		Placebo-Chemo (n = 167)	
All AESIs	115 (70.1)		101 (60.5)	
Grade 3-4 AESI	24 (14.6)		20 (12.0)	
Serious AESI	11 (6.7)		[illegible]	
AESI requiring systemic corticosteroids	21 (1[illegible]		[illegible]	
Specific AESIs, n (%)	**Any Grade**			
Hepatitis	2 (1.2)			
Hypothyroidism	11 (6.7)			
Hyperthyroidism	5 (3.0)			
Adrenal insufficiency	0		[illegible]	
Pneumonitis	2 (1.2)	1 (0.6)	2 (1.2)	0
Colitis	1 (0.6)	1 (0.6)	1 (0.6)	0
Guillain-Barré syndrome	0	0	2 (1.2)	1 (0.6)
Diabetes	1 (0.6)	0	1 (0.6)	0
Encephalitis[b]	1 (0.6)	1 (0.6)	0	0
Myositis	1 (0.6)	1 (0.6)	0	0
Rash	80 (48.8)	6 (3.7)	82 (49.1)	6 (3.6)
Infusion-related reactions	17 (10.4)	1 (0.6)	11 (6.6)	1 (0.6)
Ocular inflammatory toxicity	2 (1.2)	0	0	0
Severe cutaneous reactions	0	0	1 (0.6)	0

KN522

Hypothyroidism	14.9%
Hyperthyroidism	5.1%
Adrenal insufficiency	2.7%

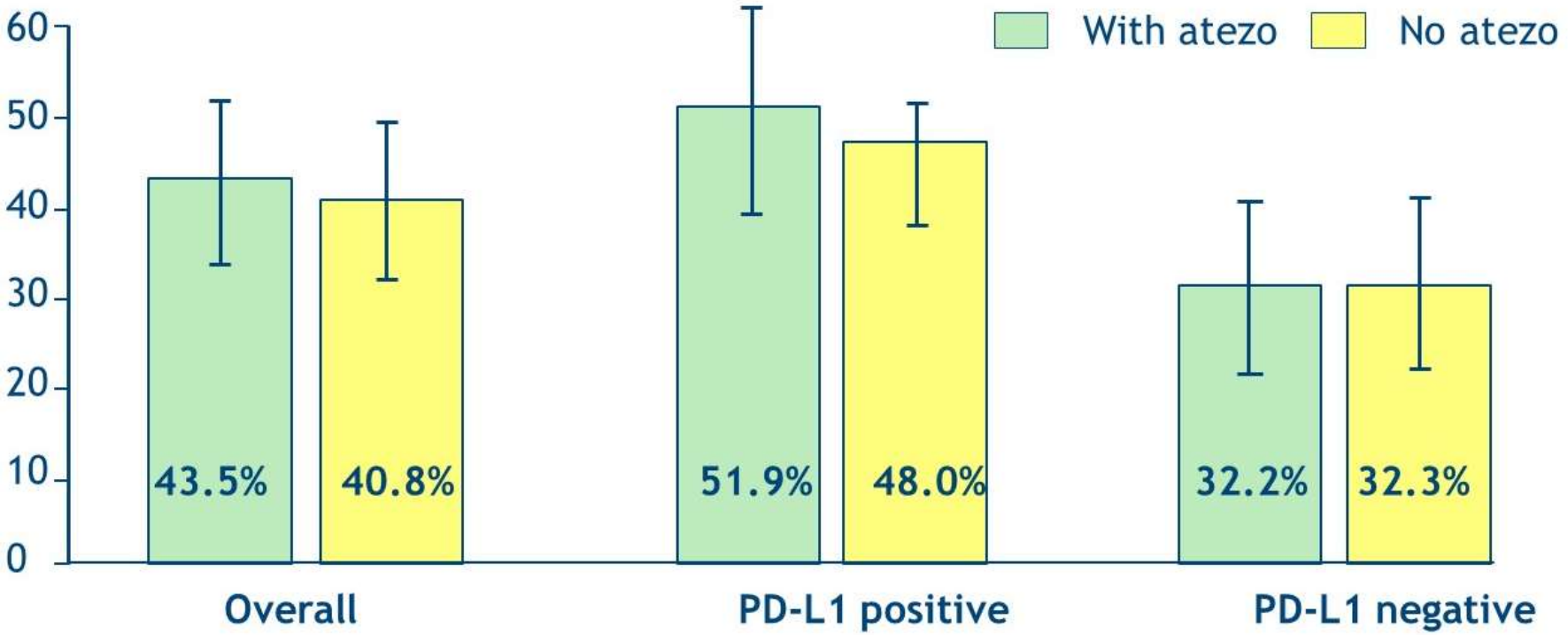
Mittendorf EA, et al. *Lancet* 2020;396:1090-1100

NeoTRIP – Preoperative Atezolizumab



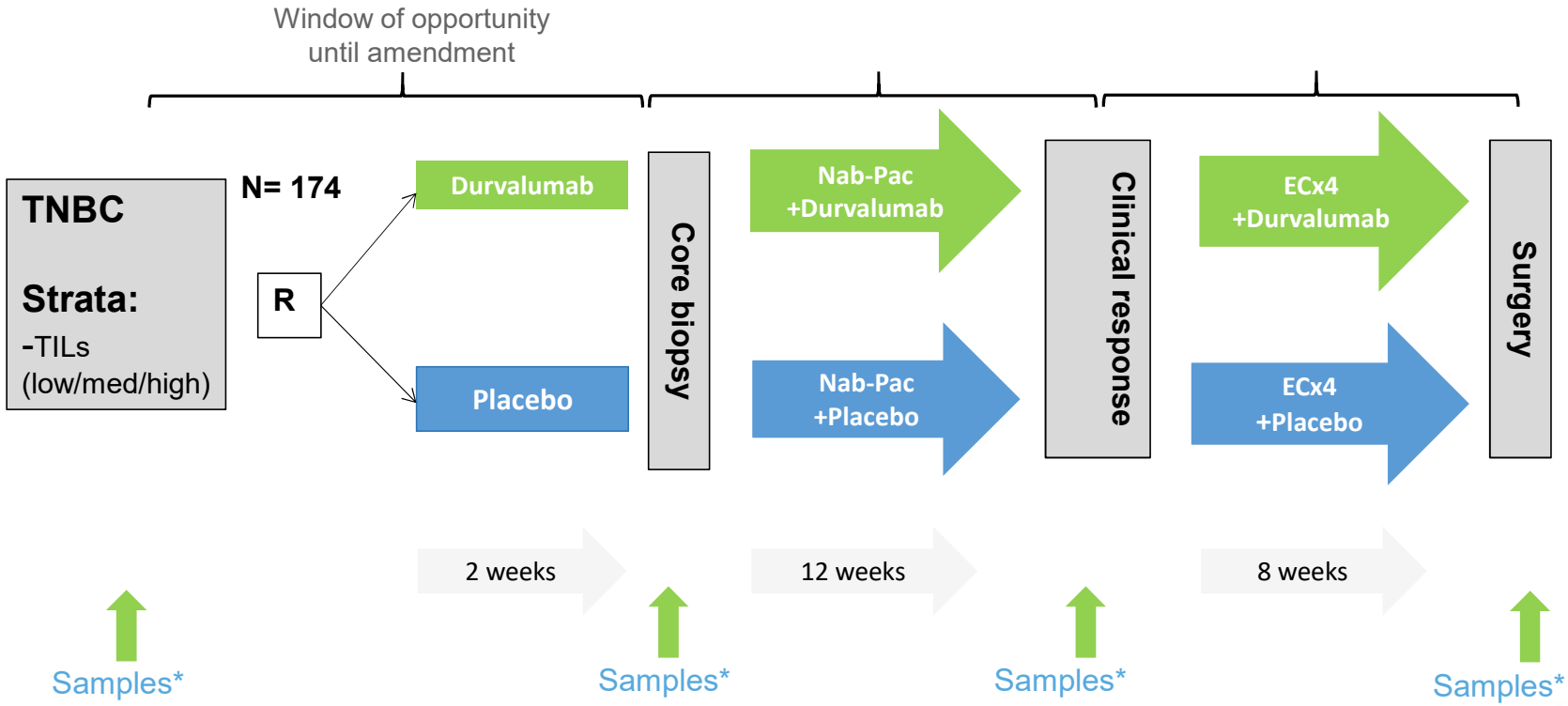
Gianni L, et al. *SABCS* 2019

pCR rates



Gianni L, et al. *SABCS* 2019

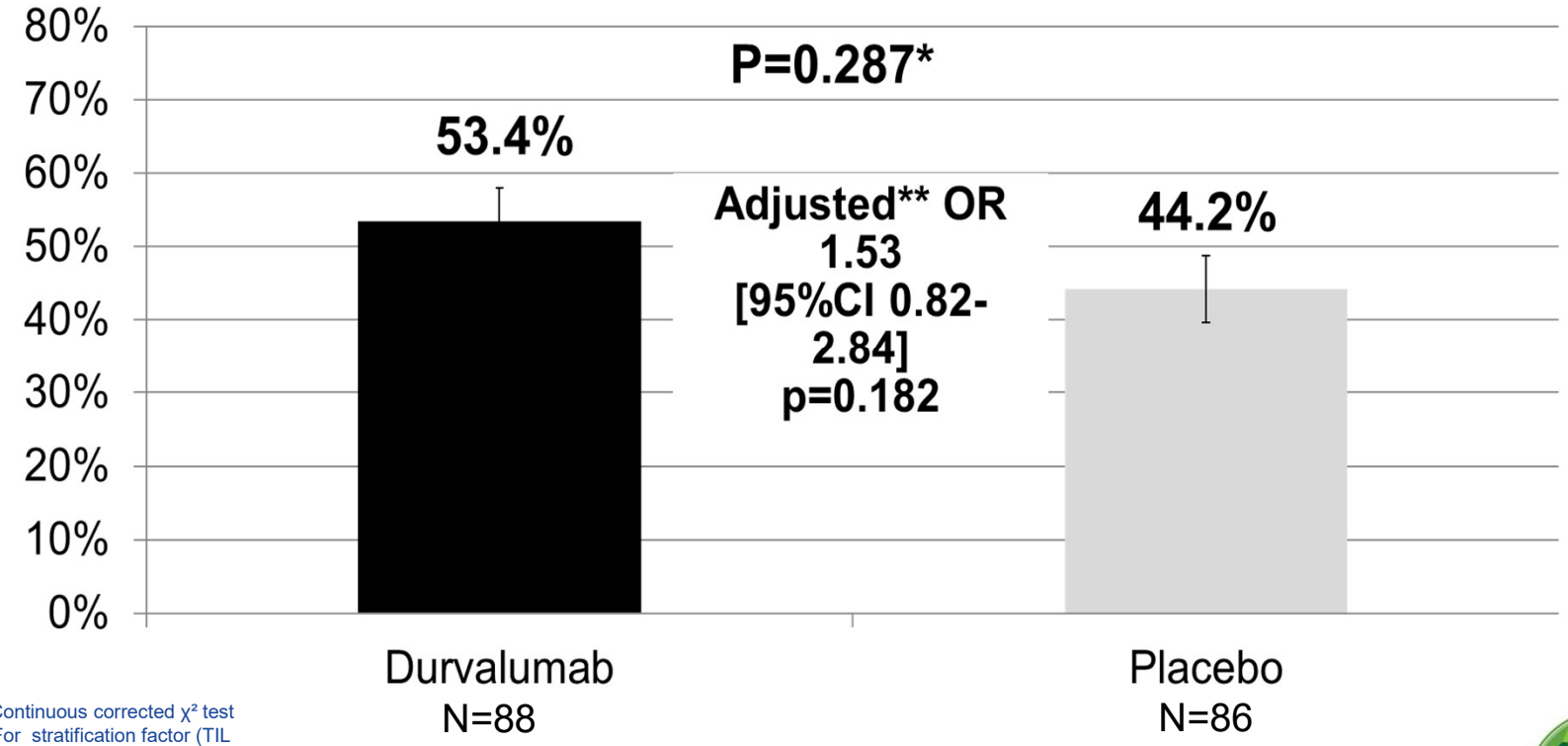
GeparNuevo



*Tissue: FFPE, fresh frozen;
Liquid biopsies: full blood; plasma, serum

Loibl S, et al. *Ann Oncol* 2019;30:1279-1288

Primary Endpoint: pCR, ypT0N0

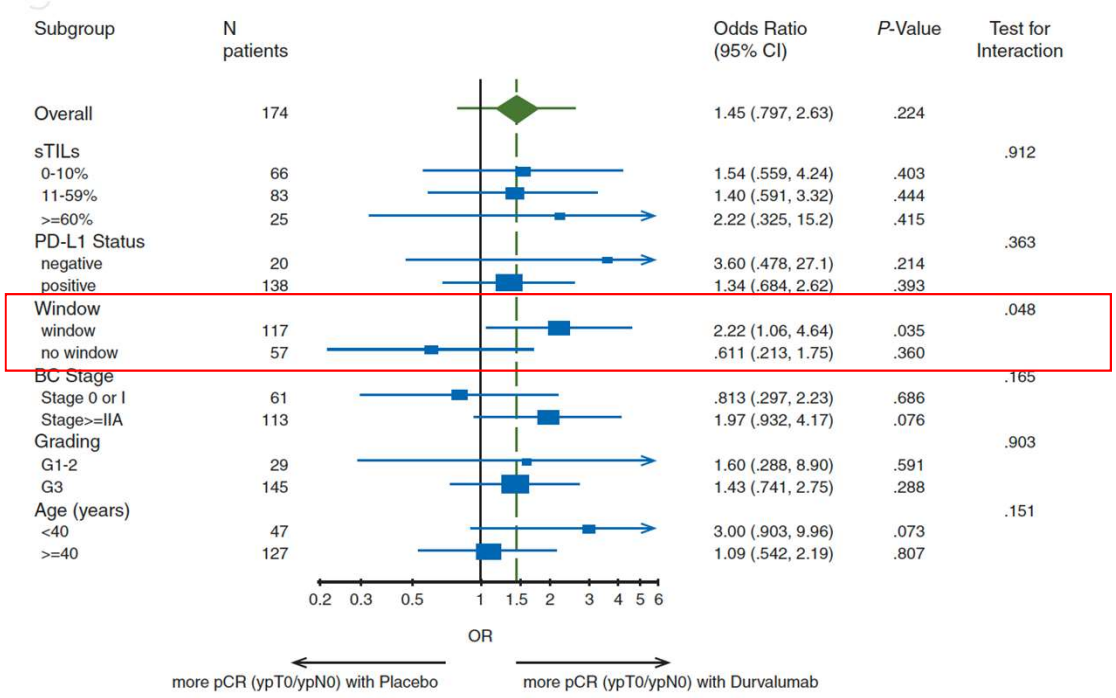


* Continuous corrected χ^2 test
** For stratification factor (TIL groups)

Loibl S, et al. *Ann Oncol* 2019;30:1279-1288

Primary Endpoint: pCR, ypT0N0

- Durva effect seen only in window cohort (n=117)
  - pCR 61% vs 41.4% (p=.035)



Loibl S, et al. *Ann Oncol* 2019;30:1279-1288

Summary Neoadjuvant IO Studies

	I-SPY2 Pembrolizumab	KEYNOTE-522 Pembrolizumab	NEOTRIP Atezolizumab	IMpassion 031 Atezolizumab	GEPARNUEVO Durvalumab
Total patients	69/181	602/1174	280	333	174
Target	PD-1	PD-1	PD-L1	PD-L1	PD-L1
Stage	II/III	II/III	I-III	II/III	35% stage I
Anthracycline	Yes	Yes	No	Yes	Yes
Carboplatin	No	Yes	Yes	No	No
pCR rate	60% vs 22% (graduated)	65% vs 51% (p=0.00055)	44% vs 41% (p=0.66)	57.6% vs 41.1% (p=0.0044)	53% vs 44% (p=0.287)

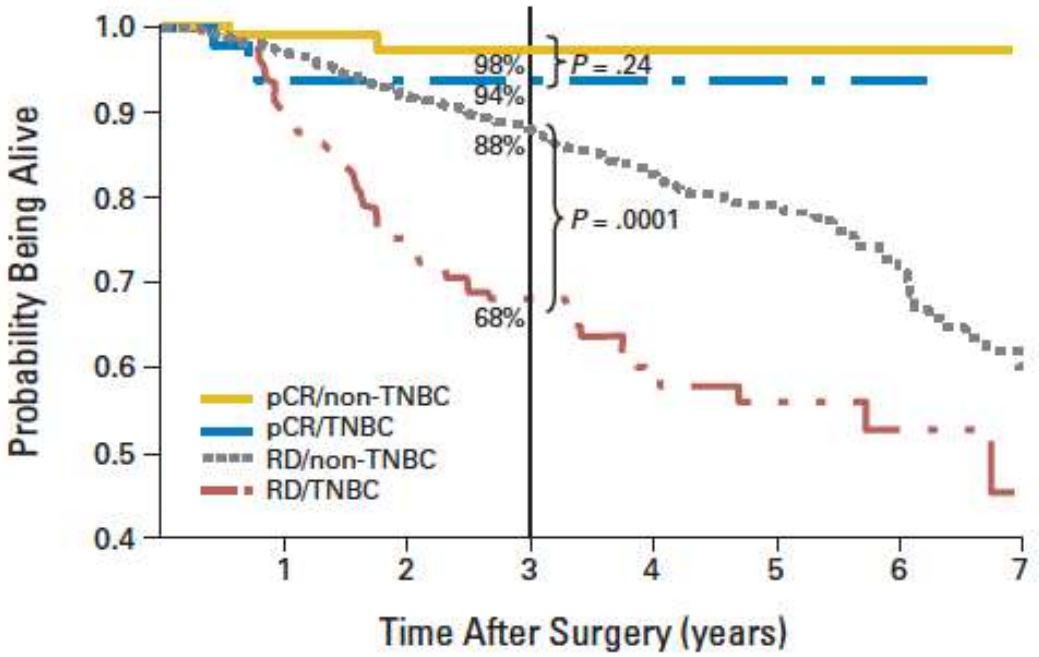
Take Home Messages

- KEYNOTE-522 and IMpassion 031 are complementary and generally supportive studies
  - ↑ pCR with addition of immunotherapy
  - Benefit seen regardless of PD-L1 status
  - EFS data in KEYNOTE-522 encouraging but need longer f/u; IMpassion 031 underpowered
    - Unclear how pCR with IO will translate to survival advantage
  - Role of adjuvant therapy unclear at this time (blinded in KN522, unblinded in IMpassion 031)
    - Duration of IO is important clinical question
  - Critical differences in chemotherapy backbone

Questions that Remain

- What is the optimal chemotherapy backbone?
- Can we de-escalate the chemotherapy?
- How should chemotherapy and checkpoint blockade be sequenced?
- Do patients need *adjuvant* checkpoint blockade?
- Can we expand the benefit to other breast cancer subtypes?
- Do all early stage TNBC patients require IO?

Do All Early Stage TNBC Patients Need Neoadjuvant Immunotherapy?



- Early stage TNBC is curable
- TNBC patients that have good response to anthracycline/taxane-based chemotherapy have good prognosis

Leidtke C, et al. *J Clin Oncol* 2008;26:1275-1281

Thank You

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