Randomized Phase II Neoadjuvant Study (GeparNuevo) to Investigate the Addition of Durvalumab to a Taxane-Anthracycline Containing Chemotherapy in Triple Negative Breast Cancer (TNBC)

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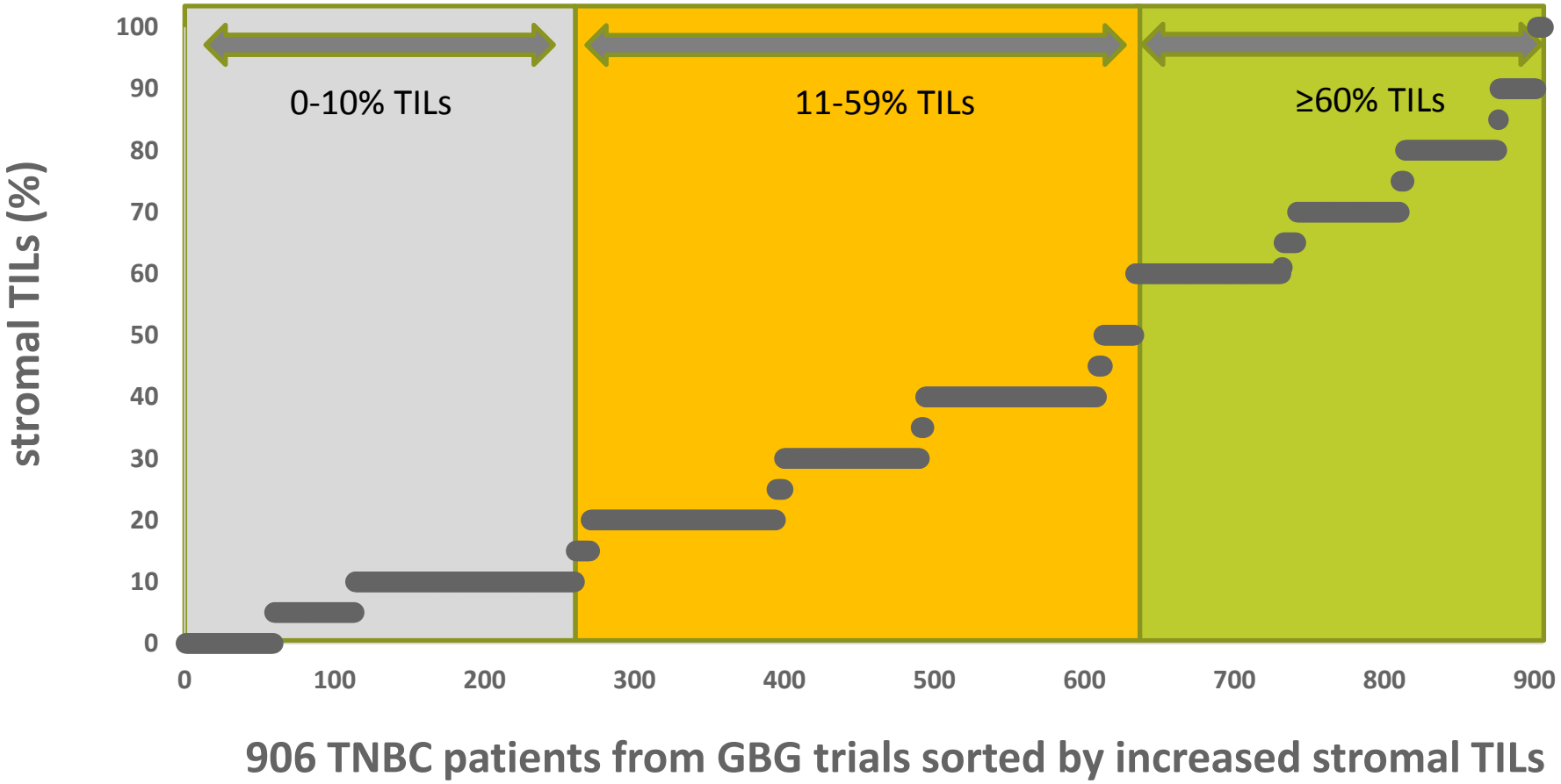
-This is a joint study by GBG and AGO-B-

Background

- Triple negative breast cancer (TNBC) is associated with a high immunogenic potential
- Several checkpoint inhibitors are being investigated in metastatic and early TNBC
- Response rates with PD-1/L1 antibodies were higher when added to chemotherapy[1]
- Tumor Infiltrating Lymphocytes (TILs) correlate highly with other immune genes, e.g. PD-L1[2]
- TILs are predictive and prognostic in TNBC[2,3]
- Durvalumab is a PD-L1 antibody with promising results in bladder and lung cancer

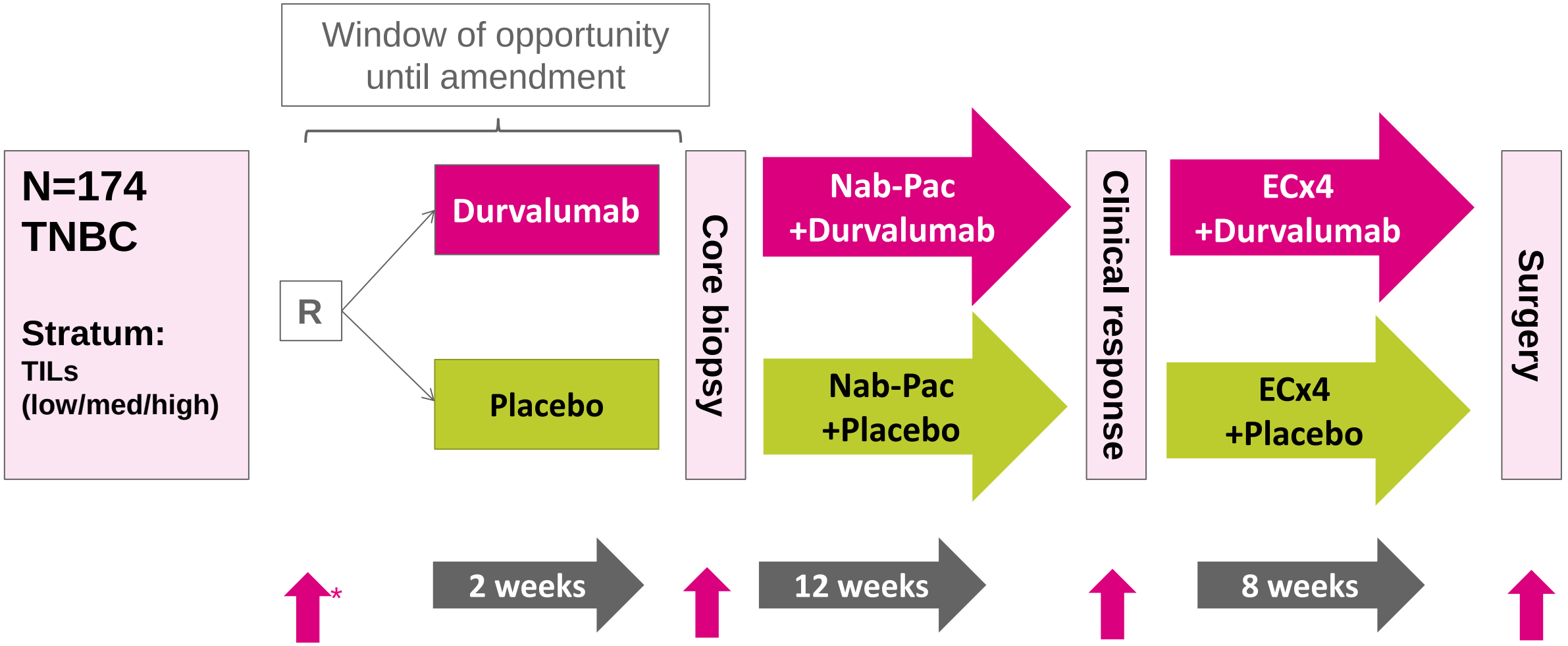
[1]Nanda R et al. J Clin Oncol 2016; [2]Denkert et al. J Clin Oncol 2015;
[3] Adams S et al. J Clin Oncol 2014; [4]Denkert et al. Lancet Oncol 2018;

Background TILs in TNBC



Denkert C et al. Lancet Oncol 2018

GeparNUEVO Study Design



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

Durvalumab (0.75g)
1.5g d1q28

nab-Paclitaxel 125mg/m² weekly

Epirubicin 90mg/m²;
Cyclophosphamide 600mg/m² d1q14

Endpoints

Primary endpoint:

- **To compare the pathological complete response (pCR= ypT0 ypN0) rates after neoadjuvant treatment with nab-Paclitaxel followed by EC +/- the PD-L1 antibody durvalumab in patients with early triple negative breast cancer**

Main secondary endpoints:

- **pCR rate in subgroups**
- **pCR rates according to different pCR definitions: ypT0/is ypN0; ypT0 ypN0/+; ypT0/is ypN0/+; $ypT_{(any)}$ ypN0.**
- **Clinical response rate**
- **Breast conservation rate**
- **Toxicity and compliance**
- **Immune-/biomarker**
- **DFS, EFS and OS**

Statistics – Sample Size

- The sample size calculation is based on the following assumptions:
  1. pCR rate in the placebo arm is expected to be **48%**, which was the pCR rate of the TNBC patients treated with nab-paclitaxel in the GeparSepto study[1,2]
  2. pCR rate in the durvalumab arm was set to **66%** because this was considered a clinically meaningful benefit in a phase II feasibility study
- 158 patients (79 in each arm) would achieve 80% power on the 2-sided significance level $\alpha=0.2$ to show the superiority of the durvalumab arm using a continuity corrected χ^2-test
- Assuming a 10% drop-out rate we planned to recruit **174** patients

[1]Untch M et al. Lancet Oncol 2016; [2] Loibl S et al. Annals Oncol 2016

Main Inclusion Criteria

- **Primary triple negative breast cancer**
- **cT1b-cT4d, any cN**
- **Centrally confirmed ER negative/PR negative/HER-2 negative status**
- **Centrally assessed Ki-67 and sTIL value.**
  - Stromal TILs were evaluated in three groups:
    low immune infiltrate (0-10% stromal TILs)
    intermediate immune infiltrate (11-59% stromal TILs)
    high immune infiltrate (60-100% stromal TILs)
- **Thyroid function within normal range**
- **No autoimmune diseases and conditions (e.g. inflammatory bowel disease)**
- **No active infections**
- **No known history of tuberculosis**

Main Baseline Characteristics

	Durvalumab N=88 N(%)	Placebo N=86 N(%)	Overall N=174 N(%)
Age (yrs), median (range)	49.5 (25.0, 74.0)	49.5 (23.0, 76.0)	49.5 (23.0, 76.0)
cT3/4	7 (8.0)	3 (3.5)	10 (5.7)
cN+	27 (30.7)	27 (31.4)	54 (31.0)
Stage IIA and higher	56 (63.6)	57 (66.3)	113 (64.9)
G3	74 (84.1)	71 (82.6)	145 (83.3)
TILs			
low (0-10%)	34 (38.6)	32 (37.2)	86 (37.9)
intermediate (11-59%)	42 (47.7)	41 (47.7)	83 (47.7)
high (≥60%)	12 (13.6)	13 (15.1)	25 (14.4)
Durvalumab/placebo alone (window)	59 (67.0)	58 (67.4)	117 (67.2)

Discontinuations

	Durvalumab N=88 N(%)	Placebo N=86 N(%)	Overall N=174 N(%)
Completed all treatments	**56 (63.6)**	**51 (59.3)**	**107 (61.5)**
Completed nabPaclitaxel and EC	**60 (68.2)**	**55 (64.0)**	**115 (66.1)**
Completed Durvalumab/Placebo	**68 (77.3)**	**69 (80.2)**	**137 (78.7)**
discontinued Durvalumab/Placebo during nabPaclitaxel	13 (14.8)	11 (12.8)	24 (13.8)
discontinued Durvalumab/Placebo during EC	7 (8.0)	6 (7.0)	13 (7.5)
Discontinued nabPaclitaxel	**19 (21.6)**	**20 (23.3)**	**39 (22.4)**
discontinued nabPaclitaxel, not started EC	5 (5.7)	7 (8.1)	12 (6.9)
discontinued nabPaclitaxel, discontinued EC	10 (11.4)	10 (11.6)	20 (11.5)
Discontinued EC	**12 (13.6)**	**14 (16.3)**	**26 (14.9)**

Reasons for Discontinuation of Durvalumab/Placebo

	Durvalumab N=88	Placebo N=86	Overall N=174
Discontinuation during nabPaclitaxel	**13**	**11**	**24**
local (pseudo)progression	3	0	3
patients/investigators decision	1	6	7
AEs	9	5	14
immune related AEs	5	3	8
Discontinuation during EC	**7**	**6**	**13**
local (pseudo)progression	1	0	1
patients/investigators decision	1	4	5
AEs	5	2	7
immune related AE	1	0	1

Haematologic Toxicities

	Durvalumab N=92* N(%)	Placebo N= 82* N(%)	Overall N=174 N(%)
Anaemia, grade 1-4	87 (94.6)	79 (96.3)	166 (95.4)
Anaemia, grade 3-4	**2 (2.2)**	**2 (2.4)**	**4 (2.3)**
Neutropenia, grade 1-4	71 (77.2)	67 (81.7)	138 (79.3)
Neutropenia, grade 3-4	**34 (37.0)**	**34 (41.5)**	**68 (39.1)**
Thrombocytopenia, grade 1-4	35 (38.0)	28 (34.1)	63 (36.2)
Thrombocytopenia, grade 3-4	**1 (1.1)**	**2 (2.4)**	**3 (1.7)**
Febrile neutropenia	**4 (4.3)**	**2 (2.4)**	**6 (3.4)**

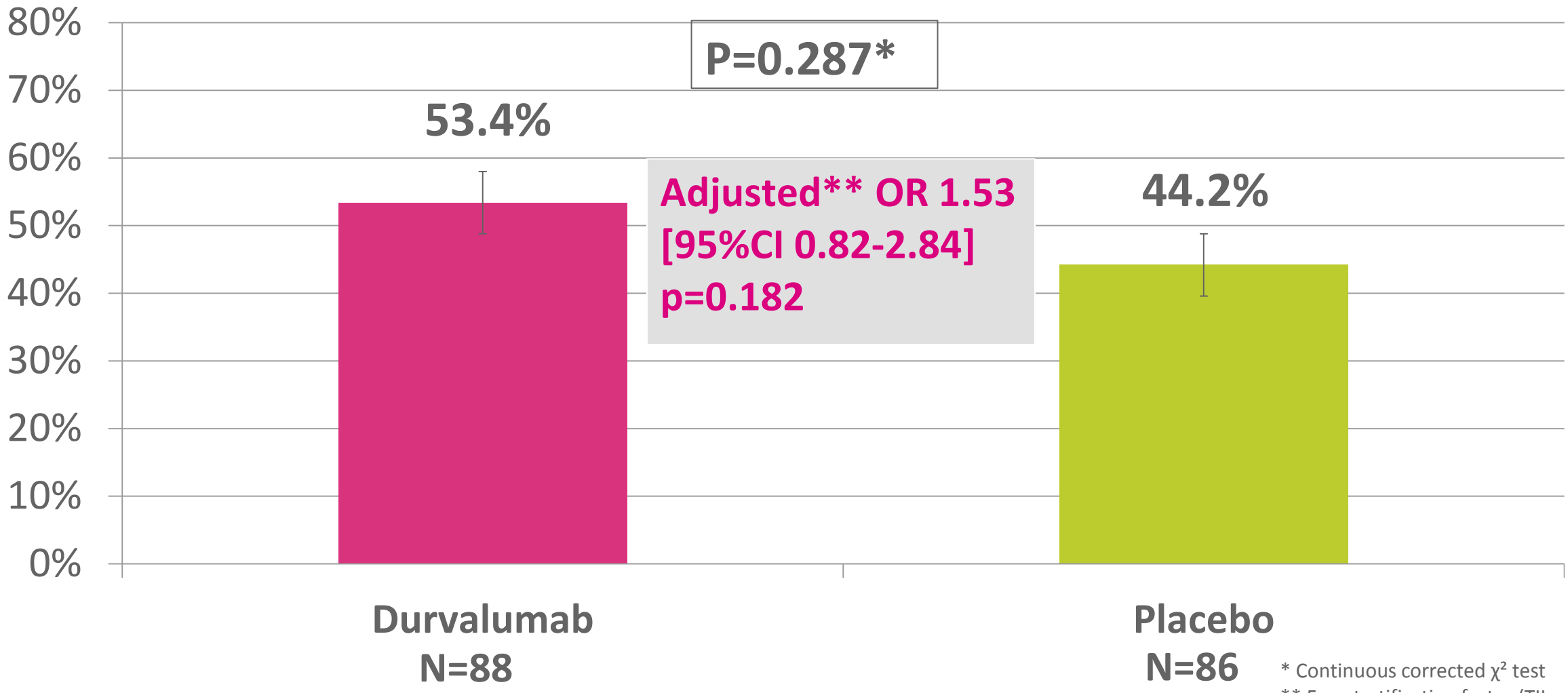
*safety population differs because 4 patients received durvalumab instead of placebo at least once

Immune Related Toxicities (any grade)

	Durvalumab N=92* N(%)	Placebo N= 82* N(%)	Overall N=174 N(%)
Hepatotoxicity	7 (7.6)	6 (7.3)	13 (7.5)
Dermatitis	13 (14.1)	12 (14.6)	25 (14.4)
Hypophysitis	1 (1.1)	0 (0.0)	1 (0.6)
Pneumonitis	1 (1.1)	1 (1.2)	2 (1.1)
Hypothyroidism	6 (6.5)	2 (2.4)	8 (4.6)
Hyperthyroidism	7 (7.6)	0 (0.0)	7 (4.0)
Neuropathy	5 (5.4)	7 (8.5)	12 (6.9)
Neuropathy, high grade	3 (3.3)	4 (4.9)	7 (4.0)

*safety population differs because 4 patients received durvalumab instead of placebo at least once

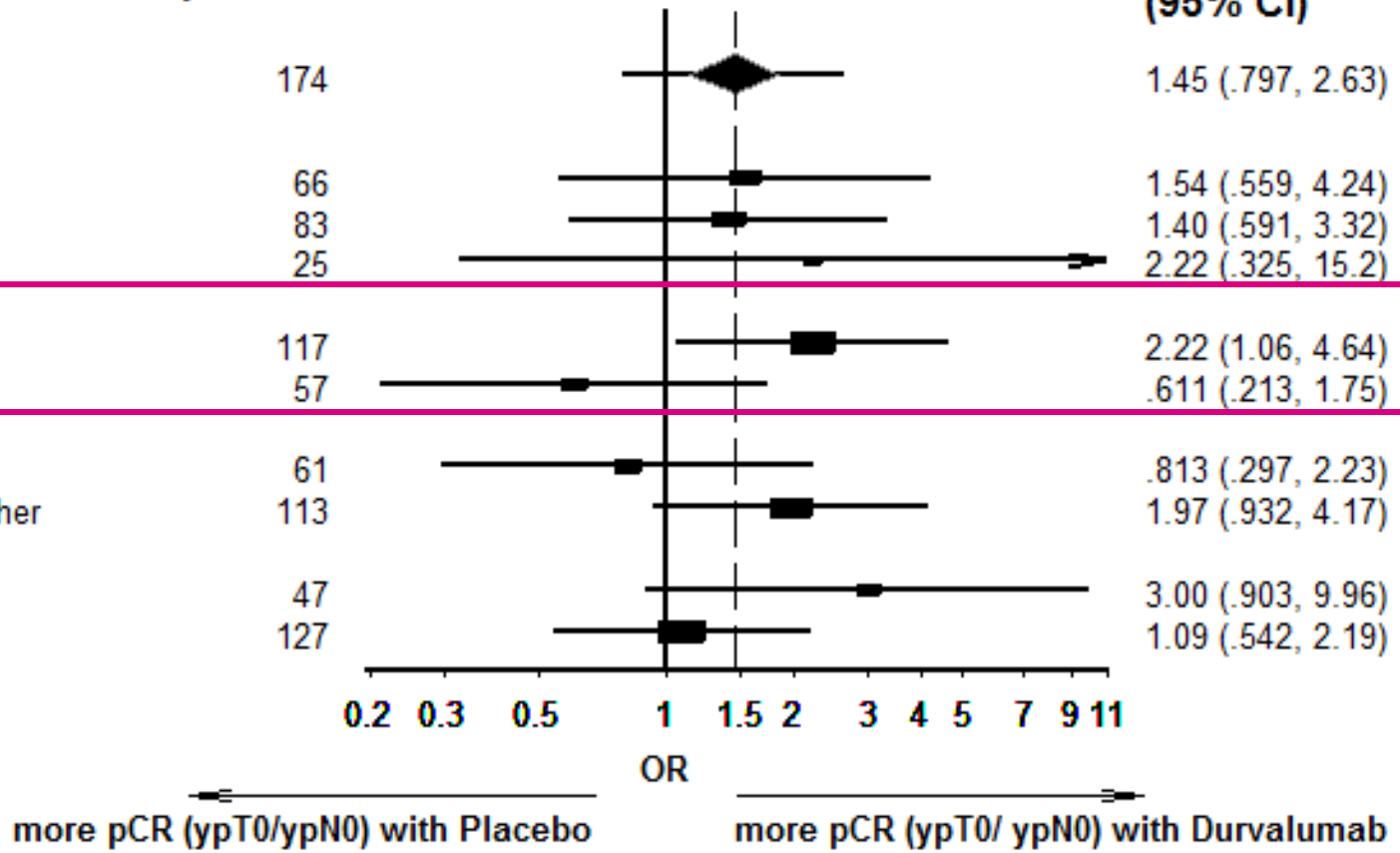
Primary Endpoint - pathological complete response pCR – ypT0, ypN0



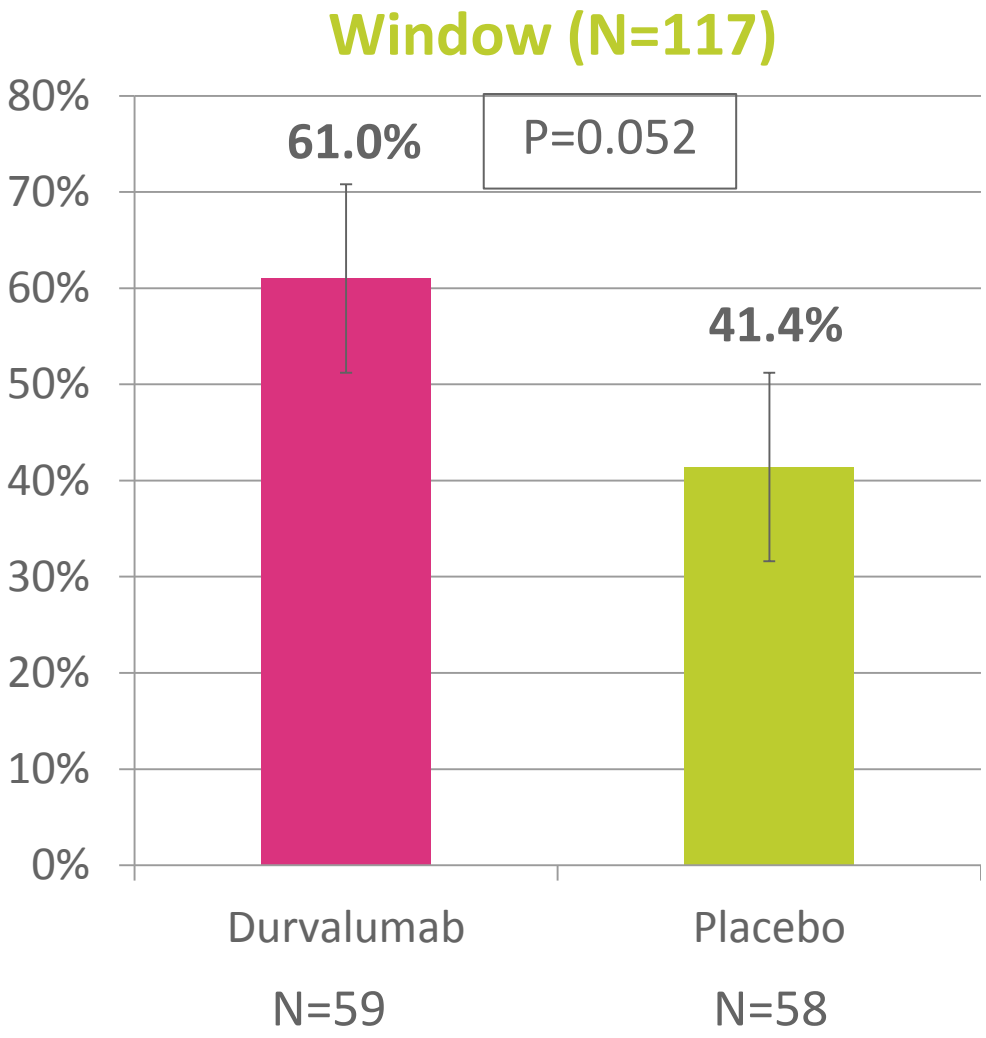
* Continuous corrected χ^2 test
** For stratification factor (TIL groups)

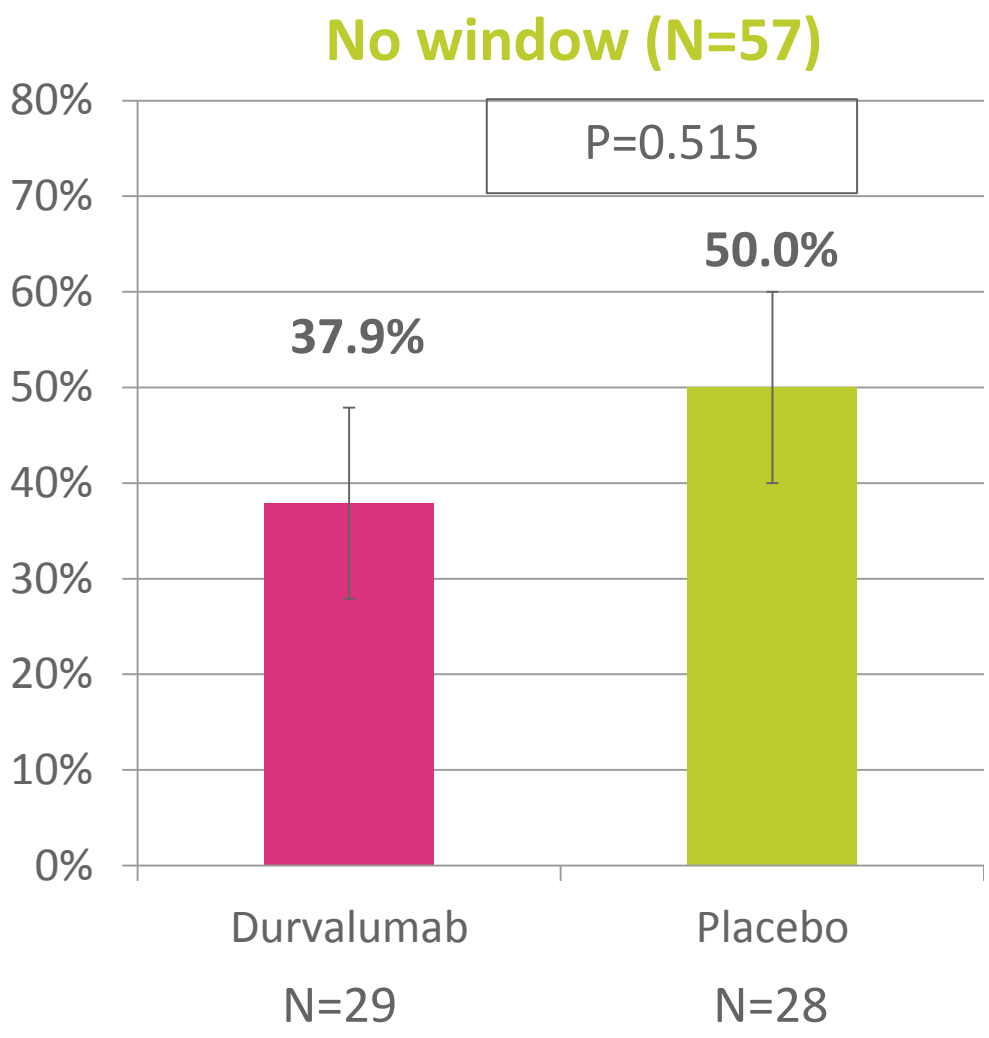
Subgroup Analyses (predefined)

Subgroup	N patients	Odds Ratio (95% CI)	p-Value	Test for Interaction
Overall	174	1.45 (.797, 2.63)	.224	
stromal TILs				.912
0-10%	66	1.54 (.559, 4.24)	.403	
11-59%	83	1.40 (.591, 3.32)	.444	
>=60%	25	2.22 (.325, 15.2)	.415	
Window				.048
window	117	2.22 (1.06, 4.64)	.035	
no window	57	.611 (.213, 1.75)	.360	
BC Stage				.165
Stage 0 or I	61	.813 (.297, 2.23)	.686	
Stage IIA and higher	113	1.97 (.932, 4.17)	.076	
Age (years)				.151
<40	47	3.00 (.903, 9.96)	.073	
>=40	127	1.09 (.542, 2.19)	.807	

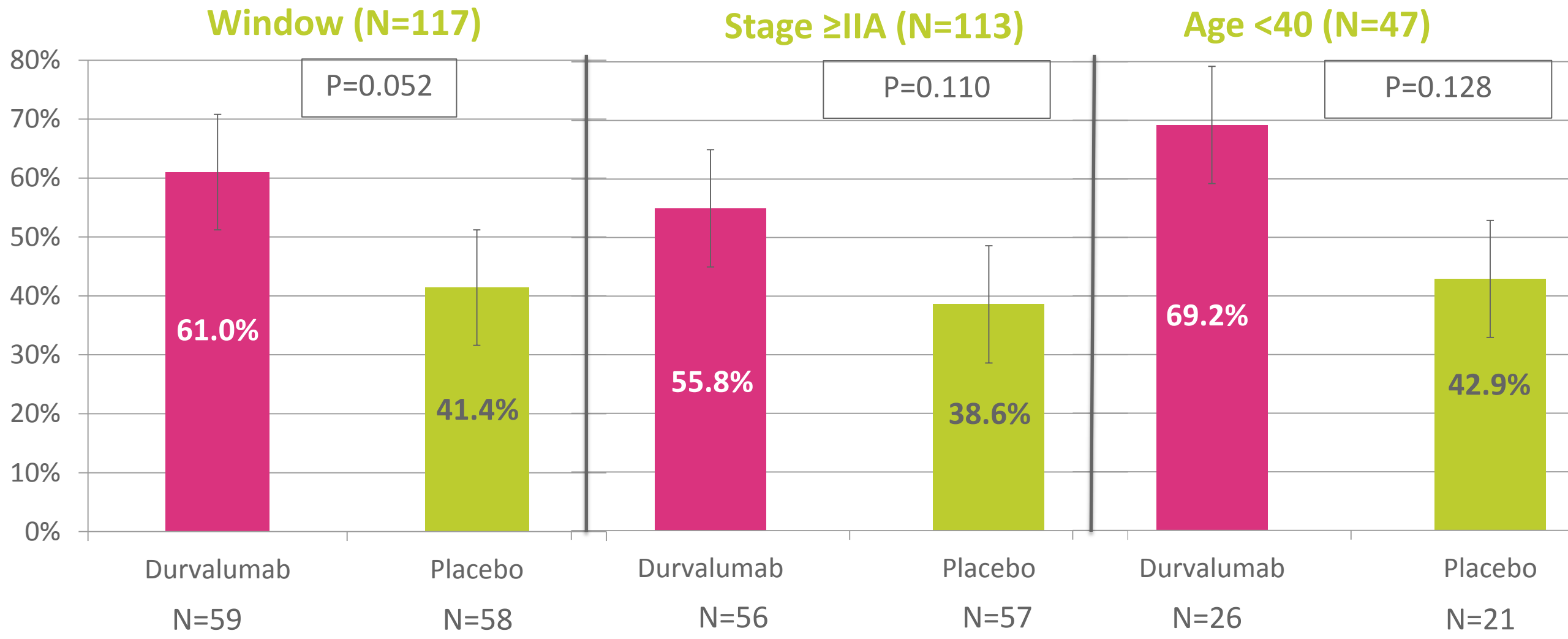


Subgroup Analysis of the Window Cohort





Subgroup Analysis – pCR rates



Neoadjuvant Chemotherapy plus anti-PD-L1/PD1 Antibodies

Phase II conventional GeparNUEVO trial

N=174

chemotherapy +/- anti-PD-L1 → surgery → ypT0 ypN0

- 44% Control (no immunotherapy)
- 53% Immunotherapy (no platinum)

(Durvalumab) → Nab Paclitaxel Q1W x12 + Durvalumab Q4W x3 → EC Q2W x4 + Durvalumab Q4W x2

Phase II adaptive Design I-SPY 2 trial[1]

N=118

chemotherapy+/- anti-PD1 → surgery → ypT0/is ypN0

- 20% Control (no immunotherapy)
- 60% Immunotherapy (no platinum)

Paclitaxel Q1W x12 + pembrolizumab Q3W x4 → AC Q3W x4

[1]Nanda R et al. ASCO 2017

Summary and Conclusion

- **The addition of durvalumab, increases the pCR rate numerically in primary TNBC patients (53% vs 44%; p=0.287; adjusted p=0.182)**
- **However, pCR rate was clinically significantly higher in the following preplanned subgroups of patients**
  - patients who started with durvalumab prior to chemotherapy (window cohort: 61.0% vs. 41.4%)
  - patients with stage IIa and higher TNBC (55.4% vs. 38.6%)
  - patients <40 years (69.2% vs. 42.9%)
- **Addition of durvalumab was well tolerated**

➡ **Durvalumab should be further investigated in patients with primary TNBC**

➡ **Induction therapy with durvalumab seems beneficial**

- **Further exploratory and translational research is ongoing**

Acknowledgement

- All patients and their families
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