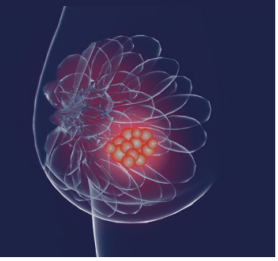


KEYconversations

in early-stage TNBC. Let's keep talking

Neo-adjuvant therapy in early-stage triple-negative breast cancer: Beyond surgical downstaging

16 May 2023

Highlights report

Summary of the MSD-sponsored symposium at the 2023 Association of Breast Surgery (ABS) Conference, Belfast, Ireland, on 16 May 2023

Mr Henry Cain
Consultant Breast Surgeon,
Newcastle upon Tyne Hospitals
NHS Foundation Trust,
Newcastle

Mr Stuart McIntosh
Consultant Breast Surgeon,
Belfast City Hospital,
Belfast

Dr Melissa Phillips
Consultant Oncologist,
St Bartholomew's Hospital,
London

Adverse events should be reported.
Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.
Adverse events should also be reported to MSD, UK (Tel: 020 8154 8000).

Prescribing information is available via the following links: GB, NI

MSD funded the logistics for ABS 2023 and had no input into the scientific content.
This promotional symposium was organised and fully funded by MSD. MSD products were discussed.
The intended audience is UK HCPs.
Please consult the SmPC for further information before making any prescribing decision.
Date of preparation: August 2023 | Job code: GB-PDO-02772

MSD

MSD symposium highlights – beyond surgical downstaging

13:20–13:25	Opening remarks and introductions
13:25–13:35	Evolving surgical treatment landscape: Where are we now?
13:35–13:45	Evolving medical treatment landscape: Summary of KEYNOTE-522 clinical trial
13:45–14:10	Early triple-negative breast cancer patient case discussion
14:10–14:20	Q&A session
14:20	Close

Click to jump to section

This MSD symposium, chaired by Consultant Breast Surgeon Mr Stuart McIntosh, took place at the ABS Conference at the International Convention and Exhibition Centre, Belfast, on 16 May 2023.

Panellists discussed the addition of IO to chemotherapy as neo-adjuvant treatment for early-stage TNBC. They presented data, including the KEYNOTE-522 study, and discussed patient eligibility and the rationale for neo-adjuvant therapy. Various considerations for eligible patients were highlighted and attendees also participated in the discussion and Q&A sessions via a digital polling system.

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

MSD

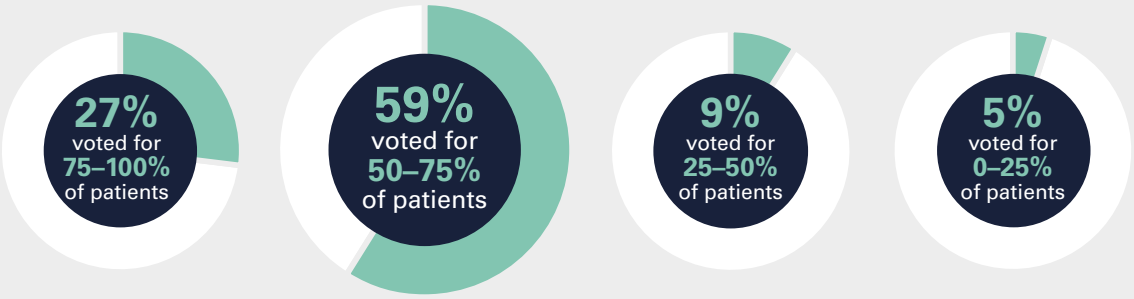
Introduction and audience polling: Attendees' initial perspectives on neo-adjuvant treatment plus IO

To gauge attendees' initial perspectives on the use of neo-adjuvant treatment plus IO, they were asked to answer two polling questions before the presentations began:

Polling question 1:

What proportion of your patients with early-stage TNBC would you consider to be at high risk of recurrence and, therefore, eligible for neo-adjuvant treatment plus IO?

1. 75–100% 2. 50–75% 3. 25–50% 4. 0–25%



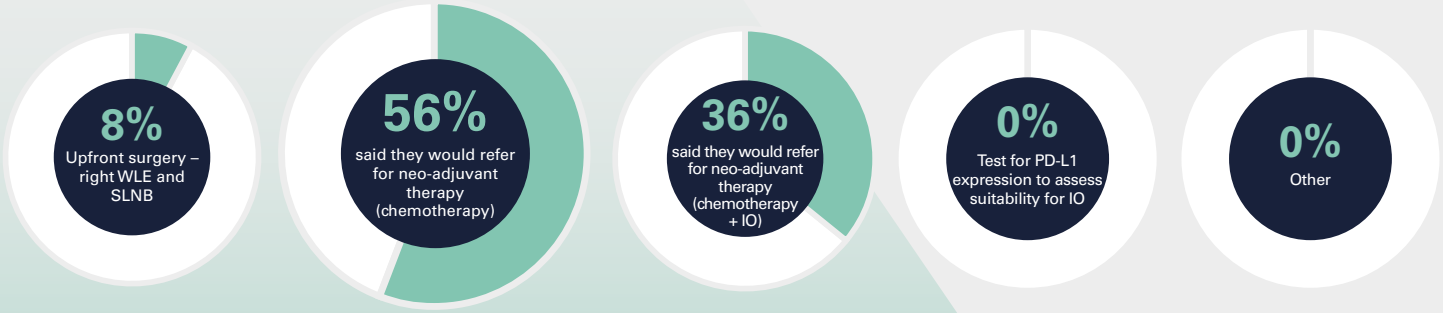
Polling question 2:

Hypothetical patient

- 52-year-old female referred to the breast unit with a 2-cm lump in the right breast
- Triple assessment confirms 2.3-cm M5 U5 lesion with normal axilla on ultrasound
- Biopsy: Grade 3 ER 0/8, PR 0/8, HER2 1+ (negative)
- No medical comorbidities and an ECOG PS 0

How would you treat this patient?

1. Upfront surgery — right WLE and SLNB
2. Refer for neo-adjuvant therapy (chemotherapy)
3. Refer for neo-adjuvant therapy plus IO
4. Test for PD-L1 expression to assess suitability for IO
5. Other



MSD

Presentation 1:

Evolving surgical treatment landscape: Where are we now?

Presented by: Mr Henry Cain, Consultant Breast Surgeon

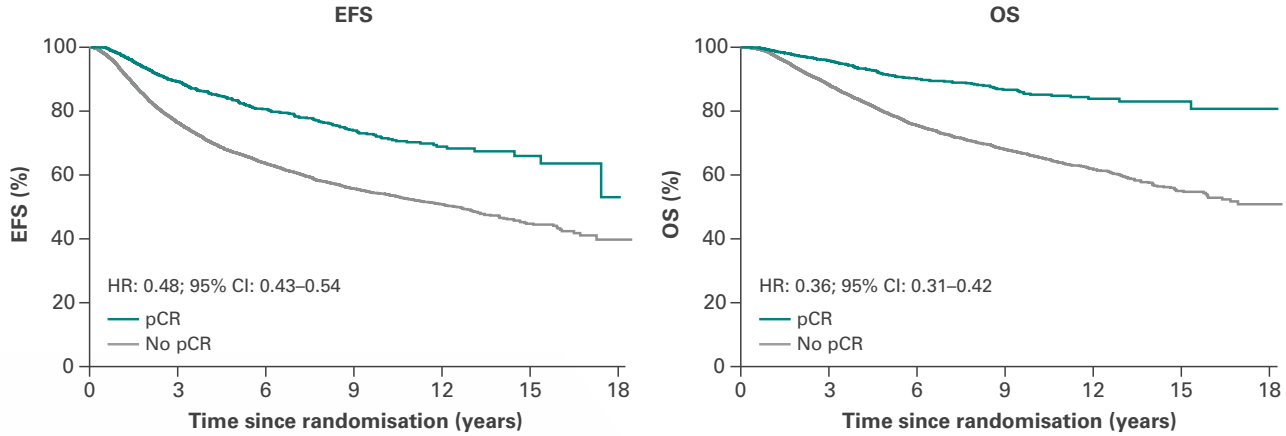
Mr Cain summarised how the treatment landscape in early-stage TNBC has evolved over the past 5 years, including the addition of IO to standard neo-adjuvant treatment. He explained how neo-adjuvant treatment plus IO may improve overall outcomes for eligible patients, including those who may not typically be expected to respond positively to standard neo-adjuvant treatment.[2,3]

Drawing on early clinical studies and local and international guidelines, Mr Cain highlighted that neo-adjuvant treatment plus IO is effective and generally well tolerated.[4–7] In particular, he stressed that its clinical benefits vs neo-adjuvant treatment alone extend beyond surgical de-escalation.[8–10]

pCR was highlighted as a useful prognostic marker of predicted patient outcomes, tumour biology and response to adjuvant chemotherapy (Figure 1).[11]

As new evidence emerges to support the use of chemotherapy plus IO beyond surgical de-escalation, it is important that all members of the MDT are involved in clinical decision-making to optimise patient outcomes.

Figure 1: The association between pCR, EFS and OS in patients who achieved pCR vs those who did not in a pooled analysis[11]



Number at risk														
PCR	2131	1513	583	337	124	35	2	2131	1618	640	383	145	43	3
No pCR	9824	6169	2674	1523	525	165	1	9824	7119	3173	1859	659	209	3

Adapted from Cortazar P et al. *Lancet* 2014.

Presentation 2:

Evolving medical treatment landscape: Summary of KEYNOTE-522 clinical trial

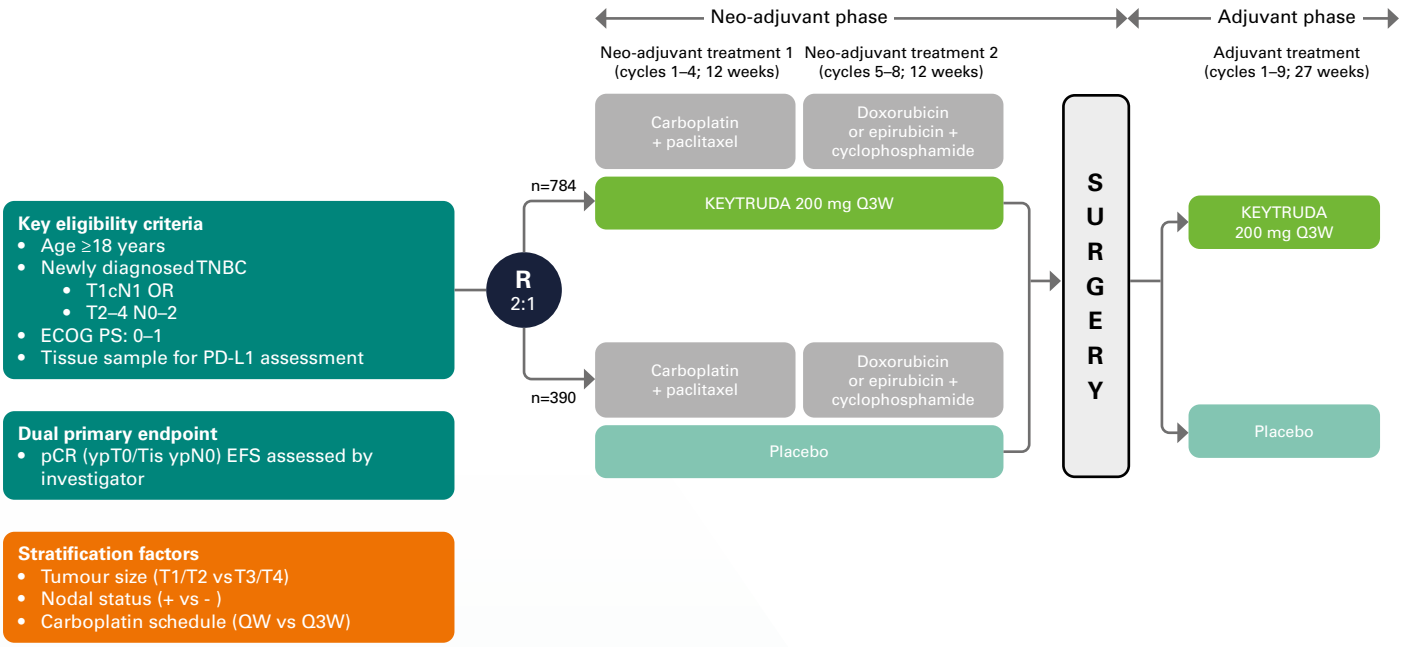
Presented by: Dr Melissa Phillips, Consultant Oncologist

Dr Phillips' presentation centred around the pivotal KEYNOTE-522 study data, exploring the benefits of neo-adjuvant treatment plus IO beyond achieving pCR and potential surgical de-escalation.[12]

Dr Phillips discussed studies that have highlighted how pCR rates have improved over the past 5 years, with rates reaching 65% on current neo-adjuvant treatment plus IO combination therapy.[12] They highlighted how the introduction of neo-adjuvant treatment plus IO provides a greater understanding of the tumour response to first-line treatment, as well as identification of non-responders based on pCR and EFS rates. Additionally, for those patients who achieve a pCR less invasive surgery may be possible.[8–10]

Dr Phillips provided an overview of the KEYNOTE-522 trial design and how the dual primary endpoints allowed for the assessment of short-term (pCR) as well as long-term EFS outcomes.[12]

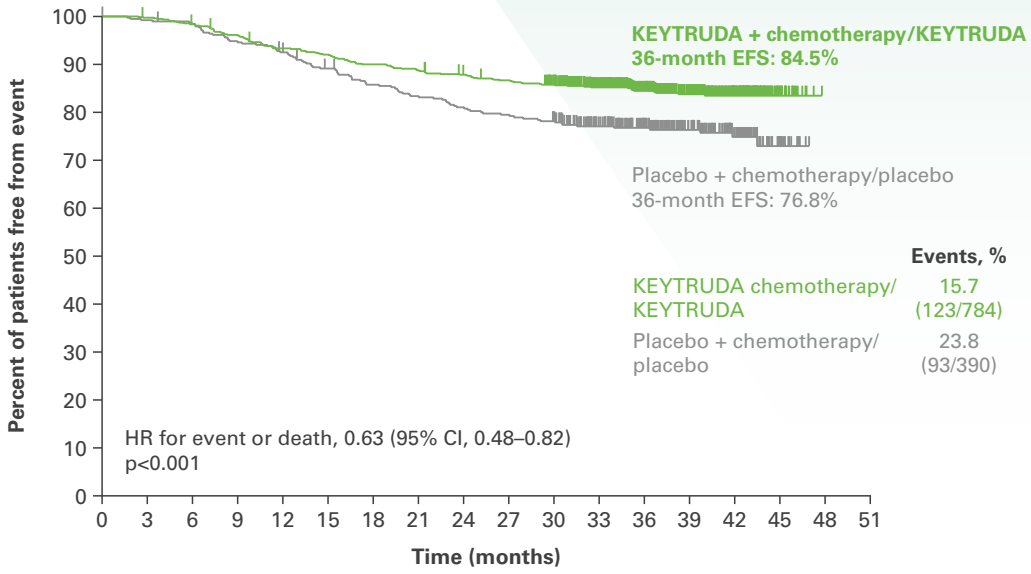
Figure 2: KEYNOTE-522 study design[12]



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

The dual primary endpoint analysis demonstrated that patients who were treated with neo-adjuvant treatment + KEYTRUDA achieved significantly higher pCR rates compared with those reached on neo-adjuvant treatment + placebo. Dr Phillips highlighted that, at a median follow-up of 13 months, pCR rates in the ITT population were 64.0% and 54.7% with KEYTRUDA and placebo, respectively (p=0.00221).[11] Similarly, EFS in the ITT population was significantly longer with neo-adjuvant treatment + KEYTRUDA vs neo-adjuvant treatment + placebo (p<0.001, Figure 3).[13]

Figure 3: KEYNOTE-522 results – EFS in the ITT population[13]



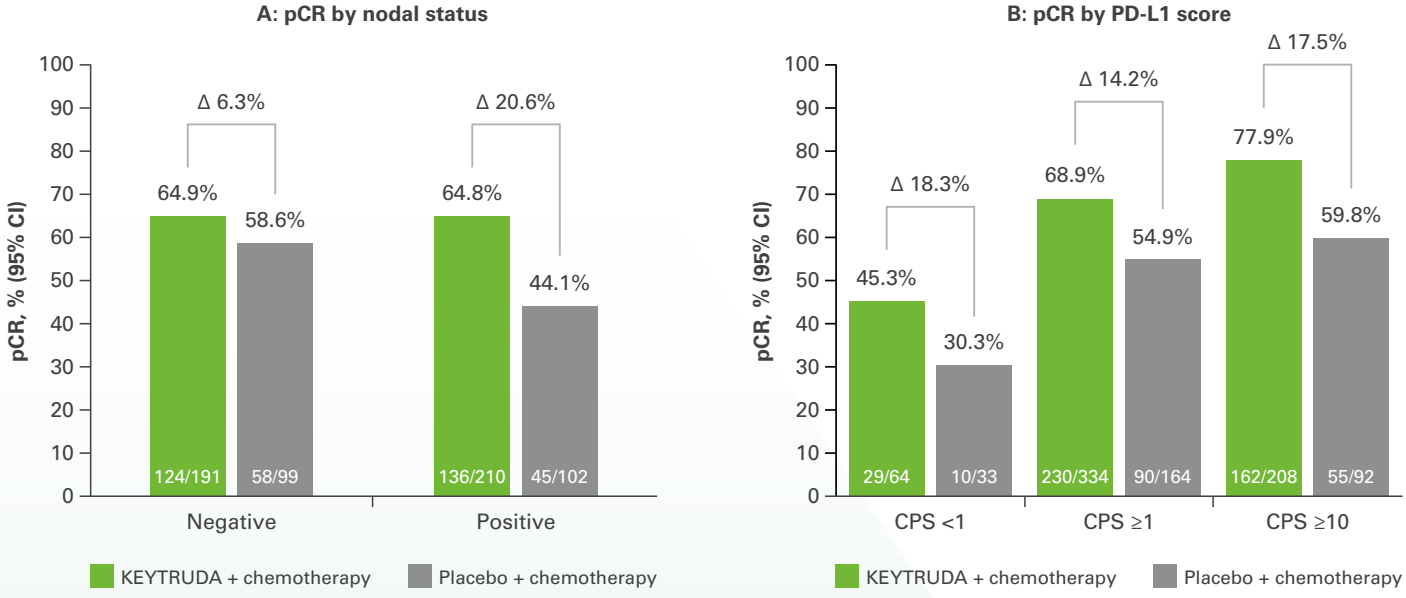
Number at risk

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.

In exploratory subgroup analyses of pCR rates by nodal status and PD-L1 CPS, improvements in pCR with KEYTRUDA + chemotherapy vs placebo + chemotherapy were suggested regardless of patients' nodal or PD-L1 status (Figure 4A,B).[14]

Figure 4: KEYNOTE-522: Exploratory analysis – pCR by nodal status and PD-L1 CPS[14]

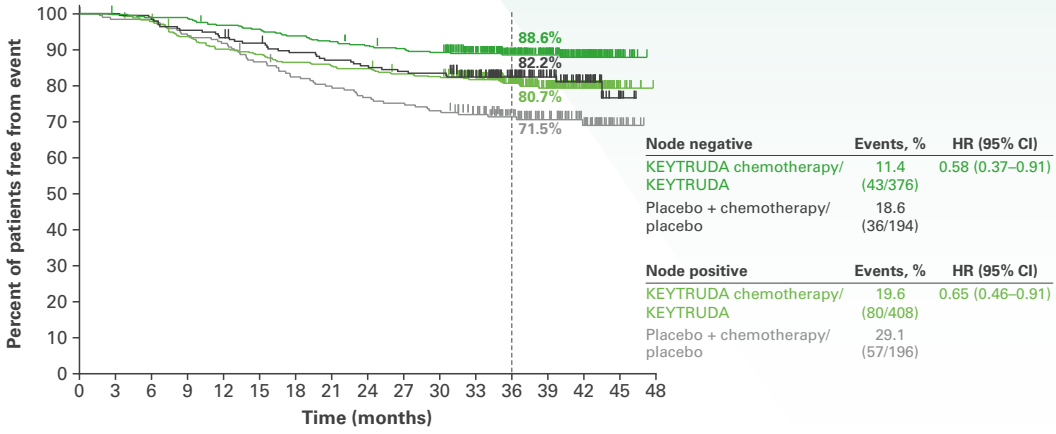


This was an exploratory analysis – results should be interpreted with caution.

Adapted from Schmid P et al. Presented at SABCS 2019.

Commenting on the subgroup analysis of EFS by nodal status, Dr Phillips noted that an EFS benefit was suggested with neo-adjuvant treatment + KEYTRUDA vs neo-adjuvant treatment + placebo, regardless of nodal status (Figure 5).[15] This is clinically significant for node-positive patients, who typically have poor outcomes from treatment.

Figure 5: KEYNOTE-522 results – Exploratory analysis: EFS by nodal status[15]



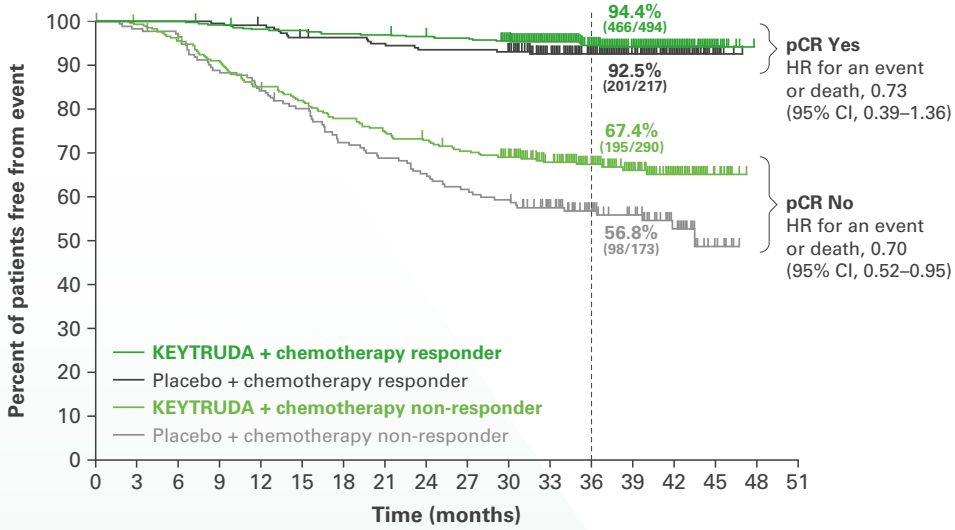
Number at risk

KEYTRUDA chemotherapy/KEYTRUDA, node negative	**376**	**374**	**371**	**371**	**362**	**358**	**351**	**345**	**338**	**335**	**322**	**272**	**212**	**151**	**81**	**16**	**0**
Placebo + chemotherapy/placebo, node negative	194	193	190	184	179	174	169	165	162	159	157	131	101	71	39	7	0
KEYTRUDA chemotherapy/KEYTRUDA, node positive	**408**	**407**	**398**	**380**	**366**	**360**	**351**	**347**	**343**	**336**	**330**	**279**	**221**	**152**	**84**	**12**	**0**
Placebo + chemotherapy/placebo, node positive	196	193	192	184	179	168	159	154	148	145	140	119	94	69	44	10	0

This was an exploratory analysis – results should be interpreted with caution.
Adapted from Schmid P et al. Presented at SABCS 2019.

Similarly, an exploratory analysis suggested that patients treated with neo-adjuvant treatment + KEYTRUDA who achieve a pCR may have improved EFS compared with those who do not (Figure 6).[13] Although patients who achieved a pCR tended to have better EFS outcomes than those who did not, this analysis of EFS by pCR status suggested that treatment with KEYTRUDA + chemotherapy may result in EFS improvements vs placebo + chemotherapy, even in patients who did not reach pCR.[13] Dr Phillips commented that this highlights the importance of considering neo-adjuvant treatment + KEYTRUDA for all eligible patients.

Figure 6: KEYNOTE-522 results – Exploratory analysis: EFS by pCR status[13]



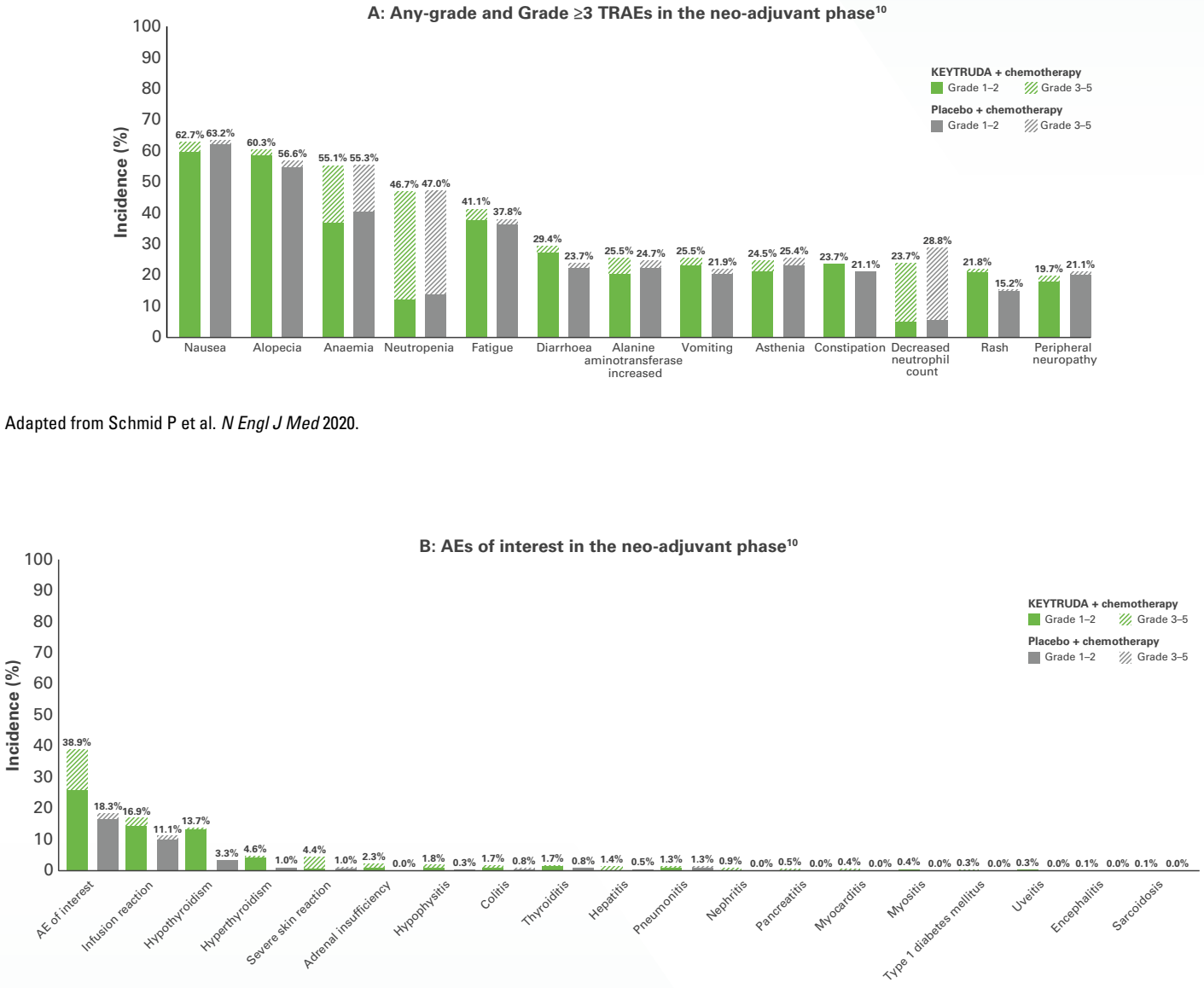
Number at risk

KEYTRUDA + chemotherapy responder	**494**	**494**	**494**	**489**	**483**	**482**	**478**	**477**	**472**	**470**	**460**	**387**	**307**	**220**	**122**	**18**	**0**	**0**
Placebo + chemotherapy responder	217	217	217	216	214	207	206	203	200	200	197	165	130	87	56	9	0	0
KEYTRUDA + chemotherapy non-responder	**290**	**287**	**275**	**262**	**245**	**236**	**224**	**215**	**209**	**201**	**192**	**164**	**126**	**83**	**43**	**10**	**0**	**0**
Placebo + chemotherapy non-responder	173	169	165	152	144	135	122	116	110	104	100	85	65	53	27	8	0	0

This is a *post hoc* exploratory analysis. No formal statistical testing was planned; therefore, no conclusions should be drawn.
Adapted from Schmid P et al. *N Engl J Med* 2022.

To conclude, Dr Phillips discussed the AE profile of neo-adjuvant chemotherapy + KEYTRUDA, followed by adjuvant KEYTRUDA monotherapy and noted that the safety data reported in KEYNOTE-522 are consistent with the known AE profiles of each regimen (Figures 7A,B),[12] suggesting that the AEs seen in the neoadjuvant phase are more generally attributable to chemotherapy. The need for treatment de-escalation was re-emphasised, as well as the need for studies that explore the potential for chemotherapy de-escalation to reduce the risk of associated AEs.

Figure 7: KEYNOTE-522 results – safety summary[12]



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

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

Panel discussion:

Early-stage TNBC patient case discussion

Speaker: Mr Henry Cain, Consultant Breast Surgeon

Mr Cain led a panel discussion focusing on a real-patient case study. He explored differing treatment scenarios, providing insightful commentary on their potential effects on the patient's outcome.

Patient characteristics:

52 years of age

ECOG PS: 0

No family history of TNBC

1-month history of a lump in her left breast

Tumour characteristics:

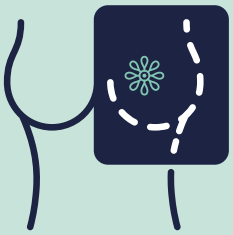
P5 2-cm lump in the upper outer quadrant

R5 28-mm lesion with a normal axillary breast ultrasound

Breast biopsy Grade 2 with no special type ductal cancer

ER-0, PR-0, HER2 negative

Conservable with oncoplastic technique



Polling questions:

Attendees were first asked which of the following approaches they would take to treat this patient:

- BCS and SNB
- Neo-adjuvant treatment

92% said they would treat this patient with neo-adjuvant treatment

Attendees were next asked if their treatment plan would change if the tumour was N1 on the axilla staging?

- BCS and SNB
- Neo-adjuvant treatment

96% said they would treat this patient with neo-adjuvant treatment

Finally, attendees were asked if their treatment would differ if the tumour was N0 and only 18 mm?

- BCS and SNB
- Neo-adjuvant treatment

33% said they would treat this patient with neo-adjuvant treatment

Before discussing the treatment approach taken for this patient, the panellists presented four hypothetical scenarios, with discussions about how each scenario might inform which treatment course is given to the patient.

MSD

Scenario 1:

- The patient had a therapeutic mammoplasty and SNB
- Results show a 25-mm TNBC tumour with all margins clear and SNB 0/1
- Treatment choice: Adjuvant chemotherapy and await test results
- HCPs must discuss what systemic treatment is available to this patient

Dr Phillips discussed Scenario 1 from an oncologist's perspective. Based on the tumour size (25 mm), they suggested referring the patient for neo-adjuvant treatment and administering dose-dense chemotherapy (without IO) in the adjuvant setting. As a surgeon, Mr Cain noted that since the patient was a surgical candidate, many surgeons would have chosen surgery as first-line treatment, skipping neo-adjuvant treatment. He outlined that this could have potentially impacted their outcomes, as they were denied the potential benefits of neo-adjuvant treatment

---

Scenario 2:

- The patient has a 35-mm Grade 2 TNBC tumour with medial margin involvement
- SNB 1/1 macro-metastases with embryonic stem cells >2 mm

Questions regarding treatment options:

- Should the patient be offered further surgery now?
- Would this change if there was axilla involvement?
- Should *BRCA* mutation testing be considered?
- Should the patient be offered chemotherapy now and surgery later?
- Would post-mastectomy radiotherapy be an appropriate option?

Mr McIntosh discussed Scenario 2, which was considered the most severe out of the four presented scenarios. He emphasised the need for both surgery and chemotherapy; however, there is no guideline-recommended order for surgery and chemotherapy. In this scenario, as surgery was chosen as the patient's first-line treatment, they were unable to receive the potential benefits of neo-adjuvant treatment plus IO. The patient ended up requiring additional surgery, which could potentially have been avoided if neo-adjuvant treatment had been used.

Scenario 3:

- Which neo-adjuvant treatment regimen should be given to the patient?
- The patient has a hereditary *BRCA2* mutation
- Post-neo-adjuvant treatment, the patient underwent a WLE and SNB, resulting in a pCR outcome in the breast and SNB 0/3 with no regression

Discussions around Scenario 3 highlighted how this strategy allowed for assessment of the genetic risk of developing future cancers, informing risk-reduction strategies based on both current disease and genetics. Additionally, pCR as a long-term prognostic marker informed the decision not to escalate surgery, based on predicted favourable clinical outcomes.

Scenario 4:

- The patient is given neo-adjuvant treatment
- The patient has a hereditary *BRCA2* mutation
- WLE and SNB show 10 mm of scattered residual Grade 3 TNBC, 0/3 node, but fibrosis and regression in one node

Discussion:

- Should further axillary treatment be considered?
- Should further systemic treatment be considered?
- Would risk-reducing surgery be beneficial?

Scenario 4 highlights a situation in which residual disease was detected in the patient. This scenario reinforces Mr Cain's previous summary of the need for neo-adjuvant treatment, by demonstrating responses to first-line neo-adjuvant plus IO treatment, as well as valuable insights into the tumour biology. This in turn can allow for early diagnosis of residual disease, as well as a more response-directed adjuvant treatment approach. Additionally, this approach can expand the range of available agents and clinical trial enrolment options, which the patient would have been ineligible for based on their baseline characteristics. Trials this patient would now be eligible for following neo-adjuvant treatment could include the OlympiA trial, due to high-risk and *BRCA2* gene mutation status.

Outcome:

Ultimately, scenario 3 was considered the preferred course of action. He emphasised that despite their eligibility for surgery as first-line treatment, neo-adjuvant treatment plus IO played a crucial role in their predicted prognostic outcomes from the index cancer.

Abbreviations:
ABS, Association of Breast Surgery; AE, adverse event; BCS, breast-conserving surgery; CI, confidence interval; CPS, combined positive score; ECOG PS, Eastern Cooperative Group performance status; EFS, event-free survival; ER, oestrogen receptor; HCP, healthcare professional; HER2, human epidermal growth factor-2; HR, hazard ratio; IO, immunotherapy; ITT, intention-to-treat; MDT, multidisciplinary team; OS, overall survival; pCR, pathologic complete response; PD-L1, programmed death ligand-1; PR, progestrone receptor; QW, every week; Q3W, every 3 weeks; R, randomisation; SLNB, sentinel lymph node biopsy; SNB; sentinel node biopsy; TNBC, triple-negative breast cancer; TRAE, treatment-related adverse event; WLE, wide local excision.

References:

1. KEYTRUDA SmPC. www.medicines.org.uk/emc/product/2498/smpc (accessed August 2023).
2. Montagna G. Presented at the San Antonio Breast Cancer Symposium (SABCS) 2022, 6–10 December 2022. Abstract GS4-02.
3. Von Minckwitz G et al. *N Engl J Med* 2019;380:617–628.
4. NCCN Breast Cancer Guidelines. Version 4, 2023.
5. AGO Breast Cancer Guidelines. Version 1, 2022.
6. Cardoso F et al. *Ann Oncol* 2019;30:1194–1220.
7. Burstein HJ et al. *Ann Oncol* 2021;32:1216–1235.
8. Korde LA et al. *J Clin Oncol* 2021;39:1485–1505.
9. Volders JH et al. *Breast Cancer Res Treat* 2018;168:1–12.
10. Marcus DM et al. *Front Oncol* 2013;3:317.
11. Cortazar P et al. *Lancet* 2014;384:164–172.
12. Schmid P et al. *N Engl J Med* 2020;382:810–821 (plus supplementary appendix).
13. Schmid P et al. *N Engl J Med* 2022;386:556–567 (plus supplementary appendix).
14. Schmid P et al. Presented at the San Antonio Breast Cancer Symposium (SABCS) 2019, 10–14 December 2019. Abstract GS3-03.
15. Schmid P et al. Presented at the San Antonio Breast Cancer Symposium (SABCS) 2021, 7–10 December 2021. Abstract GS1-01.