



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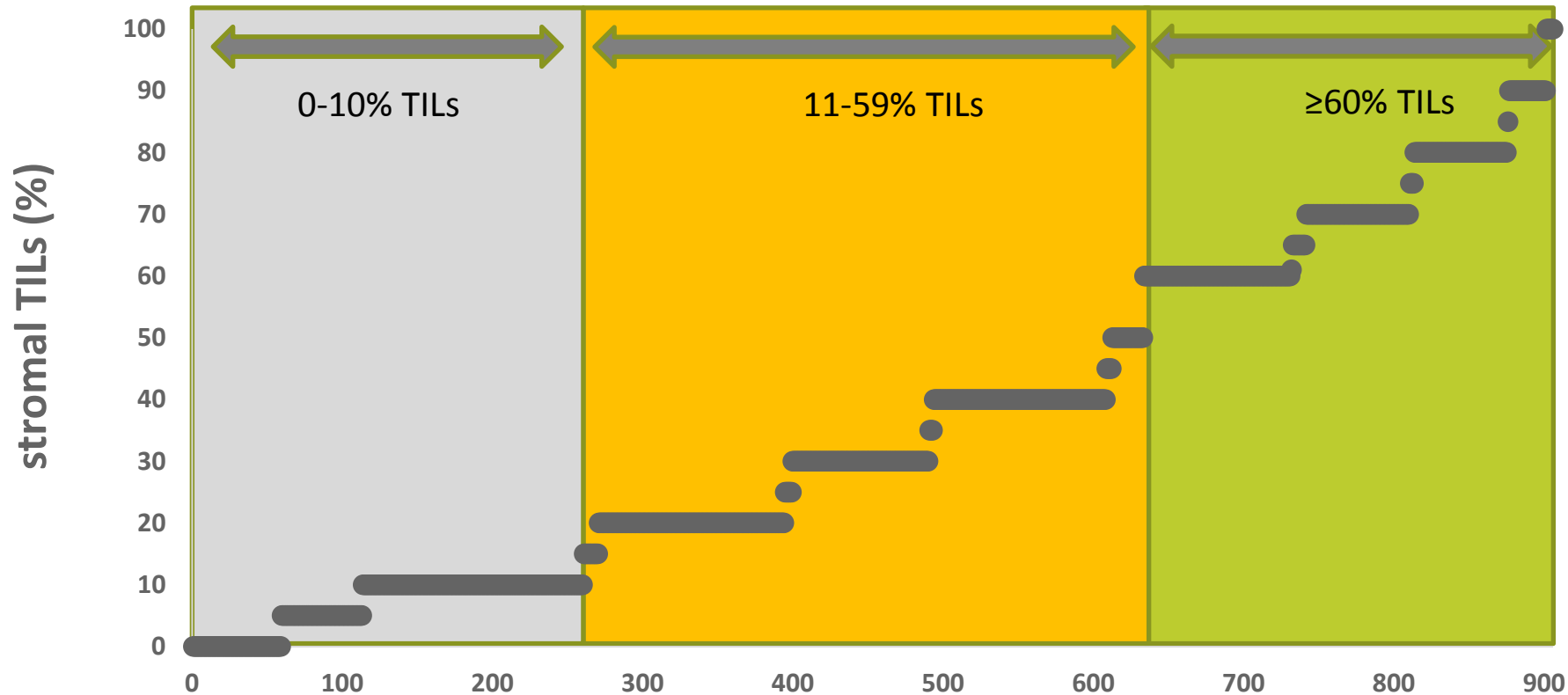
-This is a joint study by GBG and AGO-B-



- 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<sup>1</sup>
- Tumor Infiltrating Lymphocytes (TILs) correlate highly with other immune genes, e.g. PD-L1<sup>2</sup>
- TILs are predictive and prognostic in TNBC<sup>2,3</sup>
- Durvalumab is a PD-L1 antibody with promising results in bladder and lung cancer

<sup>1</sup>Nanda R et al. J Clin Oncol 2016; <sup>2</sup>Denkert et al. J Clin Oncol 2015;  
<sup>3</sup> Adams S et al. J Clin Oncol 2014; <sup>4</sup>Denkert et al. Lancet Oncol 2018;

# Background TILs in TNBC

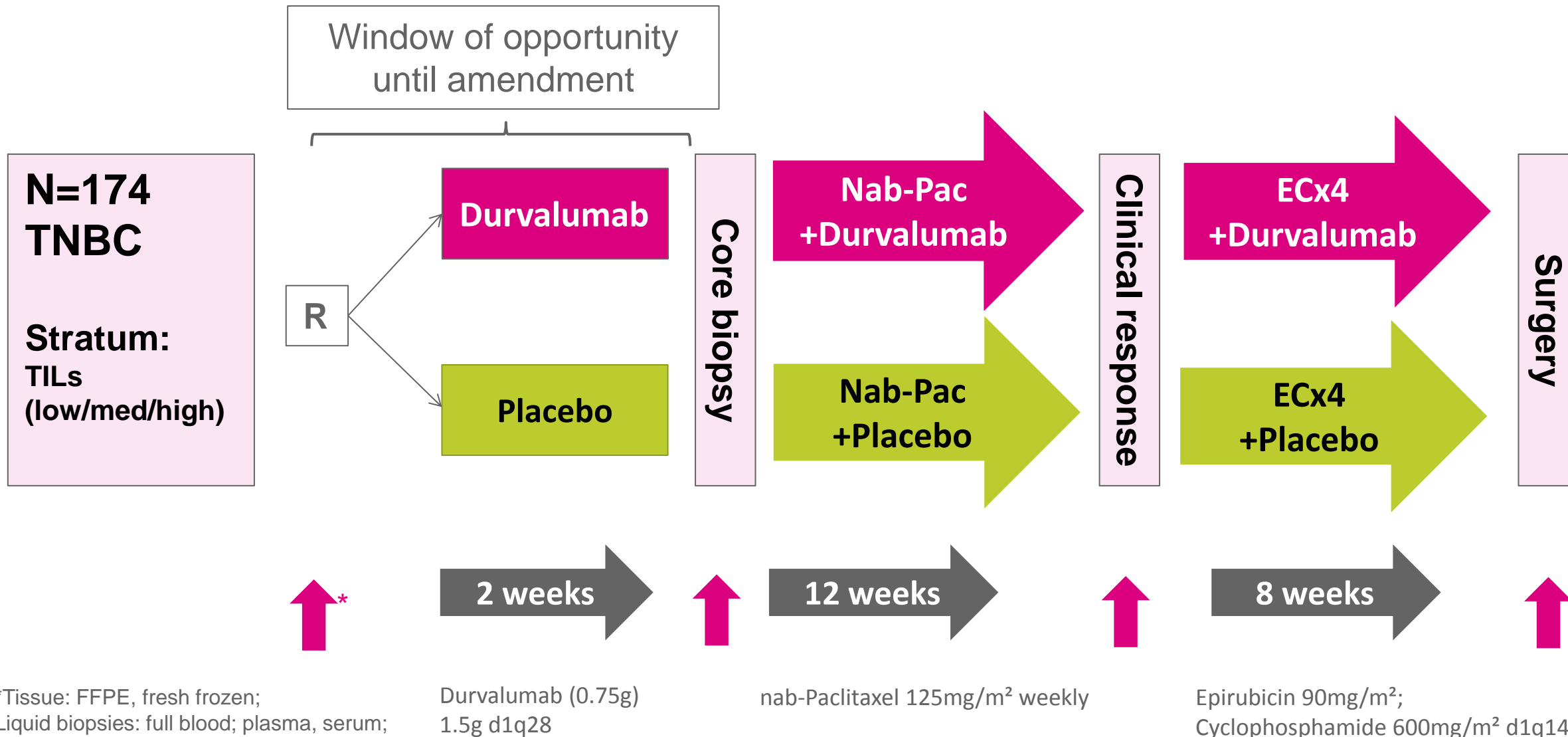


906 TNBC patients from GBG trials sorted by increased stromal TILs

Denkert C et al. Lancet Oncol 2018



# GeparNUEVO Study Design



## 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<sub>(any)</sub> ypN0.
- Clinical response rate
- Breast conservation rate
- Toxicity and compliance
- Immune-/biomarker
- DFS, EFS and OS



- 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<sup>1,2</sup>
  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  $\chi^2$ -test
- Assuming a 10% drop-out rate we planned to recruit **174** patients

<sup>1</sup>Untch M et al. Lancet Oncol 2016; <sup>2</sup> Loibl S et al. Annals Oncol 2016



- **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(%)
<b>Completed all treatments</b>	56 (63.6)	51 (59.3)	107 (61.5)
<b>Completed nabPaclitaxel and EC</b>	60 (68.2)	55 (64.0)	115 (66.1)
<b>Completed Durvalumab/Placebo</b>	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)
<b>Discontinued nabPaclitaxel</b>	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)
<b>Discontinued EC</b>	12 (13.6)	14 (16.3)	26 (14.9)



# Reasons for Discontinuation of Durvalumab/Placebo



	Durvalumab N=88	Placebo N=86	Overall N=174
<b>Discontinuation during nabPaclitaxel</b>	<b>13</b>	<b>11</b>	<b>24</b>
local (pseudo)progression	3	0	3
patients/investigators decision	1	6	7
AEs	9	5	14
immune related AEs	5	3	8
<b>Discontinuation during EC</b>	<b>7</b>	<b>6</b>	<b>13</b>
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)
<b>Anaemia, grade 3-4</b>	<b>2 ( 2.2)</b>	<b>2 ( 2.4)</b>	<b>4 ( 2.3)</b>
Neutropenia, grade 1-4	71 (77.2)	67 (81.7)	138 (79.3)
<b>Neutropenia, grade 3-4</b>	<b>34 (37.0)</b>	<b>34 (41.5)</b>	<b>68 (39.1)</b>
Thrombocytopenia, grade 1-4	35 (38.0)	28 (34.1)	63 (36.2)
<b>Thrombocytopenia, grade 3-4</b>	<b>1 ( 1.1)</b>	<b>2 ( 2.4)</b>	<b>3 ( 1.7)</b>
<b>Febrile neutropenia</b>	<b>4 (4.3)</b>	<b>2 (2.4)</b>	<b>6 (3.4)</b>

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



# Immune Related Toxicities (any grade)



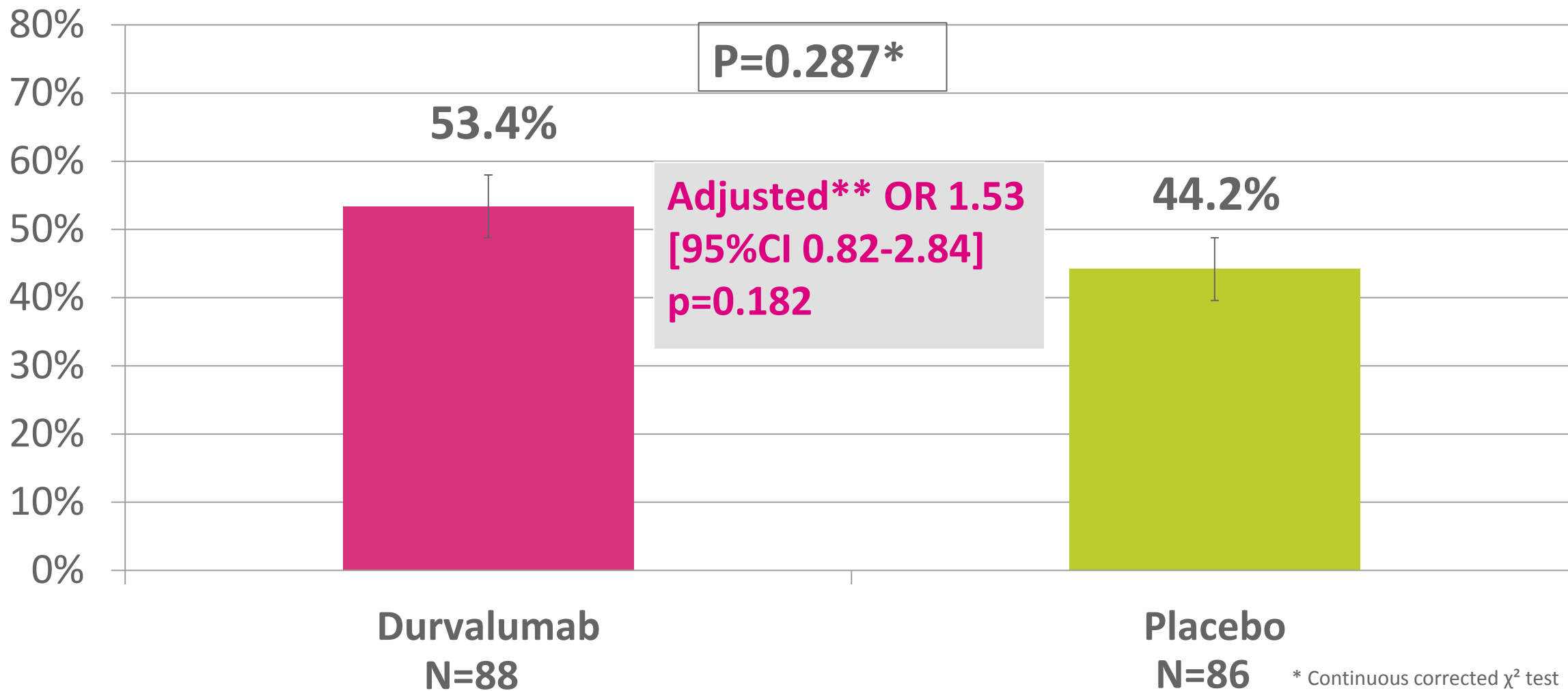
	Durvalumab N=92* N(%)	Placebo N= 82* N(%)	Overall N=174 N(%)
Hepatotoxicity	7 ( 7.6)	6 ( 7.3)	13 ( 7.5)
Dermatitis	13 (14.1)	12 (14.6)	25 (14.4)
Hypophysitis	1 ( 1.1)	0 ( 0.0)	1 ( 0.6)
Pneumonitis	1 ( 1.1)	1 ( 1.2)	2 ( 1.1)
Hypothyroidism	6 ( 6.5)	2 ( 2.4)	8 ( 4.6)
Hyperthyroidism	7 ( 7.6)	0 ( 0.0)	7 ( 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



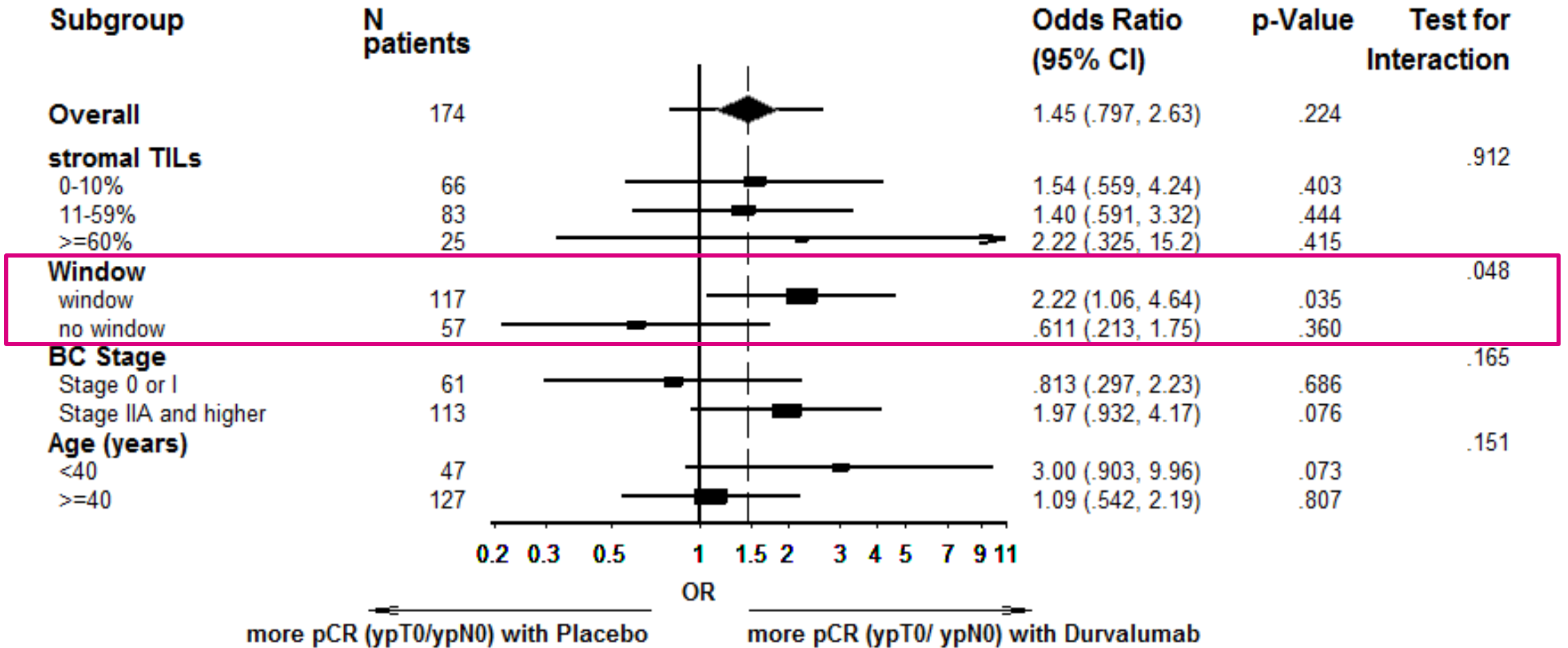
# Primary Endpoint - pathological complete response

## pCR – ypT0, ypN0



\* Continuous corrected  $\chi^2$  test  
\*\* For stratification factor (TIL groups)

# Subgroup Analyses (predefined)

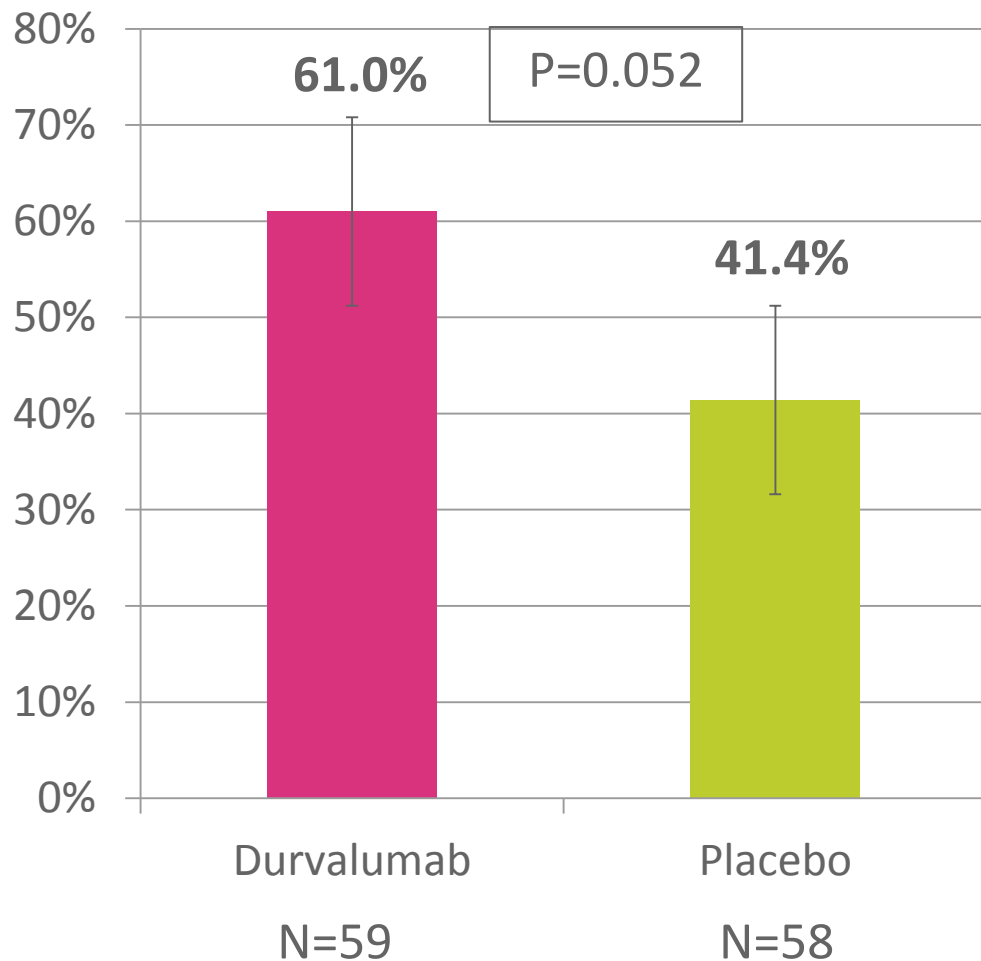




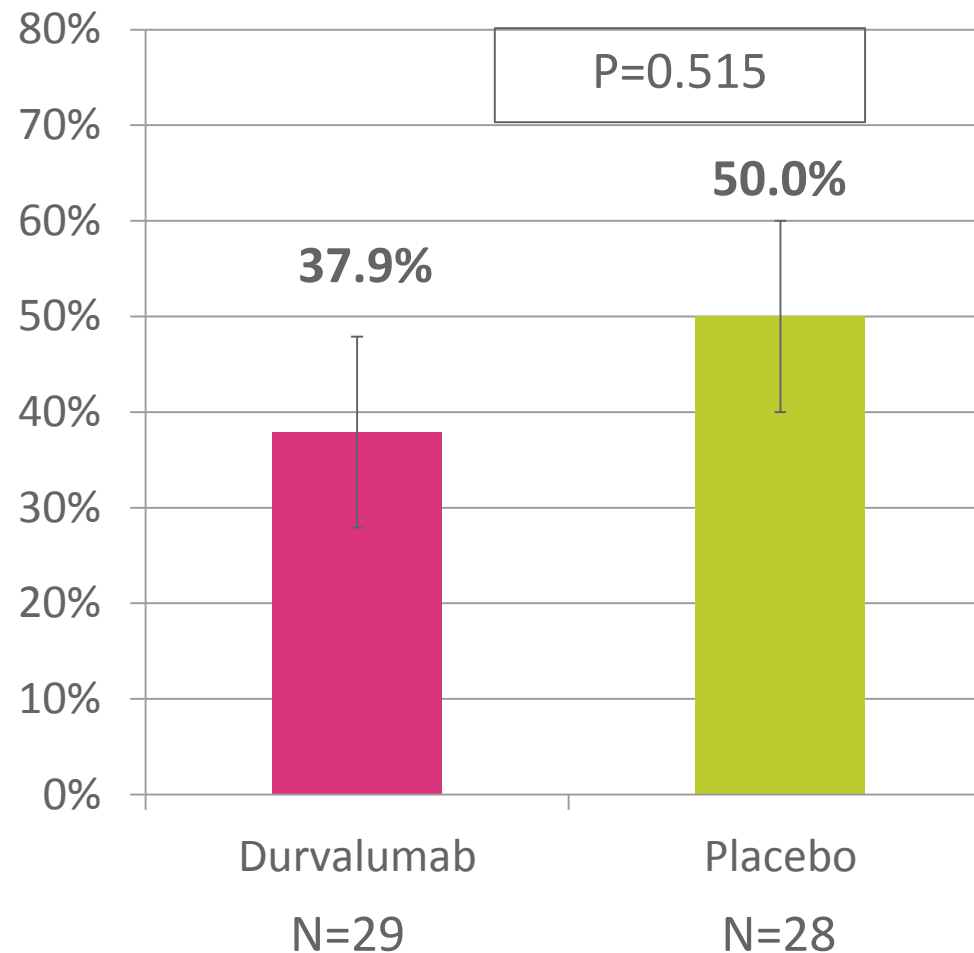
# Subgroup Analysis of the Window Cohort



**Window (N=117)**

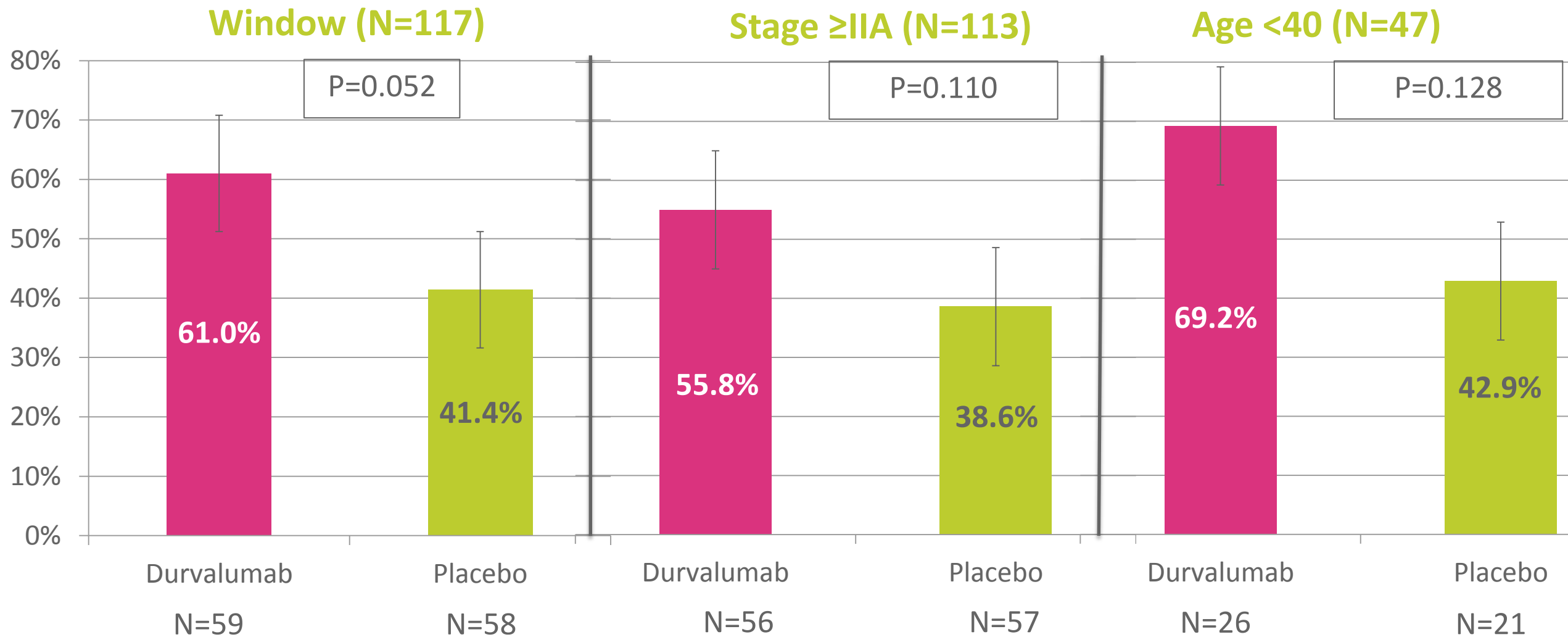


**No window (N=57)**





# 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<sup>1</sup>

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

<sup>1</sup>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



- All patients and their families
- All participating sites
- Members of the Subboard of GBG and AGO-B
- Team at GBG Headquarters (Konstantin Reissmüller, Ursula Wolf, Christiane Prätör, Bärbel Felder)
- Team at Charité for central pathology
- Knut Engels for central review of histology reports
- AstraZeneca and Celgene for financial and drug support

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