Durvalumab improves long-term outcome in TNBC: Results from the phase II randomized GeparNUEVO study investigating neodjuvant durvalumab in addition to an anthracycline/taxane based neoadjuvant chemotherapy in early triple-negative breast cancer (TNBC)

Sibylle Loibl, Andreas Schneeweiss, Jens Huober, Michael Braun, Julia Rey, Jens-Uwe Blohmer, Jenny Furlanetto, Dirk-Michael Zahm, Claus Hanusch, Jörg Thomalla, Christian Jackisch, Peter Staib, Theresa Link, Kerstin Rhiem, Christine Solbach, Peter A Fasching, Nicole Burchardi, Carsten Denkert, Michael Untch

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

Background

- PD-(L)1 inhibitors added to monochemotherapy improves PFS in PD-L1+ metastatic triple negative breast cancer (mTNBC) [1,2]
- The Safir study raised the hypothesis that durvalumab maintencance therapy improves PFS and OS in mTNBC[3]
- pCR rates with PD-(L)1 inhibitors were increased when added to neoadjuvant chemotherapy[4,5]
- The response to CPI was independent of the PD-L1 status in eTNBC
- Tumor Infiltrating Lymphocytes (TILs) correlate highly with other immune genes, e.g. PD-L1[4] and are predictive for pCR and prognostic in eTNBC[6,7,8]
- Durvalumab has demonstrated efficacy in bladder and lung cancer[9,10]

[1]Schmid et al. N Engl J Med 2018; 2 Cortes J Lancet 2020; [3] Bachelot T et al. Nature Med 2020, [4]Schmid et al. N Engl J Med 2020; [5]Mittendorf et al. Lancet. 2020; [6]Denkert et al. J Clin Oncol 2015; [7]Adams et al. Oncoimmunology 2015; [8]Denkert et al. Lancet Oncol 2018;[9] Powles et al. JAMA Oncol 2017; [10]Antonia et al. N Engl J Med 2017;

Neoadjuvant Chemotherapy plus anti-PD-L1/PD1 Antibodies Phase II/III

Phase II/III
neoTRIP
N=260

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

41% — Control (no anthracycline)
44% — Immunotherapy (no anthracycline but platinum)

Nab Paclitaxel Q1W x12 + Carbo AUC2 Atezolizumab 12x840mg Q3W 8 cycles

Gianni L et al. SABCS 2019 GS3-02

Phase III adaptive enrichment design
IMPASSION 031
N=333

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

41% — Control (no immunotherapy)
57% — Immunotherapy (no platinum)

→ Nab Paclitaxel Q1W x12 + Atezolizumab 840mg Q2W → EC Q2W x4 + Atezolizumab 840mg Q2W

Mittendorf et al. Lancet 2020

Phase III conventional design
KN522
N=602 /1174

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

51% — Control (+platinum)
65% — Immunotherapy (+platinum)

Paclitaxel Q1W x12 + Carboplatinum AUC5 Q3weeks or 1.5 Q1W +pembrolizumab Q3W x4 → AC Q3W x4+ pembrolizumab Q3W

Schmidt P et al. New Engl Journal 2020

Background

Randomized phase III trials in early-stage TNBC

- pCR rates

Trial	ΔpCR rates		
	overall	PD-L1 positive	PD-L1 negative
KEYNOTE 522[1] (pembrolizumab+CT vs placebo+CT)	+13.6%	+14%	+18%
IMpassion031[2] (atezolizumab+CT vs placebo+CT)	+17%	+20%	+14%

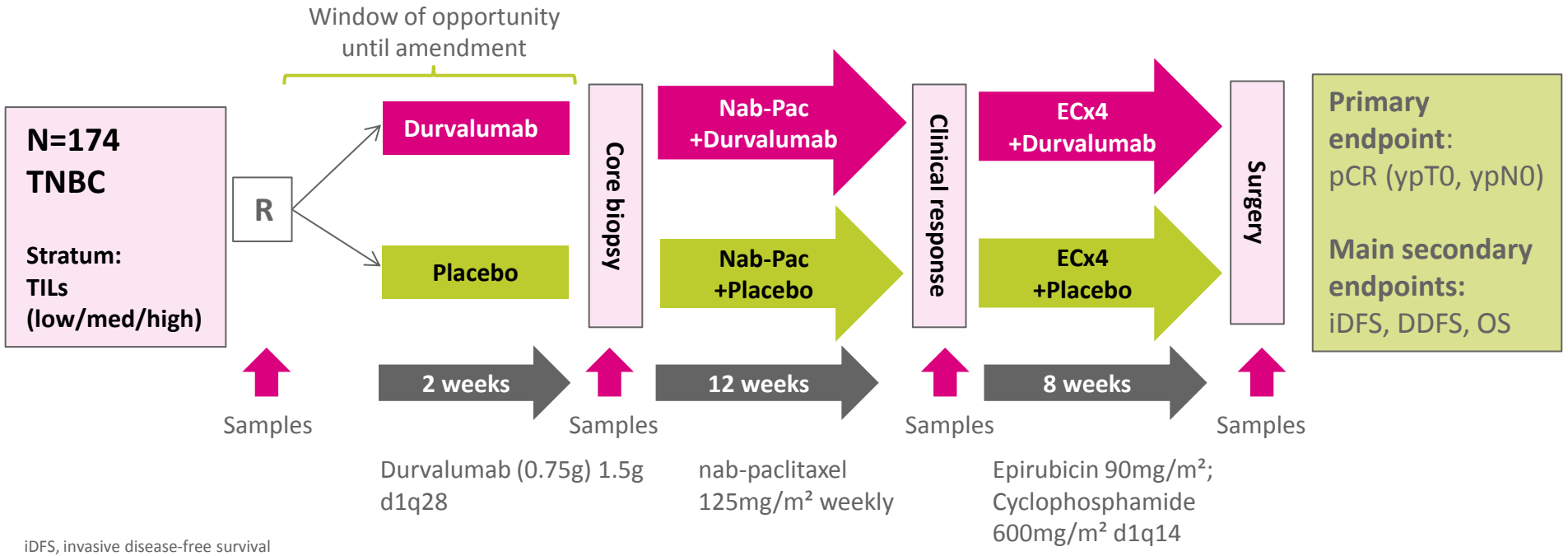
- Long-term survival

Trial	Median FU	Events	HR (95%CI)
KEYNOTE 522 (pembrolizumab+CT vs placebo+CT)	15.5 months	7.4% vs 11%	0.63 (0.43-0.93)
IMpassion031*(atezolizumab+CT vs placebo+CT)	20.6 months	10.3% vs 13.1%	0.76 (0.4-1.44)

adapted acc Loi S, 17th St Gallen 2021;
[1]Schmid, et al. N Engl J Med 2020; [2]Mittendorf et al. Lancet. 2020

*IMpassion031 is not powered for EFS
CT, chemotherapy; FU, follow-up

Study Design

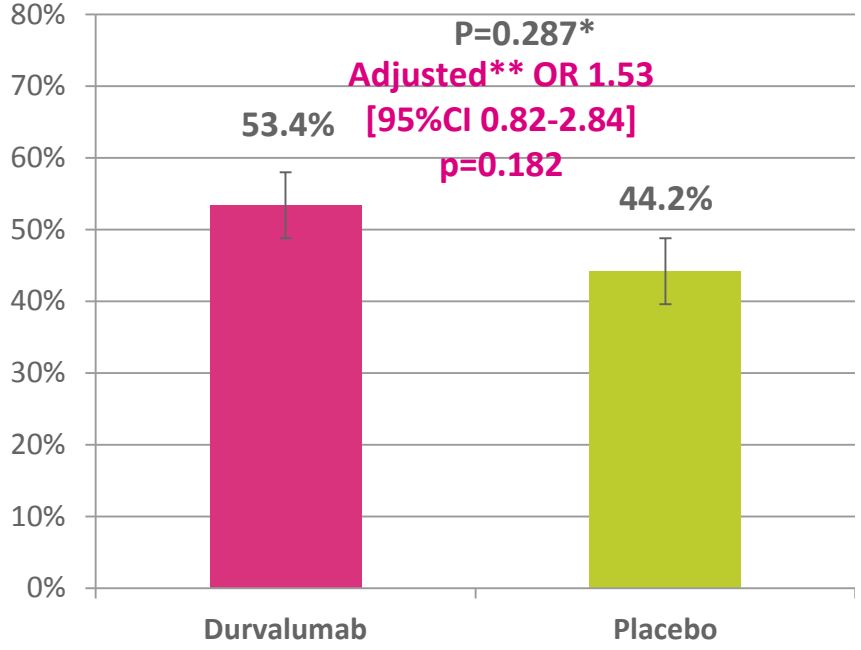


iDFS, invasive disease-free survival
DDFS, distance disease-free survival
OS, overall survival

Loibl S, et al. Ann Oncol 2019

Efficacy Endpoints

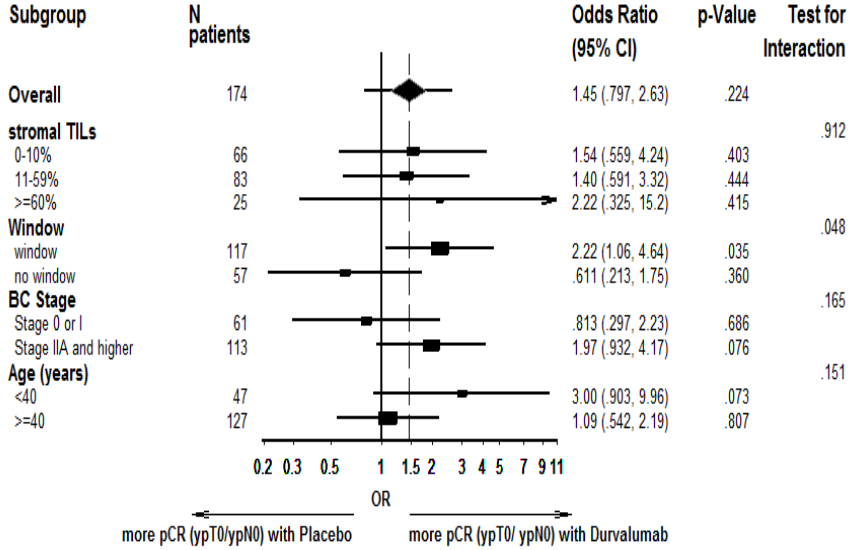
Primary endpoint: pCR – ypT0, ypN0



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

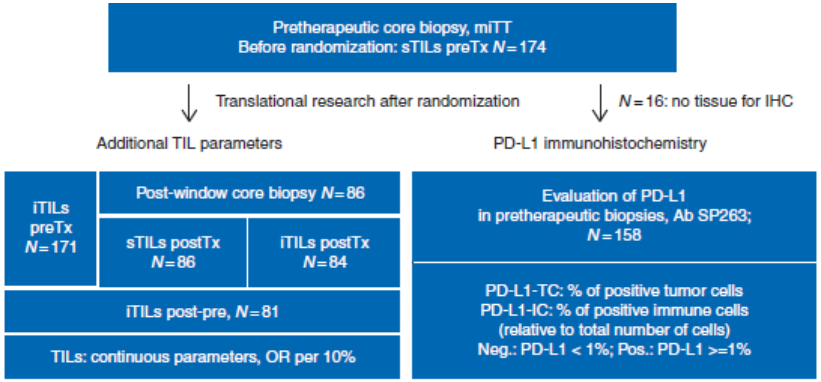
Loibl S, et al. Ann Oncol 2019

Subgroup Analyses (predefined)



Evaluation of pCR according to sTILs, iTILs change, PD-L1

A



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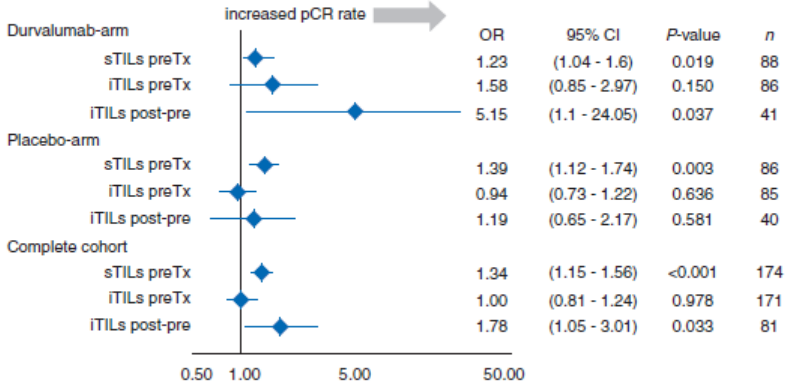
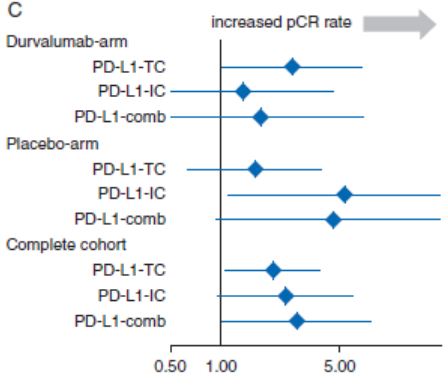


	OR	95% CI	*P*-value	*n*
Durvalumab-arm				
sTILs preTx	1.23	(1.04 - 1.6)	0.019	88
iTILs preTx	1.58	(0.85 - 2.97)	0.150	86
iTILs post-pre	5.15	(1.1 - 24.05)	0.037	41
Placebo-arm				
sTILs preTx	1.39	(1.12 - 1.74)	0.003	86
iTILs preTx	0.94	(0.73 - 1.22)	0.636	85
iTILs post-pre	1.19	(0.65 - 2.17)	0.581	40
Complete cohort				
sTILs preTx	1.34	(1.15 - 1.56)	<0.001	174
iTILs preTx	1.00	(0.81 - 1.24)	0.978	171
iTILs post-pre	1.78	(1.05 - 3.01)	0.033	81

C



	OR	95% CI	*P*-value	*n* (pos)	*n* (neg)	*n* (total)
Durvalumab-arm						
PD-L1-TC	2.63	(1.02 - 6.77)	0.045	33	45	78
PD-L1-IC	1.36	(0.40 - 4.65)	0.627	66	12	78
PD-L1-comb	1.72	(0.43 - 6.98)	0.445	69	9	78
Placebo-arm						
PD-L1-TC	1.59	(0.64 - 3.91)	0.315	32	48	80
PD-L1-IC	5.30	(1.08 - 26.03)	0.040	68	12	80
PD-L1-comb	4.63	(0.93 - 23.01)	0.061	69	11	80
Complete cohort						
PD-L1-TC	2.03	(1.06 - 3.87)	0.032	65	93	158
PD-L1-IC	2.39	(0.96 - 5.97)	0.061	134	24	158
PD-L1-comb	2.78	(1.01 - 7.65)	0.048	138	20	158

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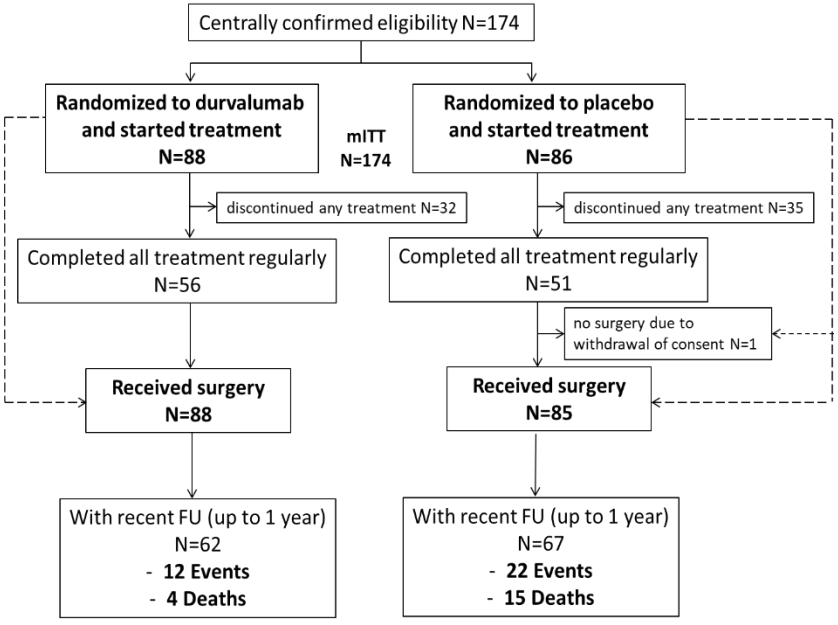
Patient and Tumor Characteristics

Consort diagram



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Main Baseline Characteristics

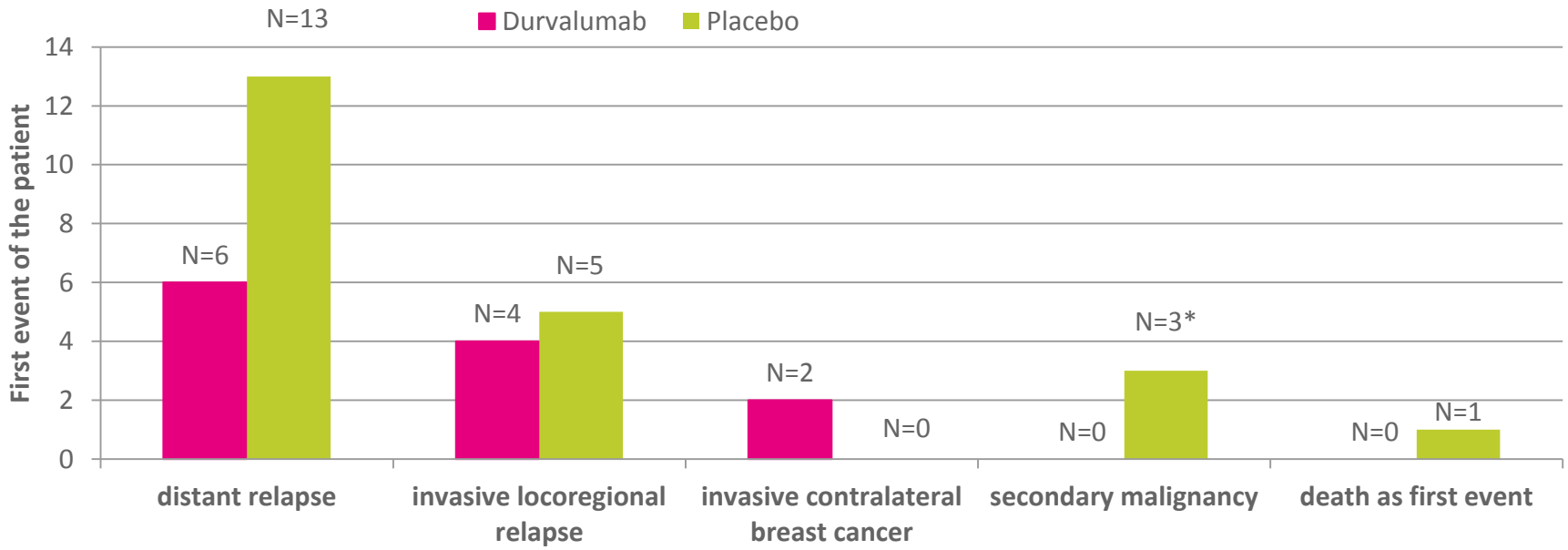
	Durvalumab N=88 N(%)	Placebo N=86 N(%)
Age (yrs), median (range)	49.5 (25.0, 74.0)	49.5 (23.0, 76.0)
cT3/4	7 (8.0)	3 (3.5)
cN+	27 (30.7)	27 (31.4)
Stage IIA and higher	56 (63.6)	57 (66.3)
G3	74 (84.1)	71 (82.6)
TILs		
low (0-10%)	34 (38.6)	32 (37.2)
intermediate (11-59%)	42 (47.7)	41 (47.7)
high (≥60%)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

Statistics

- **Primary endpoint was pCR at surgery**
- **iDFS, DDFS and OS were secondary endpoints**
- **Statistical considerations**
  - The time-to-event-analysis was changed from an initially planned event-driven analysis at 43 events (to detect HR=0.773 with 13.5% power) to a time-driven analysis after 3.5 years median follow-up.
  - No adjustment for multiple testing

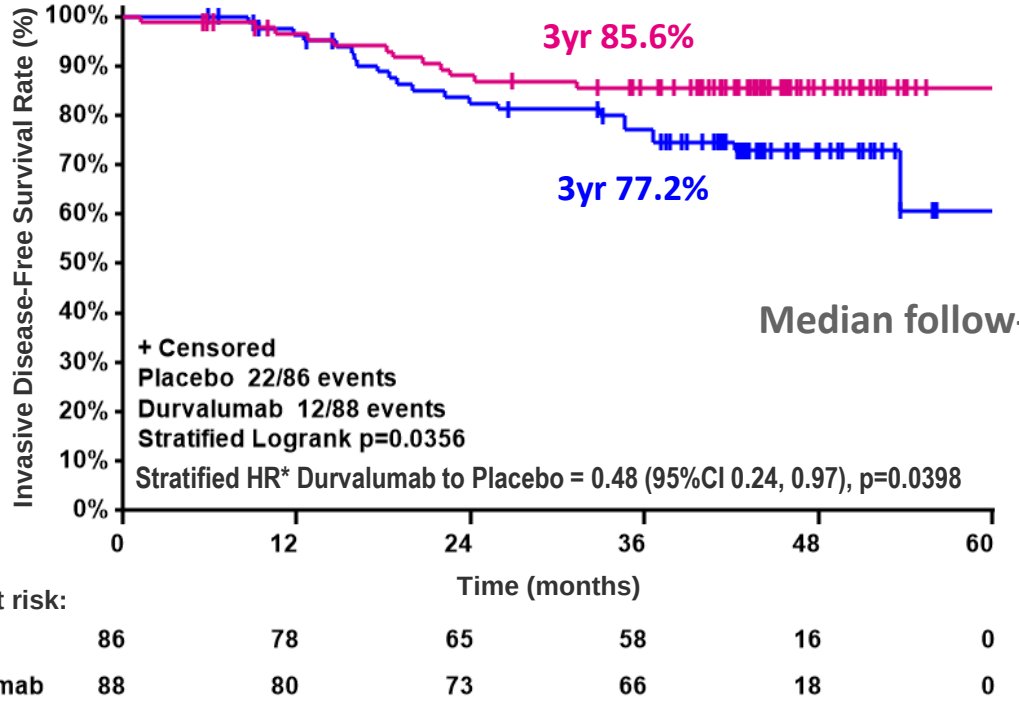
Time-To-Event Analysis

After a median follow-up 43.7 (range 4.9-56.1) months 34 iDFS events were reported (12 in the durvalumab arm and 22 in the placebo arm)



* malignant melanoma, cholangiocarcinoma with liver metastases, non-small-cell lung cancer

iDFS Between Treatment Arms

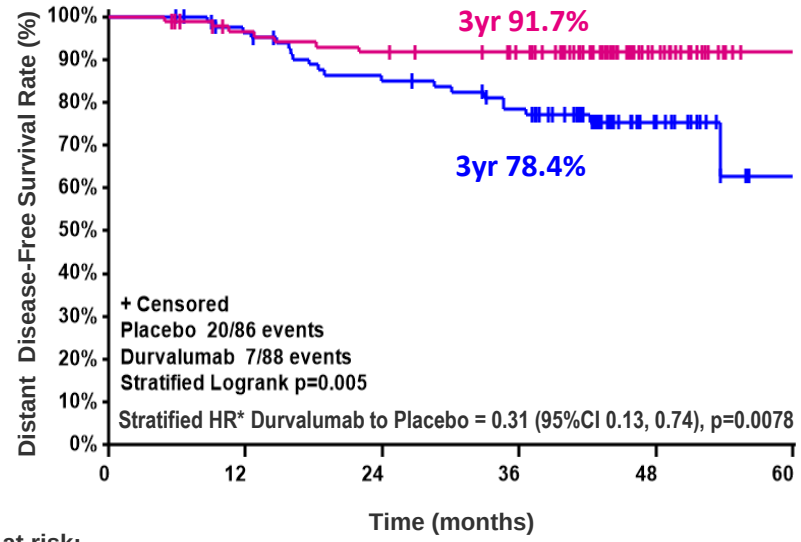


Median follow-up 43.7 (range 4.9-56.1) months

* Stratified by sTILs

DDFS and OS Between Treatment Arms

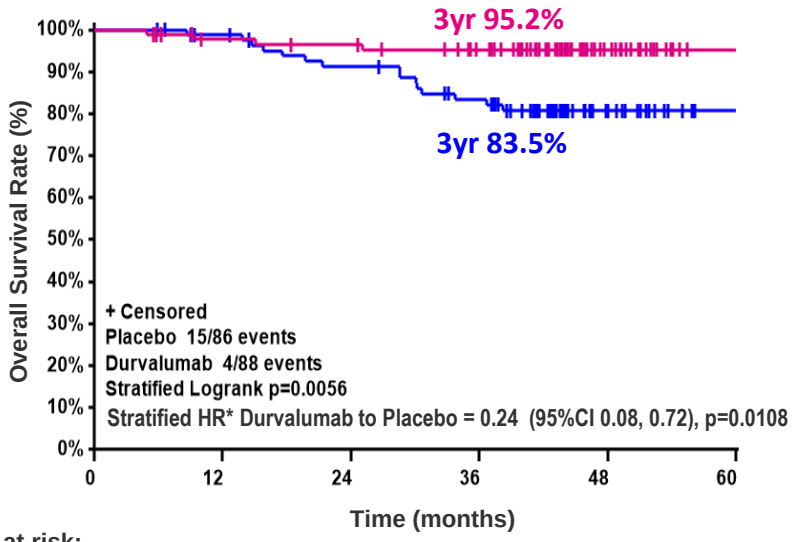
DDFS



Patients at risk:

Placebo	86	78	67	59	16	0
Durvalumab	88	80	76	70	20	0

OS



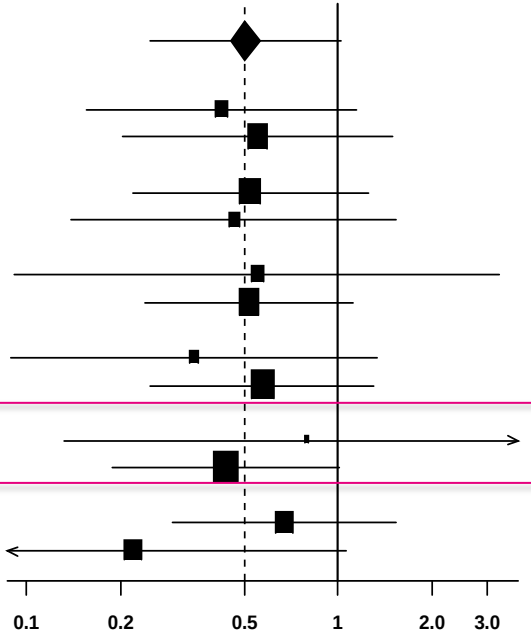
Patients at risk:

Placebo	86	80	72	63	16	0
Durvalumab	88	81	79	71	20	0

* Stratified by sTILs

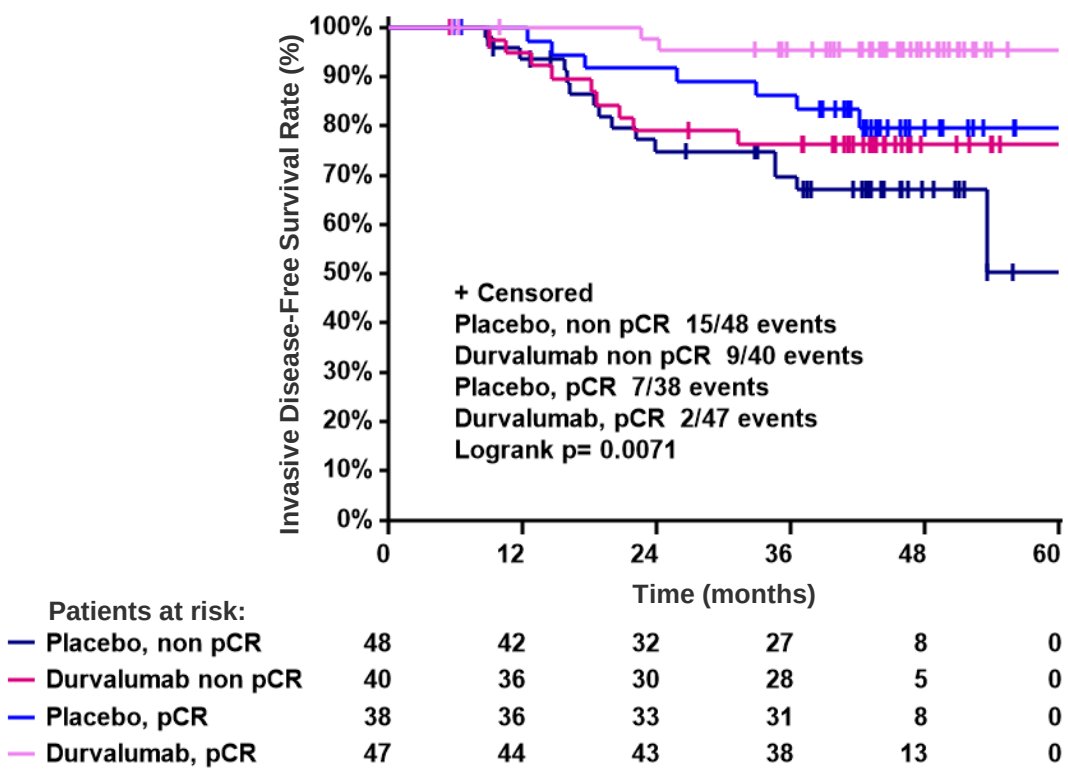
iDFS in Subgroups (univariate Cox regression model)

Subgroup	N patients	Hazard Ratio (95% CI)	p-Value	Test for Interaction
Overall *	174	0.48 (0.24, 0.97)	.0398	
sTILs				0.705
low (0-10%)	66	.423 (.156, 1.15)	0.090	
intermediate/high (11-100%)	108	.553 (.205, 1.50)	0.244	
Window Arm				0.891
window	117	.524 (.220, 1.25)	0.145	
no window	57	.465 (.140, 1.55)	0.211	
Breast Cancer Stage				0.940
Stage 0 or I	61	.553 (.092, 3.31)	0.517	
Stage IIA and higher	113	.519 (.241, 1.12)	0.093	
Age				0.552
<40	47	.344 (.089, 1.33)	0.122	
>=40	127	.573 (.251, 1.31)	0.187	
PD-L1				0.463
negative	20	.795 (.133, 4.76)	0.801	
positive	138	.436 (.188, 1.01)	0.053	
pCR (ypT0 ypN0)				0.222
no	88	.674 (.295, 1.54)	0.350	
yes	85	.220 (.046, 1.06)	0.059	



* Stratified by sTILs

iDFS by pCR and Treatment Arm



3yr 95.5%

3yr 86.1%

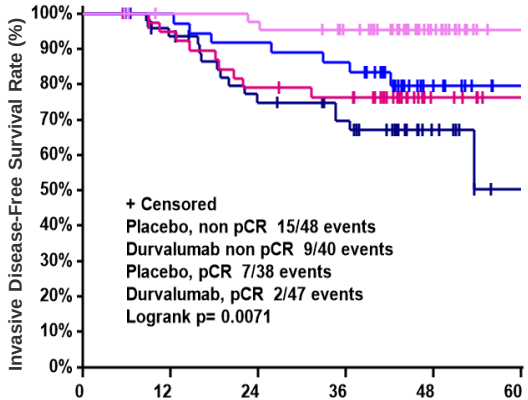
3yr 76.3%

3yr 69.7%

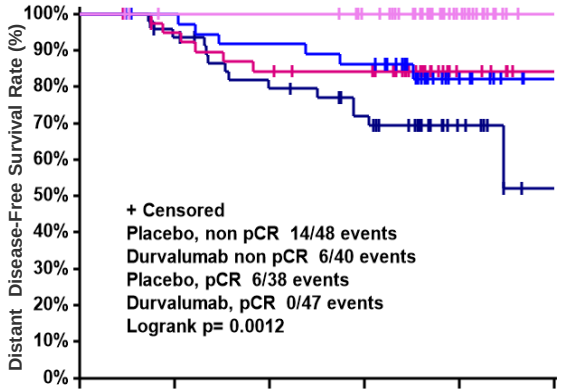
HR (pCR vs non-pCR) 0.34 (95%CI 0.16-0.73)
log-rank p=0.004

iDFS, DDFS and OS by pCR and Treatment Arm

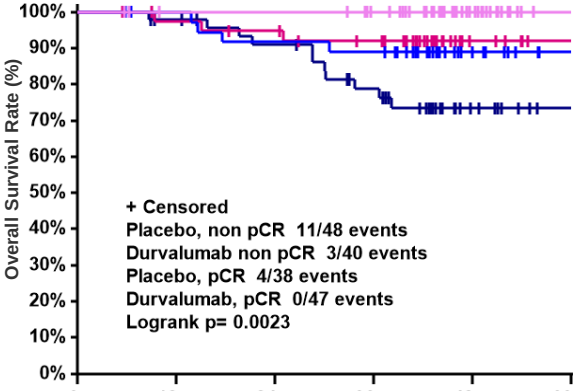
iDFS



DDFS



OS



Patients at risk:						
Placebo, non pCR	48	42	32	27	8	0
Durvalumab non pCR	40	36	30	28	5	0
Placebo, pCR	38	36	33	31	8	0
Durvalumab, pCR	47	44	43	38	13	0

Placebo, non pCR	48	42	34	28	8	0
Durvalumab non pCR	40	36	32	30	5	0
Placebo, pCR	38	36	33	31	8	0
Durvalumab, pCR	47	44	44	40	15	0

Placebo, non pCR	48	44	39	31	8	0
Durvalumab non pCR	40	37	35	31	5	0
Placebo, pCR	38	36	33	32	8	0
Durvalumab, pCR	47	44	44	40	15	0

HR (non pCR vs pCR)=0.34
(95%CI 0.16-0.73)
log-rank p=0.004

HR (non-pCR vs pCR) 0.28
(95%CI 0.11-0.69)
log-rank p=0.003

HR (non-pCR vs pCR)=0.27
(95%CI 0.09-0.81)
log-rank p=0.012

iDFS, DDFS and OS by pCR and Treatment Arm

Endpoint	Category	Durvalumab 3-year rates % (95%CI)	Placebo 3-year rates % (95%CI)	HR (durvalumab vs placebo) (95%CI)	Log-rank p-value
iDFS	Non-pCR	76.3% (59.3%, 86.9%)	69.7% (53.4%, 81.2%)	0.67 (0.29-1.54)	0.346
	pCR	95.5% (83.0%, 98.8%)	86.1% (69.8%, 94.0%)	0.22 (0.05-1.06)	0.038
DDFS	Non-pCR	84.3% (68.3%, 92.6%)	71.9% (55.8%, 83.0%)	0.48 (0.18-1.25)	0.124
	pCR	100% (100%, 100%)	86.1% (69.8%, 94.0%)	0.00 (0.00-.)*	0.005
OS	Non-pCR	92.0% (77.1%, 97.3%)	78.8% (63.2%, 88.4%)	0.30 (0.08-1.09)	0.053
	pCR	100% (100%, 100%)	88.9% (73.1%, 95.7%)	0.00 (0.00-.)*	0.024

*no events in durvalumab arm

Summary and Conclusions

- **Durvalumab added to neoadjuvant chemotherapy in TNBC significantly improved survival**
  - iDFS: HR 0.48 (95%CI; 0.24, 0.97), p=0.0398
  - DDFS: HR 0.31 (95%CI 0.13, 0.74), p=0.0078
  - OS: HR 0.24 (95%CI 0.08, 0.72), p=0.0108
- **Patients with pCR seem to have a better survival with durvalumab than pCR patients on placebo**
- **The value of PD-L1 for long-term outcome needs to be further explored**
- **pCR improvement with durvalumab was modest requiring further assessment of association of pCR and longer term outcomes with CPI therapies**
- **Given these results, the value of adjuvant therapy with CPI needs to be further assessed**

Acknowledgement

- All patients and their families
- All participating sites
- Slides are available on the webpage of GBG: www.gbg.de

Cooperating partners

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Patient Self-Registry:	**Zentrum für klinische Studien (ZKS), Köln**

GBG

Members of the Subboard GBG and AGO-B

Project Management:
Konstantin Reissmüller
Translational Research:
Bärbel Felder
Data Management:
Christiane Prätor
Medical Department:
Natalie Donde, Jenny Furlanetto, Sabine Seiler
Medical Writing:
Valentina Vladimirova, Bianca Lederer