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NCCN Guidelines Panel: Breast Cancer

Dear Sir or Madam:

On behalf of AstraZeneca, this letter is a formal request to the National Comprehensive Cancer Network (NCCN) Panel for Breast Cancer to review the enclosed data supporting use of IMFINZI® (durvalumab) as neoadjuvant therapy in addition to an anthracycline/taxane based regimen in early triple negative breast cancer (TNBC). This request is based on the GeparNUEVO updated analysis that was presented at the American Society of Clinical Oncology 2021 annual meeting and original publication from the Annals of Oncology in 2019.

Specific Changes:
We respectfully request your consideration of the following changes:

- Page BINV-L 1 of 7: Within table, under "Other Recommended Regimens", add "nab-paclitaxel and durvalumab followed by dose-dense epirubicin/cyclophosphamide (EC) and durvalumab"

- Discussion section starting on page MS-1: Add a section overviewing the GeparNUEVO study and results.

FDA Status:
Durvalumab is a programmed death-ligand 1 (PD-L1) blocking antibody indicated:
- for the treatment of adult patients with unresectable, Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.
- in combination with etoposide and either carboplatin or cisplatin, as first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

Durvalumab does not have an FDA indication in breast cancer.

Rationale:
This request is based on the results of GeparNUEVO, a randomized, double-blinded, placebo controlled, phase II trial investigating the pathological complete response (pCR) of neoadjuvant chemotherapy followed by dose-dense EC with durvalumab versus placebo in patients with primary non-metastatic TNBC.[2]

Eligible patients included women with previously untreated unilateral or bilateral primary, non-metastatic invasive TNBC with a tumor size of at least 2 cm (cT2-cT4a-d).

Patients received one injection of durvalumab 0.75 g IV/placebo monotherapy 2 weeks before start of chemotherapy followed by durvalumab 1.5 g IV/placebo every 4 weeks plus nab-paclitaxel 125 mg/m^2 weekly for 12 weeks, followed by durvalumab 1.5 g IV/placebo every 4 weeks plus EC every 2 weeks for 4 cycles.

The primary end point was pCR defined as no invasive and no non-invasive tumor residuals in breast and in axillary lymph nodes (ypT0 ypN0) after neoadjuvant therapy.

Key secondary endpoints included:

- Invasive disease free survival (iDFS)
- Distant disease free survival (DDFS)
- Overall survival

TABLE 1. Main baseline characteristics[1]

	Durvalumab n=88 n (%)	Placebo n=86 n (%)
Age (years), 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)

FIGURE 1: Primary endpoint - pathological complete response rate

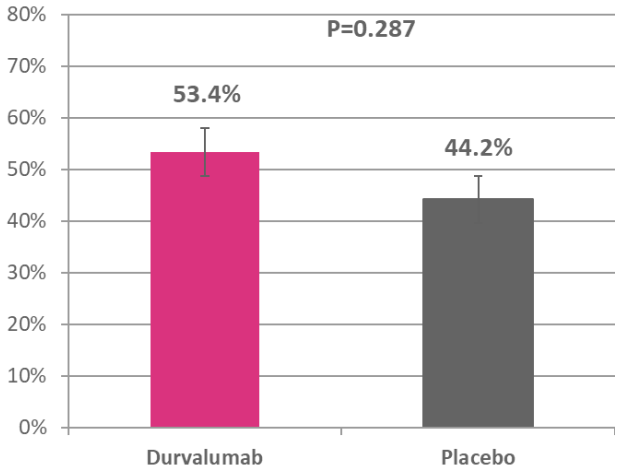


FIGURE 2: Invasive disease free survival (iDFS) between arms

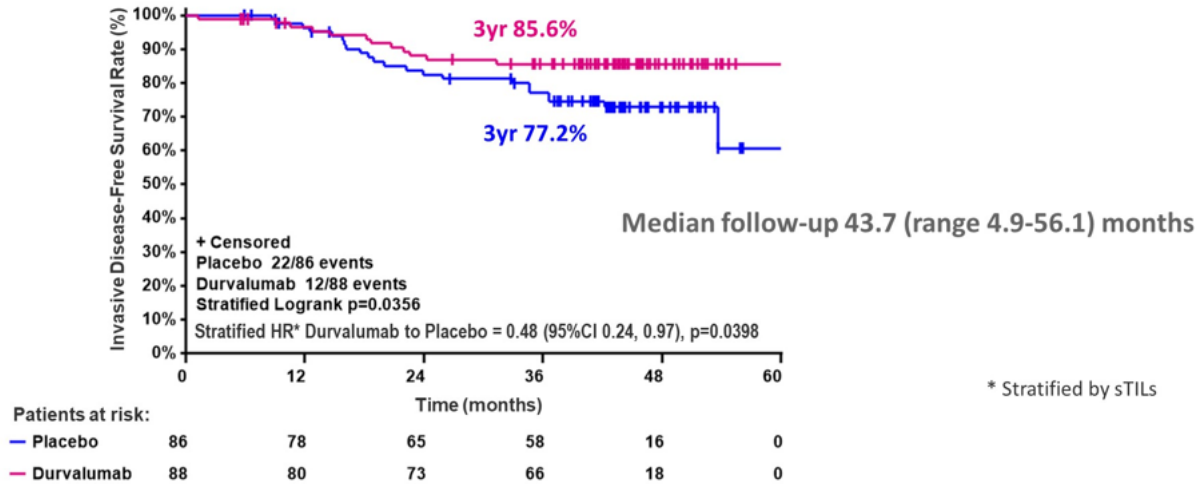


FIGURE 3: Distant disease free survival (DDFS) between arms

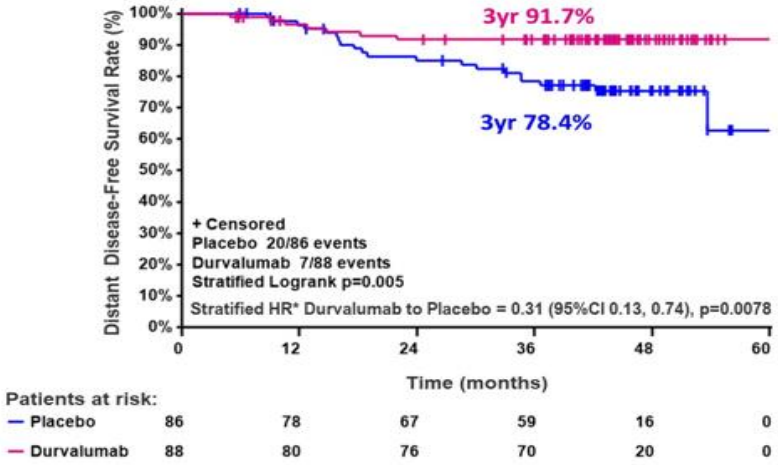
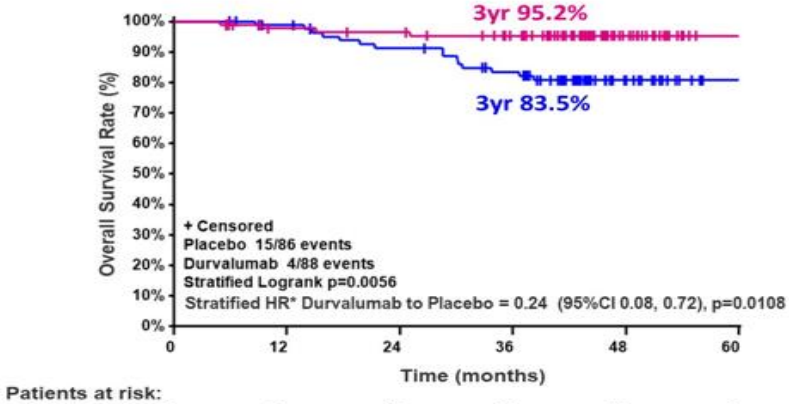
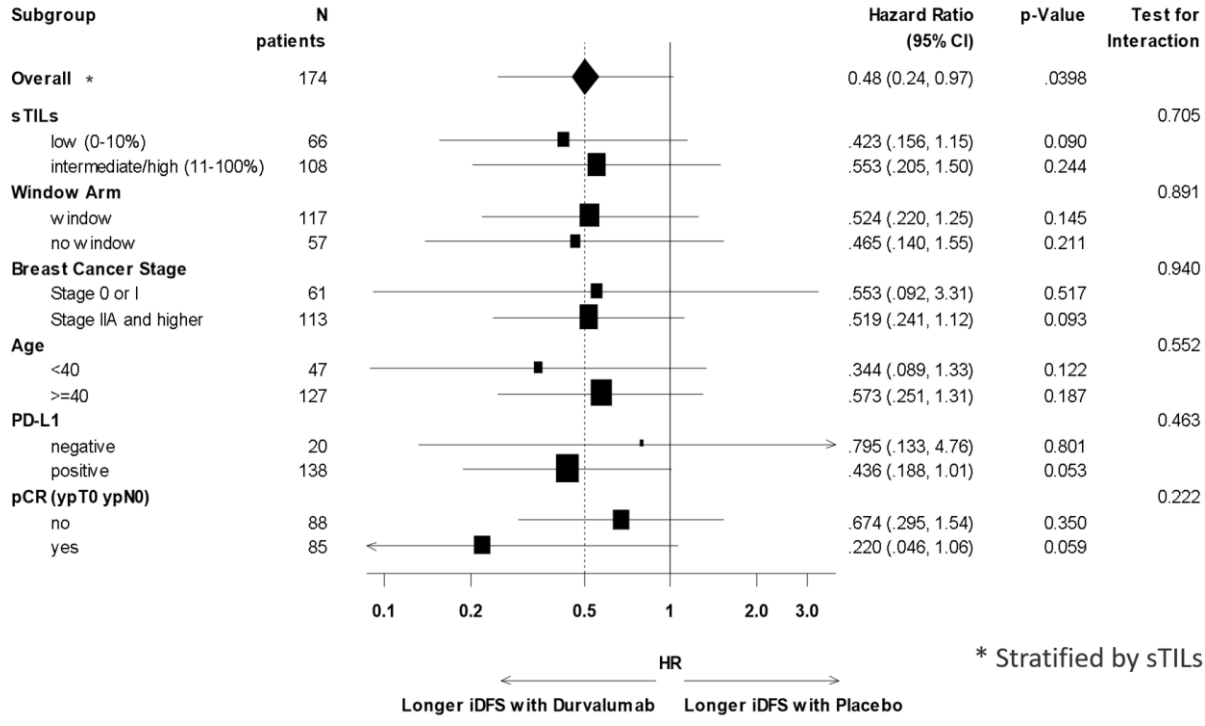


FIGURE 4: Overall survival between arms



* Stratified by sTILs

FIGURE 5: Invasive disease free survival (iDFS) in subgroups



* Stratified by sTILs

FIGURE 6: iDFS, DDFS and OS by pCR between treatment arms

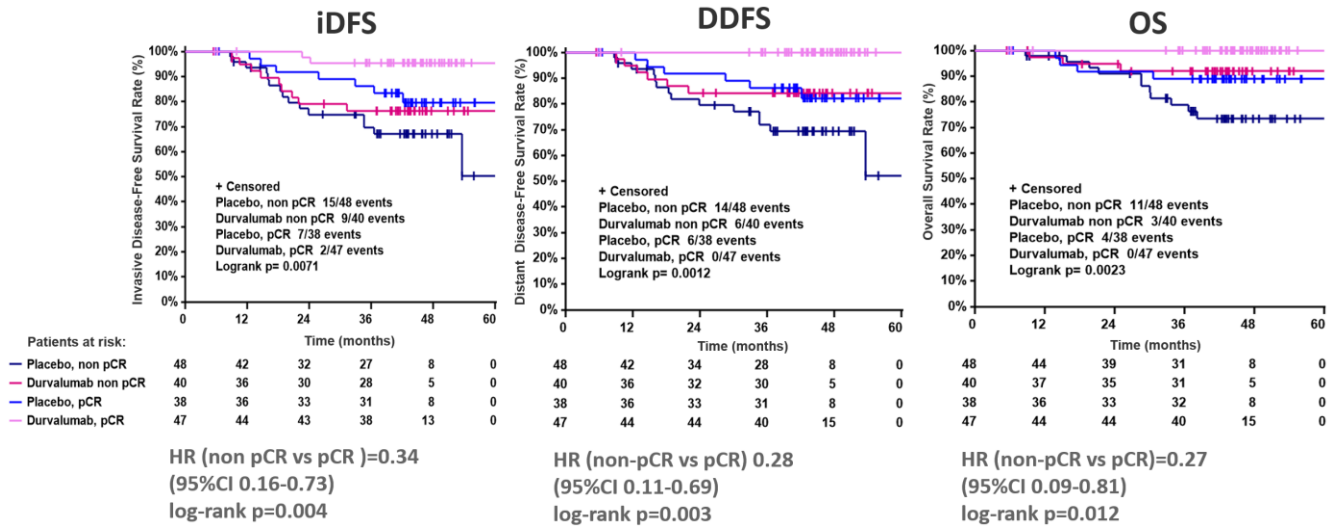


TABLE 2. iDFS, DDFS and OS by pCR and treatment arm

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

TABLE 3: Safety (≥30% any grade)

Adverse events n (%)	Durvalumab n=92		Placebo n=82		P-value any grade	P-value grade 3-4
	Any grade	Grade 3-4	Any grade	Grade 3-4		
Anemia	87 (94.6)	2 (2.2)	79 (96.3)	2 (2.4)	0.724	1.000
Leukopenia	81 (88.0)	30 (32.6)	79 (96.3)	30 (36.6)	0.053	0.633
Neutropenia	71 (77.2)	34 (37.0)	67 (81.7)	34 (41.5)	0.574	0.641
Thrombocytopenia	35 (38.0)	1 (1.1)	28 (34.1)	2 (2.4)	0.637	0.602
Increased AP	43 (46.7)	0 (0.0)	40 (48.8)	0 (0.0)	0.879	NA
Increased ASAT	45 (48.9)	3 (3.3)	28 (34.1)	0 (0.0)	0.065	0.248
Increased ALAT	53 (57.6)	4 (4.3)	45 (54.9)	3 (3.7)	0.761	1.000
Hyperglycemia	32 (38.6)	0 (0.0)	37 (51.4)	0 (0.0)	0.145	NA
Fatigue	70 (76.1)	5 (5.4)	68 (82.9)	9 (11.0)	0.349	0.264
Headache	38 (41.3)	1 (1.1)	28 (34.1)	0 (0.0)	0.352	1.000
Alopecia	85 (92.4)	–	78 (95.1)	–	0.543	–
Nausea	54 (58.7)	0 (0.0)	53 (64.6)	7 (8.5)	0.439	0.004
Diarrhea	26 (28.3)	3 (3.3)	34 (41.5)	0 (0.0)	0.080	0.248
Constipation	29 (31.5)	1 (1.1)	34 (41.5)	1 (1.2)	0.207	1.000
Mucositis	32 (34.8)	2 (2.2)	33 (40.2)	0 (0.0)	0.531	0.499
Skin reactions	45 (48.9)	2 (2.2)	39 (47.6)	1 (1.2)	0.880	1.000
Peripheral sensory neuropathy	76 (82.6)	9 (9.8)	69 (84.1)	9 (11.0)	0.840	0.809
Arthralgia	39 (42.4)	2 (2.2)	38 (46.3)	1 (1.2)	0.648	1.000
Myalgia	34 (37.0)	4 (4.3)	25 (30.5)	2 (2.4)	0.424	0.685
Epistaxis	22 (23.9)	0 (0.0)	28 (34.1)	0 (0.0)	0.179	NA
Dyspnea	30 (32.6)	0 (0.0)	20 (24.4)	0 (0.0)	0.245	NA
Infection	50 (54.3)	5 (5.4)	39 (47.6)	4 (4.9)	0.448	1.000
Nail changes	46 (50.0)	8 (8.7)	43 (52.4)	3 (3.7)	0.763	0.220
Thyroid dysfunction	46 (50.0)	0 (0.0)	36 (43.9)	0 (0.0)	0.514	NA
Other AEs	89 (96.7)	21 (22.8)	78 (95.1)	15 (18.3)	0.708	0.574

References submitted in support of this proposal:

1. IMFINZI [prescribing information]. AstraZeneca Pharmaceuticals LP, Wilmington, DE 2021.
2. Loibl S, Untch M, Burchardi N, et al. A randomised phase II study investigating durvalumab in addition to an anthracycline taxane-based neoadjuvant therapy in early triple-negative breast cancer: clinical results and biomarker analysis of GeparNuevo study. *Ann Oncol* 2019; 30(8) 1279-1288.
3. Loibl S, Schneeweiss A, Huober J, et al. Durvalumab improves long-term outcome in TNBC: Results from the phase II randomized GeparNUEVO study investigating neoadjuvant durvalumab in addition to an anthracycline/taxane based neoadjuvant chemotherapy in early triple-negative breast cancer (TNBC). Presented at: The American Society of Clinical Oncology (ASCO) Virtual Annual Meeting; June 4-8, 2021.

Sincerely,

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