KEYNOTE-522: Neoadjuvant KEYTRUDA® (pembrolizumab) + chemotherapy followed by adjuvant KEYTRUDA monotherapy in patients with triple-negative breast cancer (TNBC)

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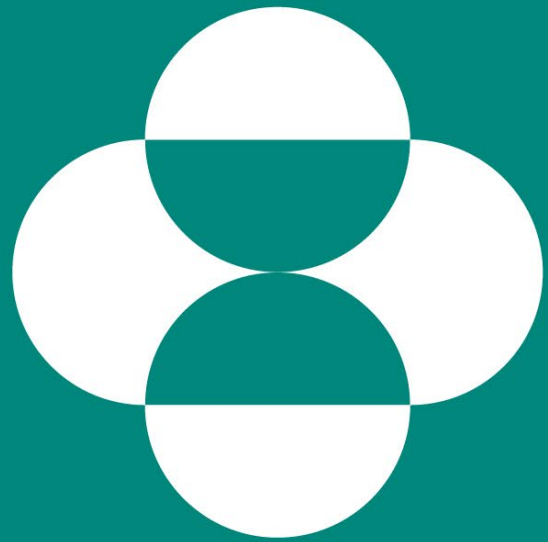
Please refer to the full Summary of Product Characteristics for KEYTRUDA and patient-targeted Risk Minimisation Materials before prescribing, to minimise the risk of treatment. Patients should also receive the Risk Minimisation Materials.



Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/ (please note that the MHRA Yellow Card link will redirect you to an external website, for which MSD does not review or control the content) or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Merck Sharp & Dohme (UK) Limited (Tel: 020 8154 8000).

Please click the following links for the KEYTRUDA SmPC and prescribing information: Great Britain; Northern Ireland.

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Job code: GB-PDO-02996 Date of preparation: January 2024

MSD

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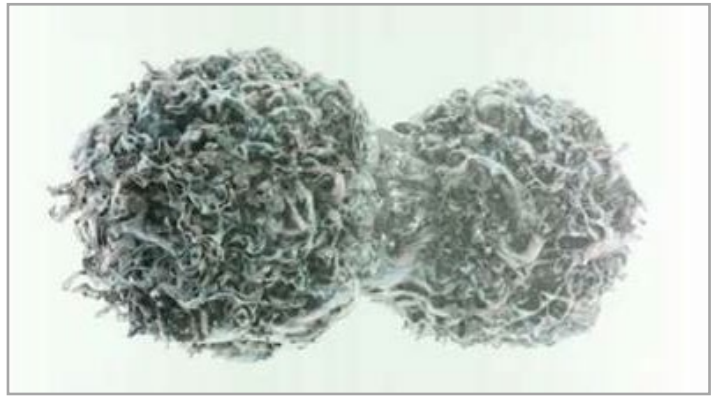
KEYTRUDA + chemotherapy licence in early-stage TNBC

KEYTRUDA in the early-stage TNBC pathway

MoA, mode of action; TNBC, triple-negative breast cancer.

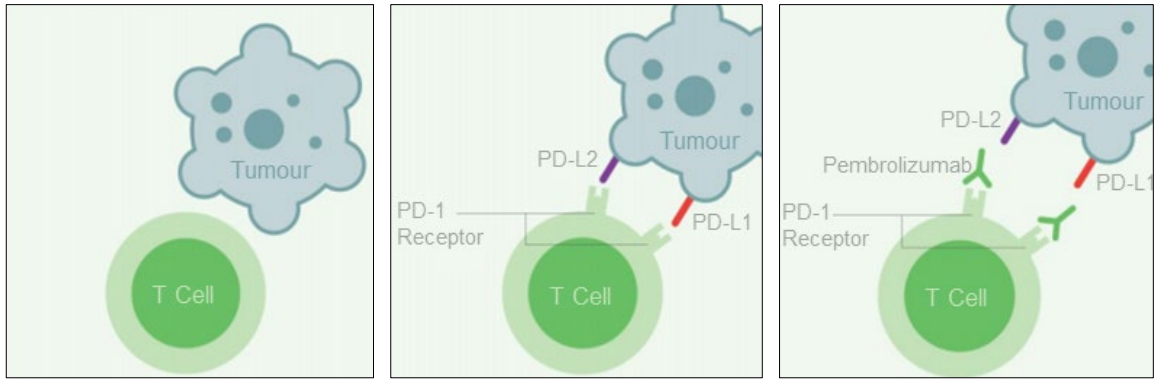
KEYTRUDA and chemotherapy: Two different mechanisms of action

Chemotherapy induces immunogenic cell death



- Chemotherapy results in the immunogenic death of tumour cells, leading to the release of tumour antigens that can be recognised by the immune system[1]
- Chemotherapy has been shown to increase tumour expression of PD-L1[2]

KEYTRUDA activates the anti-tumour immune response



- PD-L1 (and PD-L2) on tumour cells bind to PD-1 on T cells to prevent their activation, leading to immune evasion[3]
- KEYTRUDA is a humanised monoclonal antibody that binds to PD-1, blocking its interaction with PD-L1/-L2 and leading to activation of the anti-tumour response[4,5]

When combined with immunotherapies such as KEYTRUDA, chemotherapy may increase tumour immunogenicity and activate an immune response by increasing antigen shedding and presentation, and by stimulating T-cell infiltration[2]

PD-1, programmed death receptor-1; PD-L1, programmed death ligand-1; PD-L2, programmed death ligand-2; SmPC, Summary of Product Characteristics.

1. Emens LA and Middleton G. *Cancer Immunol Res* 2015;3:436–443; 2. Bailly C et al. *NAR Cancer* 2020;2(1):zcaa002; 3. Yi M et al. *J Hematol Oncol* 2021;14:10; 4. KEYTRUDA SmPC. https://www.medicines.org.uk/emc/product/2498/smpc (accessed January 2024); 5. Pardoll DM. *Nat Rev Cancer* 2012;12:252–264.

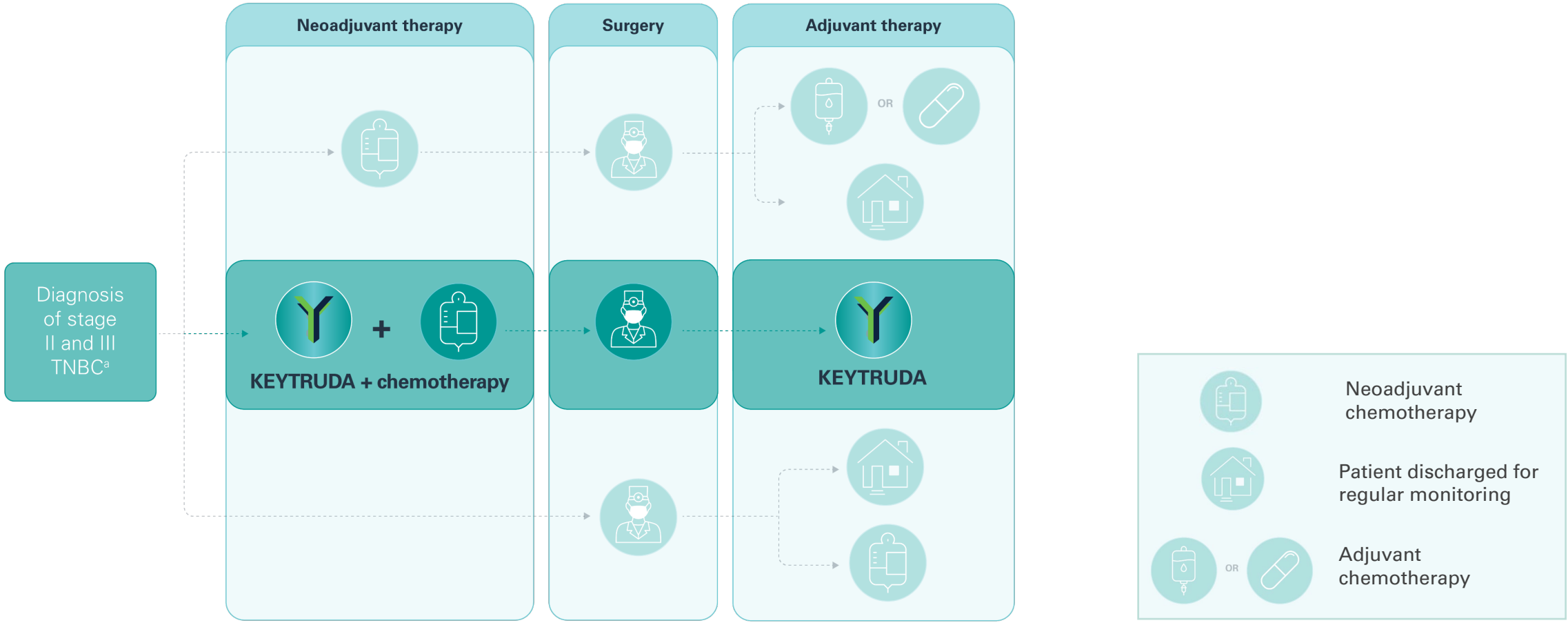
KEYTRUDA + chemotherapy licence in early-stage TNBC

KEYTRUDA, in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, is indicated in the treatment of adults with locally advanced or early-stage TNBC at high risk of recurrence

TNBC, triple-negative breast cancer.
KEYTRUDA SmPC. https://www.medicines.org.uk/emc/product/2498/smpc (accessed January 2024).

Prescribing Information: GB; NI

KEYTRUDA in the early-stage TNBC pathway[1,2]



[a]**Stage IIA, IIB, IIIA and IIIB early TNBC, and IIIC metastatic TNBC, as defined by the primary tumour-regional lymph node staging criteria of the American Joint Committee on Cancer (7th Edition).**
TNBC, triple-negative breast cancer.

1. NICE. Early and locally advanced breast cancer: diagnosis and management. https://www.nice.org.uk/guidance/ng101/chapter/Recommendations (accessed January 2024);
2. KEYTRUDA SmPC. https://www.medicines.org.uk/emc/product/2498/smpc (accessed January 2024).

Prescribing Information: GB; NI

KEYNOTE-522: Study overview

Click the links below to navigate to the section of interest

KEYNOTE-522: Study design

KEYNOTE-522: Primary endpoints

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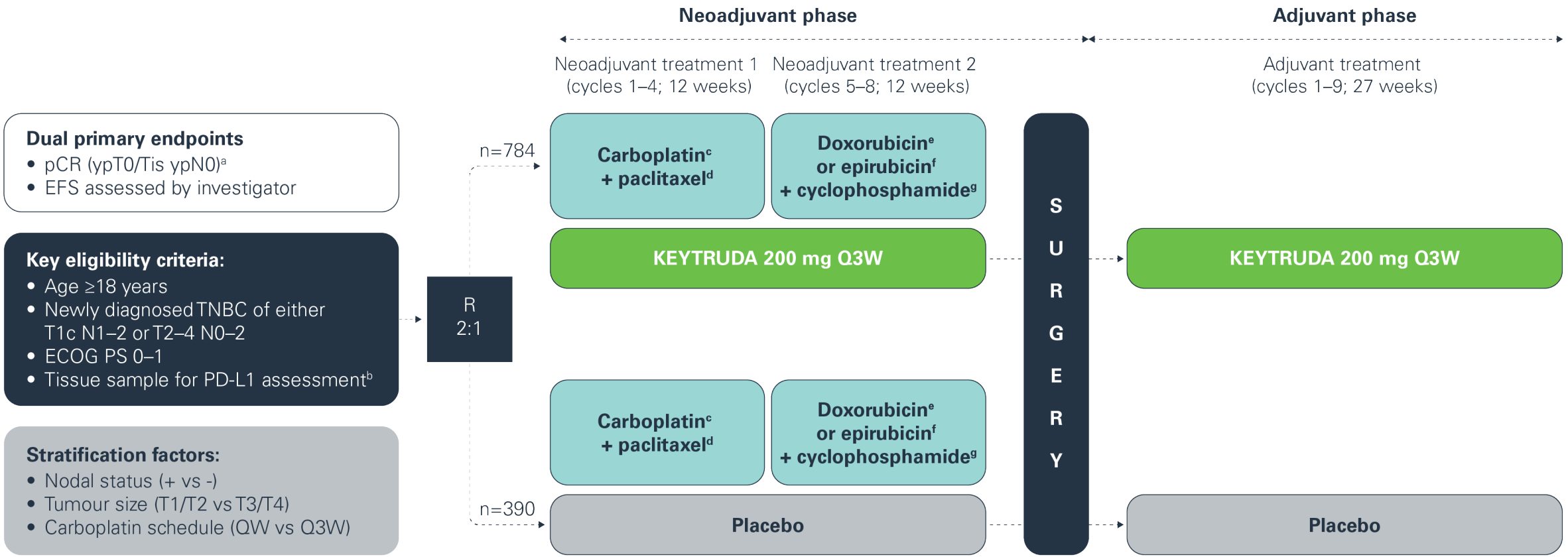
KEYNOTE-522: Patient baseline characteristics

pCR, pathologic complete response; EFS, event-free survival.

KEYNOTE-522: Study design[1,2]



Adapted from Schmid P et al. 2020 and Schmid P et al. 2022.

AEs were assessed during each phase of the study, as well as the study as a whole.
[a]Blinded assessment performed by local pathologist; [b]Must consist of at least two separate tumour cores from the primary tumour; [c]Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW; [d]Paclitaxel dose was 80 mg/m² QW; [e]Doxorubicin dose was 60 mg/m² Q3W; [f]Epirubicin dose was 90 mg/m² Q3W; [g]Cyclophosphamide dose was 600 mg/m² Q3W.
AE, adverse event; AUC, area under curve; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; pCR, pathologic complete response; PD-L1, programmed death ligand-1; QW, every week; Q3W, every 3 weeks; R, randomisation; TNBC, triple-negative breast cancer.

1. Schmid P et al. *N Engl J Med* 2020;382:810–821 (plus supplementary appendix); 2. Schmid P et al. *N Engl J Med* 2022;386:556–567 (plus supplementary appendix).

Prescribing Information: GB; NI

KEYNOTE-522: Primary endpoints[1,2]

The primary endpoints of the KEYNOTE-522 trial were pCR and EFS, and were defined as follows:

pCR: The absence of invasive cancer in the breast and lymph nodes (ypT0/Tis ypN0). Blinded assessment performed by local pathologist at the time of definitive surgery

EFS: The time from randomisation to the first occurrence of any of the following events:

- Progression of disease that precludes definitive surgery
- Local or distant recurrence
- Second primary malignancy, OR
- Death due to any cause

EFS, event-free survival; pCR, pathologic complete response.

1. Schmid P et al. *N Engl J Med* 2020;382:810–821 (plus supplementary appendix); 2. Schmid P et al. *N Engl J Med* 2022;386:556–567.

KEYNOTE-522: Key patient characteristics

Key characteristics of the KEYTRUDA + chemotherapy arm of the KEYNOTE-522 trial:

Median patient age of 49 years (range: 22–80 years)

Primary tumour classification of 74% for T1/2 and 26% for T3/4

Nodal involvement was positive for 52% and negative for 48%

75% of patients with Stage II disease and 25% with Stage III disease

Total population: 1174 patients (KEYTRUDA + chemotherapy [n=784] and placebo + chemotherapy [n=390])

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

KEYNOTE-522: Baseline characteristics[1,2]

Characteristic, n (%)	KEYTRUDA + chemotherapy (n=784)	Placebo + chemotherapy (n=390)
Median age (range), years	49 (22–80)	48 (24–79)
≤65 years	701 (89.4)	342 (87.7)
Menopausal status		
Premenopausal	438 (55.9)	221 (56.7)
Postmenopausal	345 (44.0)	169 (43.3)
PD-L1 status[a]		
Positive	656 (83.7)	317 (81.3)
Negative	127 (16.2)	69 (17.7)
ECOG PS		
0	678 (86.5)	341 (87.4)
1	106 (13.5)	49 (12.6)
Lactase dehydrogenase level		
≤ULN	631 (80.5)	309 (79.2)
>ULN	149 (19.0)	80 (20.5)
Administration of carboplatin		
QW	449 (57.3)	223 (57.2)
Q3W	335 (42.7)	167 (42.8)
Primary tumour classification		
T1/T2	580 (74.0)	290 (74.4)
T3/T4	204 (26.0)	100 (25.6)
Nodal involvement		
Positive	405 (51.7)	200 (51.3)
Negative	379 (48.3)	190 (48.7)

Characteristic, n (%)	KEYTRUDA + chemotherapy (n=784)	Placebo + chemotherapy (n=390)
Overall disease stage		
Stage II	590 (75.3)	291 (74.6)
Stage III	194 (24.7)	98 (25.1)
HER2 status score		
0–1	595 (75.9)	286 (73.3)
≥2	188 (24.0)	104 (26.7)
Race		
American Indian or Alaskan Native	14 (1.8)	7 (1.8)
Asian	149 (19.0)	89 (22.8)
Black or African American	38 (4.8)	15 (3.8)
Multiple	13 (1.7)	6 (1.5)
Native Hawaiian/Pacific Islander	1 (0.1)	0
White	504 (64.3)	242 (62.1)
Missing	65 (8.3)	31 (7.9)
Geographic region		
Asia	166 (21.2)	91 (23.3)
Europe	388 (49.5)	180 (46.2)
Australia	23 (2.9)	16 (4.1)
North America	166 (21.2)	78 (20.0)
Rest of the world	41 (5.2)	25 (6.4)

Adapted from Schmid P et al. *N Engl J Med* 2020.

[a]PD-L1 assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay and measured using the CPS (number of PD-L1-positive tumour cells, lymphocytes and macrophages divided by the total number of viable tumour cells x100).

CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; PD-L1, programmed death ligand-1; QW, every week; Q3W, every 3 weeks; ULN, upper limit of normal range.

1. Schmid P et al. *N Engl J Med* 2020;382:810–821 (plus supplementary appendix); 2. FDA Oncologic Drugs Advisory Committee (February 2021). KEYNOTE-522. https://www.fda.gov/media/145771/download (accessed January 2024).

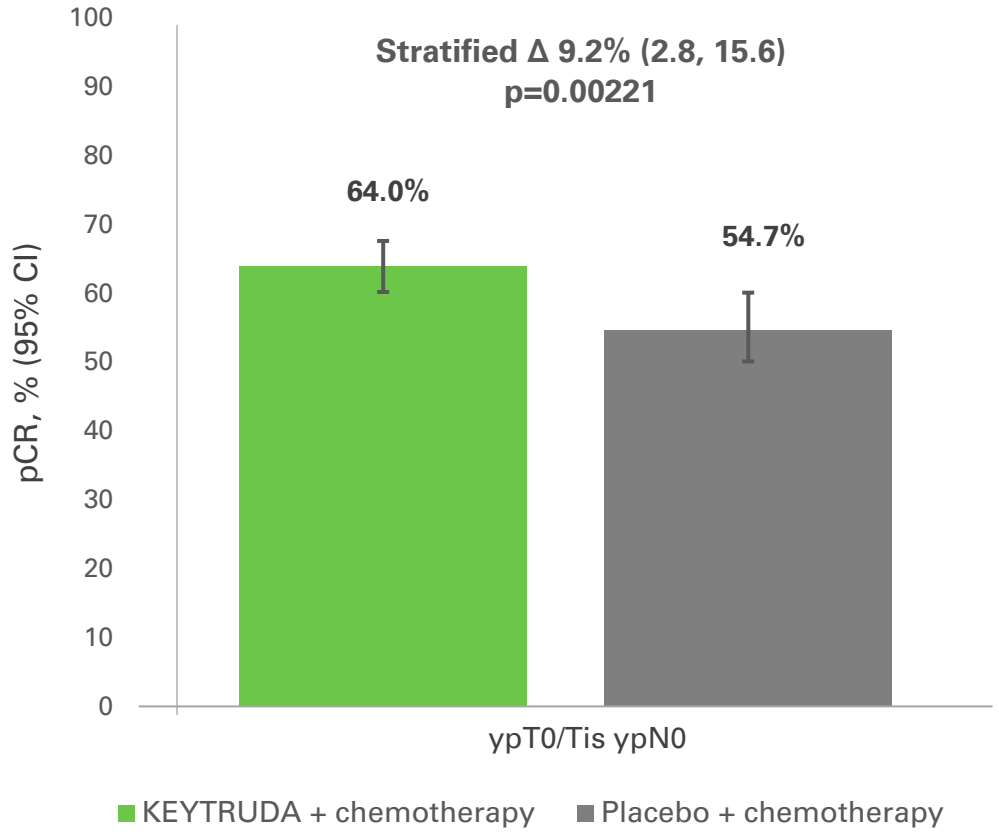
KEYNOTE-522: Results – Efficacy

Click the links below to navigate to the section of interest

- KEYNOTE-522: pCR in the ITT population
- KEYNOTE-522: EFS in the ITT population (primary analysis)
- KEYNOTE-522: EFS in the ITT population (60-month follow up)
- KEYNOTE-522: EFS in key subgroups (primary analysis)
- KEYNOTE-522: EFS in key subgroups (60-month follow up)
- KEYNOTE-522: EFS by pCR (36- and 60-month follow up)
- KEYNOTE-522: EFS by disease stage (60-month follow up)
- KEYNOTE-522: EFS by nodal status (60-month follow up)
- KEYNOTE-522: EFS by disease stage with and without pCR (60-month follow up)
- KEYNOTE-522: EFS by nodal status with and without pCR (60-month follow up)
- KEYNOTE-522: EFS by T2N0 status (60-month follow up)
- KEYNOTE-522: Disease recurrence as first EFS event (60-month follow up)
- KEYNOTE-522: Disease recurrence as first EFS event by pCR (60-month follow up)
- KEYNOTE-522: DPFS or DRFS (36- and 60-month follow up)

DPFS, distant progression-free survival; DRFS, distant recurrence-free survival; EFS, event-free survival; ITT, intention-to-treat; pCR, pathologic complete response.

KEYNOTE-522: pCR in the ITT population

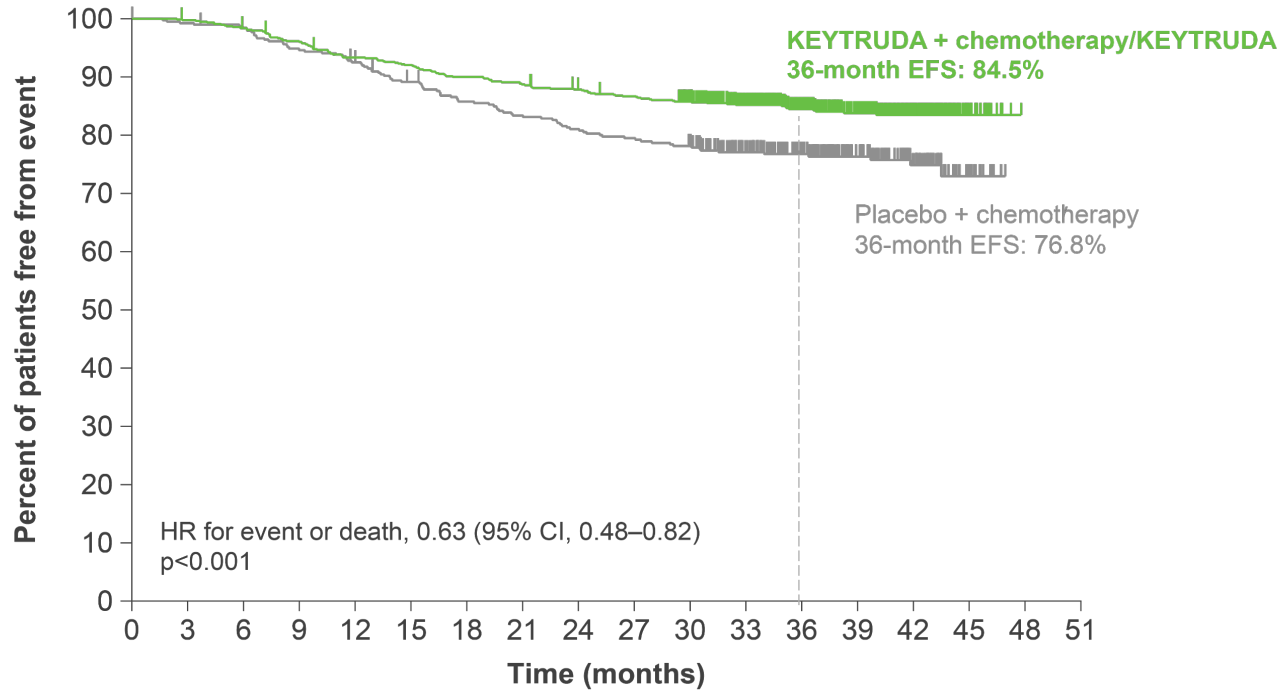


- Statistically significant improvement in pCR rates with KEYTRUDA + chemotherapy vs placebo + chemotherapy in KEYNOTE-522 (p=0.00221)
- 64.0% of patients (95% CI, 60.2–67.6) achieved pCR in the KEYTRUDA + chemotherapy (neoadjuvant treatment) group vs 54.7% of patients (95% CI, 49.1–60.1) in the placebo + chemotherapy (neoadjuvant treatment) group

Adapted from KEYTRUDA SmPC.

KEYTRUDA + chemotherapy (n=669); (placebo + chemotherapy n=333); data cut-off: 23 March 2021.
The analysis is based on the Miettinen and Nurminen method stratified according to nodal status (+ vs −), tumour size (T1 [diameter >1–2 cm] to T2 [diameter >2–5 cm] or T3 [diameter >5 cm] to T4 [locally advanced disease]), and frequency of carboplatin administration (QW or Q3W). For the other subgroups, the analysis is based on the unstratified Miettinen and Nurminen method.
CI, confidence interval; EFS, event-free survival; ITT, intention to treat; pCR, pathologic complete response.
KEYTRUDA SmPC. https://www.medicines.org.uk/emc/product/2498/smpc (accessed January 2024).

KEYNOTE-522: EFS in the ITT population at primary analysis



KEYTRUDA + chemotherapy/KEYTRUDA	784	781	769	751	728	718	702	692	681	671	652	551	433	303	165	28	0	0
Placebo + chemotherapy/placebo	390	386	382	368	358	342	328	319	310	304	297	250	195	140	83	17	0	0

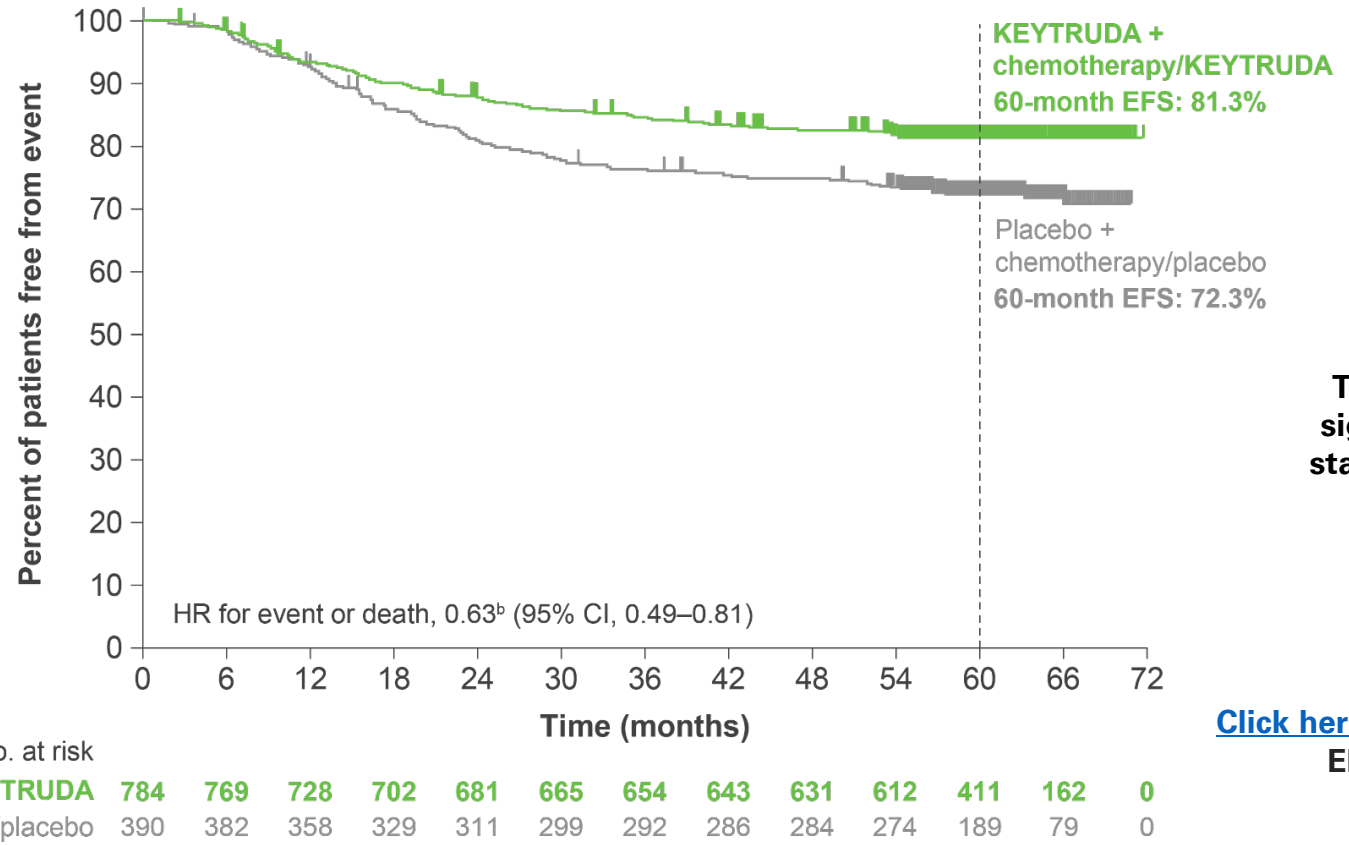
Adapted from Schmid P et al. *N Engl J Med* 2022.

- Completion of KEYTRUDA + chemotherapy in the neoadjuvant setting, followed by KEYTRUDA monotherapy as adjuvant treatment, resulted in a statistically significant improvement in EFS vs neoadjuvant placebo + chemotherapy followed by adjuvant placebo
- At 36 months, the estimated EFS in the KEYTRUDA + chemotherapy/ KEYTRUDA group was 84.5% (95% CI, 81.7–86.9) (neoadjuvant/adjuvant) vs 76.8% (95% CI, 72.2–80.7) of patients in the placebo + chemotherapy/placebo group (the median EFS was not reached for either group)

Click here to view the forest plot for EFS in key subgroups

Data cut-off: 23 March 2021.
Tick marks indicate data censored at the last time the patient was known to be alive and without an event (disease progression that precludes definitive surgery; local or distant recurrence or a second primary tumour; or death from any cause). The HR and CI were analysed with the use of a Cox regression model with treatment as a covariate stratified according to the randomisation stratification factors of nodal status (+ or −), tumour size (T1/T2 or T3/T4) and frequency of carboplatin administration (QW or Q3W).
CI, confidence interval; EFS, event-free survival; HR, hazard ratio; ITT, intention to treat; QW, every week; Q3W, every 3 weeks.
Schmid P et al. *N Engl J Med* 2022;386:556–567.

KEYNOTE-522: Exploratory analysis – EFS in the ITT population at 60-month follow up[a]



This was an exploratory analysis; significance was not tested and no statistical conclusions can be drawn

Click here to view the forest plot for EFS in key subgroups

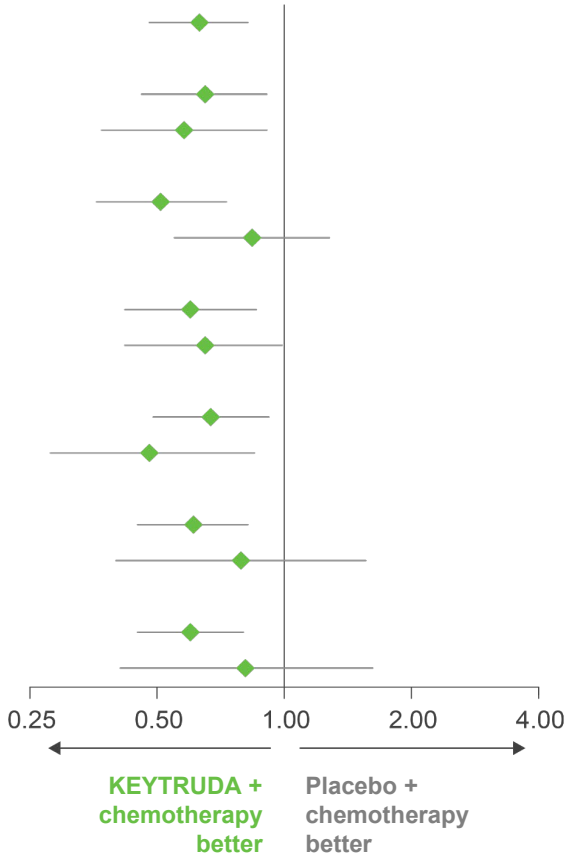
Adapted from Schmid P et al. Presented at ESMO 2023.

Data cut-off: 23 March 2023.
Tick marks indicate data censored at the last time the patient was known to be alive and without an event (disease progression that precludes definitive surgery; local or distant recurrence or a second primary tumour; or death from any cause). The HR and CI were analysed with the use of a Cox regression model with treatment as a covariate stratified according to the randomisation stratification factors of nodal status (+ or −), tumour size (T1/T2 or T3/T4) and frequency of carboplatin administration (QW or Q3W). [a]The sixth prespecified interim analysis of EFS was calendar driven and planned to occur ~72 months after the first participant was randomised; [b]HR (CI) analysed based on a Cox regression model with treatment as a covariate stratified by the randomisation stratification factors.
CI, confidence interval; EFS, event-free survival; HR, hazard ratio; ITT, intention-to-treat; QW, every week; Q3W, every 3 weeks.
Schmid P et al. Presented at the European Society of Medical Oncology (ESMO) Congress 2023, 20–24 September 2023, Madrid, Spain.

Prescribing Information: GB; NI

KEYNOTE-522: EFS in key subgroups at primary analysis

Subgroup	KEYTRUDA + chemotherapy	Placebo + chemotherapy	HR for event or death (95% CI)
	no. of patients with event/total no. (%)		
Overall	123/784 (15.7)	93/390 (23.8)	0.63 (0.48–0.82)
Nodal status			
Positive	80/408 (19.6)	57/196 (29.1)	0.65 (0.46–0.91)
Negative	43/376 (11.4)	36/194 (18.6)	0.58 (0.37–0.91)
Tumour size			
T1 to T2	64/581 (11.0)	59/290 (20.3)	0.51 (0.36–0.73)
T3 to T4	59/203 (29.1)	34/100 (34.0)	0.84 (0.55–1.28)
Carboplatin schedule			
QW	71/444 (16.0)	56/220 (25.5)	0.60 (0.42–0.86)
Q3W	50/334 (15.0)	37/167 (22.2)	0.65 (0.42–0.99)
PD-L1 status			
Positive	98/656 (14.9)	68/317 (21.5)	0.67 (0.49–0.92)
Negative	25/128 (19.5)	25/69 (36)	0.48 (0.28–0.85)
Age			
<65 yr	103/700 (14.7)	79/342 (23.1)	0.61 (0.45–0.82)
≥65 yr	20/84 (24)	14/48 (29)	0.79 (0.40–1.56)
ECOG PS			
0	101/678 (14.9)	80/341 (23.5)	0.60 (0.45–0.80)
1	22/106 (20.8)	13/49 (27)	0.81 (0.41–1.62)



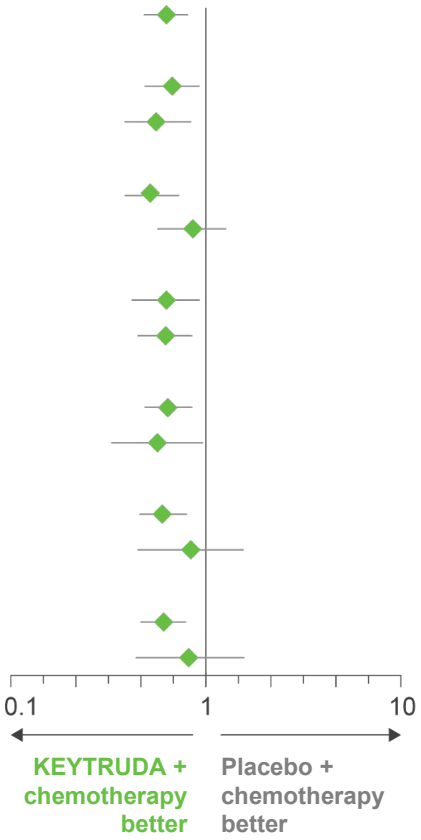
KEYNOTE-522 was not powered to detect differences in treatment effect between these subgroups. Results from exploratory analyses should be interpreted with caution due to modest patient numbers and potential imbalances in baseline characteristics

Adapted from Schmid P et al. *N Engl J Med* 2022.

Data cut-off: 23 March 2021.
The HR and CI were analysed with the use of a Cox regression model, with treatment as a covariate and stratified according to the randomisation stratification factors of nodal status (+ or −), tumour size (T1/T2 or T3/T4) and frequency of carboplatin administration (QW or Q3W).
CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; HR, hazard ratio; ITT, intention-to-treat; pCR, pathologic complete response; PD-L1, programmed death ligand-1; QW, every week; Q3W, every 3 weeks; Yr, years.
Schmid P et al. *N Engl J Med* 2022;386:556–567 (plus supplementary appendix).

KEYNOTE-522: Exploratory analysis – EFS in key subgroups at 60-month follow up

Subgroup	KEYTRUDA + chemotherapy	Placebo + chemotherapy	HR for event or death (95% CI)
	no. of patients with events/total no. (%)		
Overall	145/784 (18.5)	108/390 (27.7)	0.63 (0.49–0.81)
Nodal status			
Positive	94/408 (23.0)	64/196 (32.6)	0.67 (0.49–0.93)
Negative	51/376 (13.6)	44/194 (22.7)	0.56 (0.38–0.84)
Tumour size			
T1 to T2	80/581 (13.8)	71/290 (24.5)	0.52 (0.38–0.72)
T3 to T4	65/203 (32.0)	37/100 (37.0)	0.85 (0.57–1.27)
Carboplatin schedule			
QW	58/334 (17.4)	44/167 (26.3)	0.63 (0.42–0.93)
Q3W	85/444 (19.1)	64/220 (29.1)	0.62 (0.45–0.86)
PD-L1 status			
Positive	115/656 (17.5)	81/317 (25.5)	0.64 (0.48–0.85)
Negative	30/128 (23.4)	25/69 (36.2)	0.57 (0.33–0.98)
Age			
<65 yr	121/700 (17.3)	92/342 (26.9)	0.61 (0.46–0.80)
≥65 yr	24/84 (28.6)	16/48 (33.3)	0.83 (0.44–1.56)
ECOG PS			
0	119/678 (17.5)	93/341 (27.3)	0.60 (0.46–0.79)
1	26/106 (24.5)	15/49 (30.6)	0.83 (0.44–1.57)

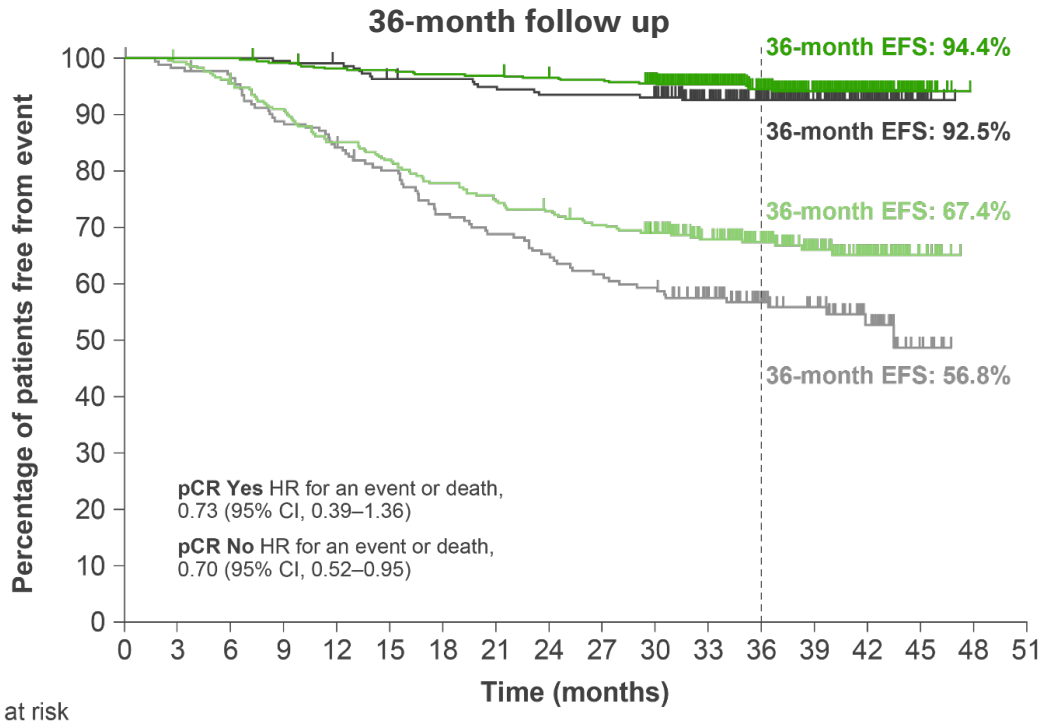


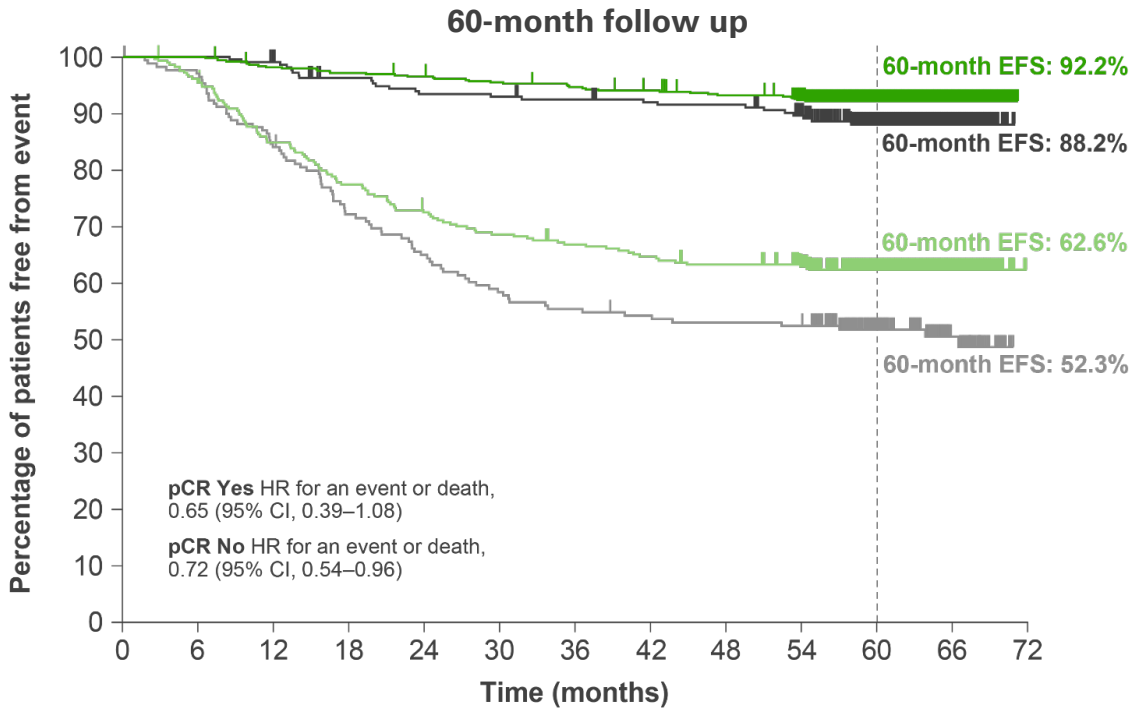
KEYNOTE-522 was not powered to detect differences in treatment effect between these subgroups. Results from exploratory analyses should be interpreted with caution due to modest patient numbers and potential imbalances in baseline characteristics

Adapted from Schmid P et al. Presented at ESMO 2023.

Data cut-off: 23 March 2023.
For the overall population and PD-L1 subgroups, analyses were based on a Cox regression model with Efron's method of tie handling, with treatment as a covariate and stratification by nodal status (positive vs negative), tumour size (T1/T2 vs T3/T4) and frequency of carboplatin administration (QW vs Q3W); for other subgroups, analysis was based on an unstratified Cox model.
CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; HR, hazard ratio; pCR, pathologic complete response; PD-L1, programmed death ligand-1; QW, every week; Q3W, every 3 weeks; yr, years.
Schmid P et al. Presented at the European Society of Medical Oncology (ESMO) Congress 2023, 20–24 September 2023, Madrid, Spain.

KEYNOTE-522: Exploratory analysis – EFS by pCR





No. at risk																		
KEYTRUDA + chemotherapy/ KEYTRUDA responder	494	494	494	489	483	482	478	477	472	470	460	387	307	220	122	18	0	0
Placebo + chemotherapy/ placebo responder	217	217	217	216	214	207	206	203	200	200	197	165	130	87	56	9	0	0
KEYTRUDA + chemotherapy/ KEYTRUDA non-responder	290	287	275	262	245	236	224	215	209	201	192	164	126	83	43	10	0	0
Placebo + chemotherapy/ placebo non-responder	173	169	165	152	144	135	122	116	110	104	100	85	65	53	27	8	0	0

KEYTRUDA + chemotherapy/ KEYTRUDA responder	495	495	484	479	473	468	463	458	451	439	295	120	0					
Placebo + chemotherapy/ placebo responder	217	217	214	206	200	199	197	195	194	185	130	53	0					
KEYTRUDA + chemotherapy/ KEYTRUDA non-responder	289	274	244	223	208	197	191	185	180	173	116	42	0					
Placebo + chemotherapy/ placebo non-responder	173	165	144	123	111	100	95	91	90	89	59	26	0					

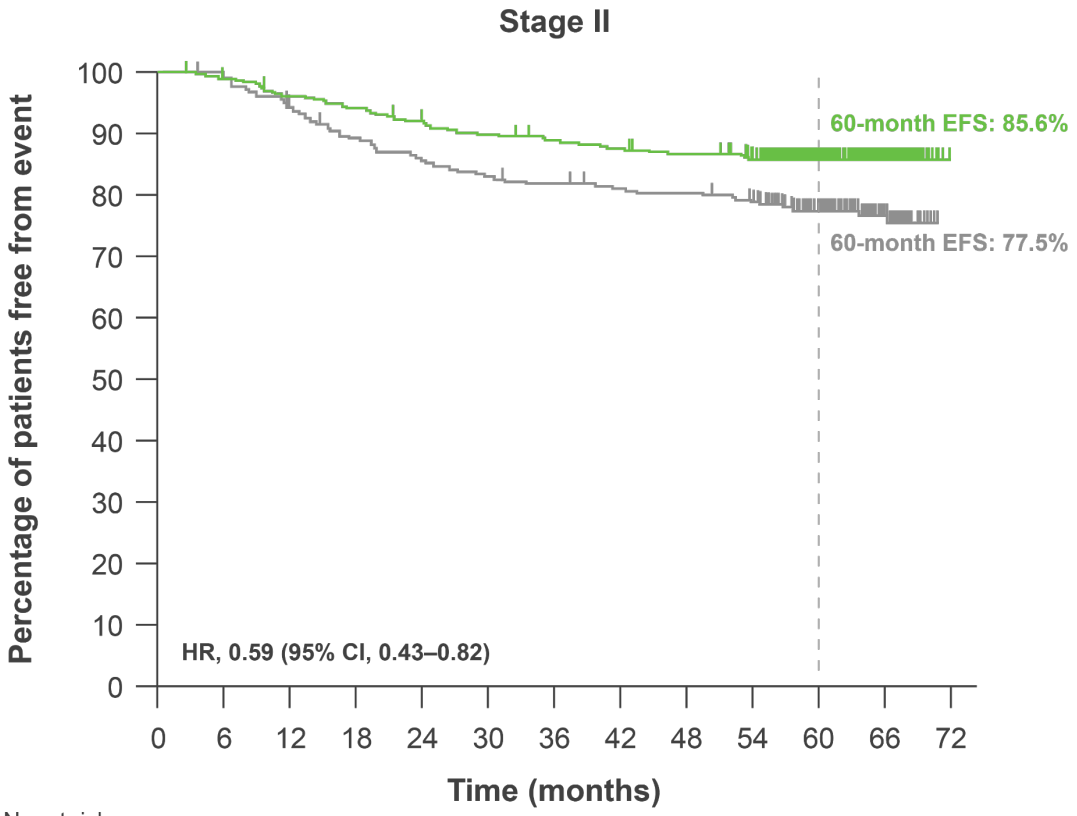
Adapted from Schmid P et al. Presented at ESMO 2023.

This was an exploratory analysis; significance was not tested and no statistical conclusions can be drawn

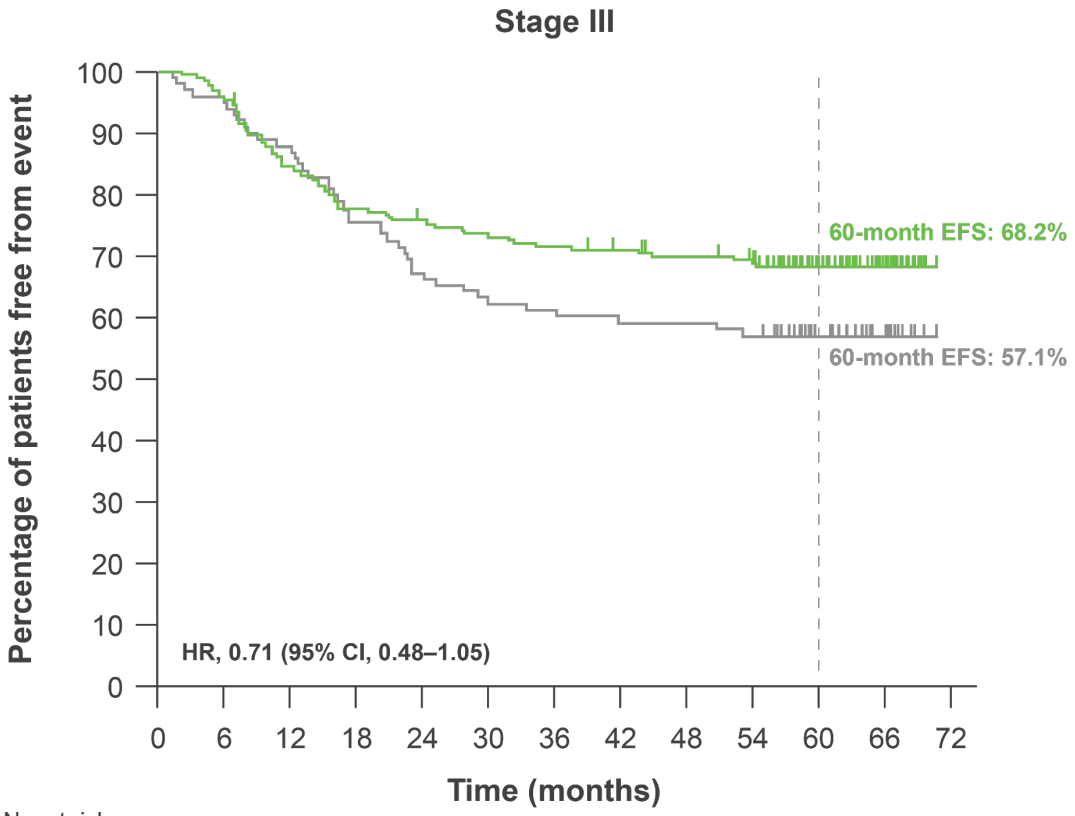
Data cut-off: 23 March 2021 and 23 March 2023.
CI, confidence interval; EFS, event-free survival; HR, hazard ratio; pCR, pathologic complete response.
Schmid P et al. Presented at the European Society of Medical Oncology (ESMO) Congress 2023, 20–24 September 2023, Madrid, Spain.

Prescribing Information: GB; NI

KEYNOTE-522: Exploratory analysis – EFS by disease stage at 60-month follow up



No. at risk													
KEYTRUDA + chemotherapy/ KEYTRUDA	590	583	565	552	536	524	517	509	501	486	331	125	0
Placebo + chemotherapy/ placebo	291	287	271	255	245	237	232	228	226	218	153	60	0



No. at risk													
KEYTRUDA + chemotherapy/ KEYTRUDA	194	186	163	150	145	141	137	134	130	126	80	37	0
Placebo + chemotherapy/ placebo	98	94	86	74	66	62	60	58	58	56	36	19	0

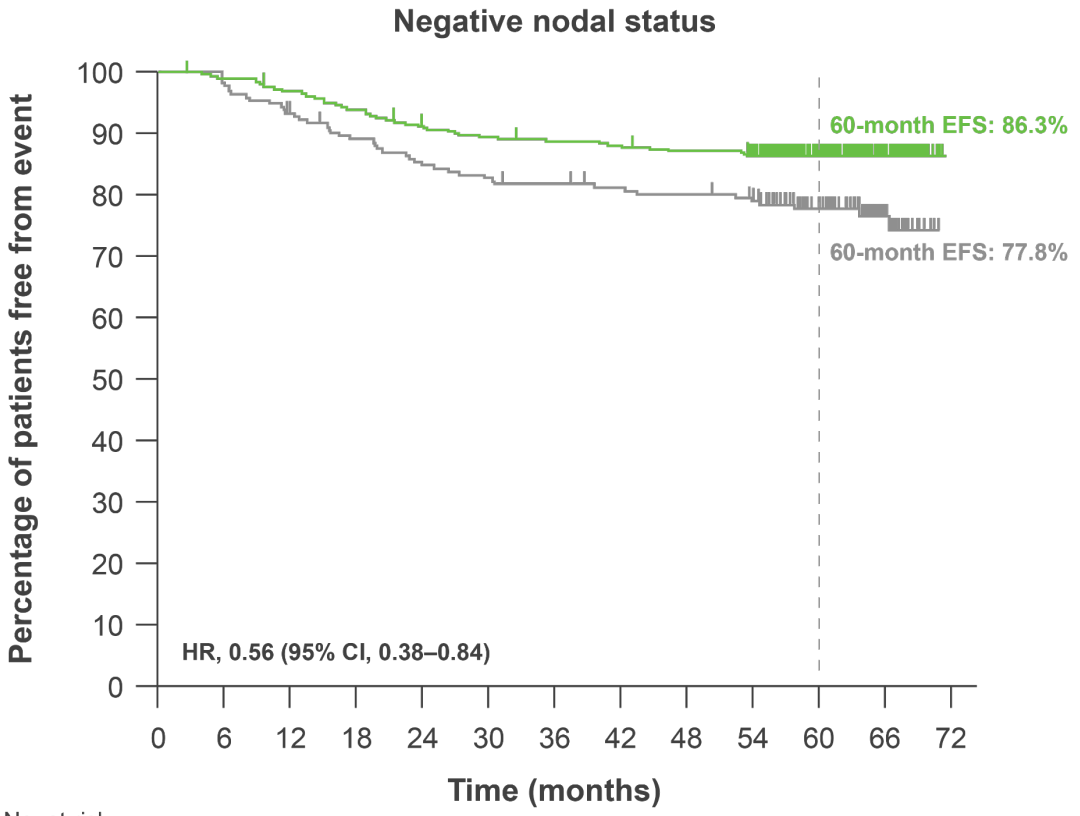
Adapted from Schmid P et al. Presented at SABCS 2023.

This was an exploratory analysis; significance was not tested and no statistical conclusions can be drawn

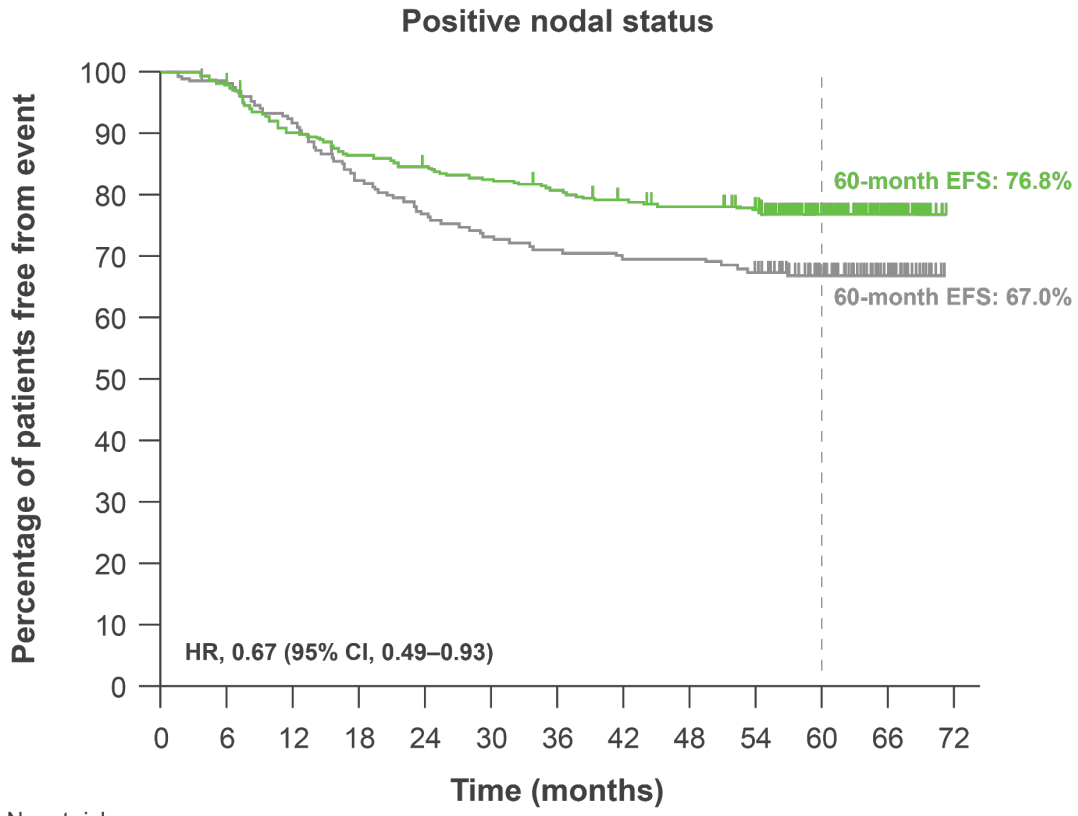
Data cut-off: 23 March 2023.
CI, confidence interval; EFS, event-free survival; HR, hazard ratio.
Schmid P et al. Presented at the San Antonio Breast Cancer Symposium (SABCS) Congress 2023, 5–9 December 2023, San Antonio, USA.

Prescribing Information: GB; NI

KEYNOTE-522: Exploratory analysis – EFS by nodal status at 60-month follow up



No. at risk													
KEYTRUDA + chemotherapy/ KEYTRUDA	376	371	362	351	338	331	328	325	320	309	210	80	0
Placebo + chemotherapy/ placebo	194	190	179	169	162	157	154	151	149	144	98	38	0



No. at risk													
KEYTRUDA + chemotherapy/ KEYTRUDA	408	398	366	351	343	334	326	318	311	303	201	82	0
Placebo + chemotherapy/ placebo	196	192	179	160	149	142	138	135	135	130	91	41	0

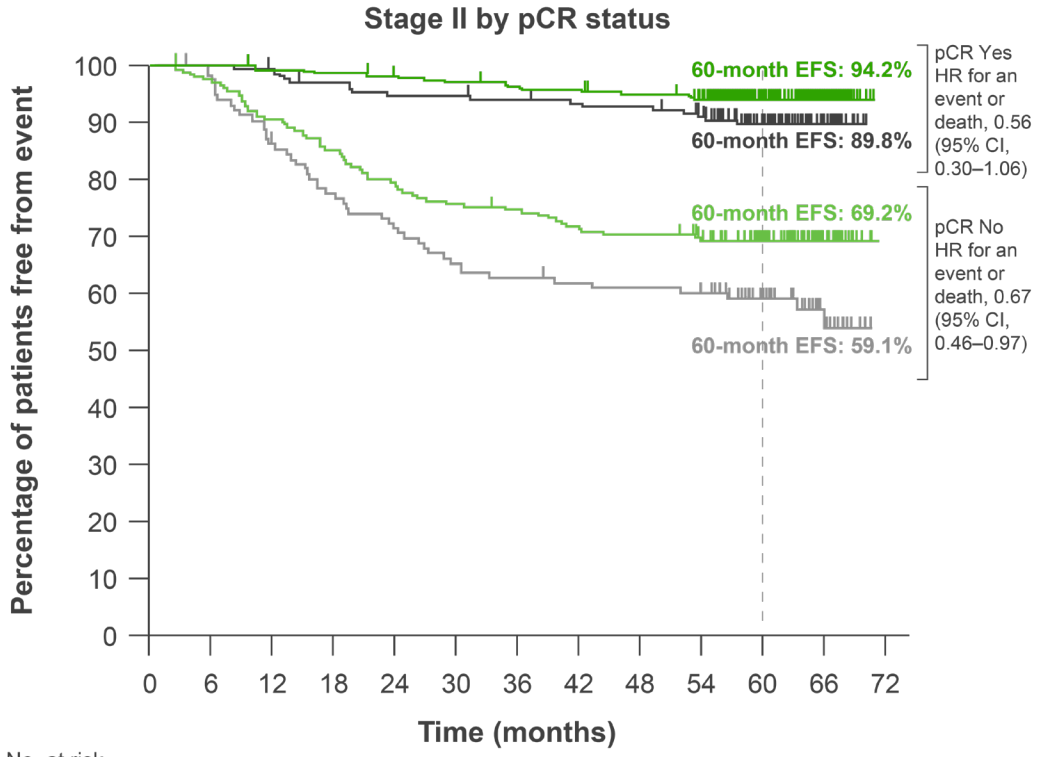
Adapted from Schmid P et al. Presented at SABCS 2023.

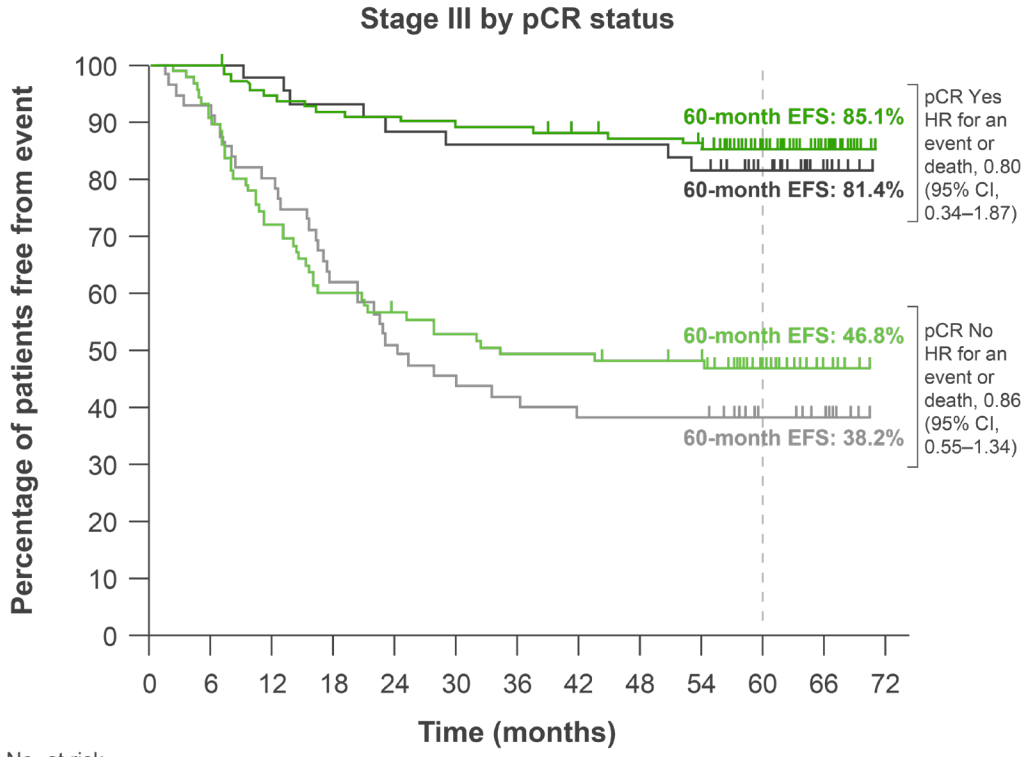
This was an exploratory analysis; significance was not tested and no statistical conclusions can be drawn

Data cut-off: 23 March 2023.
CI, confidence interval; EFS, event-free survival; HR, hazard ratio.
Schmid P et al. Presented at the San Antonio Breast Cancer Symposium (SABCS) Congress 2023, 5–9 December 2023, San Antonio, USA.

Prescribing Information: GB; NI

KEYNOTE-522: Exploratory analysis – EFS by disease stage in patients with and without pCR at 60-month follow up





No. at risk

KEYTRUDA + chemotherapy/ KEYTRUDA responder	386	386	382	380	375	371	367	365	360	351	236	90	0
Placebo + chemotherapy/ placebo responder	173	173	171	166	162	162	160	158	157	150	106	42	0
KEYTRUDA + chemotherapy/ KEYTRUDA non-responder	204	197	183	172	161	153	150	144	141	135	95	35	0
Placebo + chemotherapy/ placebo non-responder	118	114	100	89	83	75	72	70	69	68	47	18	0

No. at risk

KEYTRUDA + chemotherapy/ KEYTRUDA responder	109	109	102	99	98	97	96	93	91	88	59	30	0
Placebo + chemotherapy/ placebo responder	43	43	42	40	38	37	37	37	37	35	24	11	0
KEYTRUDA + chemotherapy/ KEYTRUDA non-responder	85	77	61	51	47	44	41	41	39	38	21	7	0
Placebo + chemotherapy/ placebo non-responder	55	51	44	34	28	25	23	21	21	21	12	8	0

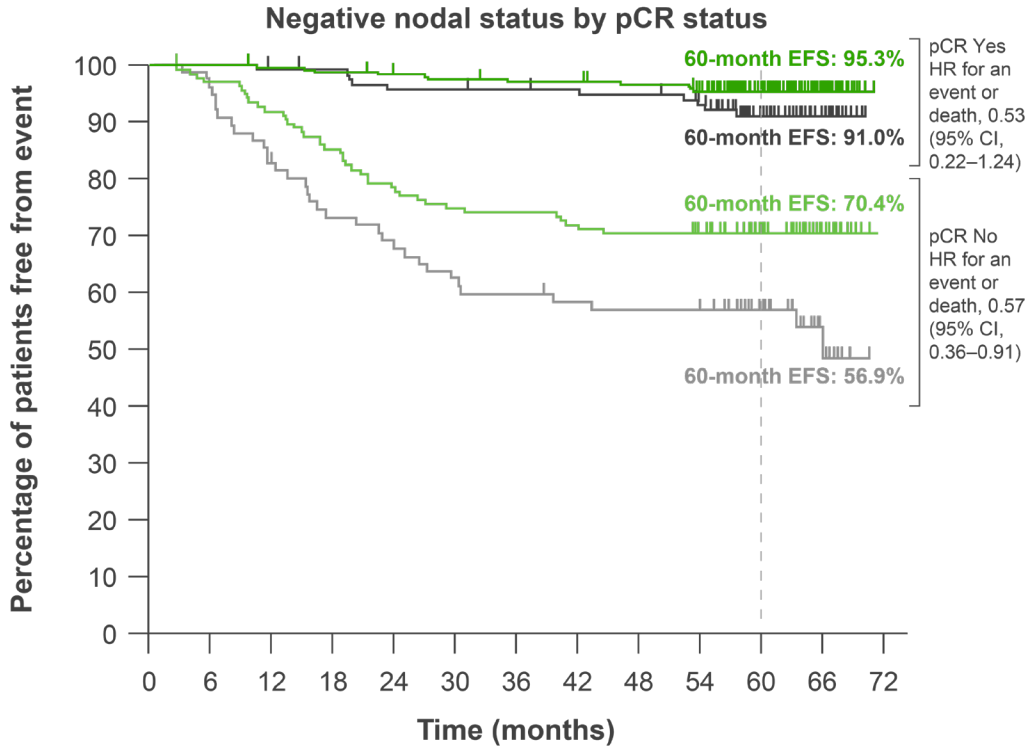
Adapted from Schmid P et al. Presented at SABCS 2023.

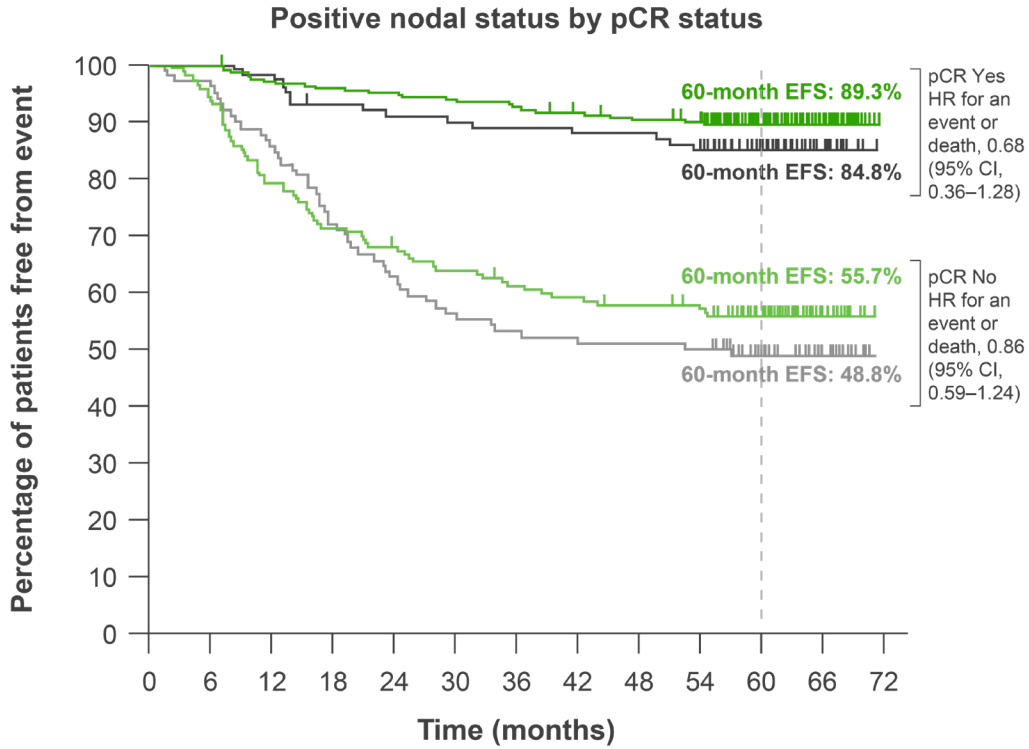
This was an exploratory analysis; significance was not tested and no statistical conclusions can be drawn

Data cut-off: 23 March 2023.
CI, confidence interval; EFS, event-free survival; HR, hazard ratio; pCR, pathologic complete response.
Schmid P et al. Presented at the San Antonio Breast Cancer Symposium (SABCS) Congress 2023, 5–9 December 2023, San Antonio, USA.

Prescribing Information: GB; NI

KEYNOTE-522: Exploratory analysis – EFS by nodal status in patients with and without pCR at 60-month follow up





No. at risk

KEYTRUDA + chemotherapy/ KEYTRUDA responder	240	240	238	236	232	230	228	228	225	218	149	55	0
Placebo + chemotherapy/ placebo responder	118	118	117	115	111	111	110	109	108	103	70	28	0
KEYTRUDA + chemotherapy/ KEYTRUDA non-responder	136	131	124	115	106	101	100	97	95	91	61	25	0
Placebo + chemotherapy/ placebo non-responder	76	72	62	54	51	46	44	42	41	41	28	10	0

No. at risk

KEYTRUDA + chemotherapy/ KEYTRUDA responder	255	255	246	243	241	238	235	230	226	221	146	65	0
Placebo + chemotherapy/ placebo responder	99	99	97	91	89	88	87	86	86	82	60	25	0
KEYTRUDA + chemotherapy/ KEYTRUDA non-responder	153	143	120	108	102	96	91	88	85	82	55	17	0
Placebo + chemotherapy/ placebo non-responder	97	93	82	69	60	54	51	49	49	48	31	16	0

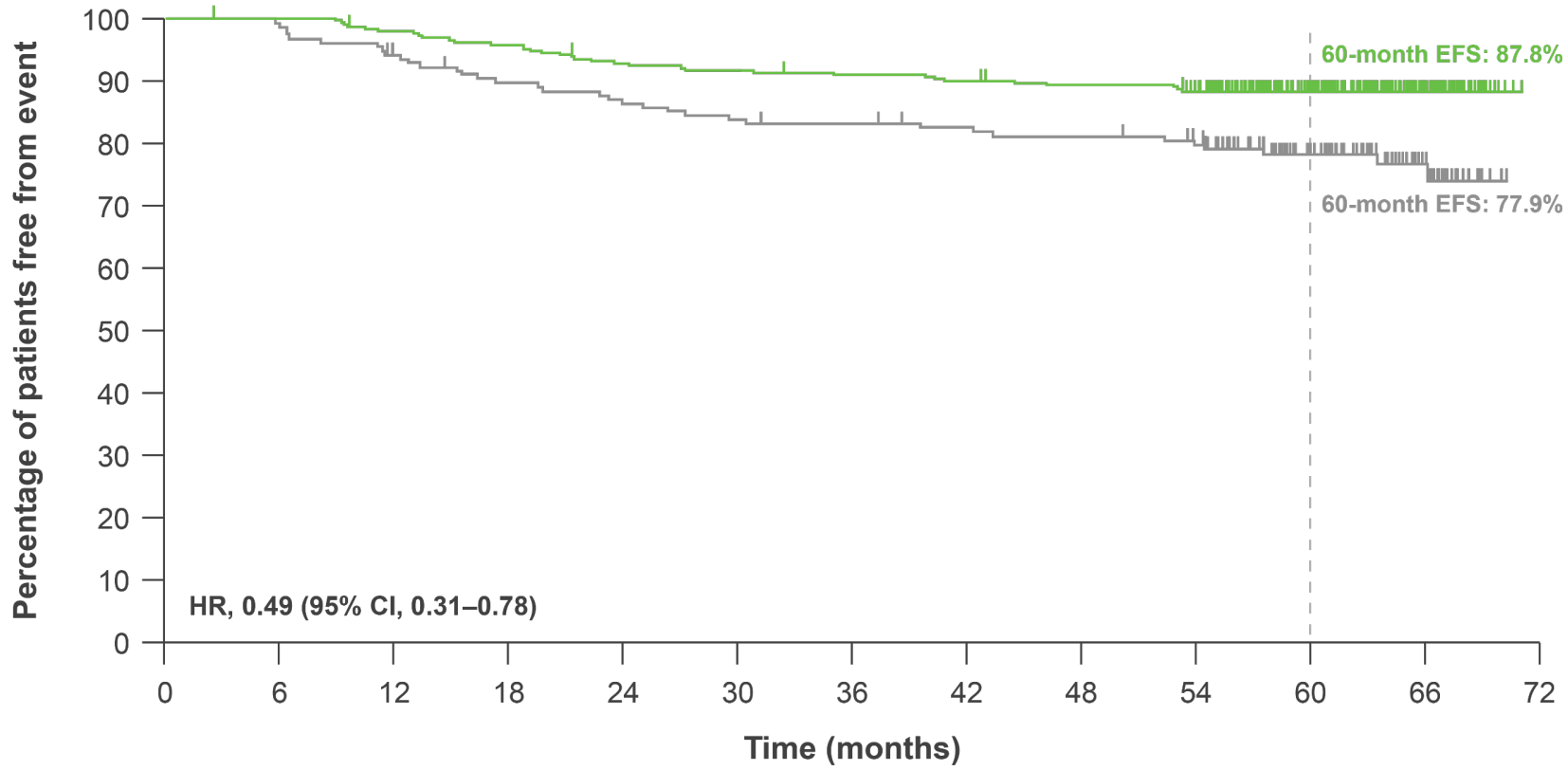
Adapted from Schmid P et al. Presented at SABCS 2023.

This was an exploratory analysis; significance was not tested and no statistical conclusions can be drawn

Data cut-off: 23 March 2023.
CI, confidence interval; EFS, event-free survival; HR, hazard ratio; pCR, pathologic complete response.
Schmid P et al. Presented at the San Antonio Breast Cancer Symposium (SABCS) Congress 2023, 5–9 December 2023, San Antonio, USA.

Prescribing Information: GB; NI

KEYNOTE-522: Exploratory analysis – EFS by T2N0 status at 60-month follow up



No. at risk													
KEYTRUDA + chemotherapy/ KEYTRUDA	316	314	306	299	288	284	281	278	274	265	179	71	0
Placebo + chemotherapy/ placebo	159	156	147	138	134	129	127	124	122	117	78	32	0

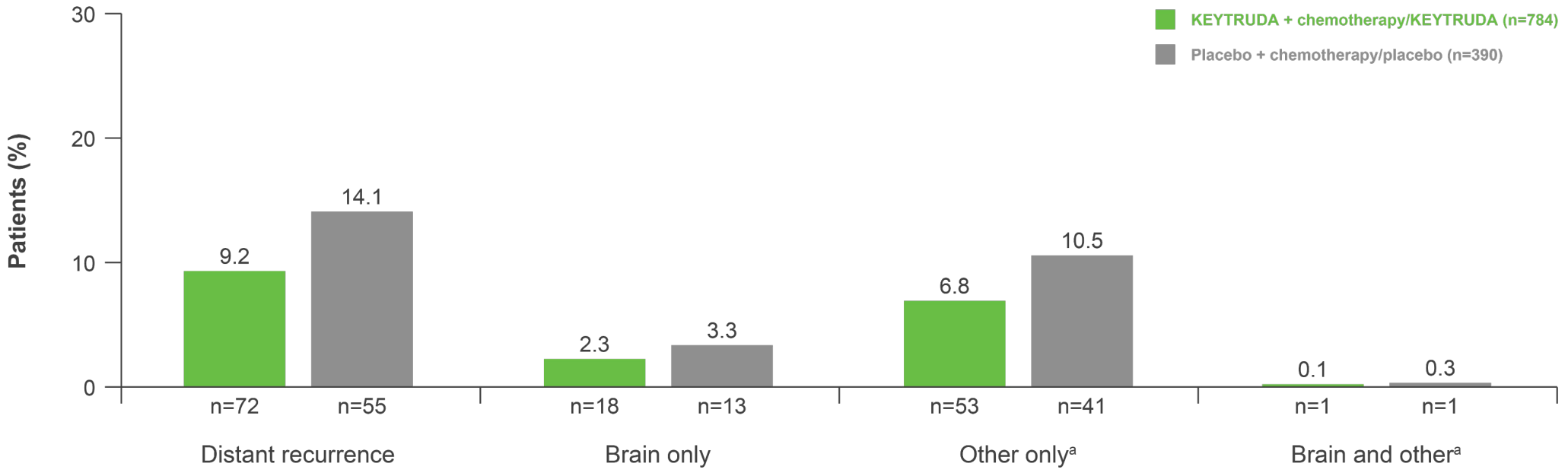
Adapted from Schmid P et al. Presented at SABCS 2023.

This was an exploratory analysis; significance was not tested and no statistical conclusions can be drawn

Data cut-off: 23 March 2023.
CI, confidence interval; EFS, event-free survival; HR, hazard ratio.
Schmid P et al. Presented at the San Antonio Breast Cancer Symposium (SABCS) Congress 2023, 5–9 December 2023, San Antonio, USA.

Prescribing Information: GB; NI

KEYNOTE-522: Exploratory analysis – Distant recurrence as first EFS event at 60-month follow up

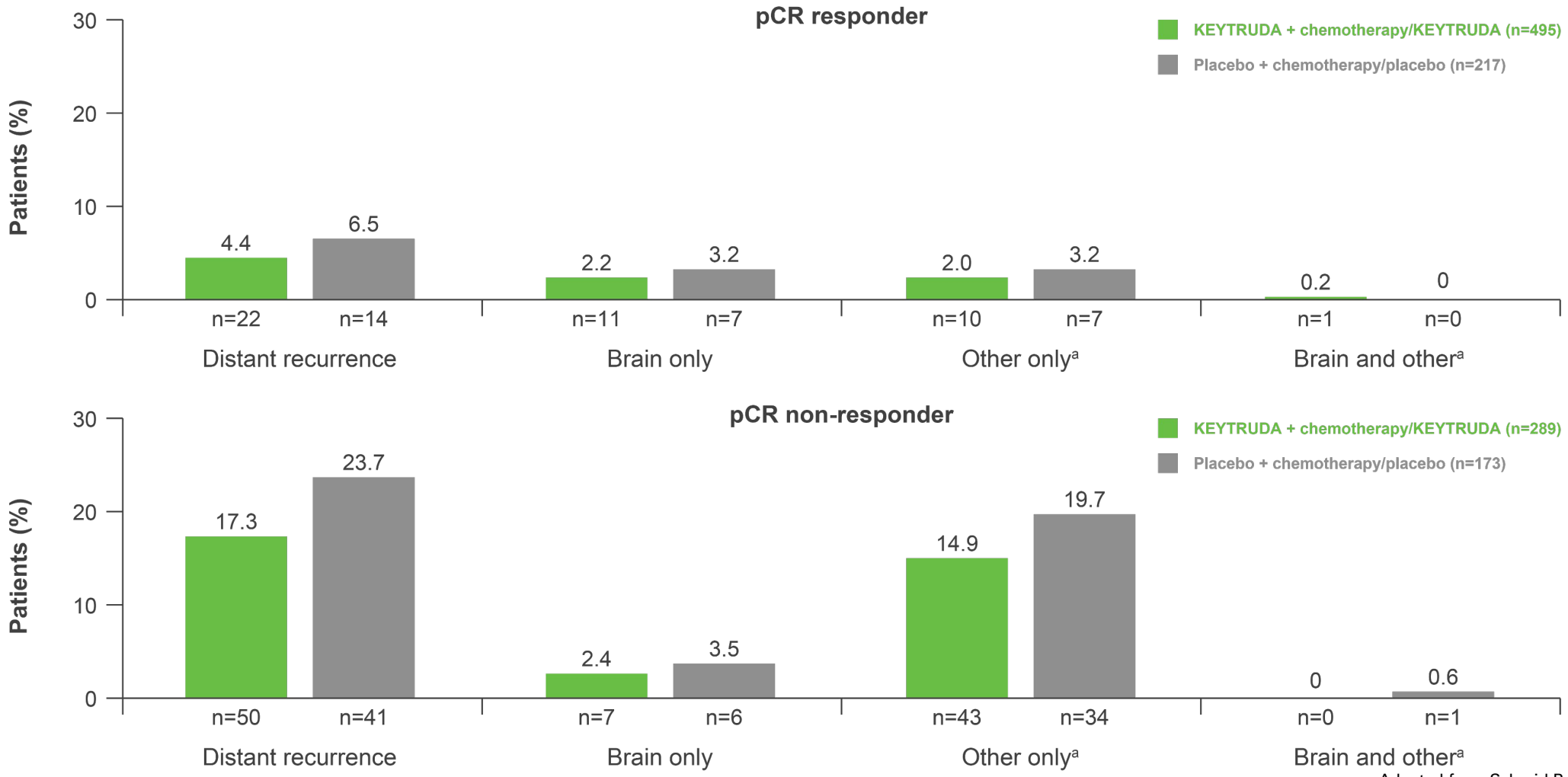


Adapted from Schmid P et al. Presented at SABCS 2023.

This was an exploratory analysis; significance was not tested and no statistical conclusions can be drawn

Data cut-off: 23 March 2023.
[a]Other refers to non-brain distant recurrence sites, which were classified per clinical identification.
CI, confidence interval; EFS, event-free survival; HR, hazard ratio.
Schmid P et al. Presented at the San Antonio Breast Cancer Symposium (SABCS) Congress 2023, 5–9 December 2023, San Antonio, USA.

KEYNOTE-522: Exploratory analysis – Distant recurrence as first EFS event by pCR (ypT0/Tis ypN0) at 60-month follow up



Adapted from Schmid P et al. Presented at SABCS 2023.

This was an exploratory analysis; significance was not tested and no statistical conclusions can be drawn

Data cut-off: 23 March 2023.

[a]Other refers to non-brain distant recurrence sites, which were classified per clinical identification.

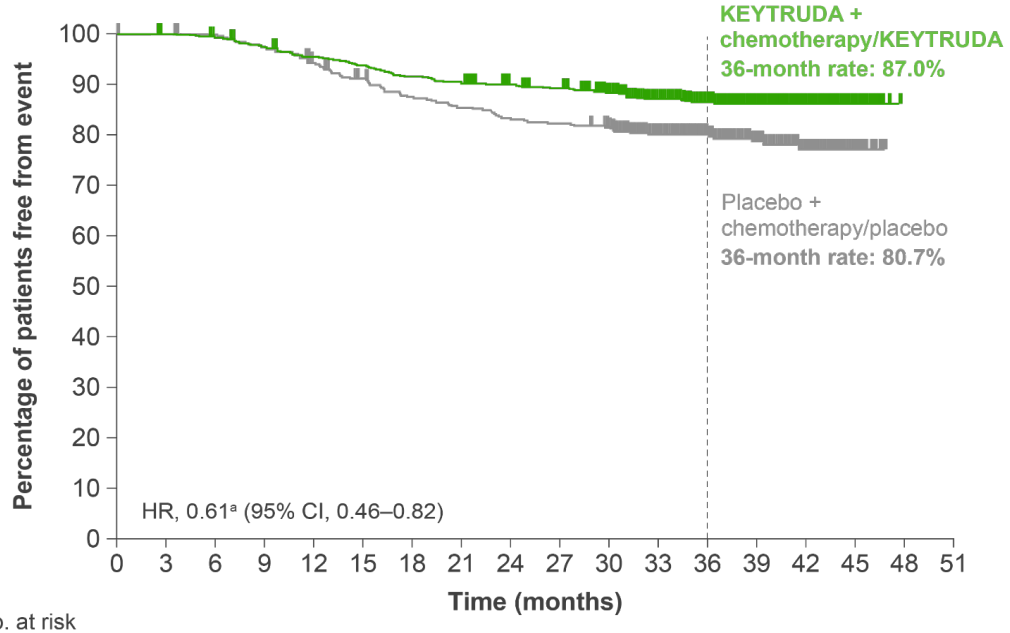
CI, confidence interval; EFS, event-free survival; HR, hazard ratio; pCR, pathologic complete response.

Schmid P et al. Presented at the San Antonio Breast Cancer Symposium (SABCS) Congress 2023, 5–9 December 2023, San Antonio, USA.

Prescribing Information: GB; NI

KEYNOTE-522: Exploratory analysis – DPFS or DRFS

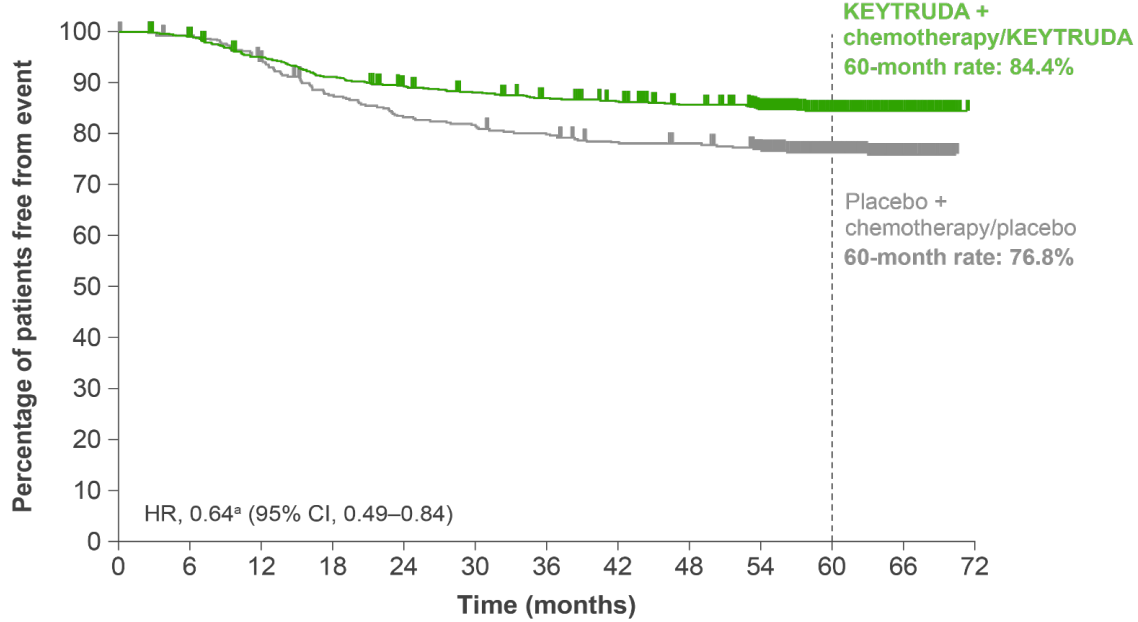
36-month follow up



No. at risk

KEYTRUDA + chemotherapy/KEYTRUDA	784	782	773	758	741	728	711	702	692	685	663	561	439	308	167	29	0	0
Placebo + chemotherapy/placebo	390	389	387	379	367	352	337	330	321	317	312	259	202	143	84	17	0	0

60-month follow up



784	774	742	711	692	681	667	659	645	626	416	164	0
390	387	367	338	322	316	308	298	295	287	195	82	0

Adapted from Schmid P et al. Presented at ESMO 2023.

This was an exploratory analysis; significance was not tested and no statistical conclusions can be drawn

Data cut-off: 23 March 2021 and 23 March 2023.
[a]HR (CI) analysed based on a Cox regression model with treatment as a covariate stratified by randomisation stratification factors.
CI, confidence interval; DPFS, distant progression-free survival; DRFS, distant recurrence-free survival; HR, hazard ratio.
Schmid P et al. Presented at the European Society of Medical Oncology (ESMO) Congress 2023, 20–24 September 2023, Madrid, Spain.

Prescribing Information: GB; NI

KEYNOTE-522: Results – Safety

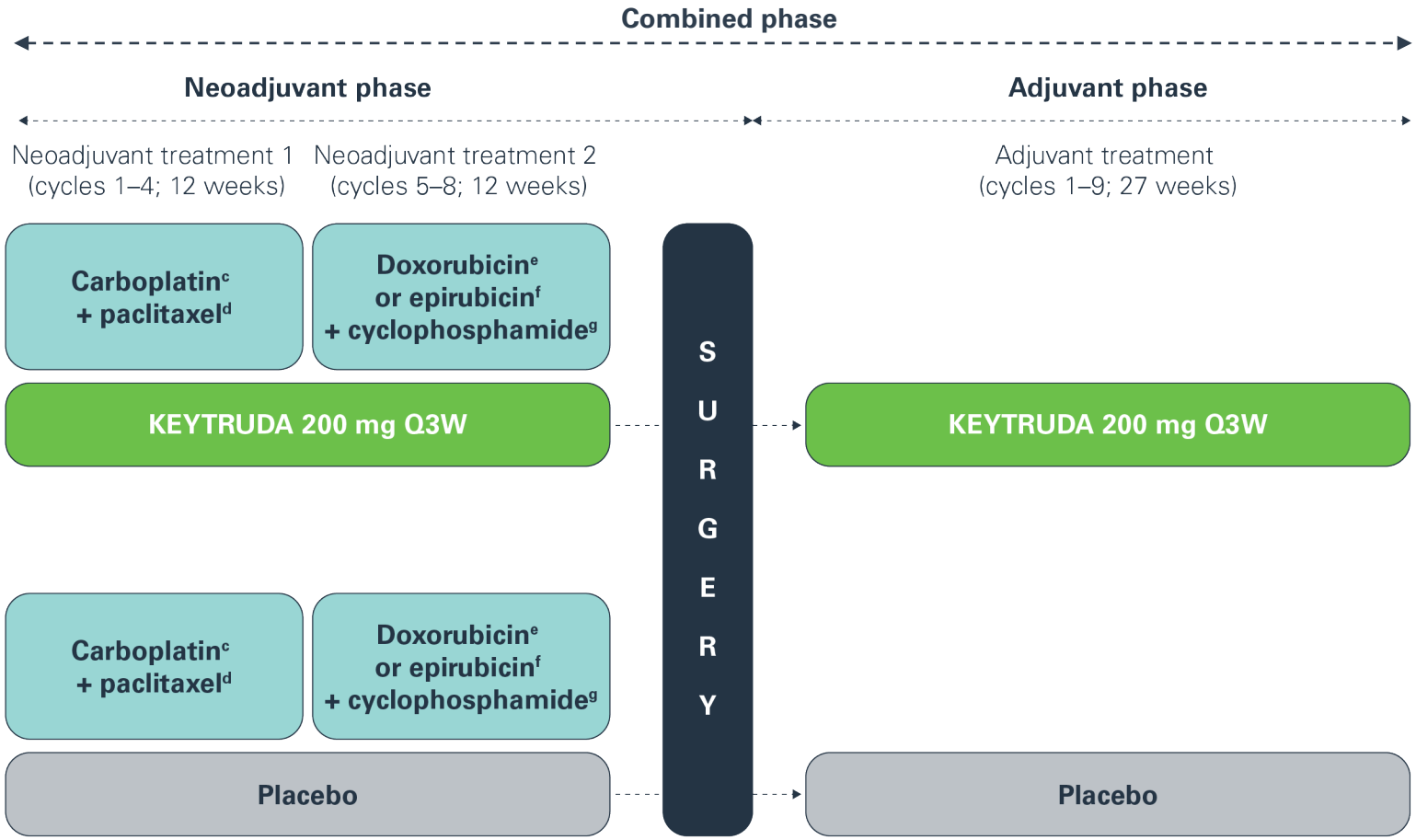
Click the links below to navigate to the section of interest

KEYNOTE-522: Safety assessments	**KEYNOTE-522: Summary of any-grade AEs in the neoadjuvant phase (primary analysis)**	**KEYNOTE-522: AEs of interest in the neoadjuvant phase (primary analysis)**	**KEYNOTE-522: TRAEs in the adjuvant phase (36-month follow up)**
KEYNOTE-522: Immune-mediated AEs and infusion reactions in the adjuvant phase (36-month follow up)	**KEYNOTE-522: Summary of any-grade AEs in the combined phase (36-month follow up)**	**KEYNOTE-522: Immune-mediated AEs in the combined phase (36-month follow up)**	**KEYNOTE-522: Summary of safety results in the combined phase (36-month follow up)**

AE, adverse event; TRAE, treatment-related adverse event.

Prescribing Information: GB; NI

KEYNOTE-522: Safety assessments[1,2]



AEs were assessed during each phase of the study, as well as the study as a whole

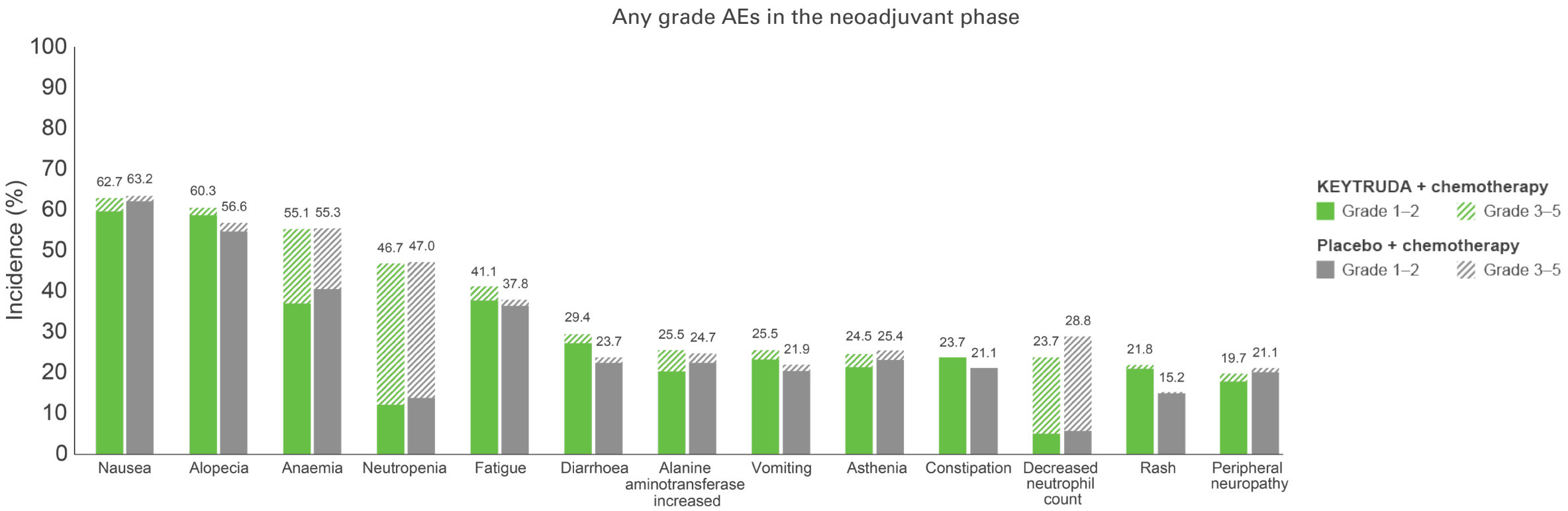
Adapted from Schmid P et al. 2020 and Schmid P et al. 2022.

[a]Blinded assessment performed by local pathologist; [b]Must consist of at least two separate tumour cores from the primary tumour; [c]Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW; [d]Paclitaxel dose was 80 mg/m² QW; [e]Doxorubicin dose was 60 mg/m² Q3W; [f]Epirubicin dose was 90 mg/m² Q3W; [g]Cyclophosphamide dose was 600 mg/m² Q3W.

AE, adverse event; AUC, area under curve; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; pCR, pathologic complete response; PD-L1, programmed death ligand-1; QW, every week; Q3W, every 3 weeks; R, randomisation; TNBC, triple-negative breast cancer.

1. Schmid P et al. *N Engl J Med* 2020;382:810–821 (plus supplementary appendix); 2. Schmid P et al. *N Engl J Med* 2022;386:556–567 (plus supplementary appendix).

KEYNOTE-522: Summary of any-grade AEs occurring in ≥20% of patients in the neoadjuvant phase at primary analysis



The tabular data for this plot is shown in the appendix. Click here to view.

Adapted from Schmid P et al. *N Engl J Med* 2020.

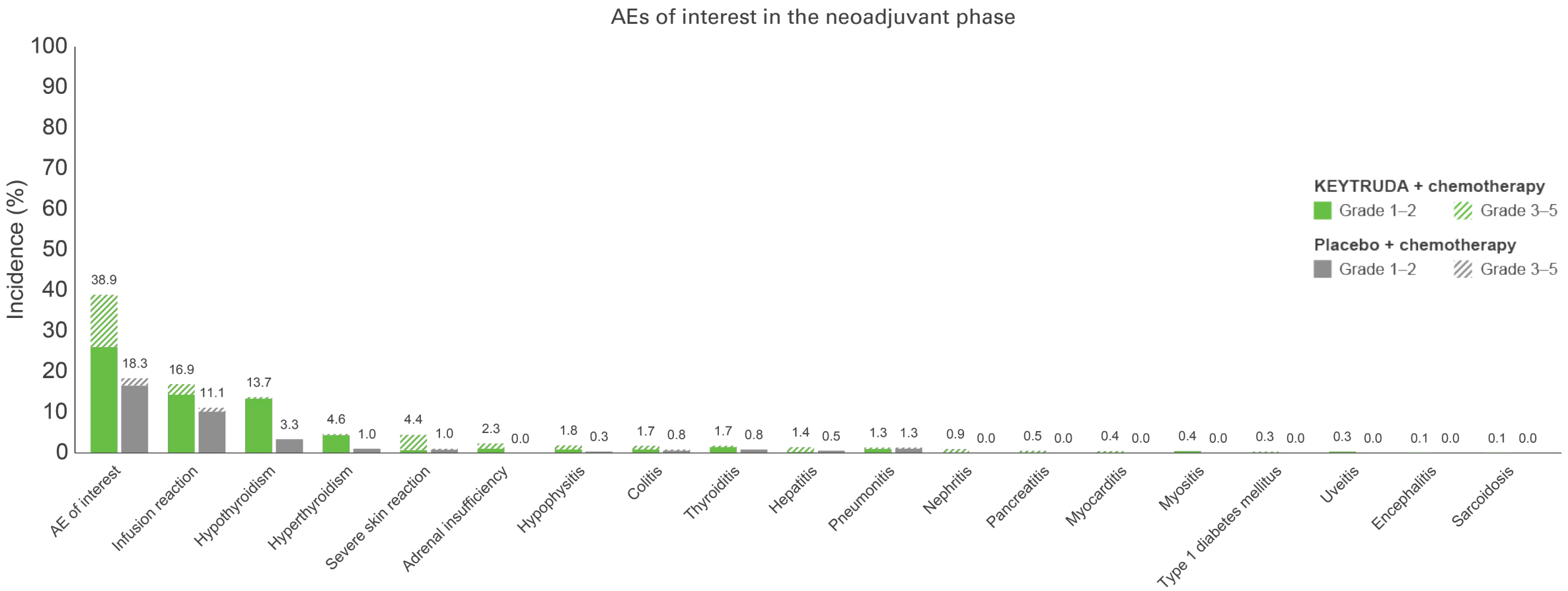
Listed are AEs that occurred during the treatment period or within 30 days after the treatment period (or, for serious AEs, within 90 days) in patients who were randomised and received at least one trial drug or surgery. The severity of the AEs was graded according to the Common Terminology Criteria for Adverse Events, v4.0, of the National Cancer Institute. Patients may have had more than one event.

AE, adverse event.

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

Prescribing Information: GB; NI

KEYNOTE-522: AEs of interest occurring in ≥20% of patients in the neoadjuvant phase at primary analysis[a]



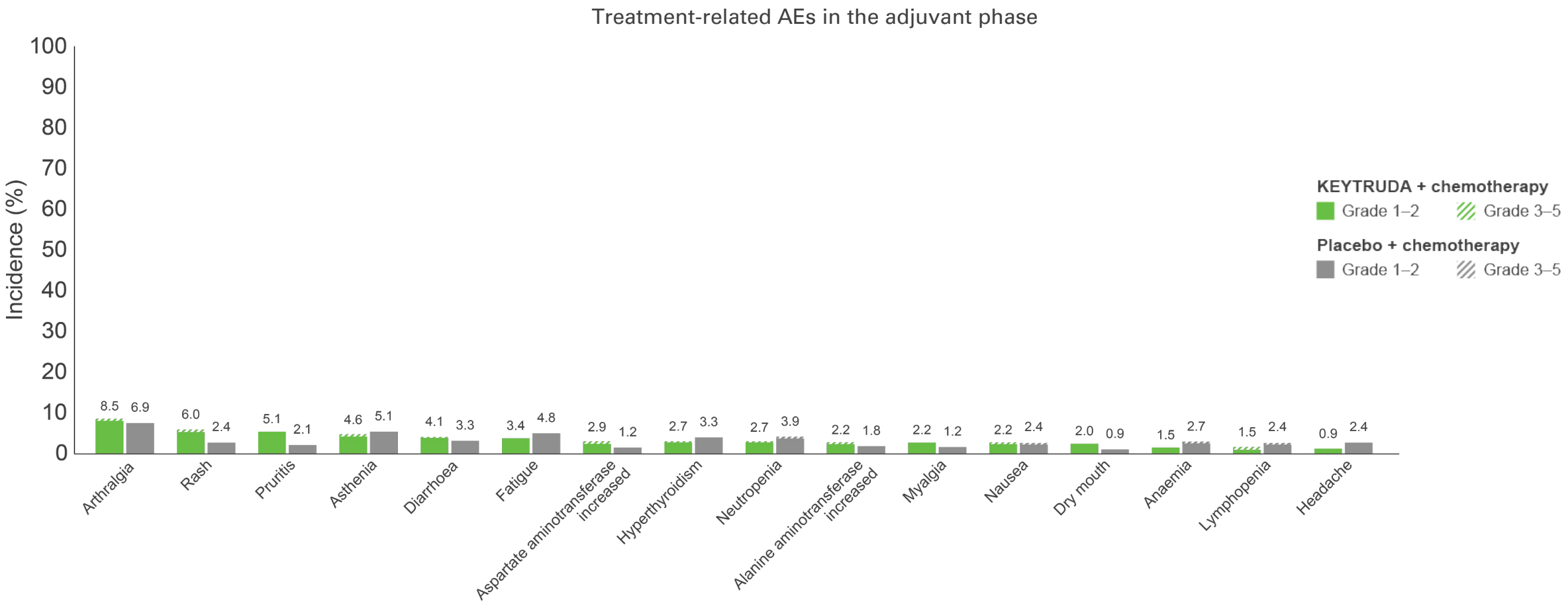
The tabular data for this plot is shown in the appendix. Click here to view.

Adapted from Schmid P et al. *N Engl J Med* 2020.

Listed are AEs that occurred during the treatment period or within 30 days after the treatment period (or, for serious AEs, within 90 days) in patients who were randomised and received at least one trial drug or surgery. The severity of the AEs was graded according to the Common Terminology Criteria for Adverse Events, v4.0, of the National Cancer Institute. Patients may have had more than one event.
[a]AEs of interest were determined according to a list of terms specified by the sponsor, regardless of attribution to any trial treatment by the investigators.
AE, adverse event.
Schmid P et al. *N Engl J Med* 2020;382:810–821 (plus supplementary appendix).

Prescribing Information: GB; NI

KEYNOTE-522: TRAEs occurring in ≥20% of patients in the adjuvant phase at primary analysis at 36-month follow up



The tabular data for this plot is shown in the appendix. Click here to view.

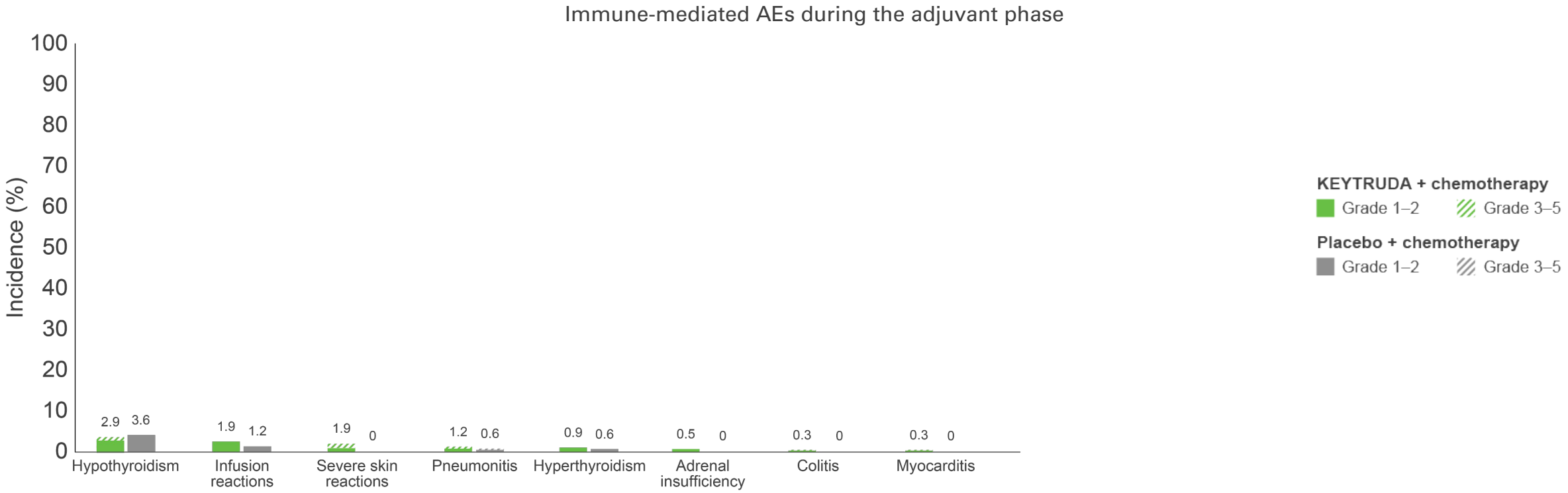
Adapted from Schmid P et al. Presented at ESMO 2021.

Listed are AEs that occurred during the treatment period or within 30 days after the treatment period (or, for serious AEs, within 90 days) in patients who were randomised and received at least one trial drug or surgery. The severity of the AEs was graded according to the Common Terminology Criteria for Adverse Events, v4.0, of the National Cancer Institute. Patients may have had more than one event.

AE, adverse event; TRAE, treatment-related adverse event.

Schmid P et al. Presented at the European Society for Medical Oncology (ESMO) Virtual Plenary 2021, 16–21 September 2021. Abstract VP7-2021.

KEYNOTE-522: Immune-mediated AEs and infusion reactions in the adjuvant phase at primary analysis at 36-month follow up



The tabular data for this plot is shown in the appendix. Click here to view.

Adapted from Schmid P et al. Presented at ESMO 2021.

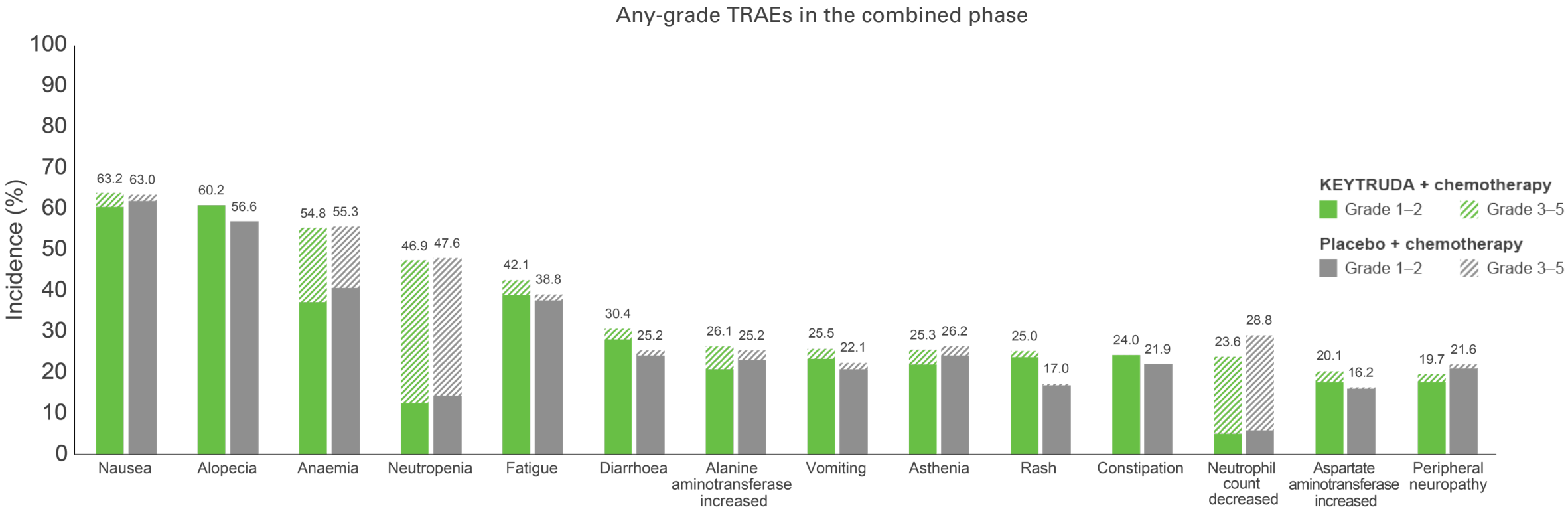
Listed are AEs that occurred during the treatment period or within 30 days after the treatment period (or, for serious AEs, within 90 days) in patients who were randomised and received at least one trial drug or surgery. The severity of the AEs was graded according to the Common Terminology Criteria for Adverse Events, v4.0, of the National Cancer Institute. Patients may have had more than one event. Immune-mediated AEs were determined according to the sponsor, regardless of attribution to any trial treatment. Grade 5 immune-mediated AEs were pulmonary embolism and autoimmune encephalitis (n=1 each) in the KEYTRUDA + chemotherapy group.

AE, adverse event.

Schmid P et al. Presented at the European Society for Medical Oncology (ESMO) Virtual Plenary 2021, 16–21 September 2021. Abstract VP7-2021.

Prescribing Information: GB; NI

KEYNOTE-522: Summary of any-grade TRAEs occurring in ≥20% of patients in the combined phase at 36-month follow up



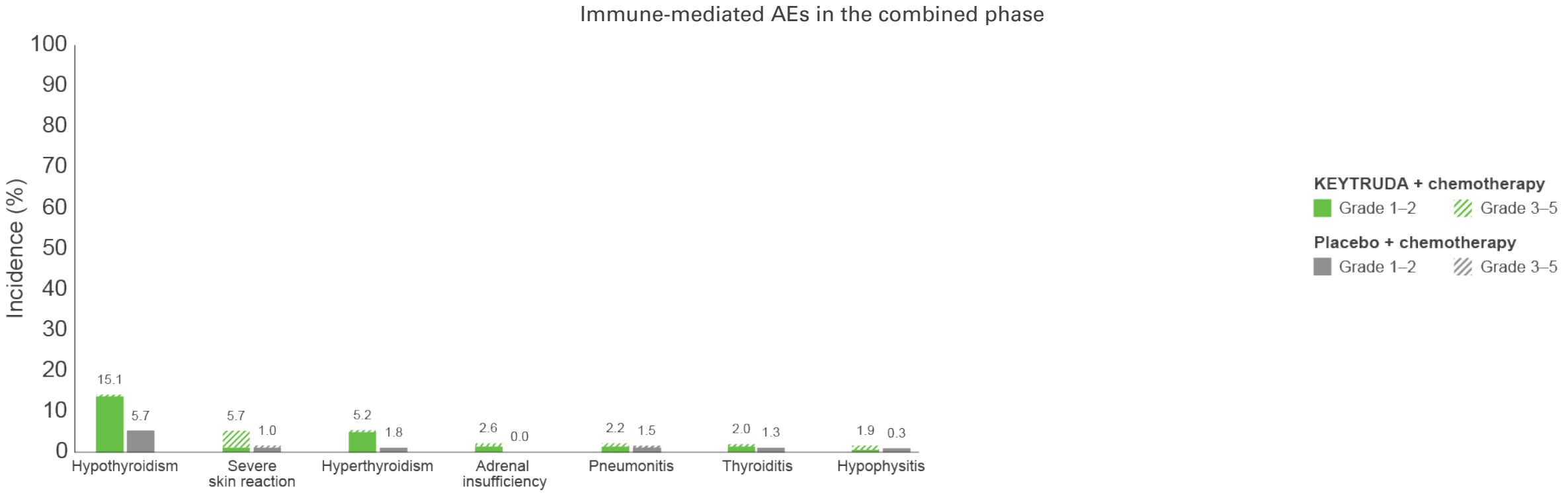
The tabular data for this plot is shown in the appendix. Click here to view.

Adapted from Schmid P et al. *N Engl J Med* 2022.

AEs were assessed during each phase of the study, as well as the study as a whole.
Listed are AEs that occurred during the treatment period or within 30 days after the treatment period (or, for serious AEs, within 90 days) in patients who were randomised and received at least one trial drug or surgery. The severity of the AEs was graded according to the Common Terminology Criteria for Adverse Events, v4.0, of the National Cancer Institute. Patients may have had more than one event.
Grade 5 AEs were sepsis and multiple organ dysfunction syndrome (n=1) and pneumonitis, pulmonary embolism and autoimmune encephalitis (n=1 in each group) in the KEYTRUDA + chemotherapy arm and septic shock (n=1) in the placebo + chemotherapy arm.
AE, adverse event; TRAE, treatment-related adverse event.
Schmid P et al. *N Engl J Med* 2022;386:556–567.

Prescribing Information: GB; NI

KEYNOTE-522: Immune-mediated AEs occurring in ≥20% of patients in the combined phase at 36-month follow up[a]



The tabular data for this plot is shown in the appendix. Click here to view.

Adapted from Schmid P et al. *N Engl J Med* 2022.

AEs were assessed during each phase of the study, as well as the study as a whole.
Listed are AEs that occurred during the treatment period or within 30 days after the treatment period (or, for serious AEs, within 90 days) in patients who were randomised and received at least one trial drug or surgery. The severity of the AEs was graded according to the Common Terminology Criteria for Adverse Events, v4.0, of the National Cancer Institute. Patients may have had more than one event.
[a]Immune-mediated AEs were determined according to the sponsor, regardless of attribution to any trial treatment. Grade 5 immune-mediated AEs were pulmonary embolism and autoimmune encephalitis (n=1 each) in the KEYTRUDA + chemotherapy group.
AE, adverse event.
Schmid P et al. *N Engl J Med* 2022;386:556–567.

Prescribing Information: GB; NI

KEYNOTE-522: Summary of safety results in the combined (neoadjuvant and adjuvant) phase at 36-month follow up

Immune-mediated AEs and infusion reactions

	KEYTRUDA + chemotherapy/ KEYTRUDA (n=783)	Placebo + chemotherapy/ placebo (n=389)
Any	341 (43.6)	85 (21.9)
Grade 1–2	224 (28.6)	77 (19.8)
Grade 3–4	115 (14.7)	8 (2.1)[a]
Grade 5	2 (0.3)[b]	0
Led to dose reduction[c]		
Chemotherapy[d]	1 (0.1)[e]	0
Led to treatment interruption		
KEYTRUDA/placebo	43 (5.5)	9 (2.3)
Chemotherapy[d]	88 (11.2)	25 (6.4)
Led to discontinuation of any drug		
KEYTRUDA/placebo	61 (7.8)	4 (1.0)
Chemotherapy[d]	45 (5.7)	7 (1.8)

Time to onset and management of the most common (≥20 patients) immune-mediated AEs and infusion reactions

	KEYTRUDA + chemotherapy/ KEYTRUDA (n=783)	Placebo + chemotherapy/ placebo (n=389)
Infusion reactions, n (%)	141 (18.0)	45 (11.6)
Median time to onset (range), days	16 (1–458)	22 (1–325)
Treated with corticosteroids, n	85	28
Hypothyroidism, n (%)	118 (15.1)	22 (5.7)
Median time to onset (range), days	105 (7–510)	255 (7–527)
Treated with thyroid replacement, n	106	13
Severe skin reactions, n (%)	45 (5.7)	4 (1.0)
Median time to onset (range), days	64 (4–479)	50.5 (32–186)
Treated with corticosteroids, n	28	0
Hyperthyroidism, n (%)	41 (5.2)	7 (1.8)
Median time to onset (range), days	107 (20–470)	184 (1–284)
Adrenal insufficiency, n (%)	20 (2.6)	0
Median time to onset (range), days	175.5 (100–383)	-
Treated with hormone replacement, n	20	-

Adapted from Cortés J et al. Presented at SABCS 2023.

[a]There were no Grade 4 immune-mediated AEs or infusion reactions; [b]n=1 with pneumonitis (neoadjuvant phase), n=1 with autoimmune encephalitis (adjuvant phase); [c]Dose reduction was not allowed for KEYTRUDA or placebo; [d]Chemotherapy was administered during the neoadjuvant phase only; [e]Due to a severe skin reaction.

AE, adverse event.

Cortés J et al. Presented at the San Antonio Breast Cancer Symposium (SABCS) Congress 2023, 5–9 December 2023, San Antonio, USA.

Implementing KEYTRUDA + chemotherapy for early-stage TNBC

Click the links below to navigate to the section of interest

KEYTRUDA dosing in KEYNOTE-522

KEYTRUDA dosing

TNBC, triple-negative breast cancer.

Prescribing Information: GB; NI

KEYTRUDA dosing in KEYNOTE-522

First neoadjuvant phase[1]

200 mg KEYTRUDA
+ paclitaxel[a] and carboplatin[b]

Q3W
up to 12 weeks

Second neoadjuvant phase[1]

200 mg KEYTRUDA + doxorubicin[c]
or epirubicin[d] and
cyclophosphamide[e]

Q3W
up to 12 weeks

Adjuvant cycle[2]

200 mg KEYTRUDA monotherapy
(radiation therapy concurrently or
2 weeks prior to adjuvant KEYTRUDA)

Q3W
up to 27 weeks

Patients should be treated with KEYTRUDA until disease progression or unacceptable toxicity[3]

Atypical responses (i.e. an initial transient increase in tumour size or new small lesions within the first few months, followed by tumour shrinkage) have been observed[3]

It is recommended to continue treatment in clinically stable patients with initial evidence of disease progression until disease progression is confirmed[3]

No dose reductions of KEYTRUDA are recommended. KEYTRUDA should be withheld or discontinued to manage AEs as described within the SmPC[3]

When administering KEYTRUDA in combination with IV chemotherapy, KEYTRUDA should be administered first[3]

Consult the full KEYTRUDA SmPC for guidance on dosing

[a]80 mg/m^2; [b]AUC of 5 mg/mm/min or 1.5 mg/mm/min QW; [c]60 mg/m^2; [d]90 mg/m^2; [e]600 mg/m^2.
AE, adverse event; AUC, area under the curve; IV, intravenous; Q3W, every 3 weeks; SmPC, Summary of Product Characteristics.
1. Schmid P et al. *N Engl J Med* 2020;382:810–821; 2. Schmid P et al. *N Engl J Med* 2022;386:556–567;
3. KEYTRUDA SmPC. https://www.medicines.org.uk/emc/product/2498/smpc (accessed January 2024).

Prescribing Information: GB; NI

KEYTRUDA dosing

KEYTRUDA dosing:[1]

Administered as an IV infusion

Over 30 minutes

200 mg Q3W or 400 mg Q6W

Patients should be treated with KEYTRUDA until disease progression or unacceptable toxicity[1]

Atypical responses (i.e. an initial transient increase in tumour size or new small lesions within the first few months, followed by tumour shrinkage) have been observed[1]

It is recommended to continue treatment in clinically stable patients with initial evidence of disease progression until disease progression is confirmed[1]

No dose reductions of KEYTRUDA are recommended. KEYTRUDA should be withheld or discontinued to manage AEs as described within the SmPC[1]

When administering KEYTRUDA in combination with IV chemotherapy, KEYTRUDA should be administered first[1]

Consult the full KEYTRUDA SmPC for guidance on dosing

The only dosing regimen assessed in all clinical Phase 2 and 3 registration studies for KEYTRUDA was 200 mg Q3W. The study that led to the approval of Q6W dosing for monotherapy and combination therapy assessed the 400 mg Q6W dosing schedule based on an exposure–response evaluation, using modelling and simulation[2]

AE, adverse event; FDA, US Food and Drug Administration; IV, intravenous; Q3W, every 3 weeks; Q6W, every 6 weeks; SmPC, Summary of Product Characteristics.

1. KEYTRUDA SmPC. https://www.medicines.org.uk/emc/product/2498/smpc (accessed January 2024); 2. FDA (April 2020). FDA approves new dosing regimen for KEYTRUDA. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-new-dosing-regimen-pembrolizumab (accessed January 2024).

KEYNOTE-522: Summary

Click the links below to navigate to the section of interest

Summary: Efficacy

Summary: Safety

Summary: Efficacy

KEYTRUDA, in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, is indicated in the treatment of adults with locally advanced or early-stage TNBC at high risk of recurrence[1]

- There was a statistically significant improvement in pCR rates with KEYTRUDA + chemotherapy vs placebo + chemotherapy in KEYNOTE-522 (64.0% vs 54.7%, respectively; p=0.00221)[1]
- KEYTRUDA + chemotherapy in the neoadjuvant setting, followed by KEYTRUDA monotherapy as adjuvant treatment, resulted in a statistically significant improvement in EFS compared with placebo + chemotherapy followed by placebo at the 36-month analysis (HR: 0.63; 95% CI: 0.48–0.82 [p<0.001])[a,2]
  - With longer follow up, 60-month EFS rates were 81.3% with KEYTRUDA + chemotherapy/KEYTRUDA vs 72.3% with placebo + chemotherapy/placebo (HR 0.63; 95% CI: 0.49–0.81)[b,3]
- An exploratory analysis of EFS in key subgroups, including disease stage, nodal status and T2N0 status, suggested a benefit for patients treated with KEYTRUDA + chemotherapy vs placebo + chemotherapy[4]
- An exploratory analysis suggested a benefit for KEYTRUDA + chemotherapy/KEYTRUDA vs placebo + chemotherapy/placebo regardless of pCR outcome after 36 months and the difference was maintained with 60 months of follow up[3,4]
- After 60 months of follow up, the incidence of brain metastases as the first EFS event was generally low in both treatment groups[4]

[a]HR (CI) analysed based on a Cox regression model with treatment as a covariate stratified by the randomisation stratification factors; [b]Prespecified p-value boundary of 0.00517 was crossed.
CI, confidence interval; EFS, event-free survival; HR, hazard ratio; pCR, pathologic complete response; TNBC, triple-negative breast cancer.
1. KEYTRUDA SmPC. https://www.medicines.org.uk/emc/product/2498/smpc (accessed January 2024); 2. Schmid P et al. *N Engl J Med* 2022;386:556–567;
3. Schmid P et al. Presented at the European Society of Medical Oncology (ESMO) Congress 2023, 20–24 September 2023, Madrid, Spain;
4. Schmid P et al. Presented at the San Antonio Breast Cancer Symposium (SABCS) Congress 2023, 5–9 December 2023, San Antonio, USA.

Summary: Safety

KEYTRUDA, in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, is indicated in the treatment of adults with locally advanced or early-stage TNBC at high risk of recurrence[1]

- The safety data for KEYTRUDA + chemotherapy as neoadjuvant treatment, followed by KEYTRUDA monotherapy as adjuvant treatment, are consistent with the known AE profiles of each regimen, being generally manageable in both phases[2,3]
- No indication-specific immune-mediated AEs were identified at the 36-month analysis[4]
  - Most immune-mediated AEs and infusion reactions were Grade 1–2 in severity, manageable with corticosteroids, treatment interruption and/or hormone replacement, and did not result in treatment discontinuation[4]

AE, adverse event; TNBC, triple-negative breast cancer.

1. KEYTRUDA SmPC. https://www.medicines.org.uk/emc/product/2498/smpc (accessed January 2024); 2. Schmid P et al. *N Engl J Med* 2022;386:556–567;
3. Schmid P et al. *N Engl J Med* 2020;382:810–821; 4. Cortés J et al. Presented at the San Antonio Breast Cancer Symposium (SABCS) Congress 2023, 5–9 December 2023, San Antonio, USA.

Appendix

Click the links below to navigate to the section of interest

AE, adverse event; TRAE, treatment-related adverse event.

KEYNOTE-522: Summary of any-grade AEs occurring in ≥20% of patients in the neoadjuvant phase at primary analysis

AE, n (%)	KEYTRUDA + chemotherapy (n=781)		Placebo + chemotherapy (n=389)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any AE	777 (99.2)	633 (81.0)	389 (100.0)	295 (75.8)
Treatment-related AE[a]	773 (99.0)	600 (76.8)	388 (99.7)	281 (72.2)
Nausea	490 (62.7)	26 (3.3)	246 (63.2)	5 (1.3)
Alopecia	471 (60.3)	14 (1.8)	220 (56.6)	8 (2.1)
Anaemia	430 (55.1)	142 (18.2)	215 (55.3)	58 (14.9)
Neutropenia	365 (46.7)	270 (34.6)	183 (47.0)	129 (33.2)
Fatigue	321 (41.1)	27 (3.5)	147 (37.8)	6 (1.5)
Diarrhoea	230 (29.4)	17 (2.2)	92 (23.7)	5 (1.3)
Alanine aminotransferase increased	199 (25.5)	41 (5.2)	96 (24.7)	9 (2.3)
Vomiting	199 (25.5)	18 (2.3)	85 (21.9)	6 (1.5)
Asthenia	191 (24.5)	25 (3.2)	99 (25.4)	9 (2.3)
Constipation	185 (23.7)	0	82 (21.1)	0
Decreased neutrophil count	185 (23.7)	146 (18.7)	112 (28.8)	90 (23.1)
Rash	170 (21.8)	7 (0.9)	59 (15.2)	1 (0.3)
Peripheral neuropathy	154 (19.7)	15 (1.9)	82 (21.1)	4 (1.0)

Adapted from Schmid P et al. *N Engl J Med* 2020.

Listed are AEs that occurred during the treatment period or within 30 days after the treatment period (or, for serious AEs, within 90 days) in patients who were randomised and received at least one trial drug or surgery. The severity of the AEs was graded according to the Common Terminology Criteria for Adverse Events, v4.0, of the National Cancer Institute. Patients may have had more than one event.
AE, adverse event.
Schmid P et al. *N Engl J Med* 2020;382:810–821.

Prescribing Information: GB; NI

KEYNOTE-522: AEs of interest in the neoadjuvant phase at primary analysis (1/2)

AE, n (%)	KEYTRUDA + chemotherapy (n=781)		Placebo + chemotherapy (n=389)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any AE	777 (99.5)	633 (81.0)	389 (100.0)	295 (75.8)
Treatment-related AE	773 (99.0)	600 (76.8)	388 (99.7)	281 (72.2)
AE of interest	304 (38.9)	101 (12.9)	71 (18.3)	7 (1.8)
Infusion reaction	132 (16.9)	20 (2.6)	43 (11.1)	4 (1.0)
Hypothyroidism	107 (13.7)	3 (0.4)	13 (3.3)	0
Hyperthyroidism	36 (4.6)	2 (0.3)	4 (1.0)	0
Severe skin reaction	34 (4.4)	30 (3.8)	4 (1.0)	1 (0.3)
Adrenal insufficiency	18 (2.3)	10 (1.3)	0	0
Hypophysitis	14 (1.8)	8 (1.0)	1 (0.3)	0
Colitis	13 (1.7)	7 (0.9)	3 (0.8)	1 (0.3)
Thyroiditis	13 (1.7)	2 (0.3)	3 (0.8)	0
Hepatitis	11 (1.4)	9 (1.2)	2 (0.5)	0

Adapted from Schmid P et al. *N Engl J Med* 2020.

Listed are AEs that occurred during the treatment period or within 30 days after the treatment period (or, for serious AEs, within 90 days) in patients who underwent randomisation and received at least one trial drug or surgery. The severity of the AEs was graded according to the Common Terminology Criteria for Adverse Events, v4.0, of the National Cancer Institute. Patients may have had more than one event. [a]Treatment-related AEs were events occurring in ≥20% of patients or considered medically relevant by the investigator; [b]AEs of interest were determined according to a list of terms specified by the sponsor, regardless of attribution to any trial treatment by the investigators.

AE, adverse event.

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

KEYNOTE-522: AEs of interest occurring in ≥20% of patients in the neoadjuvant phase at primary analysis[a] (2/2)

AE, n (%)	KEYTRUDA + chemotherapy (n=781)		Placebo + chemotherapy (n=389)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any AE	777 (99.5)	633 (81.0)	389 (100.0)	295 (75.8)
Treatment-related AE	773 (99.0)	600 (76.8)	388 (99.7)	281 (72.2)
AE of interest	304 (38.9)	101 (12.9)	71 (18.3)	7 (1.8)
Pneumonitis	10 (1.3)	3 (0.4)	5 (1.3)	1 (0.3)
Nephritis	7 (0.9)	7 (0.9)	0	0
Pancreatitis	4 (0.5)	4 (0.5)	0	0
Myocarditis	3 (0.4)	2 (0.3)	0	0
Myositis	3 (0.4)	0	0	0
Type 1 diabetes mellitus	2 (0.3)	2 (0.3)	0	0
Uveitis	2 (0.3)	0	0	0
Encephalitis	1 (0.1)	1 (0.1)	0	0
Sarcoidosis	1 (0.1)	0	0	0

Adapted from Schmid P et al. *N Engl J Med* 2020.

Listed are AEs that occurred during the treatment period or within 30 days after the treatment period (or, for serious AEs, within 90 days) in patients who were randomised and received at least one trial drug or surgery. The severity of the AEs was graded according to the Common Terminology Criteria for Adverse Events, v4.0, of the National Cancer Institute. Patients may have had more than one event.
[a]AEs of interest were determined according to a list of terms specified by the sponsor, regardless of attribution to any trial treatment by the investigators.
AE, adverse event.
Schmid P et al. *N Engl J Med* 2020;382:810–821.

KEYNOTE-522: TRAEs occurring in ≥20% of patients in the adjuvant phase at 36-month follow up

AE, n (%)[a]	KEYTRUDA + chemotherapy (n=588)	Placebo + chemotherapy (n=331)
Any grade	316	286
Arthralgia	50 (8.5)	41 (6.9)
Rash	35 (6.0)	14 (2.4)
Pruritis	30 (5.1)	12 (2.1)
Asthenia	27 (4.6)	30 (5.1)
Diarrhoea	24 (4.1)	19 (3.3)
Fatigue	20 (3.4)	28 (4.8)
Aspartate aminotransferase increased	17 (2.9)	7 (1.2)
Hypothyroidism	16 (2.7)	19 (3.3)
Neutropenia	16 (2.7)	23 (3.9)
Alanine aminotransferase increased	13 (2.2)	11 (1.8)
Myalgia	13 (2.2)	7 (1.2)
Nausea	13 (2.2)	14 (2.4)
Dry mouth	12 (2.0)	5 (0.9)
Anaemia	9 (1.5)	16 (2.7)
Lymphopenia	9 (1.5)	14 (2.4)
Headache	5 (0.9)	14 (2.4)

Adapted from Schmid P et al. Presented at ESMO 2021.

Listed are AEs that occurred during the treatment period or within 30 days after the treatment period (or, for serious AEs, within 90 days) in patients who were randomised and received at least one trial drug or surgery. The severity of the AEs was graded according to the Common Terminology Criteria for Adverse Events, v4.0, of the National Cancer Institute. Patients may have had more than one event.
[a]n numbers for each AE have been calculated from provided percentages.
AE, adverse event; TRAE, treatment-related adverse event.
Schmid P et al. Presented at the European Society for Medical Oncology (ESMO) Virtual Plenary 2021, 16–21 September 2021. Abstract VP7-2021.

Prescribing Information: GB; NI

KEYNOTE-522: Immune-mediated AEs and infusion reactions in the adjuvant phase at 36-month follow up[a]

AE, n (%)[b]	KEYTRUDA + chemotherapy (n=588)	Placebo + chemotherapy (n=331)
Any grade	60 (10.2)	35 (6.0)
Hypothyroidism	17 (2.9)	21 (3.6)
Infusion reactions	11 (1.9)	7 (1.2)
Severe skin reactions	11 (1.9)	0
Pneumonitis	7 (1.2)	4 (0.6)
Hyperthyroidism	5 (0.9)	4 (0.6)
Adrenal insufficiency	3 (0.5)	0
Colitis	2 (0.3)	0
Myocarditis	2 (0.3)	0

Adapted from Schmid P et al. Presented at ESMO 2021.

Listed are AEs that occurred during the treatment period or within 30 days after the treatment period (or, for serious AEs, within 90 days) in patients who were randomised and received at least one trial drug or surgery. The severity of the AEs was graded according to the Common Terminology Criteria for Adverse Events, v4.0, of the National Cancer Institute. Patients may have had more than one event.
[a]Immune-mediated AEs were considered regardless of attribution to treatment or immune-relatedness by the investigator; [b]n numbers for each AE have been calculated from provided percentages.
AE, adverse event.
Schmid P et al. Presented at the European Society for Medical Oncology (ESMO) Virtual Plenary 2021, 16–21 September 2021. Abstract VP7-2021.

KEYNOTE-522: Any-grade AEs in the combined phase occurring in ≥20% of patients at 36-month follow up[a]

AE, n (%)	KEYTRUDA + chemotherapy (n=783)		Placebo + chemotherapy (n=389)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any AE	777 (99.2)	645 (82.4)	389 (100.0)	306 (78.7)
Treatment-related AE[a]	774 (98.9)	604 (77.1)	388 (99.7)	285 (73.3)
Nausea	495 (63.2)	27 (3.4)	245 (63.0)	6 (1.5)
Alopecia	471 (60.2)	0	220 (56.6)	0
Anaemia	429 (54.8)	141 (18.0)	215 (55.3)	58 (14.9)
Neutropenia	367 (46.9)	270 (34.5)	185 (47.6)	130 (33.4)
Fatigue	330 (42.1)	28 (3.6)	151 (38.8)	6 (1.5)
Diarrhoea	238 (30.4)	20 (2.6)	98 (25.2)	5 (1.3)
Alanine aminotransferase increased	204 (26.1)	43 (5.5)	98 (25.2)	9 (2.3)
Vomiting	200 (25.5)	19 (2.4)	86 (22.1)	6 (1.5)
Asthenia	198 (25.3)	28 (3.6)	102 (26.2)	9 (2.3)
Rash	196 (25.0)	12 (1.5)	66 (17.0)	1 (0.3)
Constipation	188 (24.0)	0	85 (21.9)	0
Neutrophil count decreased	185 (23.6)	146 (18.6)	112 (28.8)	90 (23.1)
Aspartate aminotransferase increased	157 (20.1)	20 (2.6)	63 (16.2)	1 (0.3)
Peripheral neuropathy	154 (19.7)	15 (1.9)	84 (21.6)	4 (1.0)

Adapted from Schmid P et al. *N Engl J Med* 2022.

Listed are AEs that occurred during the treatment period or within 30 days after the treatment period (or, for serious AEs, within 90 days) in patients who were randomised and received at least one trial drug or surgery. The severity of the AEs was graded according to the Common Terminology Criteria for Adverse Events, v4.0, of the National Cancer Institute. Patients may have had more than one event.

[a]Grade 5 AEs were sepsis and multiple organ dysfunction syndrome (n=1) and pneumonitis, pulmonary embolism and autoimmune encephalitis (n=1 in each group) in the KEYTRUDA + chemotherapy arm and septic shock (n=1) in the placebo + chemotherapy arm.

AE, adverse event.

Schmid P et al. *N Engl J Med* 2022;386:556–567.

Prescribing Information: GB; NI

KEYNOTE-522: Immune-mediated AEs occurring in ≥20% of patients in the combined phase at 36-month follow up[a]

AE, n (%)	KEYTRUDA + chemotherapy (n=783)		Placebo + chemotherapy (n=389)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any AE	777 (99.2)	645 (82.4)	389 (100.0)	306 (78.7)
Treatment-related AE[a]	774 (98.9)	604 (77.1)	388 (99.7)	285 (73.3)
Immune-mediated AE[b]	262 (33.5)	101 (12.9)	44 (11.3)	4 (1.0)
Hypothyroidism	118 (15.1)	4 (0.5)	22 (5.7)	0
Severe skin reaction	45 (5.7)	37 (4.7)	4 (1.0)	1 (0.3)
Hyperthyroidism	41 (5.2)	2 (0.3)	7 (1.8)	0
Adrenal insufficiency	20 (2.6)	8 (1.0)	0	0
Pneumonitis	17 (2.2)	7 (0.9)	6 (1.5)	2 (0.5)
Thyroiditis	16 (2.0)	2 (0.3)	5 (1.3)	0
Hypophysitis	15 (1.9)	10 (1.3)	1 (0.3)	0

Adapted from Schmid P et al. *N Engl J Med* 2022.

Listed are AEs that occurred during, or 30 days after the treatment period (or, for serious AEs, within 90 days) in patients who were randomised and received ≥1 trial drug or surgery.
The severity of the AEs was graded according to the Common Terminology Criteria for Adverse Events, v4.0, of the National Cancer Institute. Patients may have had more than one event.
[a]Grade 5 AEs were sepsis and multiple organ dysfunction syndrome (n=1) and pneumonitis, pulmonary embolism and autoimmune encephalitis (n=1 in each group) in the KEYTRUDA + chemotherapy arm and septic shock (n=1) in the placebo + chemotherapy arm; [b]Immune-mediated AEs were determined according to the sponsor, regardless of attribution to any trial treatment. Grade 5 immune-mediated AEs were pulmonary embolism and autoimmune encephalitis (n=1 each) in the KEYTRUDA + chemotherapy group.
AE, adverse event.
Schmid P et al. *N Engl J Med* 2022;386:556–567.

Prescribing Information: GB; NI