Tossicità da immunoterapia in neoadiuvante: i dati real world

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Declaration of Interests

Emilia Montagna

Institutional financial interests with commercial entities:

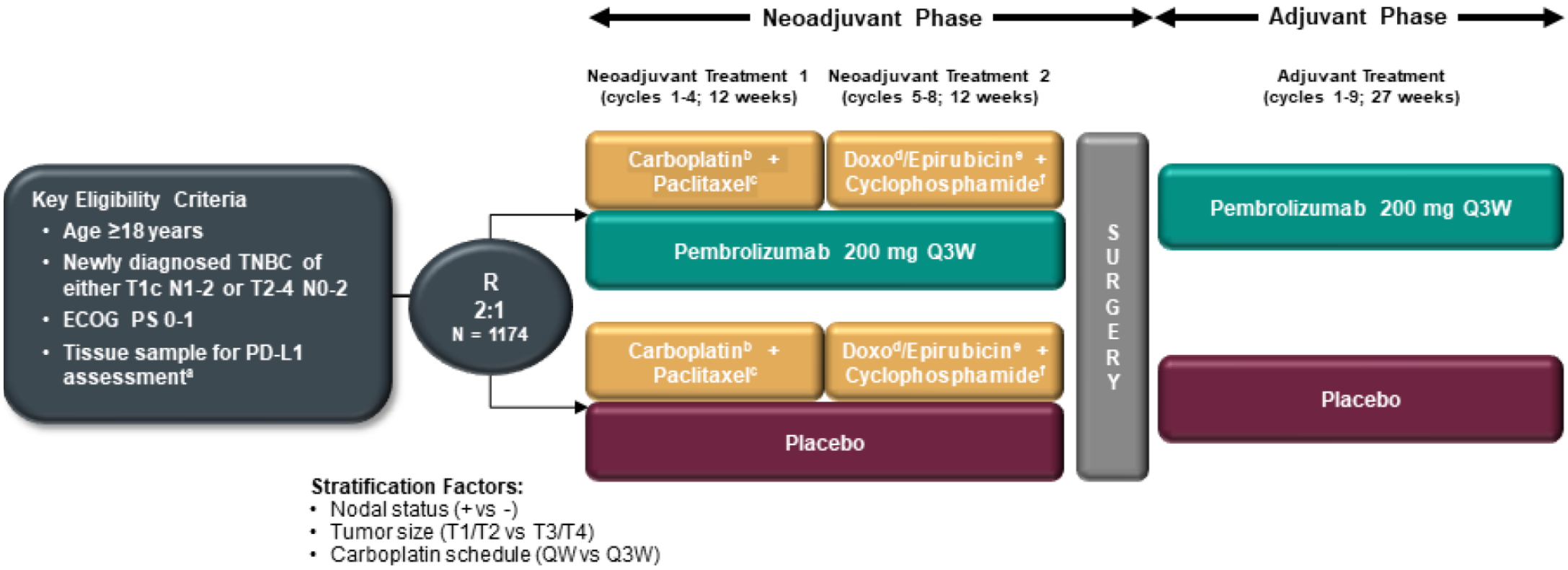
- Novartis
- Pierre fabre

- **No personal financial interests with any commercial entity**

Agenda

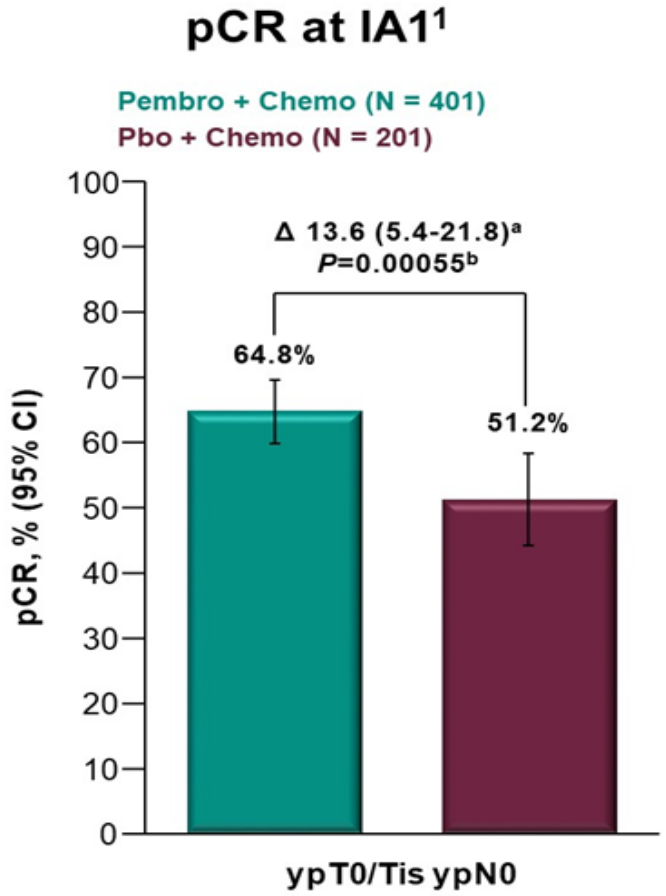
- Dati di efficacia della immunoterapia nella terapia neoadiuvante nel tumore mammario triplo negativo

KEYNOTE 522 – Study DESIGN



No T1a-T1b; No T1cN0; No T4d (inflammatory)

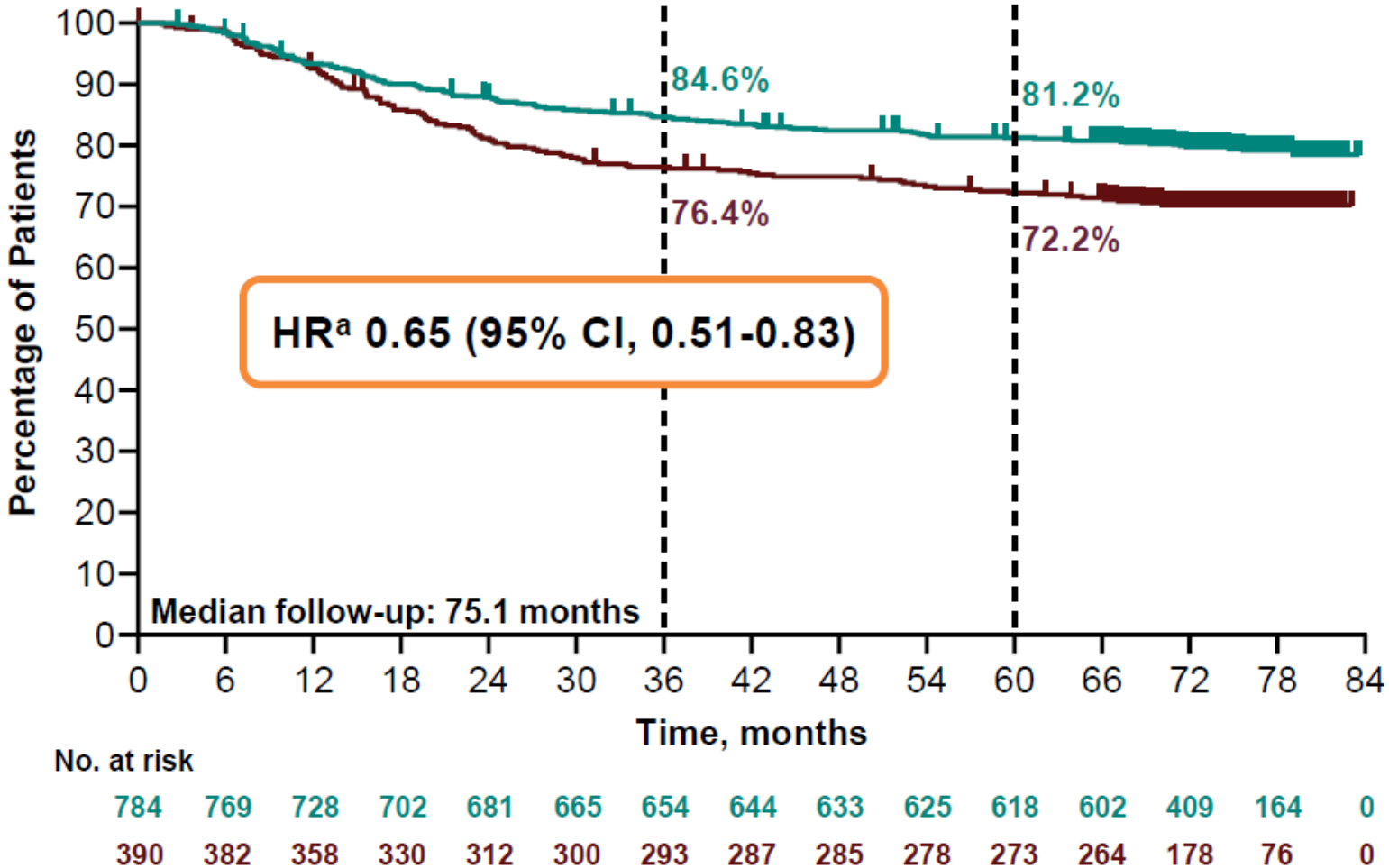
Primary Analyses of KEYNOTE-522



Neoadjuvant chemo plus pembrolizumab resulted in a significantlly and clinically meaningful increase in pCR of 13,6 percentage points

1. Schmid P, et al. *N Engl J Med* 2020;382:810-21. 2. Schmid P, et al. *N Engl J Med* 2022;386:556-67. [a]Estimated treatment difference based on Miettinen & Nurminen method stratified by randomization stratification factors. [b]Prespecified *P*-value boundary for significance of 0.003 was crossed; data cutoff date: September 24, 2018. [c]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [d]Prespecified *P*-value boundary of 0.00517 was crossed. [e]Defined as the time from randomization to the data cutoff date of March 23, 2021.

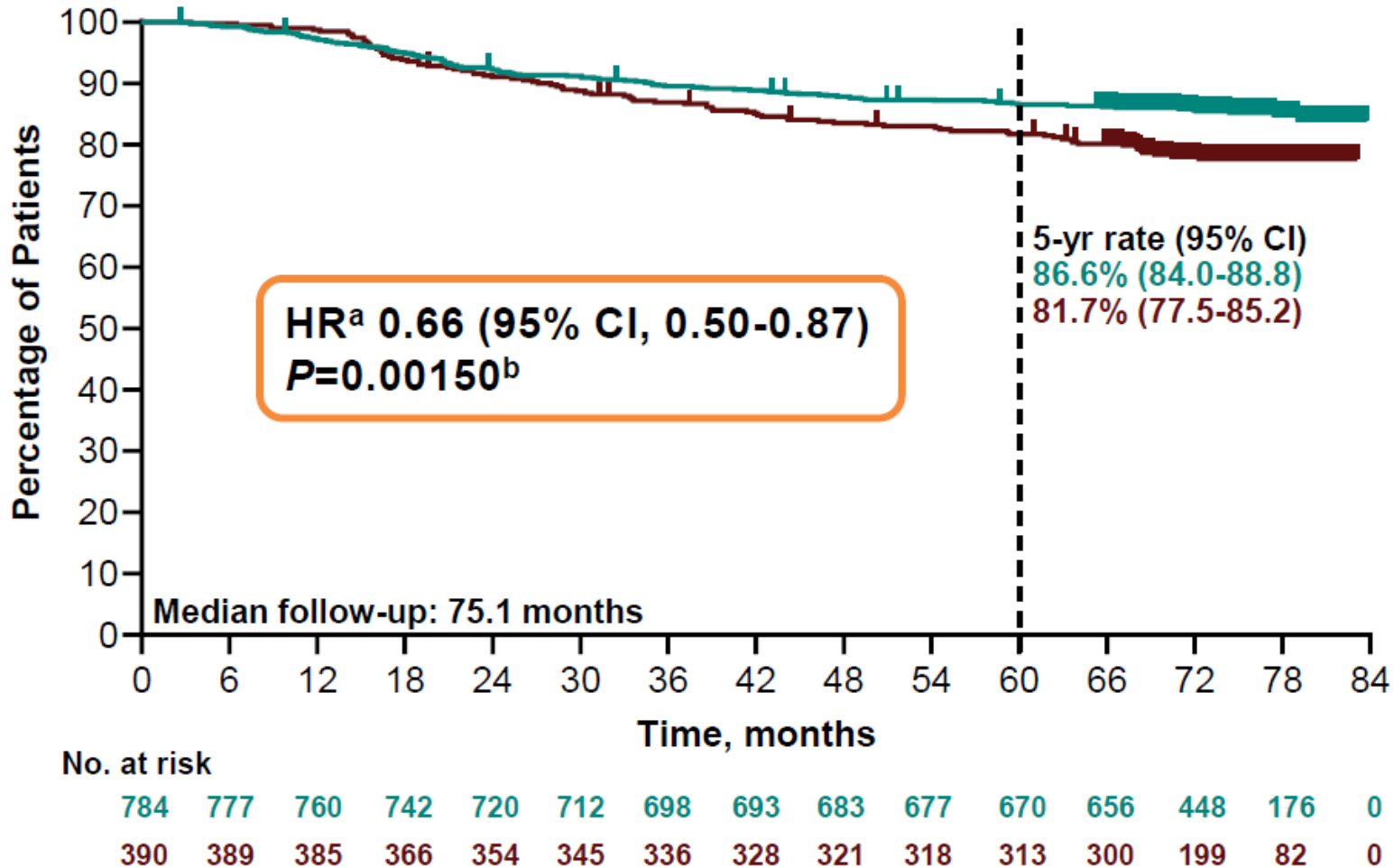
Updated Event-Free Survival



	Pts w/ Event
Pembro + Chemo/Pembro	20.3%
Placebo + Chemo/Placebo	29.2%

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff date: March 22, 2024.

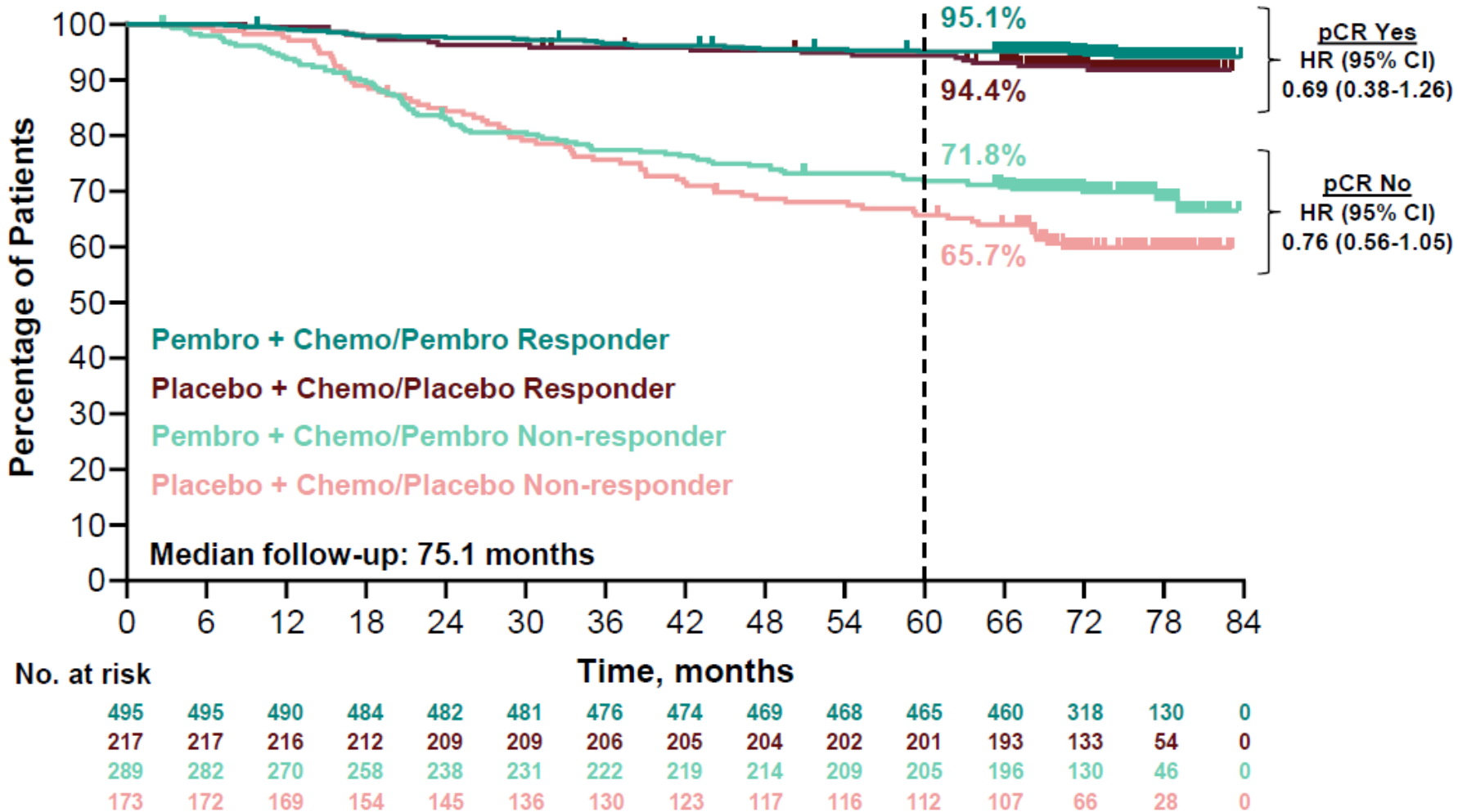
Key Secondary Endpoint: Overall Survival



	Pts w/ Event
Pembro + Chemo/Pembro	14.7%
Placebo + Chemo/Placebo	21.8%

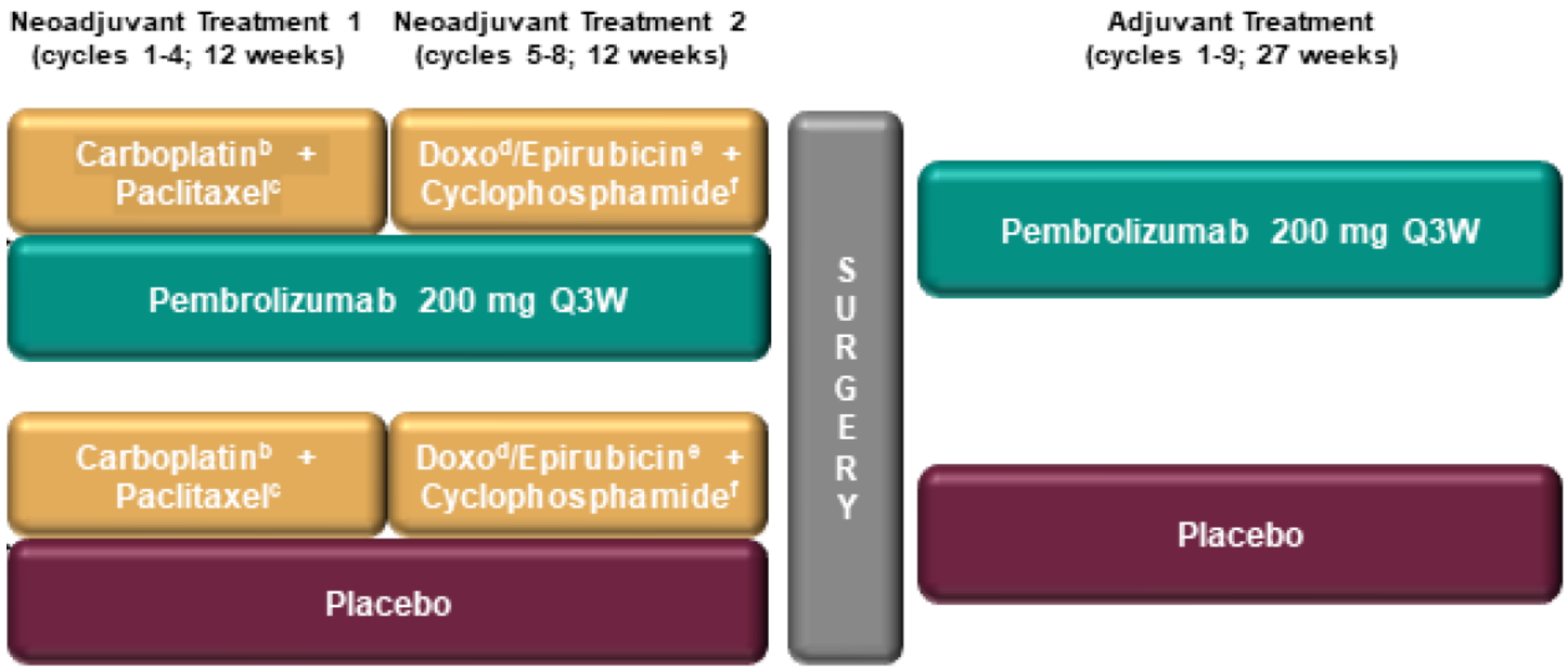
[a]The unstratified piecewise HR was 0.87 (95% CI, 0.57-1.32) before the 2-year follow-up and 0.51 (95% CI, 0.35-0.75) afterwards. The weighted average HR with weights of number of events before and after 2-year follow-up was 0.66. With 200 events (67.3% information fraction), the observed *P*-value crossed the prespecified nominal boundary of 0.00503 (1-sided) at this interim analysis. Data cutoff date: March 22, 2024.

Overall Survival by Pathologic Complete Response (yp T0/Tis ypN0)



This is a non-randomized subgroup analysis based on the post-treatment outcome of pCR and HRs should therefore be interpreted with caution. Data cutoff date: March 22, 2024.

- **These results provide further support for pembro plus platinum-containing neoadjuvant chemo followed by adjuvant pembro after surgery, regardless of the pCR outcome, as a standard-of-care treatment regimen for patients with high-risk, early-stage TNBC**



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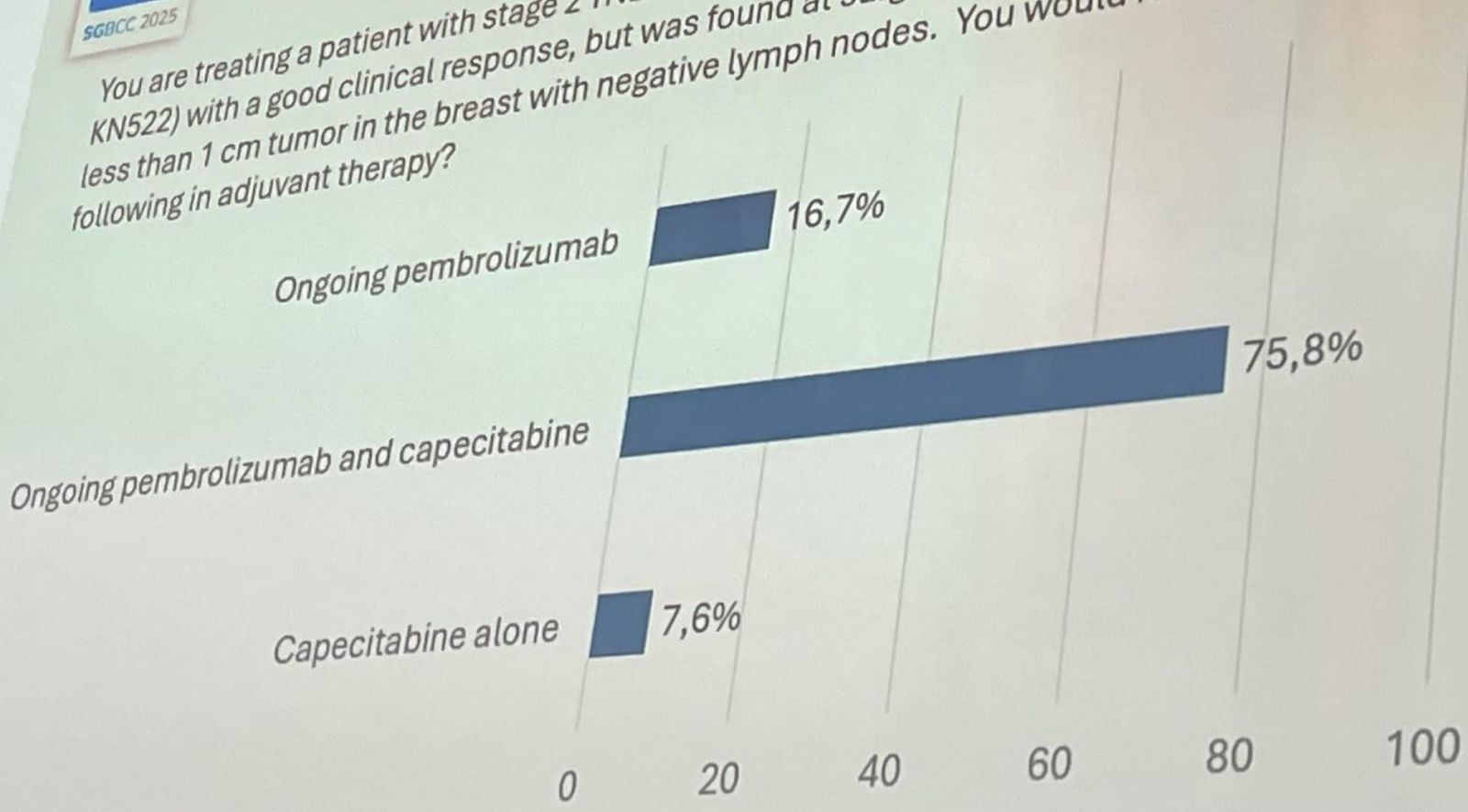
12 – 15 March 2025, Vienna / Austria

SGBCC 2025

You are treating a patient with stage 2 TNBC. She received neoadjuvant TCb/AC/pembrolizumab (ala KN522) with a good clinical response, but was found at surgery to have residual disease constituting less than 1 cm tumor in the breast with negative lymph nodes. You would recommend which of the following in adjuvant therapy?



Total votes: 66

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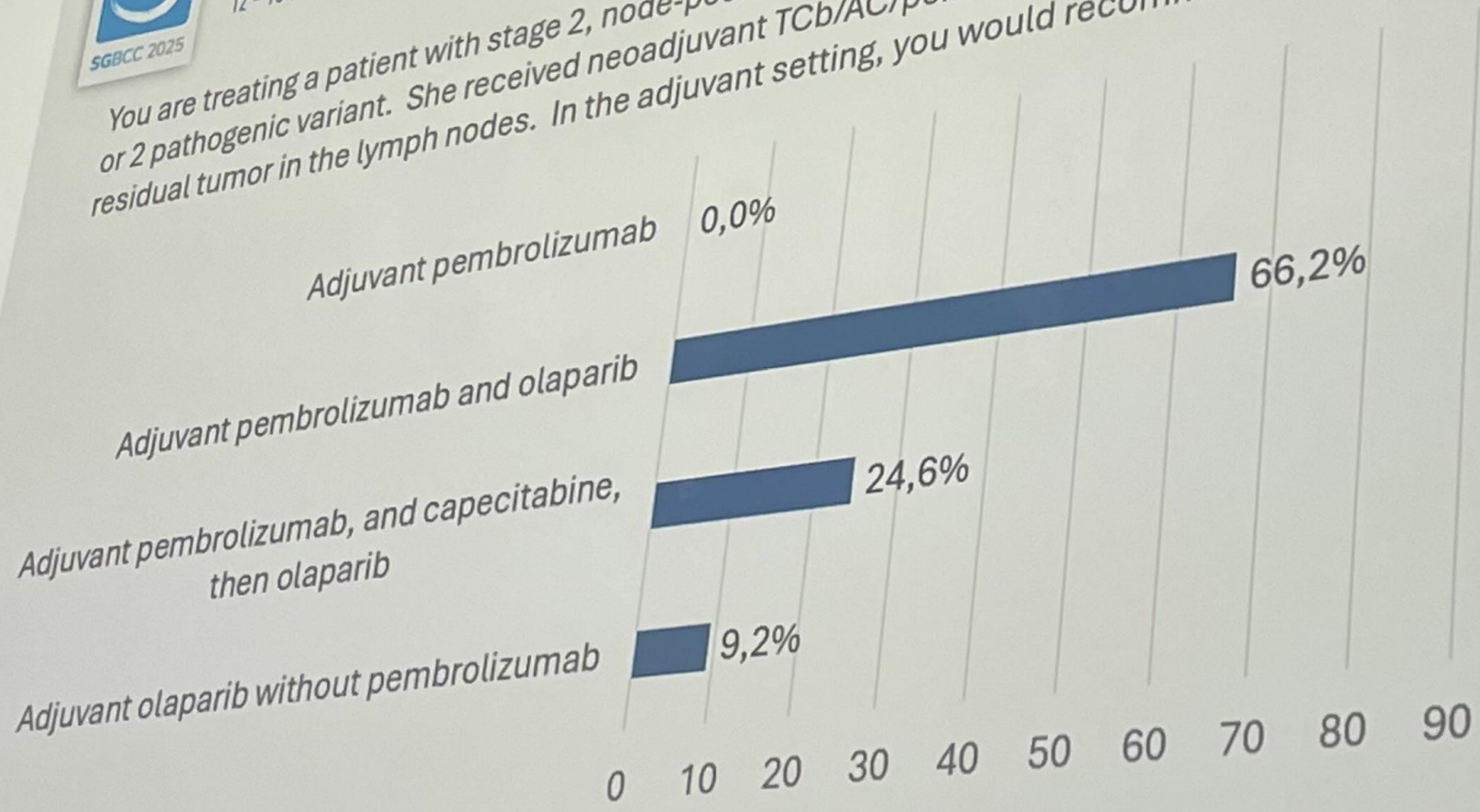
SGBCC 2025

You are treating a patient with stage 2, node-positive TNBC. She additionally has a deleterious BRCA1 or 2 pathogenic variant. She received neoadjuvant TCb/AC/pembrolizumab (ala KN522), and had residual tumor in the lymph nodes. In the adjuvant setting, you would recommend:



68

tal votes: 65

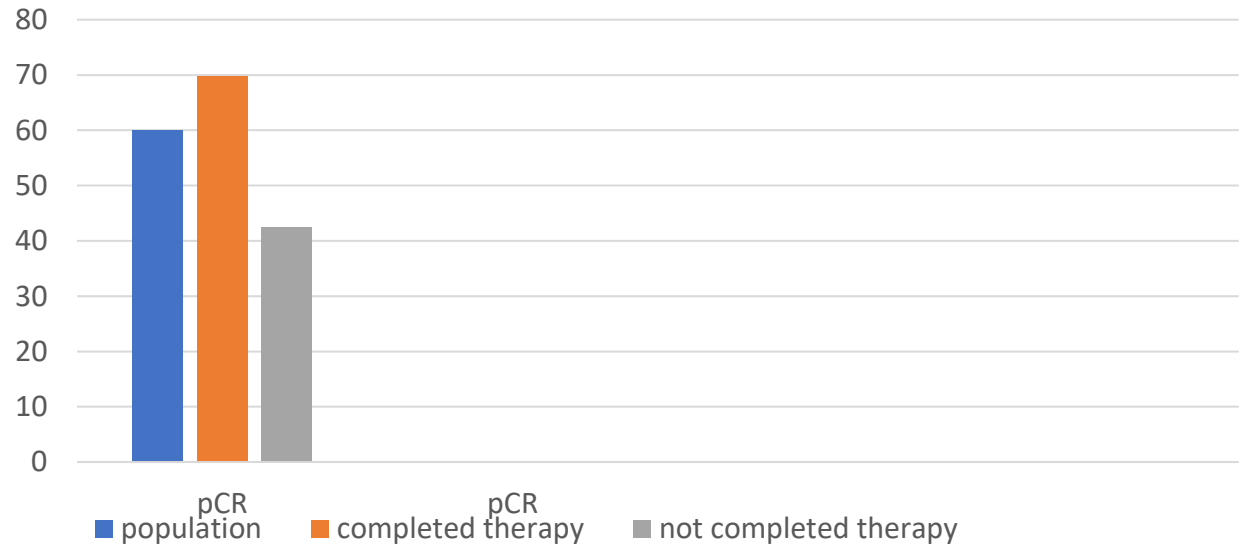
Studi retrospettivi di real world sull'efficacia dell'immunoterapia in neoadiuvante

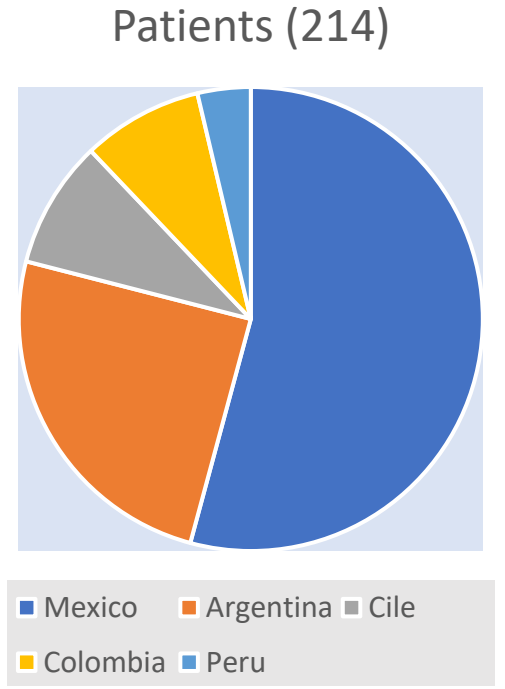
Studio	Numero pazienti	%di pCR
Botticelli A (multicentrico TIGER)	121	60
Rached	100	58
Hofherr et al	100	54,5
Wood et al	76	48,4
Krishnan J (multicentrico)	153	64,7
Deng* (multicentrico)	63	34,9
Karci E (multicentrico)	108	63,9

* pembrolizumab orcamrelizumab or anti-PD-L1 antibody (atezolizumab)

Real world data in Hispano-American women (PETRHA)

- Approximately 10% of the participants in the KEYNOTE- 522 trial were Hispanic or Latino
- Neoadjuvant pembrolizumab was administered 200 mg q3w in 83.7% and 400 mg q6w in 16.3% of patients





- Disparities in access to pembrolizumab therapy were reflected as women with private insurance were more likely to complete pembrolizumab compared to those in public or governmental settings.
- A significantly lower pCR rate among women who did not complete the planned number of pembrolizumab cycles, underscoring the importance of treatment adherence

BARCELONA 2024 ESMO congress

PROMENADE: PembROlizuMab for early ER-low/HER2- breast caNcer, reAlworlD frEnch cohort

F. Cherifi[1], L. Cabel[2], C. Bousrih[3], E. Volant[4], F. Dalenc[5], B. Mery[6], M. Auvray Kuentz[7], M. Alexandre[8], L. Benistant[9], M. Leheurteur[10], C. Bailleux[11], M. Debled[12], J-S. Frenel[13], D. Loirat[2], F.C. Bidard[2], S. Aho[14], A. Glenet[15], J.T.L. Ribeiro Mourato[3], F. Christy[16], G. Emile[1]

[1]Breast Cancer Unit, Centre Francois Baclesse, Caen, CEDEX 4, France [2]Medical Oncology, Institut Curie, Paris, CEDEX 14, France, [3]Breast unit, Gustave Roussy - Cancer Campus, Villejuif, France [4]Oncology, Cancéropôle Grand Ouest - CHU Nantes Immeuble Deurbroucq, Nantes, France, [5]Medical oncology, Oncopole Claudius Regaud- IUCT, Toulouse, France, [6]Oncology, Center Leon Berard, Lyon, France, [7] Oncology Center Eugène Marquis, Rennes, France, [8]Medical Oncology, ICM - Institut du Cancer de Montpellier, Montpellier, France, [9]Oncology, ICANS - Institut de Cancérologie Strasbourg Europe, Strasbourg, France, [10]Oncology, Centre Henri Becquerel, Rouen, CEDEX 1, France, [11]Oncology, Centre Anticancer Antoine Lacassagne, Nice, France, [12]Institute Bergonié - Centre Régional de Lutte Contre le Cancer Bordeaux,France [13]Medical Oncology Department, ICO Institut de Cancerologie de l'Ouest René Gauducheau, Saint-Herblain,France, [14]Institut de Cancérologie de Lorraine, Nancy, France [15]Oncology, IUCT Oncopole, Toulouse, France, [16]Clinical Research, Centre Francois Baclesse, Caen, Cedex, France,

METHODS

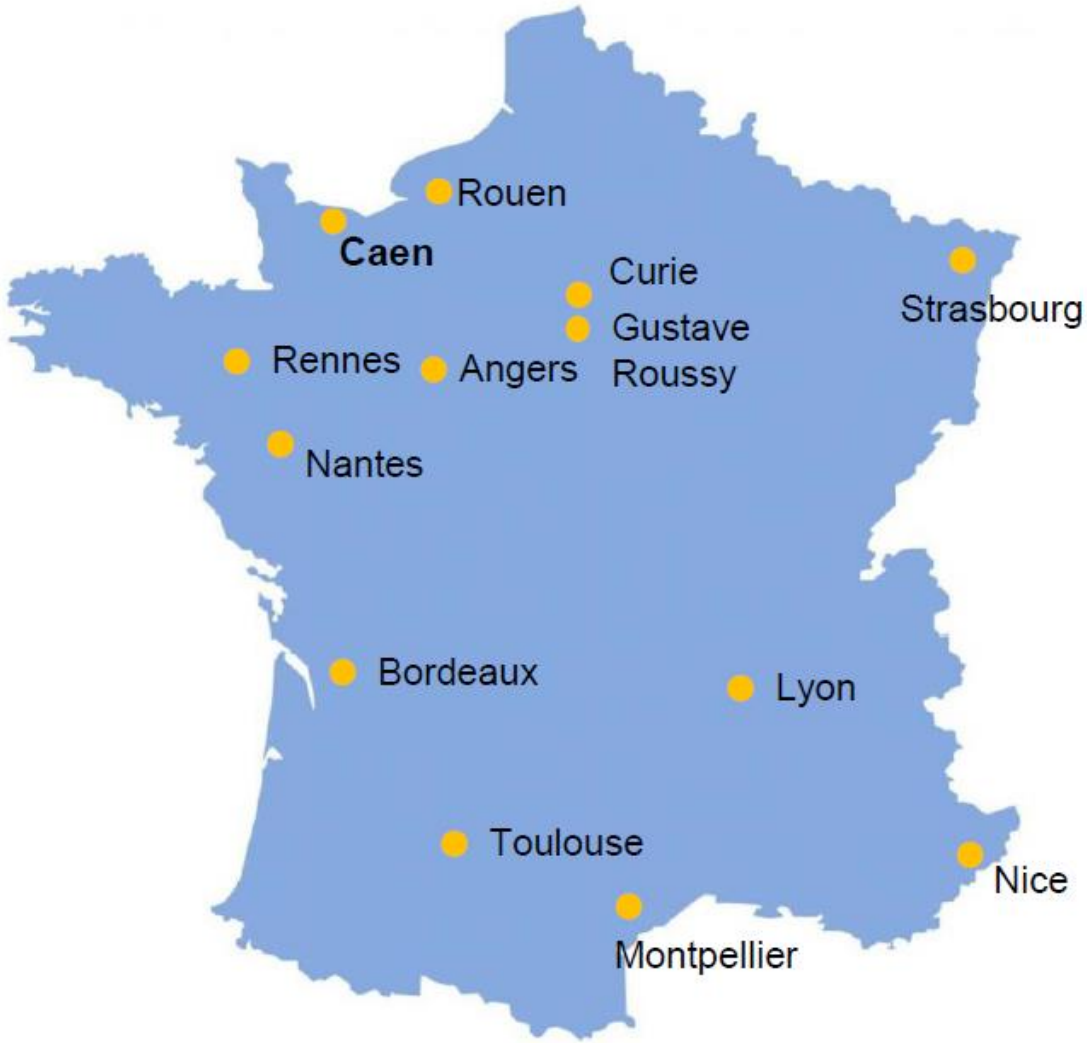
Retrospective real-life study

12 Comprehensive Cancer Centers in 13 cities in France

Inclusion Criteria:

- All patients receiving KEYNOTE 522 regimen
- Since its availability in march 2022
- Estrogen and/or progesterone receptor low **(1-9%)**
- HER2 negative (0, 1+, 2+ ISH neg)

Primary Objective: pCR (ypT0/isN0 or RCB 0) rate



RESULTS

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General characteristics

Number of patients	**114**
Age - Median (min-max)	49 (26-80)
Missing	*2 (1.8%)*
Menopausal status - n (%)	
Pre	64 (57%)
Post	48 (43%)
Missing	*2 (1.8%)*
Tumor size - n (%)	
<T2	12 (11%)
≥T2	102 (89%)
Node - n (%)	
N0	58 (51%)
N ≥1	56 (49%)

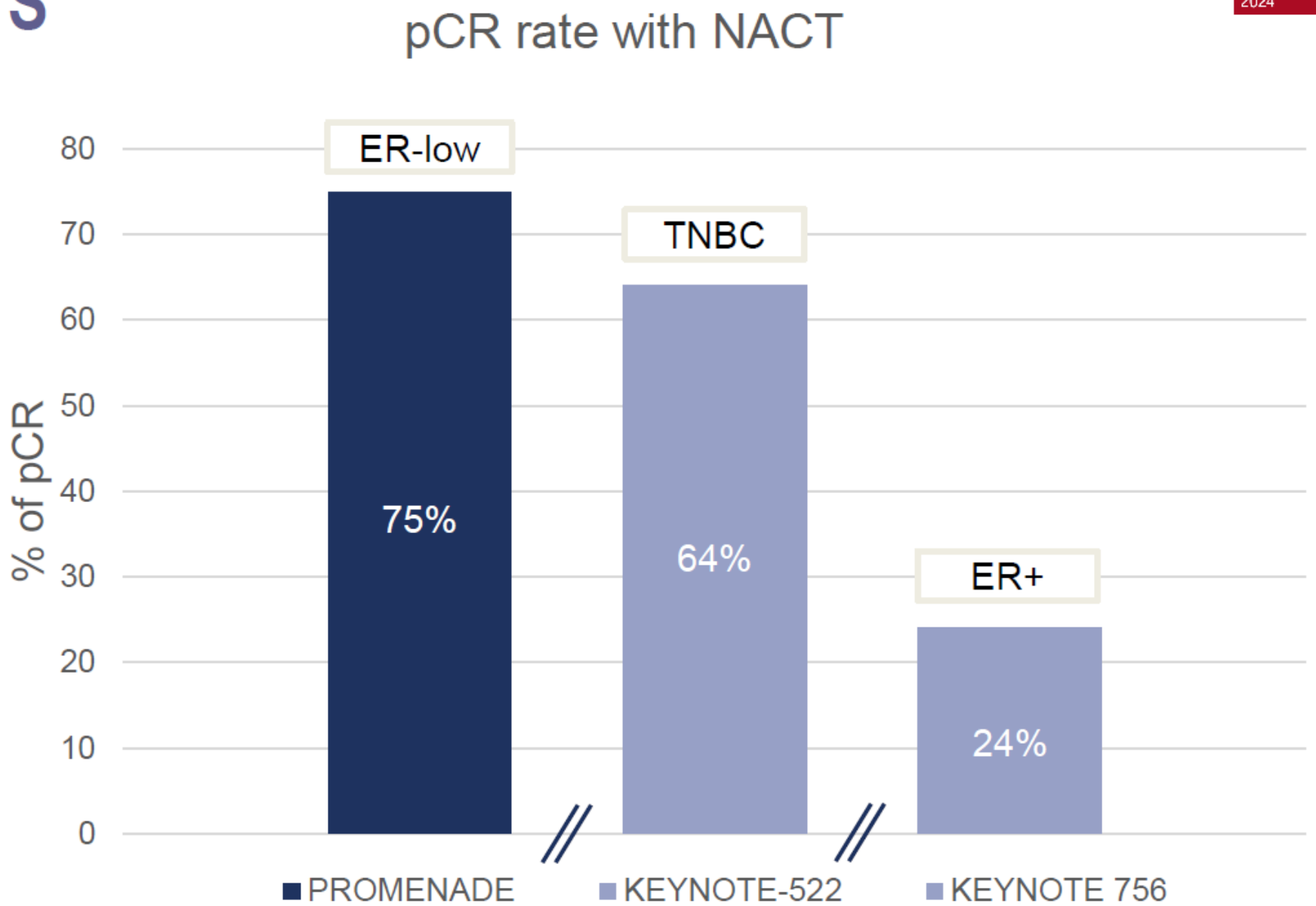
Pathology

Histology - n (%)	
Ductal	102 (90%)
Lobular	2 (2%)
Other	9 (8%)
Missing	*1 (0.9%)*
SBR grade - n (%)	
II	15 (14%)
III	95 (86%)
Missing	*4 (3.5%)*
KI67 - Mean (SD)	61 (24)
Missing	*15 (13.2%)*
Endocrine receptors - n (%)	
ER-/PR+	37 (32%)
ER+/PR-	66 (58%)
ER+/PR+	11 (10%)
HER2 – n (%)	
0	57 (50%)
1	35 (31%)
2 (ISH neg)	22 (19%)

Treatment

NACT* completed- n (%)	83 (75%)
Missing	*4 (3.5%)*
Surgery - n (%)	113 (99%)
Surgery type - n (%)	
Lumpectomy	62 (54.3%)
Mastectomy	50 (44%)
Not done (PD)	1 (0.8%)
Other	1 (0.8%)
Nodal intervention - n (%)	
Sentinel lymph node	57 (50%)
Axillary dissection	54 (47%)
Not done (PD)	1 (0.8%)
Other	2 (1.7%)

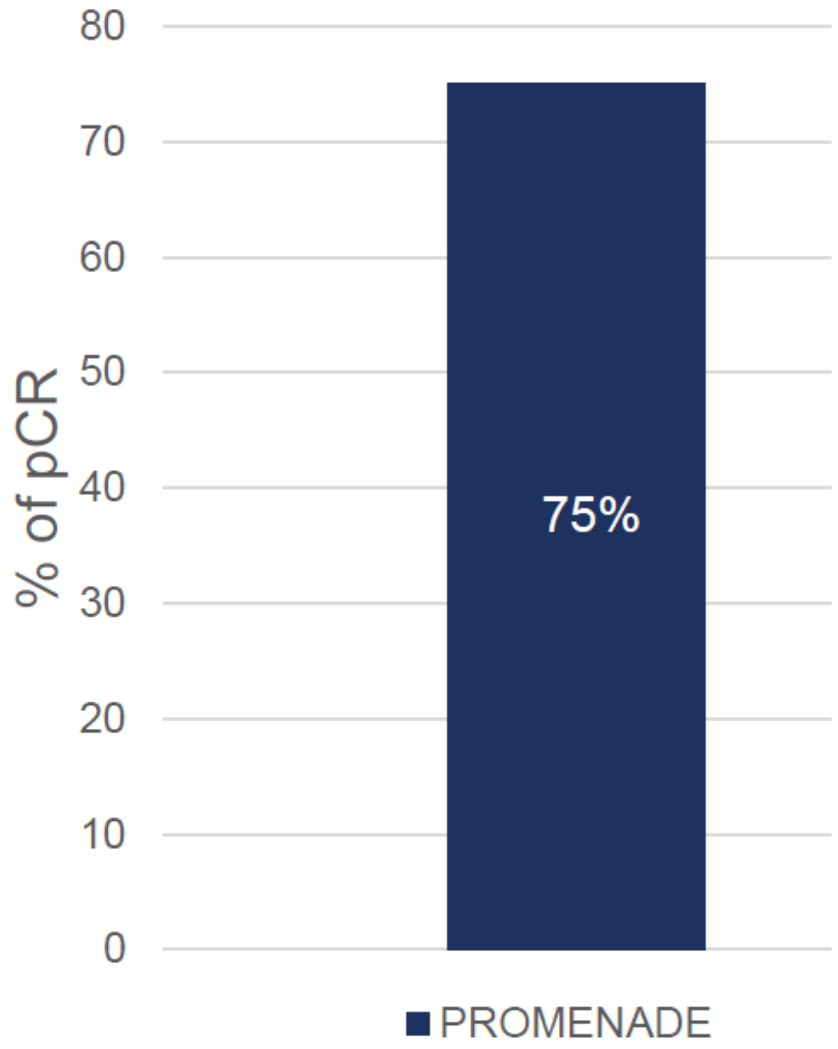
RESULTS



Data are not intended to be directly comparative

RESULTS

pCR rate with KEYNOTE-522 regimen in ER-low BC



RCB	n (%)
0	85 (75 %)
1	9 (8 %)
2	12 (11 %)
3	7 (6 %)
Progressive disease	1 (1 %)

TAKE HOME MESSAGE

- Tumors with ER-low status have:
  - A high rate of pCR after KEYNOTE 522 regimen
  - Respond differently than ER-positive and more like Triple-negative BC

- KEYNOTE 522 regimen seems to be useful for this population

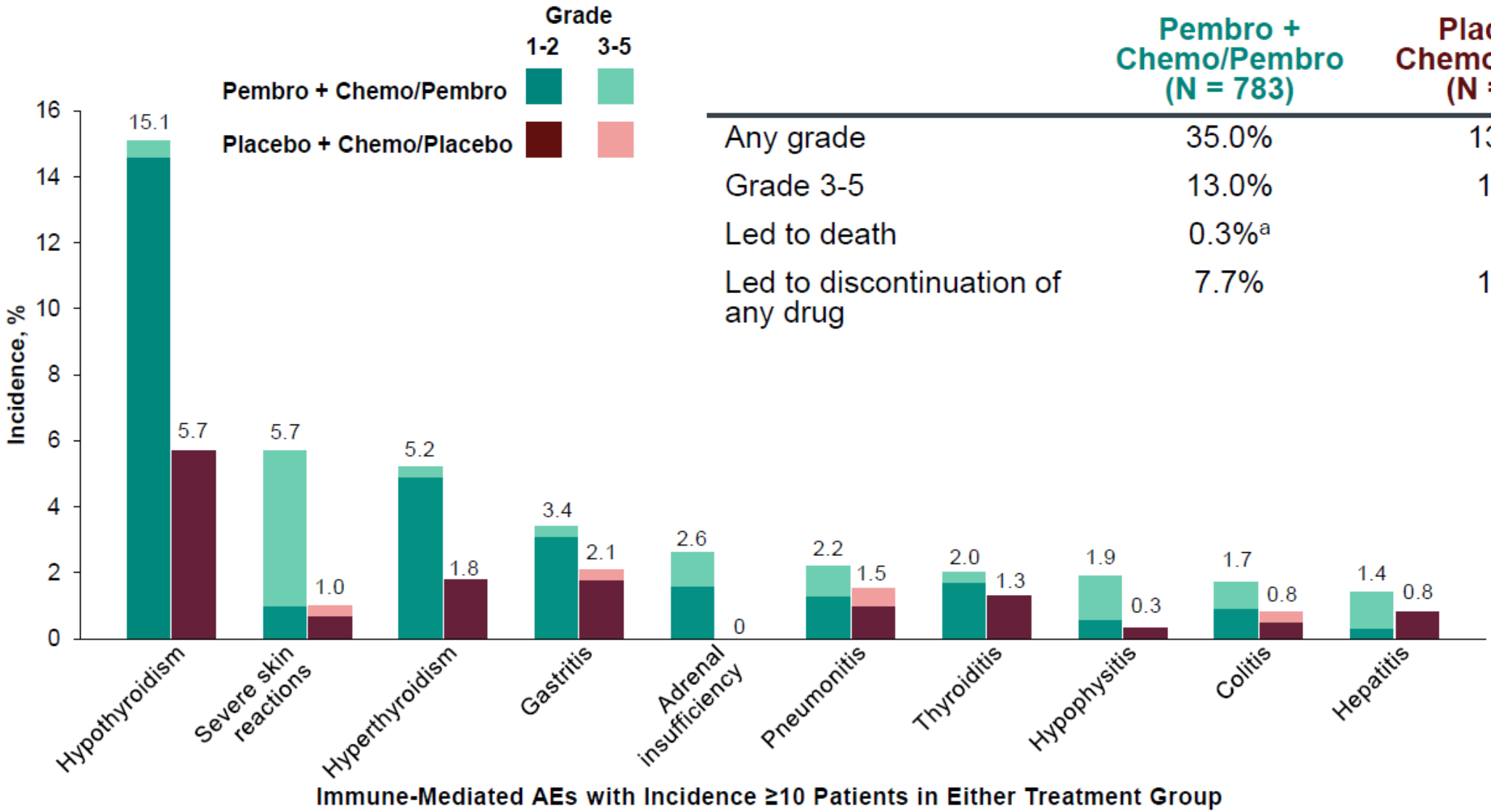
→ What is the best treatment in the adjuvant setting ?

Agenda

- Dati di efficacia della immunoterapia nella terapia neoadiuvante nel tumore mammario triplo negativo

- Dati di tossicità

Immune-Mediated Adverse Events



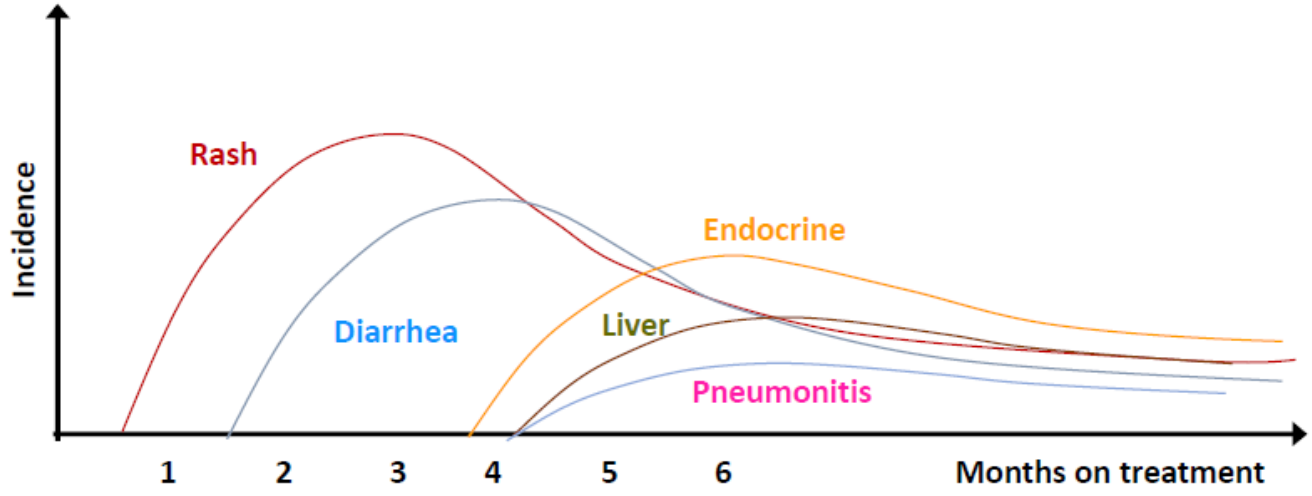
	Pembro + Chemo/Pembro (N = 783)	Placebo + Chemo/Placebo (N = 389)
Any grade	35.0%	13.1%
Grade 3-5	13.0%	1.5%
Led to death	0.3%[a]	0
Led to discontinuation of any drug	7.7%	1.0%

Immune-Mediated AEs with Incidence ≥10 Patients in Either Treatment Group

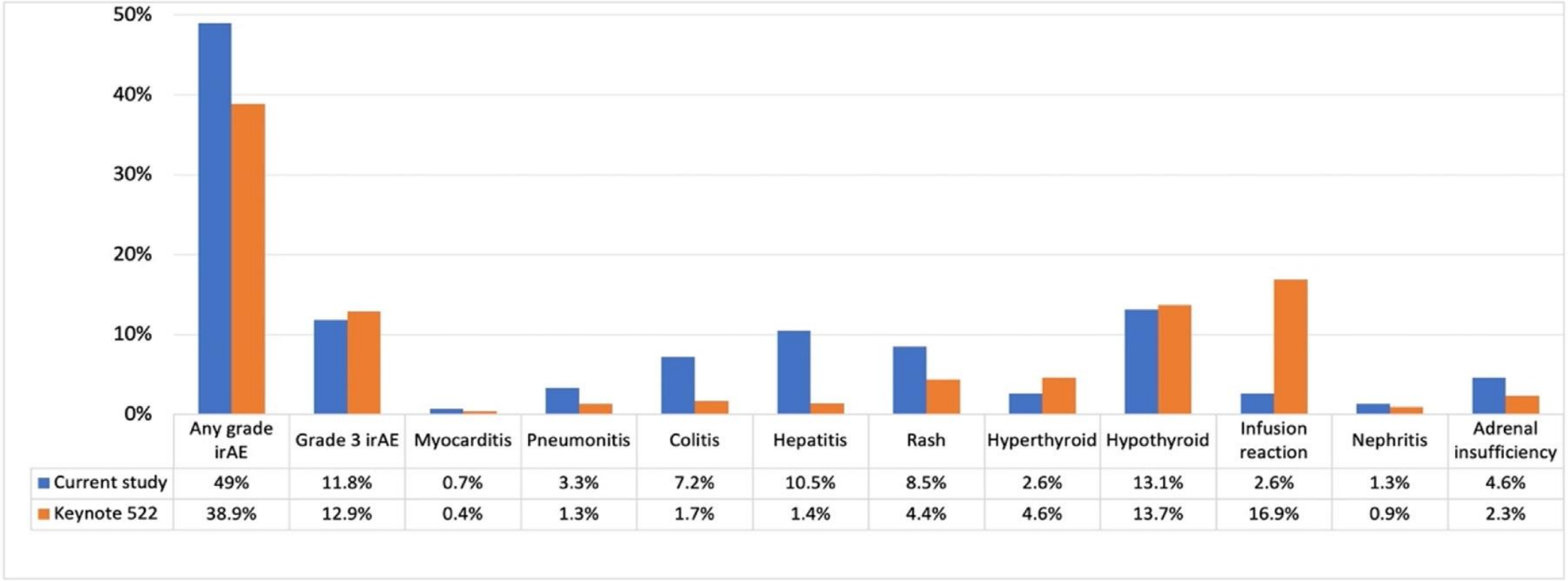
[a]1 patient from pneumonitis and 1 patient from autoimmune encephalitis. Considered regardless of attribution to treatment or immune relatedness by the investigator. Related terms included in addition to preferred terms listed.
Data cutoff date: March 22, 2024.

Toxicities With Immune Checkpoint Inhibitors

- Timing can be highly variable
- irAE can occur months or even a year after the end of treatment
- Time course might be even more variable with novel combinations



Real world data of toxicity



	Any grade irAE	Grade 3 irAE	Myocarditis	Pneumonitis	Colitis	Hepatitis	Rash	Hyperthyroid	Hypothyroid	Infusion reaction	Nephritis	Adrenal insufficiency
Current study	49%	11.8%	0.7%	3.3%	7.2%	10.5%	8.5%	2.6%	13.1%	2.6%	1.3%	4.6%
Keynote 522	38.9%	12.9%	0.4%	1.3%	1.7%	1.4%	4.4%	4.6%	13.7%	16.9%	0.9%	2.3%

Table 4 Comparison of Treatment Discontinuation Rates During the Neoadjuvant Phase With the Keynote-522 Trial

Variable	Current Study ($n = 153$)	Keynote-522 ($n = 781$)
Any drug discontinuation	47 (30.7%)	182 (23.3%)
Chemotherapy discontinuation	33 (21.6%)	45 (5.7%)[27]
Pembrolizumab discontinuation	32 (20.9%)	105 (13.4%)

Krishnan J Clin breast cancer 2024

High-grade (grade 3-5) irAEs occurred in 30% of patients in the study of Rached

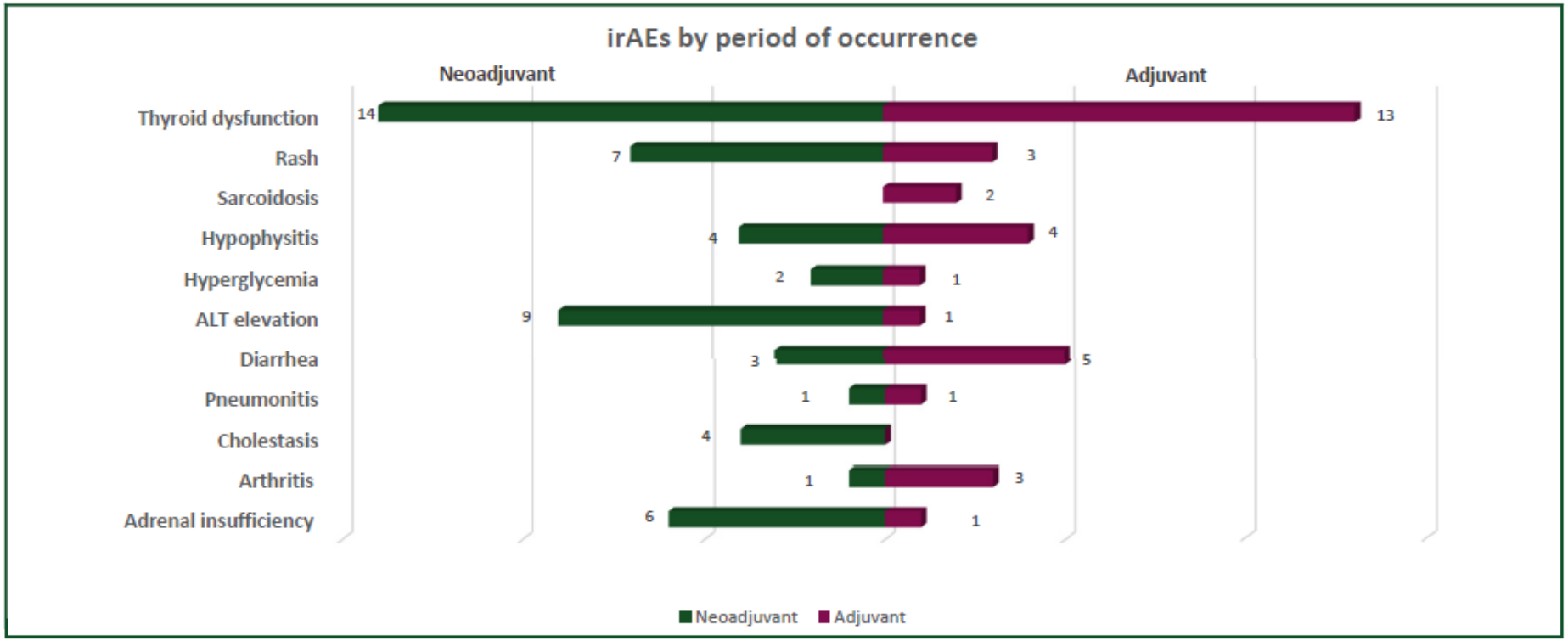


Figure 2. irAEs by period of occurrence. Comparison of irAEs occurring in two periods: the neoadjuvant period (left) and the adjuvant period (right). Numbers and bar sizes represent the count of these adverse events in each respective period.
ALT, alanine aminotransferase; irAEs, immune-related adverse events.

66% of irAEs during the neoadjuvant phase
34% during the adjuvant phase of treatment

ESMO Real World Data and Digital Oncology 2024

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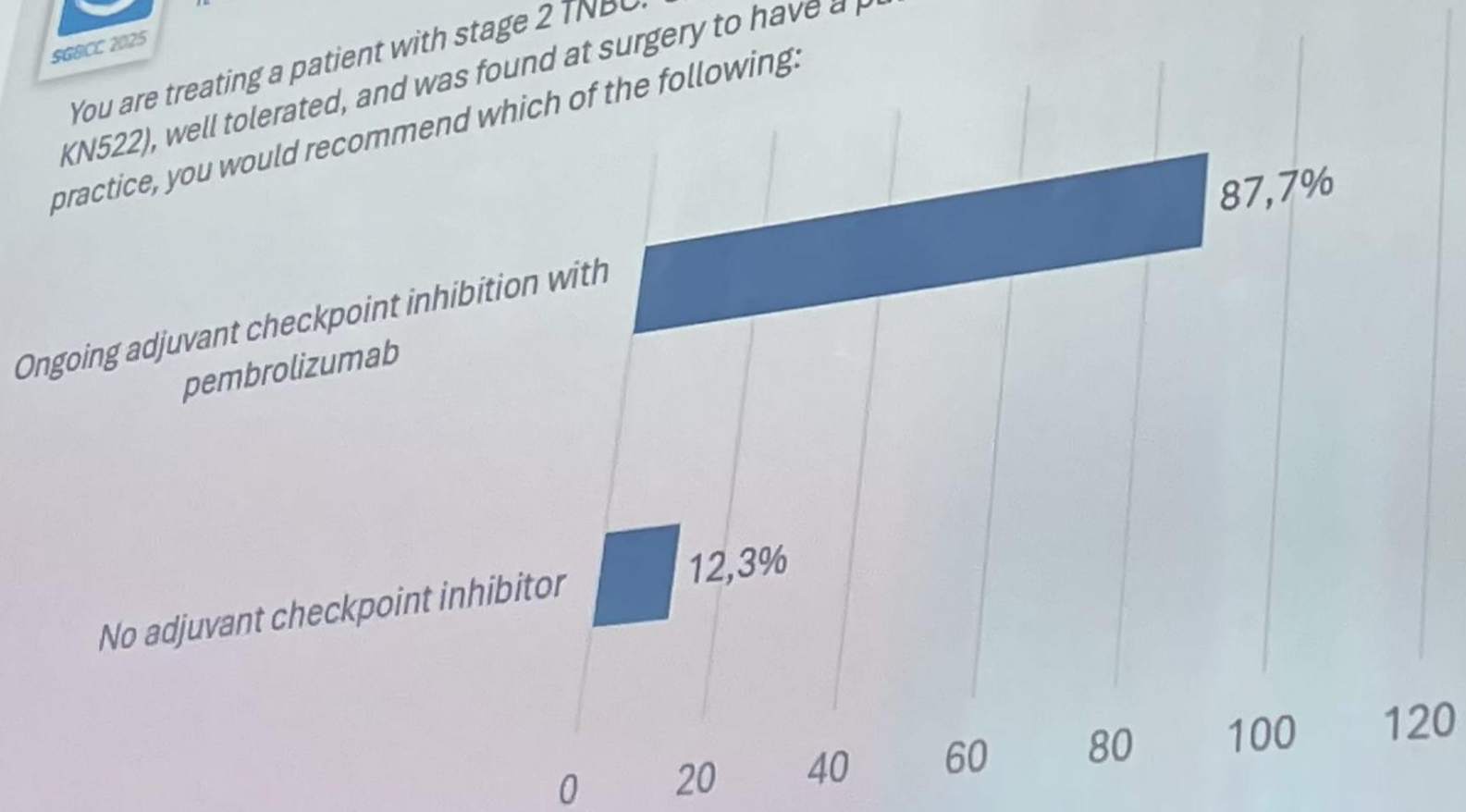
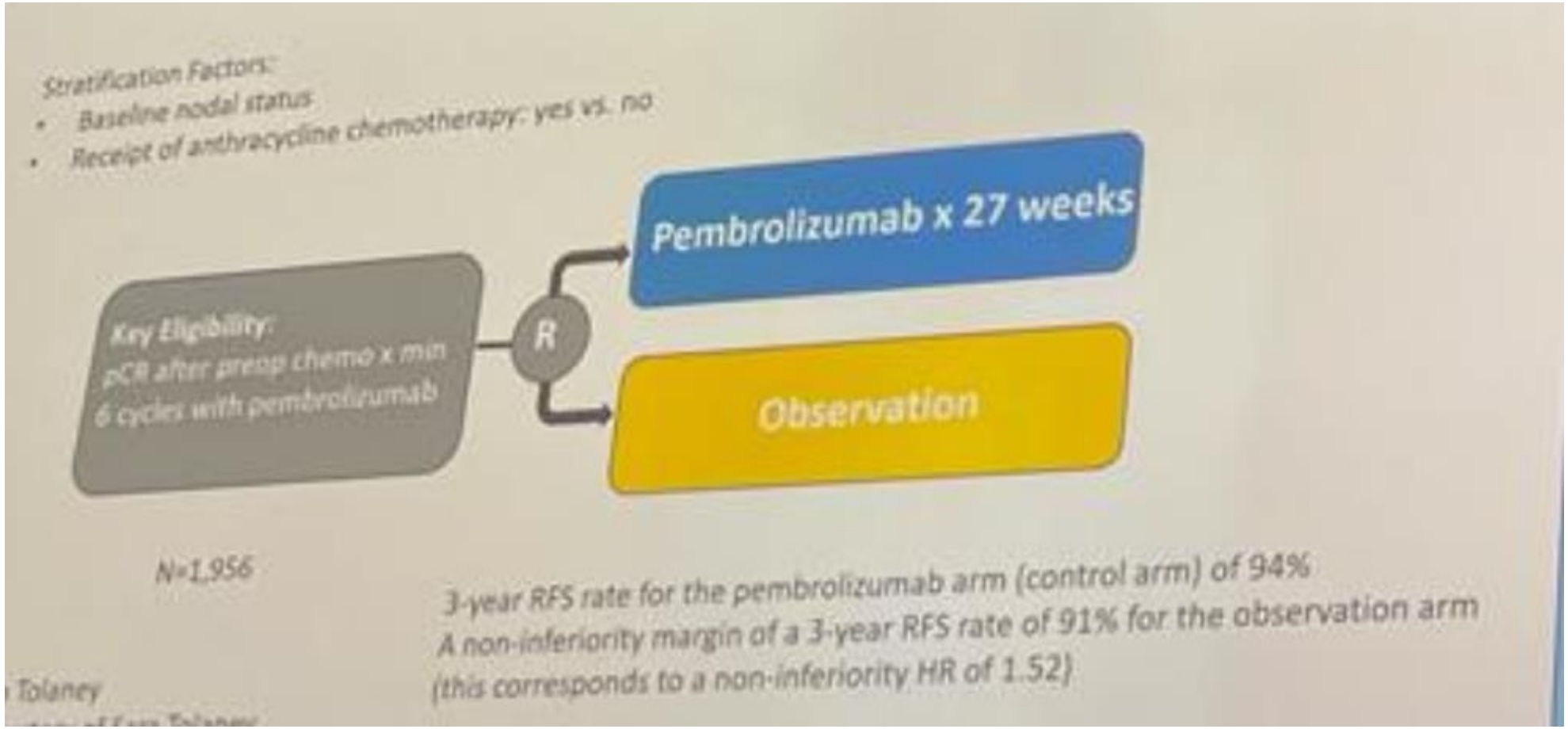
SGBCC 2025

You are treating a patient with stage 2 TNBC. She received neoadjuvant TCb/AC/pembrolizumab (a la KN522), well tolerated, and was found at surgery to have a pathological complete response. In routine practice, you would recommend which of the following:



Total votes: 65

OptimICE-PCR:
De-Escalation of Therapy in Early-Stage TNBC Patients Who Achieve pCR After Neoadjuvant Chemotherapy With Checkpoint Inhibitor Therapy



MDA Cancer center and and Lyndon B Johnson (233 patients)

- Grade≥ 3 irAE occurred in 26 instances
- The most common irAEs were endocrine (52%) followed by gastrointestinal (23%).
- Grade≥ 3 irAE occurred in 26 instances, with the most common being gastrointestinal (13 instances). A fatal irAE occurred in 2 pts where both were colitis
- In this real-world diverse population, was identified a similar rate and severity of irAEs as reported in the KEYNOTE-522 trial (as in the TIGER trial)

RWD: ADDRESSING GAPS IN GENERALIZABILITY

Clinical Trials represent only a proportion of real-world populations

Clinical Trials

Real World

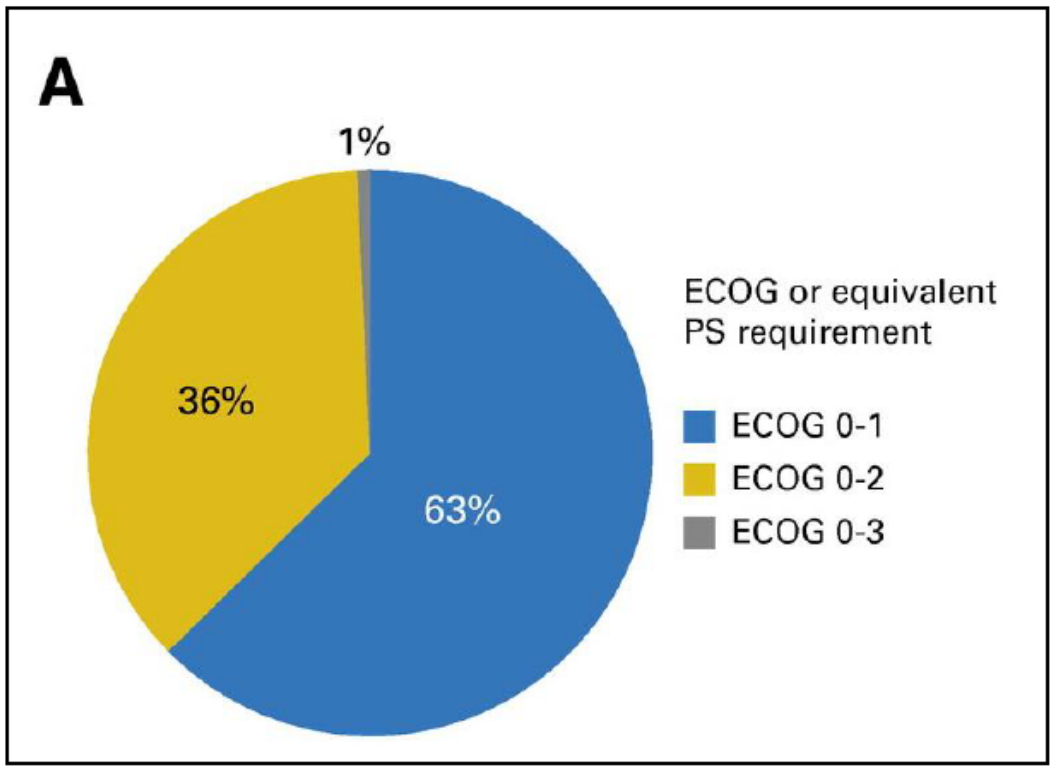
WHY IS RWE SO DIFFERENT FROM RCT

Table 2
Reasons for clinical trial ineligibility among patients in Alberta between 2004 and 2015 ($n = 125\ 316$)

Criteria for ineligibility	Number of patients (%)
Age > 75 years	30,661 (25%)
Presence of heart disease	10,996 (16%)
Kidney disease	6840 (5%)
Uncontrolled diabetes	5984 (5%)
Liver disease	4778 (4%)
Abnormal bloodwork	2339 (2%)
Prior malignancy	1872 (1%)
Any immunosuppression	1642 (1%)

= 38 % non-eligible for RCTs

Karim et al. Clin Oncol (R Coll Radiol). 2019 Sep;31(9):e160-e166.



Pazdur et al. J Clin Oncol. 2017 Nov 20;35(33):3745-3752.

→ Patients **often do not « match »** those included in RCTs

A TOXICITY GAP? CHALLENGES

INTUITIVELY

→ Patients who are frailer, older, and have more comorbidities tend to suffer more from side effects.

Capturing Adverse Events in RCTs

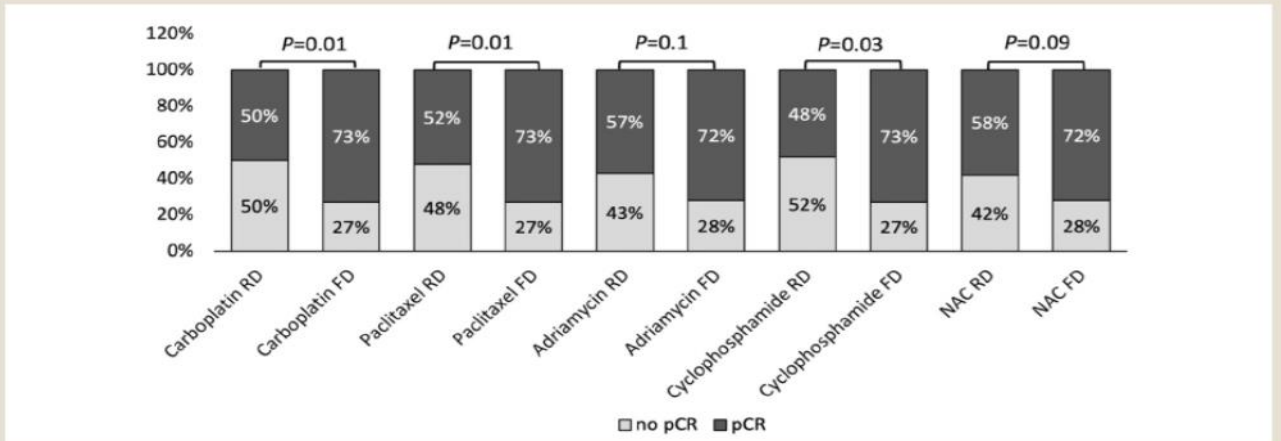
Capturing Adverse Events in the Real-World

La gestione della tossicità correlata al trattamento è fondamentale per garantire di completare la terapia pianificata e ottenere risultati ottimali

- L'interruzione precoce della chemioterapia neoadiuvante prima della settimana 12 è stata correlata a un tasso di pCR minore

Detrimental Impact of Chemotherapy Dose Reduction or Discontinuation

Figure 2 pCR rate by the relative dose intensity of chemotherapy. The number of patients who received reduced dose of carboplatin, paclitaxel, adriamycin and cyclophosphamide are 46, 56, 33 and 25, respectively. Of these patients, 23, 29, 19, and 12, achieved pCR, respectively. The number of patients who received full dose of carboplatin, paclitaxel, adriamycin and cyclophosphamide are 103, 93, 111 and 110, respectively. Of these patients, 75, 68, 81, and 81, achieved pCR, respectively.
Abbreviations: FD = full dose (100% RDI); NAC = neoadjuvant chemotherapy; pCR = pathologic complete response; RD = reduced dose (<100% RDI); RDI = relative dose intensity.



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Agenda

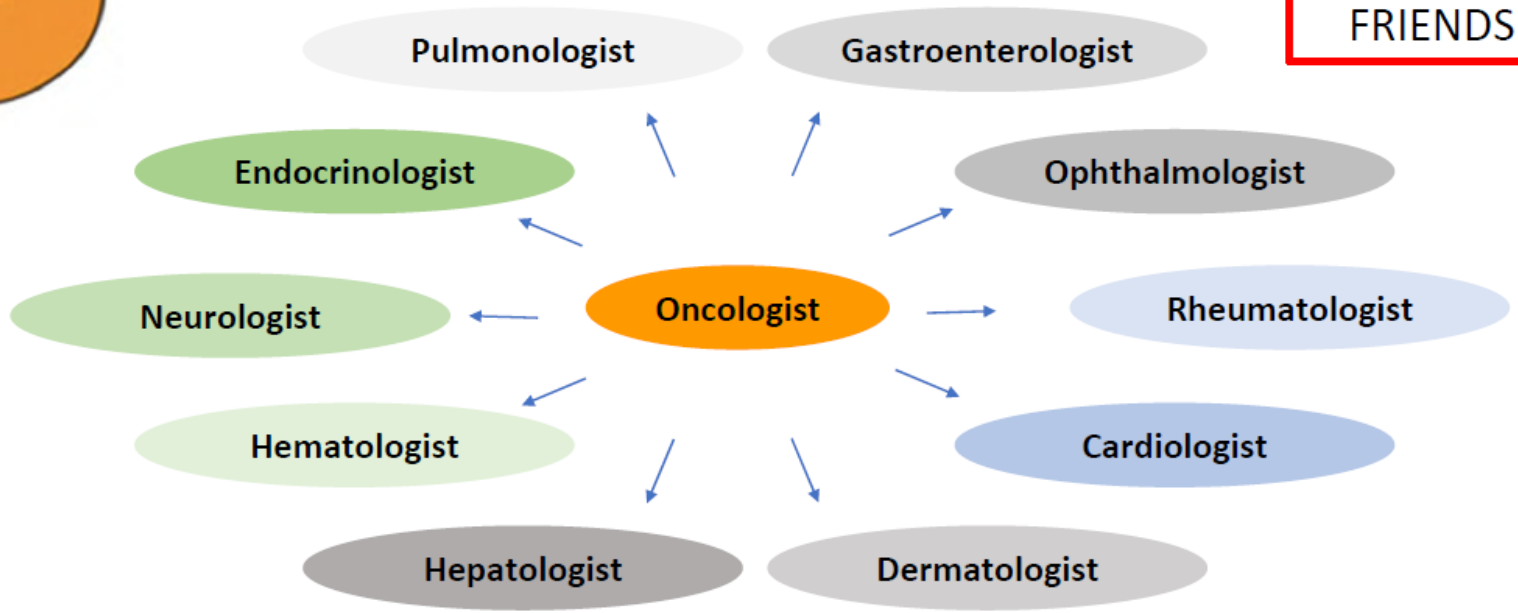
- Dati di efficacia della immunoterapia nella terapia neoadiuvante nel tumore mammario triplo negativo
- Dati di tossicità
- Monitoraggio

KFP0

Multidisciplinary Management Coordinated by Oncologist

TREAT

TALK TO YOUR FRIENDS!



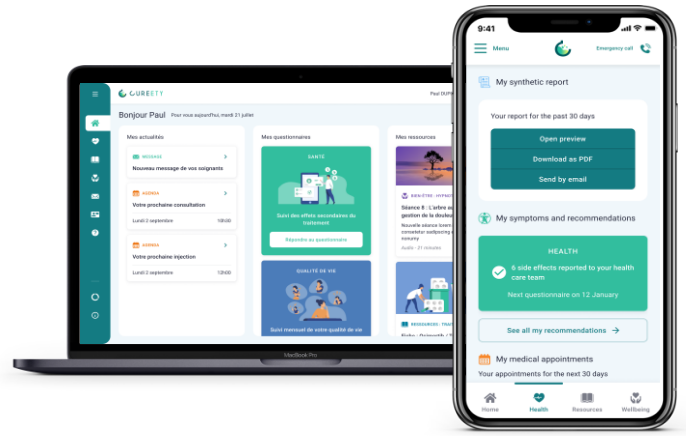
Must learn from each other and feedback and follow up!

PHARMACOVIGILANCE studies and **large** Real-World Datasets
→ Allow to capture rare events (that can remain uncaptured in RCTs)

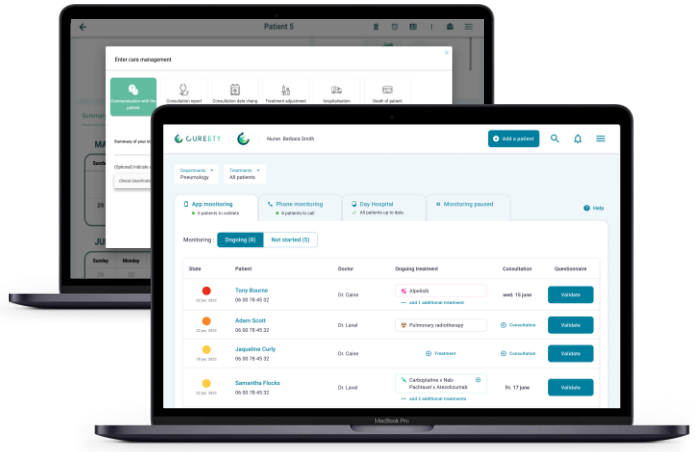
Cos’è il monitoraggio remote dei pazienti (RPM)?

Monitoraggio remoto attraverso i patient-reported outcomes (PROs)

PROMs **ospitati su una piattaforma software** per collegare i pazienti a distanza con il loro team sanitario, dove questo meccanismo viene definito "monitoraggio remoto del paziente"



Interfaccia paziente



Interfaccia professionisti sanitari

US Department of Health Human Services F.D.A. Center for Drug Evaluation Research, U.S. Department of Health Human Services F.D.A. Center for Biologics Evaluation Research, U.S. Department of Health Human Services F.D.A. Center for Devices Radiological Health. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. Health Qual Life Outcomes 2006; 4: 79-79.

Virtual Hospital – APP per monitoraggio

Monitoraggio continuo

Rilevamento precoce di **eventi avversi**

Maggiore **coinvolgimento** del paziente

Personalizzazione delle cure

Comunicazione efficace

Raccolta **dati**

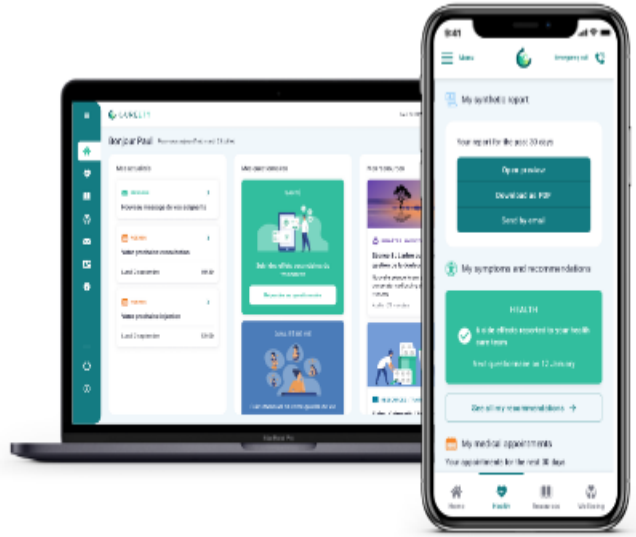
Limitazione autopresentazioni

Riduzione messaggi email e whatsapp

La nostra esperienza in IEO:

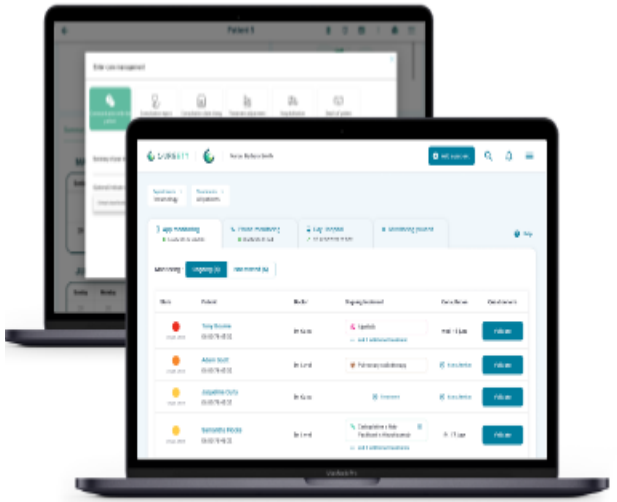
MONITORING

EDUCATION



Interfaccia paziente
(web-app or mobile)

CUREETY



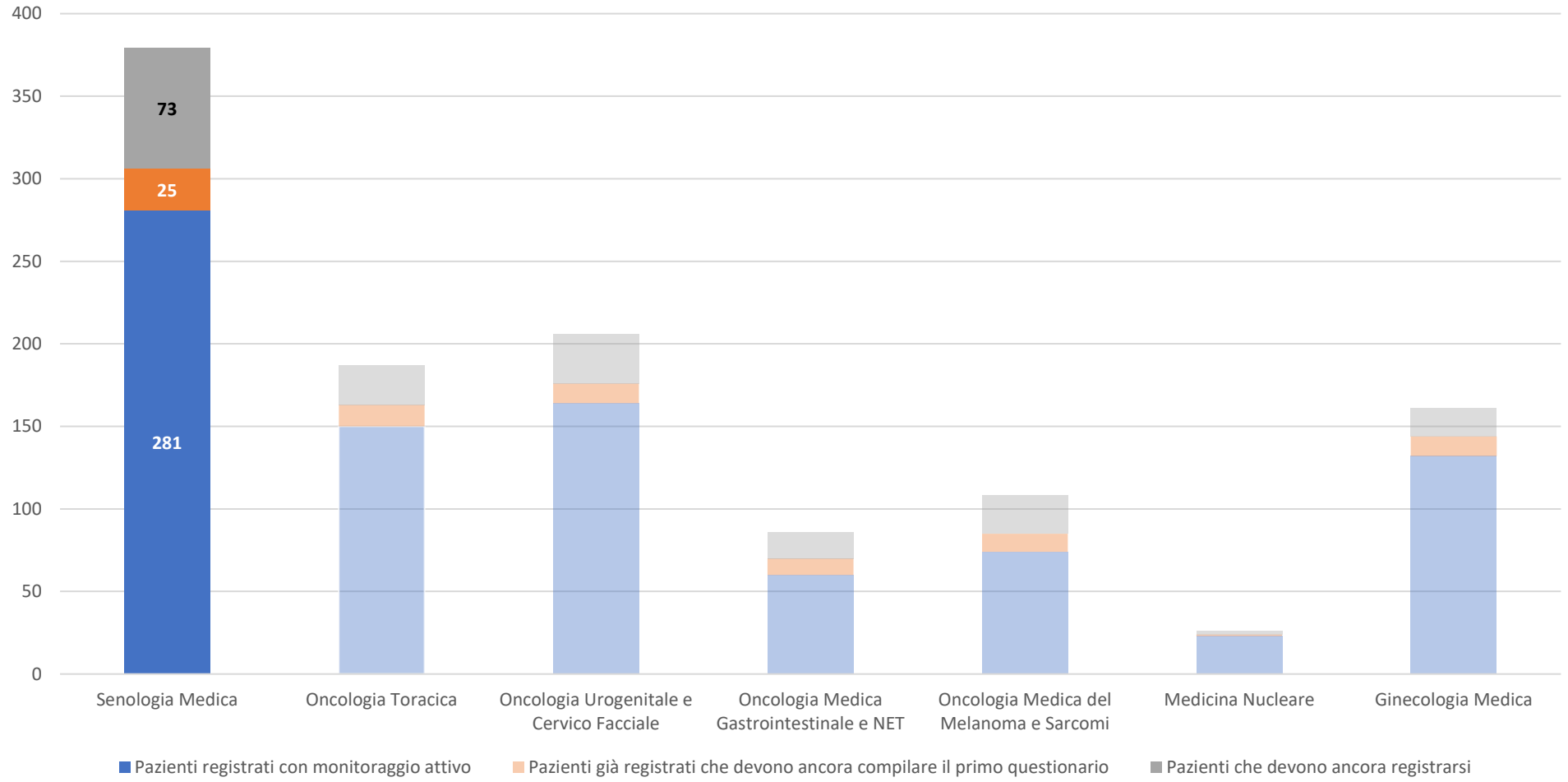
Interfaccia Operatore Sanitario (HCP)

Cureety è un'applicazione certificata come dispositivo medico di classe II
(Certificazione CE, ISO 13485:2016, ISO 27001:2017)

DIVISIONE DI SENOLOGIA MEDICA

50% delle pazienti in terapia registrate su Cureety

57
Età media



Agenda

- Dati di efficacia della immunoterapia nella terapia neoadiuvante nel tumore mammario triplo negativo
- Dati di tossicità
- Monitoraggio
- Conclusioni

Conclusions

- Long-term toxicities.
- The crucial importance of a close follow-up for the patients throughout the entire duration of the treatment with extensive work-up to ensure an early detection of potentially serious toxicities
- The importance of collaborating with immune-toxicity teams.

The QoL for this population should be carefully evaluated, especially regarding permanent toxicities.

GRAZIE!!