Immunotherapy: Efficacy and Toxicity Considerations

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Young Women's Breast Cancer Translational Program

Agenda

- Review current efficacy results in EBC for immunotherapy
- Highlight emerging combinations under investigation
- Discuss unique safety considerations when using immunotherapy

Immune checkpoint inhibitors in early TNBC

Variable	I-SPY	KEYNOTE-522	IMPASSION 031	NeoTRIP	GeparNUEVO
Total patients	69/180	**1174 (602)**	**333**	**280**	**174**
Type of CPi	**PD1 Pembro x 4**	**PD1 Pembro x 1 year**	**PD-L1 Atezo x 1 year**	**PD-L1 Atezo x 8**	**PD-L1 Durva x 8**
Stage	**Stage II/III**	**Stage II/III**	**Stage II/III**	**+ N3 disease**	**35% stage I**
Anthracycline pre-op	**yes**	**yes**	**yes**	**no***	**yes**
Included carboplatin	**no**	**yes**	**No (nab-pac)**	**Yes (nab-pac) 2 wks on, 1 wk off x 8**	**no**
Improved pCR	**Yes**	**Yes 51.2 v 64.8% P=0.00055**	**Yes 41.1 v 57.6% P=0.0044**	**No (43.5 v 40.5%)**	**Numeric improvement (53 v 44%, p=0.18)**
Improved EFS	**NR: pCR>nonpCR**	**Yes**	**NR**	**No**	**Yes EFS, DDFS and OS**

Nanda et al, JAMA Onc 2020; Schmid et al, NEJM 2020 and ESMO Plenary 2021; Mittendorf, Lancet 2020; Gianni et al, SABCS 2019; Loibl et al, Ann Oncol 2019 and ASCO 2021;
*Callari et al, PD10-09:, SABCS 2021

BARCELONA 2024 ESMO congress

Neoadjuvant Pembrolizumab or Placebo + Chemotherapy Followed by Adjuvant Pembrolizumab or Placebo for High-Risk Early-Stage Triple-Negative Breast Cancer: Overall Survival Results from the Phase 3 KEYNOTE-522 Study

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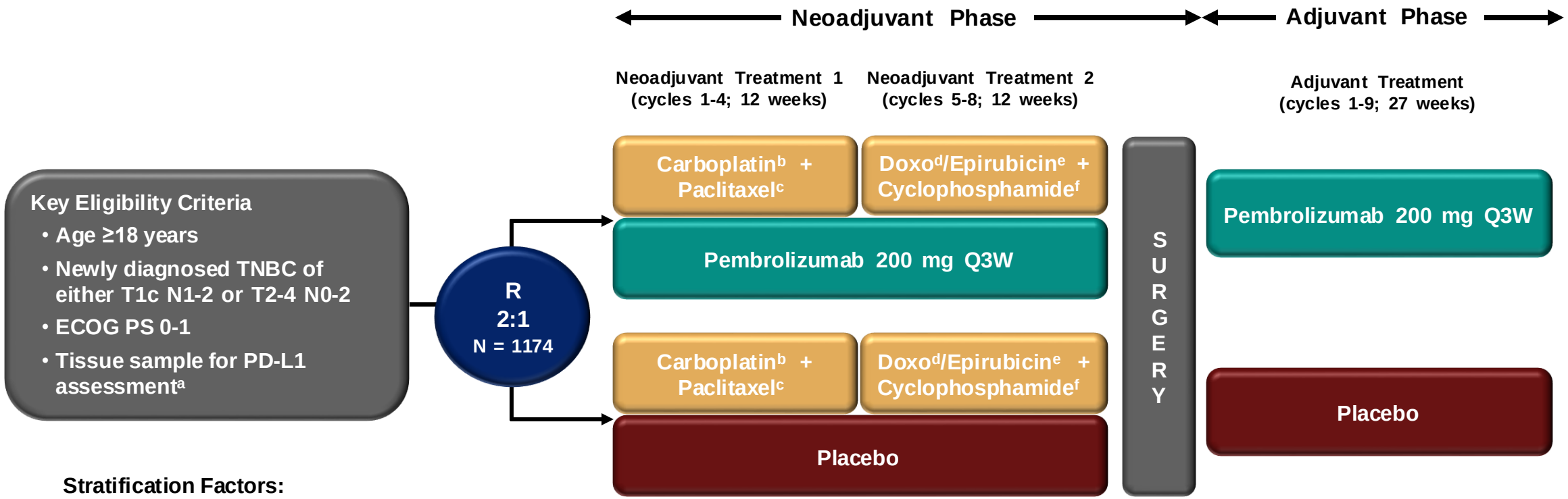
KEYNOTE-522 Study Design (NCT03036488)



Stratification Factors:

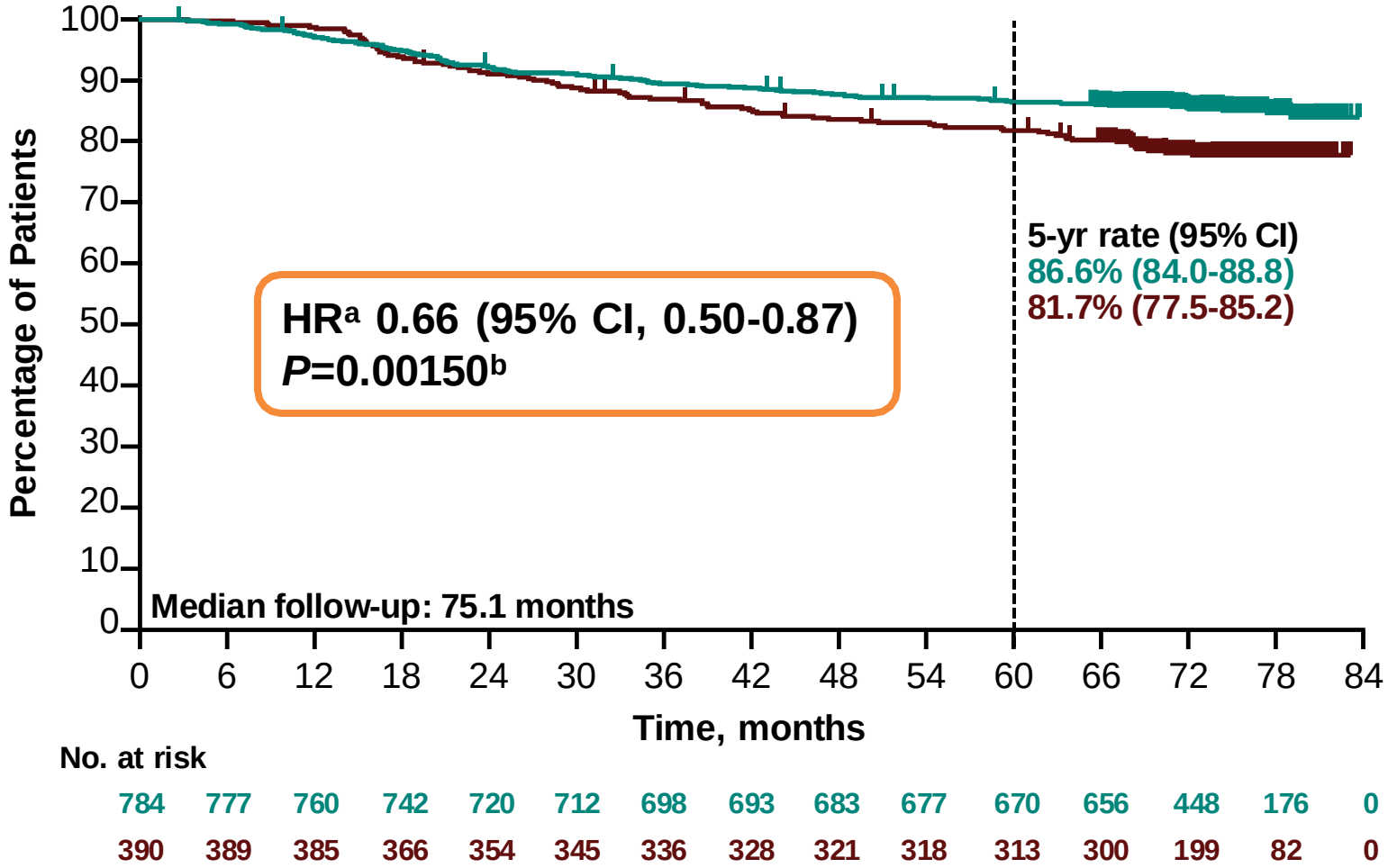
- Nodal status (+ vs -)
- Tumor size (T1/T2 vs T3/T4)
- Carboplatin schedule (QW vs Q3W)

Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post-treatment included)

Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post-treatment included)

[a]Must consist of at least 2 separate tumor cores from the primary tumor. [b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW. [c]Paclitaxel dose was 80 mg/m^2 QW. [d]Doxorubicin dose was 60 mg/m^2 Q3W. [e]Epirubicin dose was 90 mg/m^2 Q3W. [f]Cyclophosphamide dose was 600 mg/m^2 Q3W.

Key Secondary Endpoint: Overall Survival

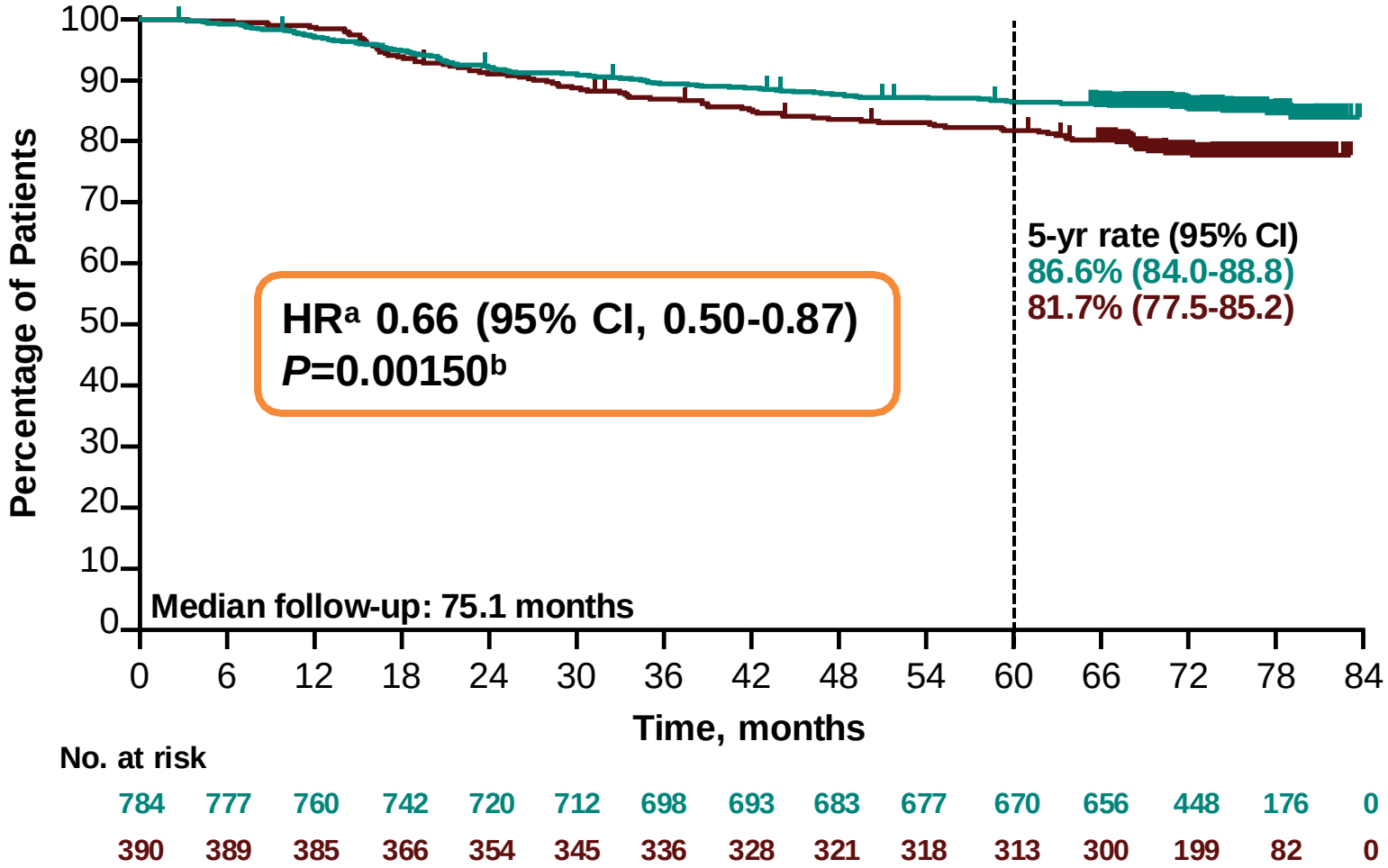


	Pts w/ Event
Pembro + Chemo/Pembro	14.7%
Placebo + Chemo/Placebo	21.8%

[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.

Peter Schmid

Key Secondary Endpoint: Overall Survival



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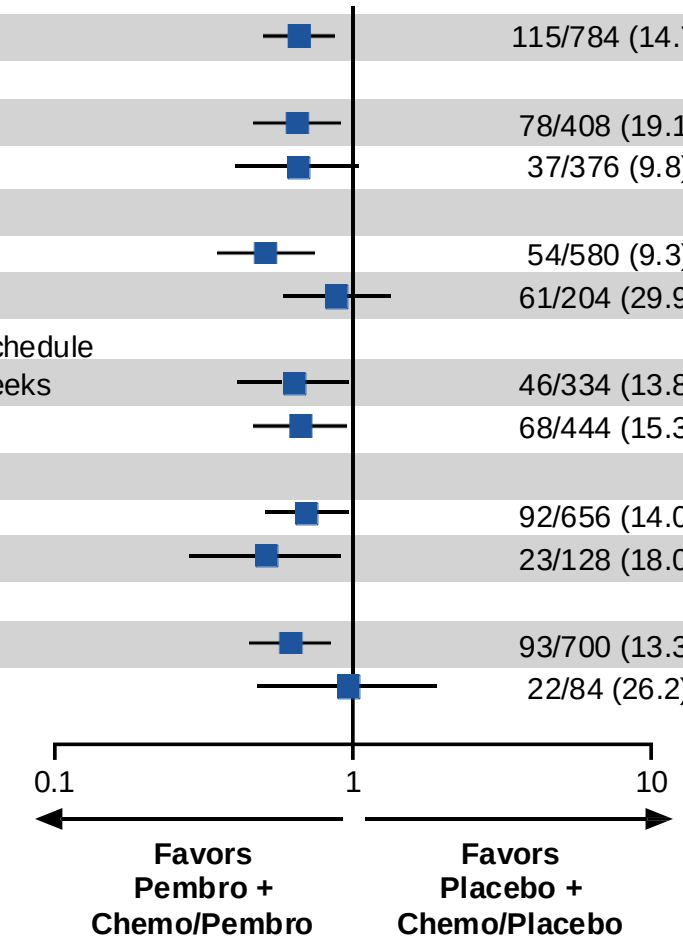
Peter Schmid

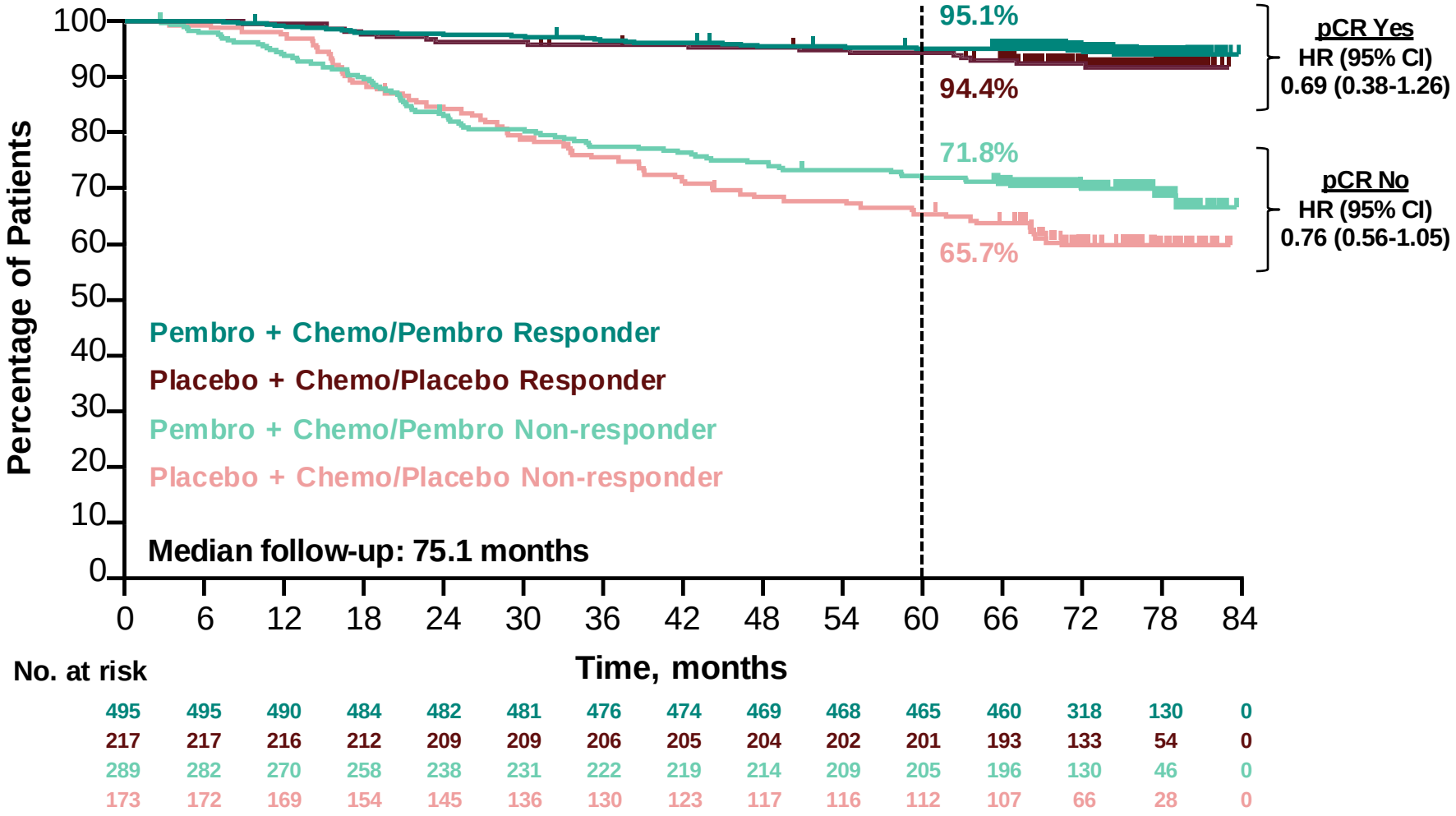
Overall Survival in Patient Subgroups

Subgroup	No. Events/No. Patients (%) Pembro + Chemo/Pembro	Placebo + Chemo/Placebo	Hazard Ratio (95% CI)
Overall	115/784 (14.7)	85/390 (21.8)	0.66 (0.50 to 0.87)
Nodal status			
Positive	78/408 (19.1)	56/196 (28.6)	0.65 (0.46 to 0.91)
Negative	37/376 (9.8)	29/194 (14.9)	0.65 (0.40 to 1.05)
Tumor size			
T1/T2	54/580 (9.3)	51/290 (17.6)	0.51 (0.35 to 0.75)
T3/T4	61/204 (29.9)	34/100 (34.0)	0.88 (0.58 to 1.34)
Carboplatin schedule			
Every 3 weeks	46/334 (13.8)	36/167 (21.6)	0.63 (0.41 to 0.97)
Weekly	68/444 (15.3)	49/220 (22.3)	0.67 (0.46 to 0.96)
PD-L1 status			
CPS ≥1	92/656 (14.0)	62/317 (19.6)	0.70 (0.51 to 0.97)
CPS <1	23/128 (18.0)	23/69 (33.3)	0.51 (0.28 to 0.91)
Age category			
<65 years	93/700 (13.3)	72/342 (21.1)	0.62 (0.45 to 0.84)
≥65 years[a]	22/84 (26.2)	13/48 (27.1)	0.96 (0.48 to 1.91)



For overall population and PD-L1 subgroups, analyses based on Cox regression model with Efron's method of tie handling with treatment as a covariate and stratified by nodal status (positive vs negative), tumor size (T1/T2 vs T3/T4), and frequency of carboplatin (once weekly vs once every 3 weeks); for other subgroups, analysis based on unstratified Cox model. [a]Based on the small sample size and few events, results should be interpreted with caution. Data cutoff date: March 22, 2024.

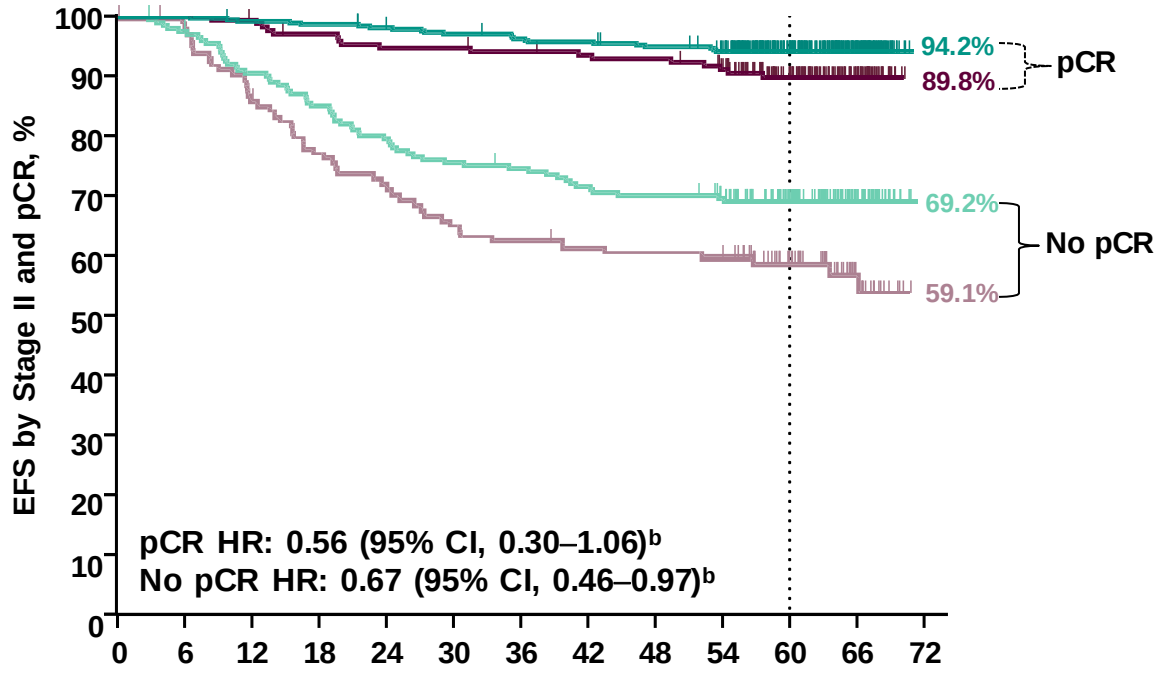
Overall Survival by Pathologic Complete Response (ypT0/Tis ypN0)



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.

EFS at IA6 by Baseline Disease Stage in Patients With and Without pCR

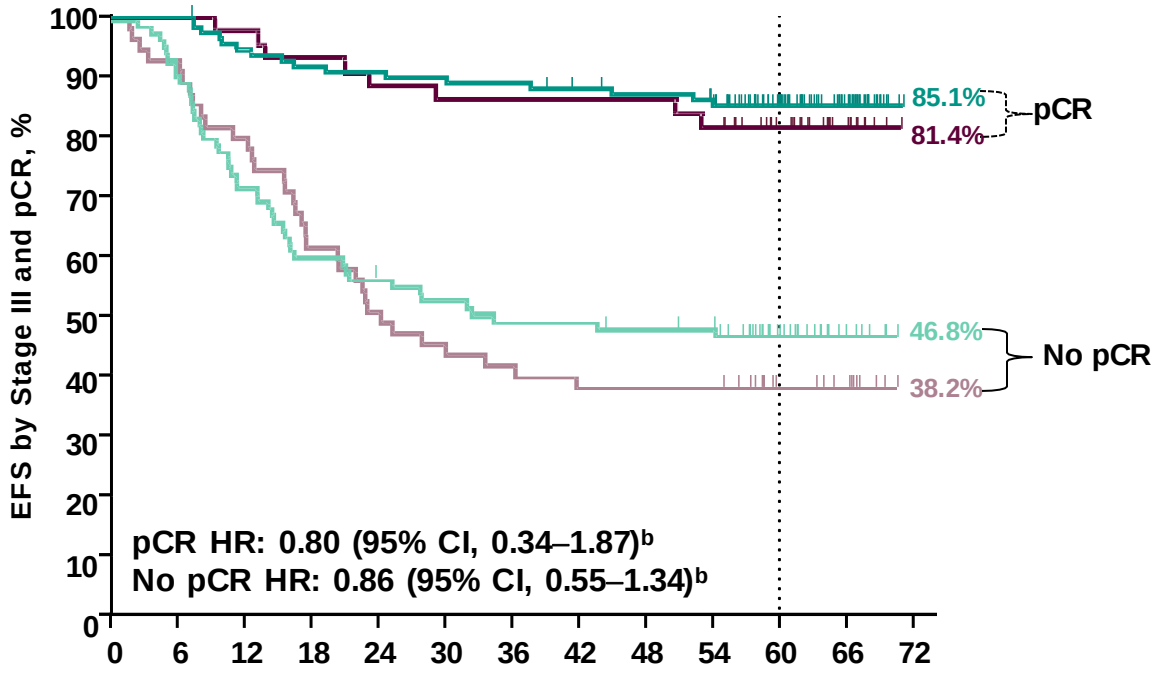
Stage II by pCR Status[a]



No. at risk

Pembro + Chemo/Pembro pCR	386	386	382	380	375	371	367	365	360	351	236	90	0
Pbo + Chemo/Pbo pCR	173	173	171	166	162	162	160	158	157	150	106	42	0
Pembro + Chemo/Pembro no pCR	204	197	183	172	161	153	150	144	141	135	95	35	0
Pbo + Chemo/Pbo no pCR	118	114	100	89	83	75	72	70	69	68	47	18	0

Stage III by pCR Status[a]



No. at risk

Pembro + Chemo/Pembro pCR	109	109	102	99	98	97	96	93	91	88	59	30	0
Pbo + Chemo/Pbo pCR	43	43	42	40	38	37	37	37	37	35	24	11	0
Pembro + Chemo/Pembro no pCR	85	77	61	51	47	44	41	41	39	38	21	7	0
Pbo + Chemo/Pbo no pCR	55	51	44	34	28	25	23	21	21	21	12	8	0

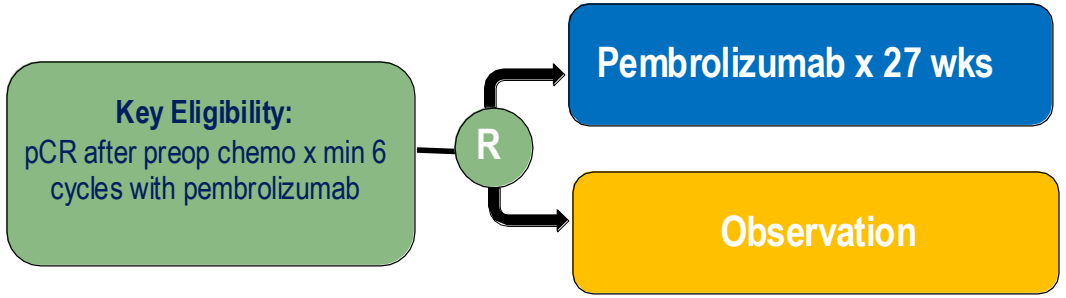
[a]Post-hoc exploratory analyses, non-randomized comparison. [b]Hazard ratio (95% CI) analyzed based on the unstratified Cox model.
Data cutoff date of March 23, 2023.

Unanswered questions:

Do we need both neoadjuvant *and* adjuvant immunotherapy for patients with early-stage TNBC, particularly for those who achieve pCR after NACT + IO?

Among patients with early-stage TNBC who do NOT achieve a pCR after neoadjuvant chemo + IO, can we improve outcomes with better adjuvant treatments?

OptimICE-pCR (NCT05812807)



Stratification Factors:
- Baseline nodal status
- Receipt of anthracycline chemotherapy: yes vs. no

Ongoing post-neoadjuvant clinical trials with ADCs:

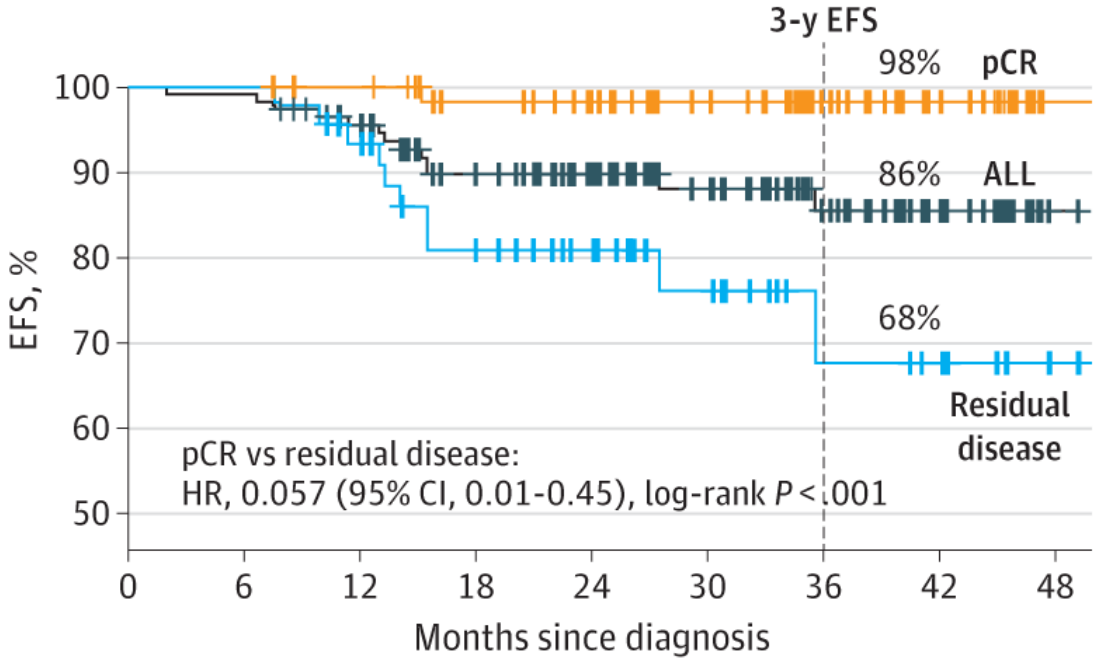
- **SASCIA** (ER+/HER2- and TNBC): Sacituzumab govitecan x 8 vs. TPC (NCT04595565)
- **Optimize RD/ASCENT-05**: Sacituzumab govitecan + pembrolizumab x 8 vs. pembrolizumab +/- capecitabine (NCT05633654)
- **Tropion Breast03**: Dato-DXd +/- durvalumab vs. capecitabine and/or pembrolizumab (NCT05629585)

JAMA Network™

From: **Clinical and Biomarker Findings of Neoadjuvant Pembrolizumab and Carboplatin Plus Docetaxel in Triple-Negative Breast Cancer: NeoPACT Phase 2 Clinical Trial**

JAMA Oncol. 2024;10(2):227-235. doi:10.1001/jamaoncol.2023.5033

Stage I-III TNBC
Carbo, docetaxel, pembro x 6 cycles
N=117
pCR 60%
IAEs 28%, ≥G3 6%



No. at risk

ALL	115	114	103	87	71	53	32	17	1
pCR	64	64	62	55	46	37	24	11	0
Residual disease	47	47	40	31	25	16	8	6	1

Figure Legend: Event-Free Survival (EFS) of Patients in the Intent-to-Treat Group (N = 115)HR indicates hazard ratio, and pCR, pathologic complete response.

From: **Clinical and Biomarker Findings of Neoadjuvant Pembrolizumab and Carboplatin Plus Docetaxel in Triple-Negative Breast Cancer: NeoPACT Phase 2 Clinical Trial**

JAMA Oncol. 2024;10(2):227-235. doi:10.1001/jamaoncol.2023.5033

Immune-mediated AEs	All grades	Grade 1-2	Grade 3-4
Any immune-mediated AE	30 (26.1)	26 (22.6)	4 (3.5)
Rash	21 (18.3)	21 (18.3)	0
Hypothyroidism	4 (3.5)	4 (3.5)	0
Colitis	2 (1.7)	0	2 (1.7)
Inflammatory dermatitis	1 (0.9)	0	1 (0.9)
Autoimmune disorder[d]	1 (0.9)	0	1 (0.9)
Hyperthyroidism	1 (0.9)	1 (0.9)	0
Thyroiditis	1 (0.9)	1 (0.9)	0
Cranial nerve palsy	1 (0.9)	1 (0.9)	0
Focal meningomyelitis	1 (0.9)	1 (0.9)	0

Abbreviation: TNBC, triple-negative breast cancer.

[a] Treatment-related adverse events that occurred in 10% or more of patients are reported. Grading scale follows the *Common Terminology Criteria for Adverse Events*.[16]

[b] Grade 1 = 40%; grade 2 = 18.3%.

[c] Grade 1 = 27.8%; grade 2 = 10.4%.

[d] Glutamic acid decarboxylase 65−positive autoimmune encephalitis.

Table Title:

Adverse Events (AEs) Among 115 Patients Treated With Neoadjuvant Pembrolizumab and Carboplatin Plus Docetaxel, by AE Grade

[d] Glutamic acid decarboxylase 65−positive autoimmune encephalitis.

Alexandra/IMpassion030 phase 3 open-label study design

SURGERY

Early TNBC
- **Stage II-III**
- **At least 50% node-positive**
- **N=2300**

R

Arm A: Atezolizumab + Chemotherapy experimental arm

Week 1 3 5 9 13 19 21 24 27 33 42 51

Induction Treatment **Maintenance Treatment**

Follow up

Arm B: Chemotherapy only control arm

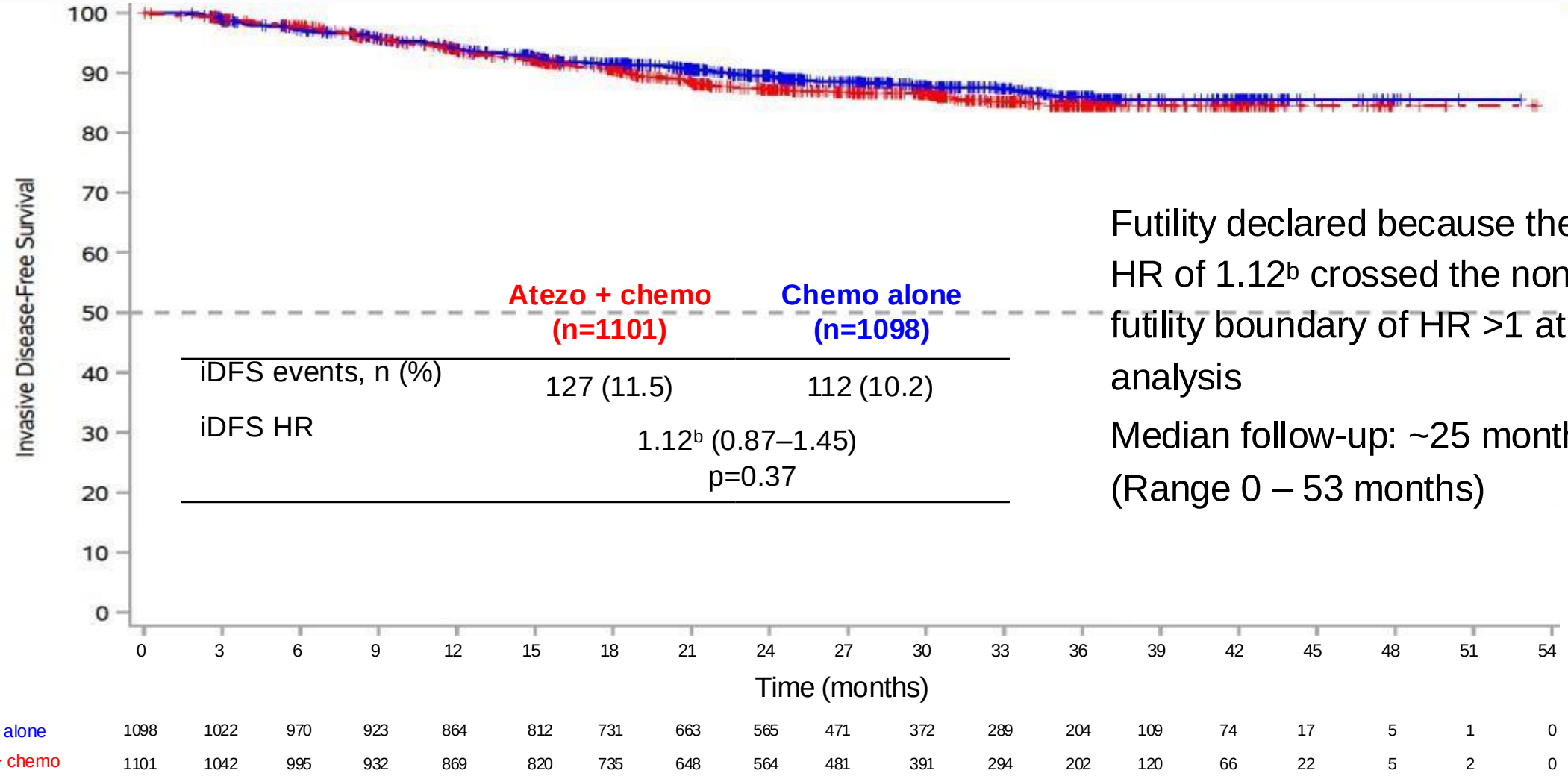
Stratification factors:

Axillary nodal status
(0 vs. 1−3 vs. ≥ 4 positive lymph nodes)
Surgery
(breast conserving vs. mastectomy)
Tumor PD-L1 status
(IC0 vs. IC1/2/3)

- Paclitaxel qw for 12 weeks
- ddAC/EC q2w for 4 doses supported with G-CSF/GM-CSF
- Atezolizumab
  - Induction: 840 mg q2w for up to 10 doses
  - Maintenance: 1200 mg q3w to complete 1 year
- Monitoring visit Arm B

★ **End of 30-day safety reporting period after last study treatment**

Primary efficacy endpoint: iDFS[a] (ITT population)



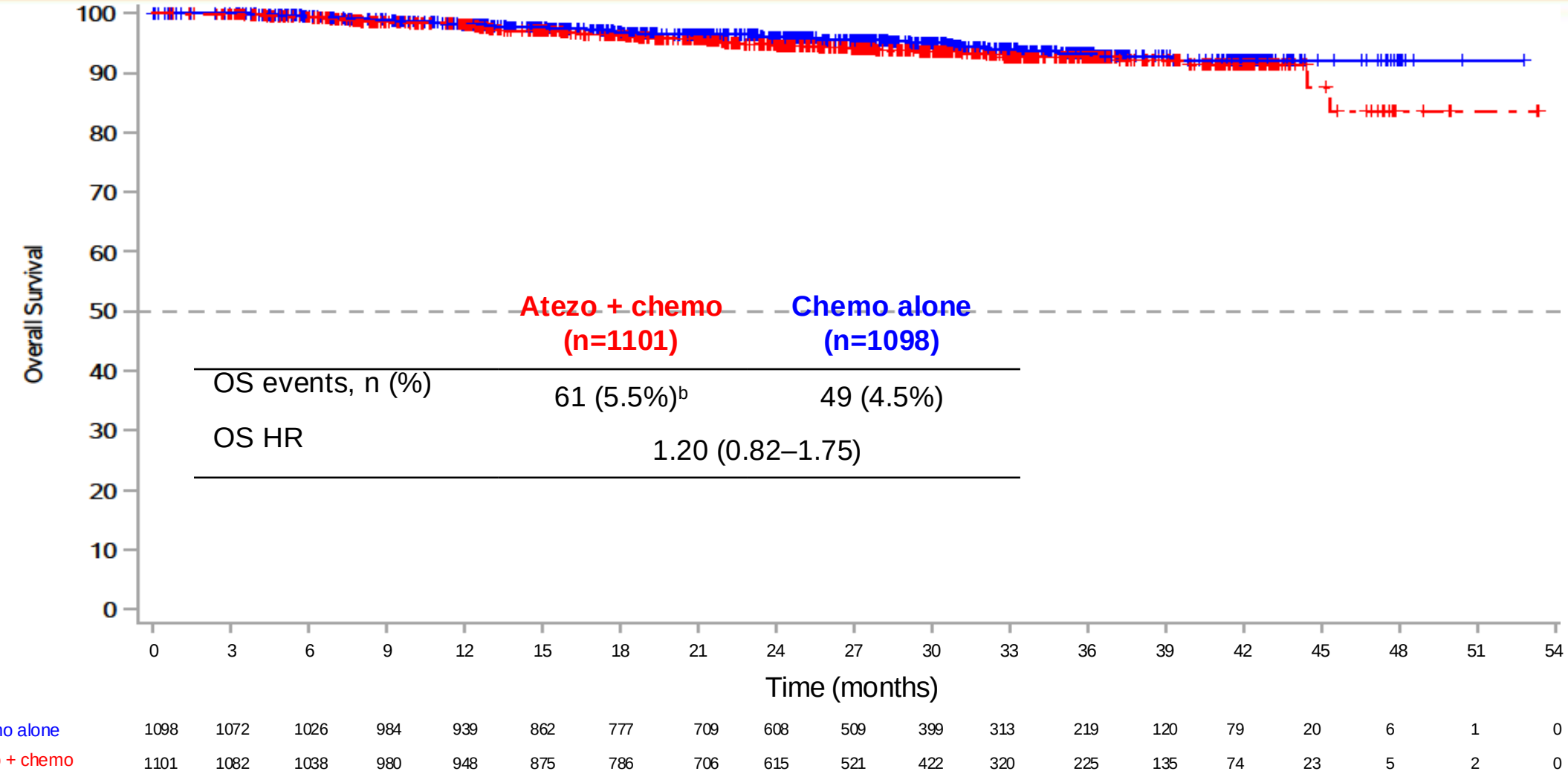
	Atezo + chemo (n=1101)	Chemo alone (n=1098)
iDFS events, n (%)	127 (11.5)	112 (10.2)
iDFS HR	1.12[b] (0.87–1.45) p=0.37	

Futility declared because the observed HR of 1.12[b] crossed the non-binding futility boundary of HR >1 at this interim analysis

Median follow-up: ~25 months (Range 0 – 53 months)

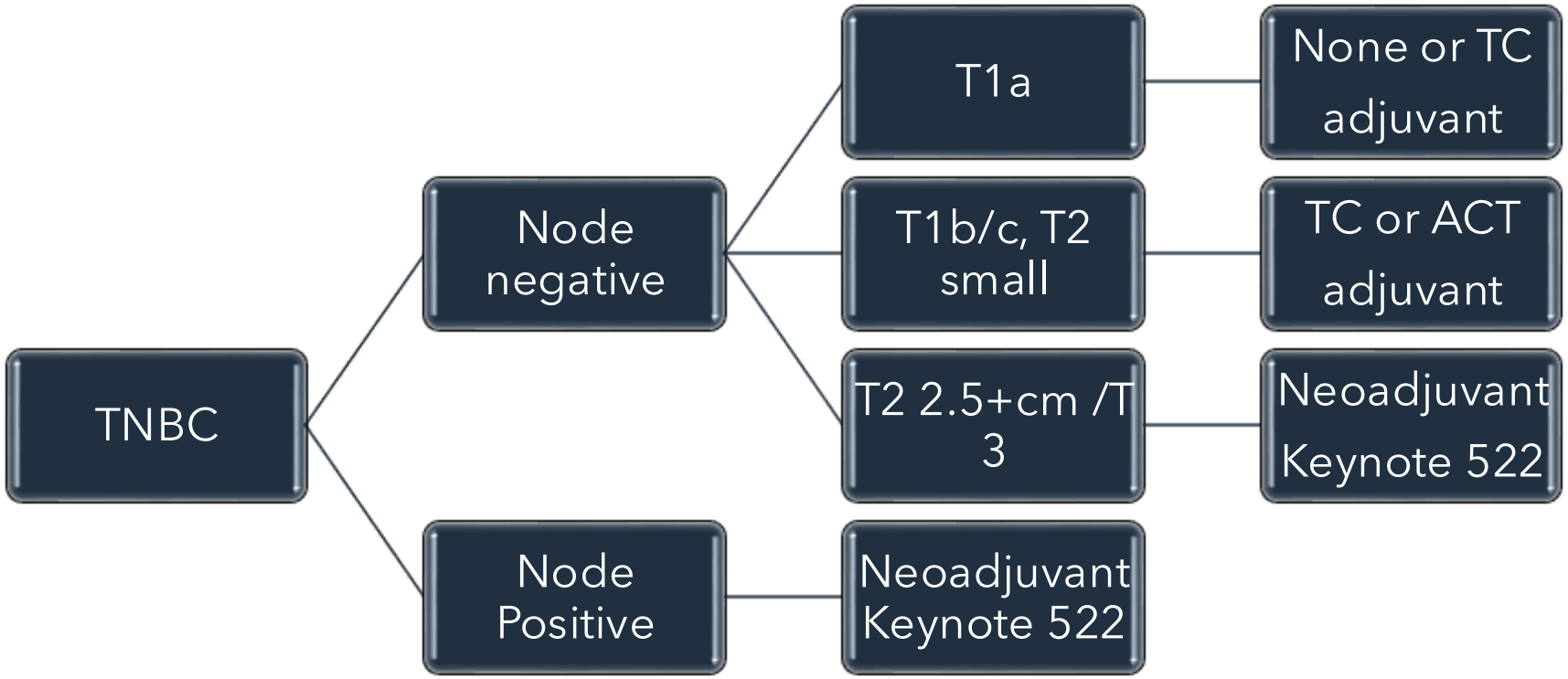
[a]Defined as the interval from randomization until date of first occurrence of an iDFS event, [b]stratified by PD-L1 status, Surgery, and Axillary Nodal Status

Key secondary efficacy endpoint: OS[a], ITT population



[a]Defined as the interval between randomization until death from any cause. [b]One patient in the atezo arm who died 25 Dec 2022 not taken into account (data issue).

TNBC Chemo Chart



Considerations:

Age

Comorbidities

Autoimmune disease

T2N0 actual size

2.1 versus >2.5

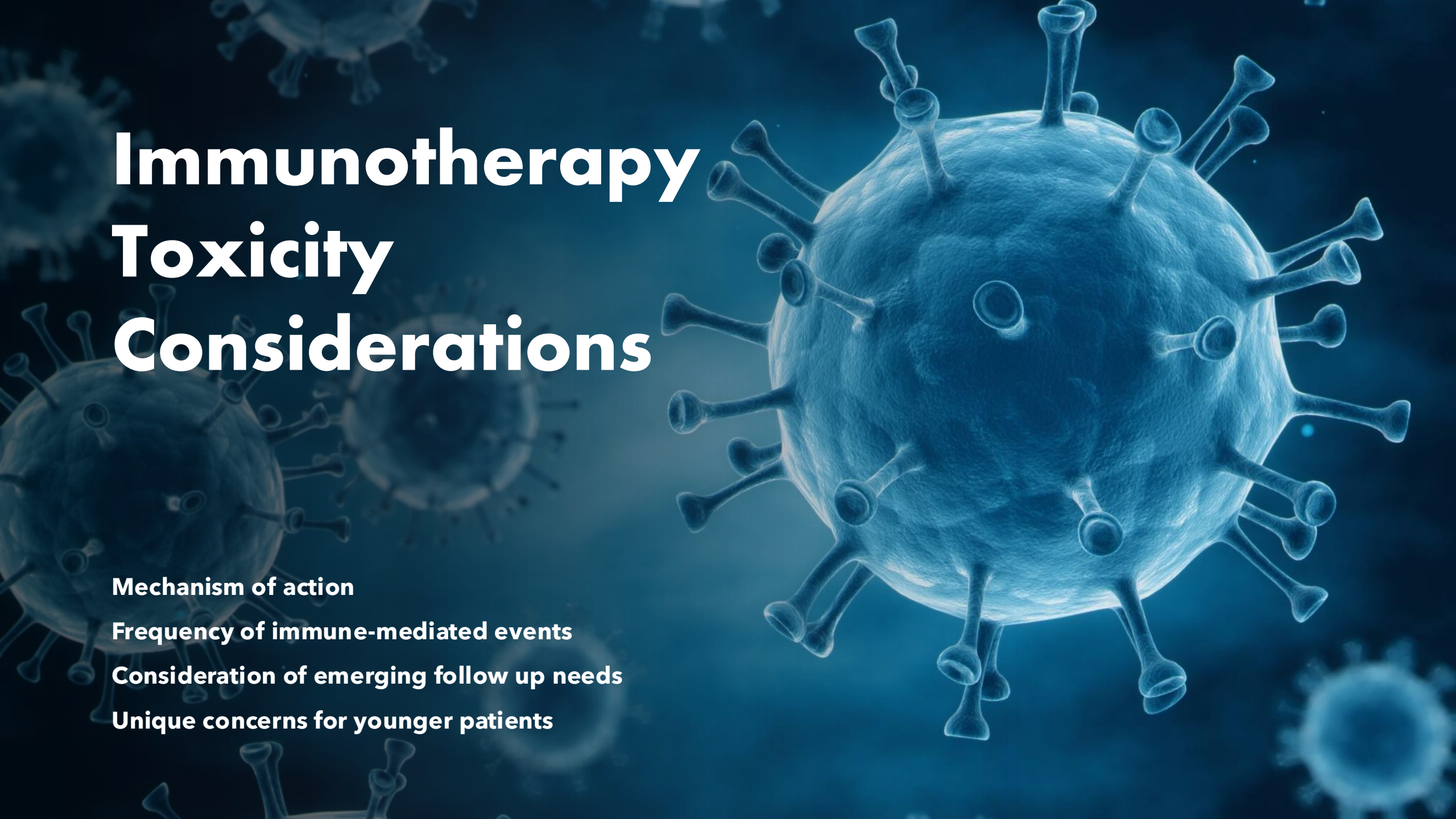
Other risk factors

Neoadjuvant Immune checkpoint inhibitors in early HR+BC

Variable	I-SPY	KEYNOTE-756	CheckMate7FL
Total patients	69/180 (40 HR+)	**1279**	**521**
Type of CPi	**PD1** **Pembro x 4**	**PD1** **Pembro x 1 year**	**PD-L1** **Nivo x 1 year**
Stage	**Stage II/III**	**Stage II/III**	**Stage II/III**
Anthracycline pre-op	**yes**	**yes**	**yes**
Included carboplatin	**no**	**yes**	**No**
Improved pCR	**Yes** **30% v. 13%**	**Yes** **24.3% v 15.6%**	**Yes** **24.5% v 13.3%**
Improved EFS	**NR**	**NR**	**NR**

Nanda, ASCO 2017; Cardosa, Ann Oncol, 2023; Loi, Ann Oncol, 2023

Immunotherapy Toxicity Considerations



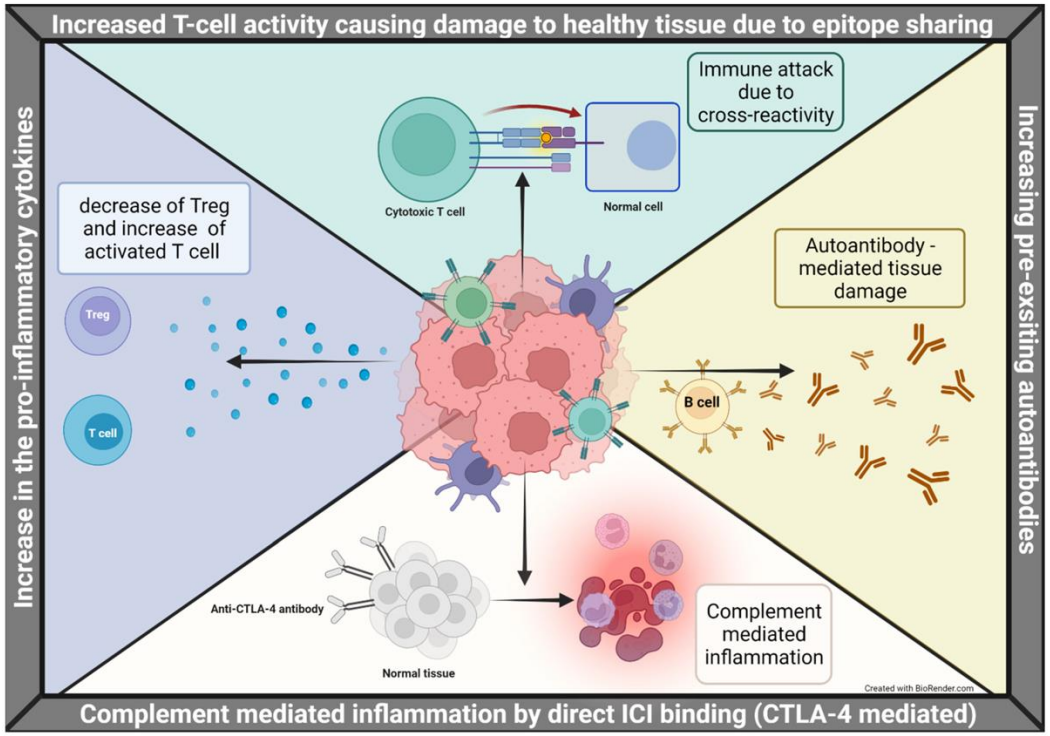
Mechanism of action

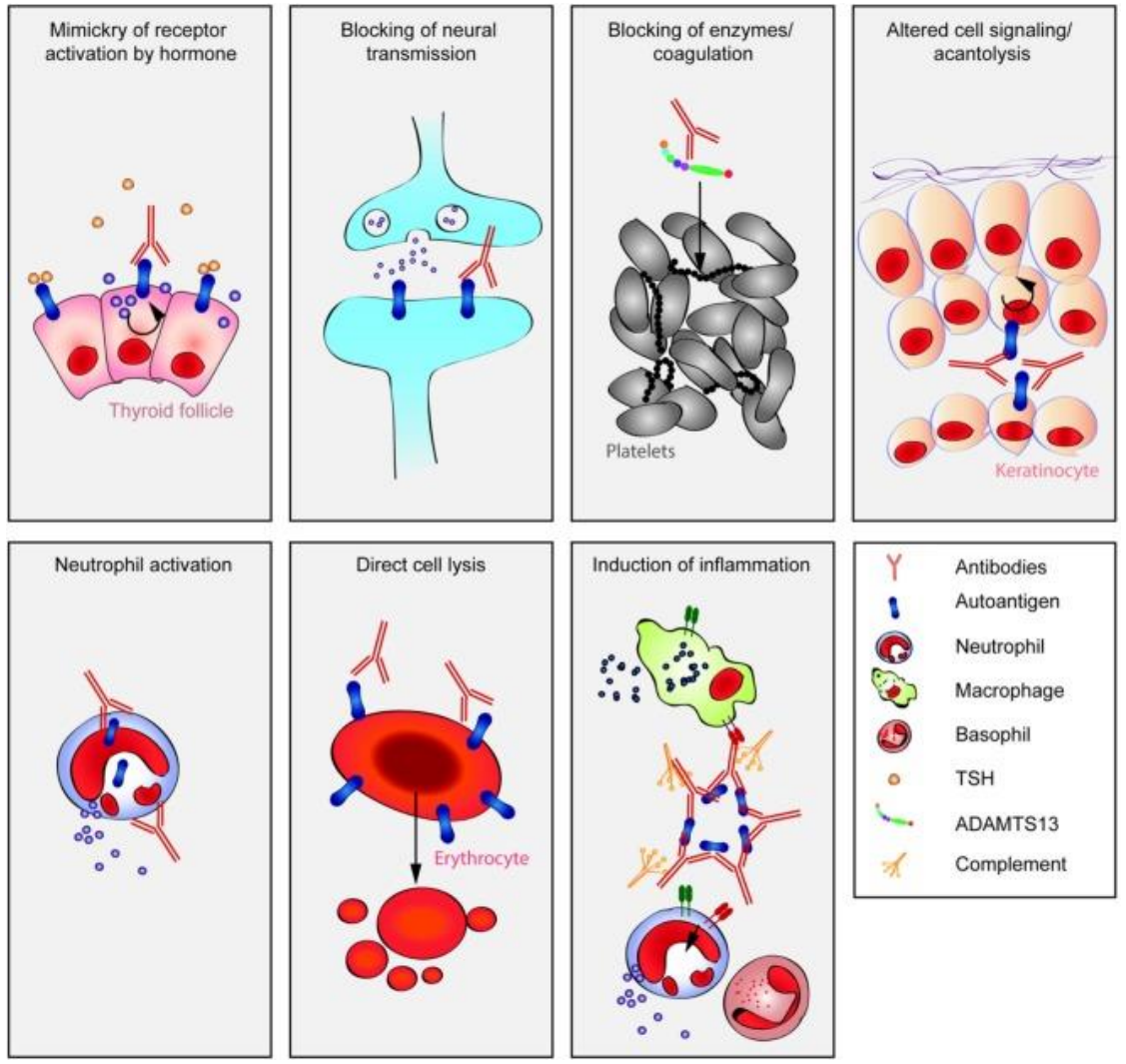
Frequency of immune-mediated events

Consideration of emerging follow up needs

Unique concerns for younger patients

Mechanisms of Check-point inhibitor related toxicities





Timeline to formation
Perpetuation of toxicity
Multiple presentation possibilities

Cancers 2022. doi:10.3390/cancers14102460; Frontiers Immunol. 2017 May 31;8:603 doi: 10.3389/fimmu.2017.00603

Immune-related adverse events by organ system

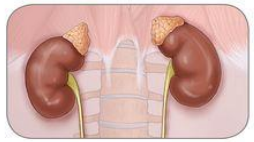
NEUROLOGIC

- Posterior Reversible Encephalopathy
- Neuropathy
- Guillian-Barre Syndrome
- Myelopathy
- Autoimmune Encephalitis
- Aseptic Meningitis
- Myasthenia gravis
- Transverse Myelitis
- Non-specific symptoms: headache, tremor, lethargy, memory disturbance, seizure

RESPIRATORY

- Cough/dyspnea
- Laryngitis
- Pneumonitis
- Bronchitis
- Pleuritis
- Sarcoid-like granulomatosis

RENAL



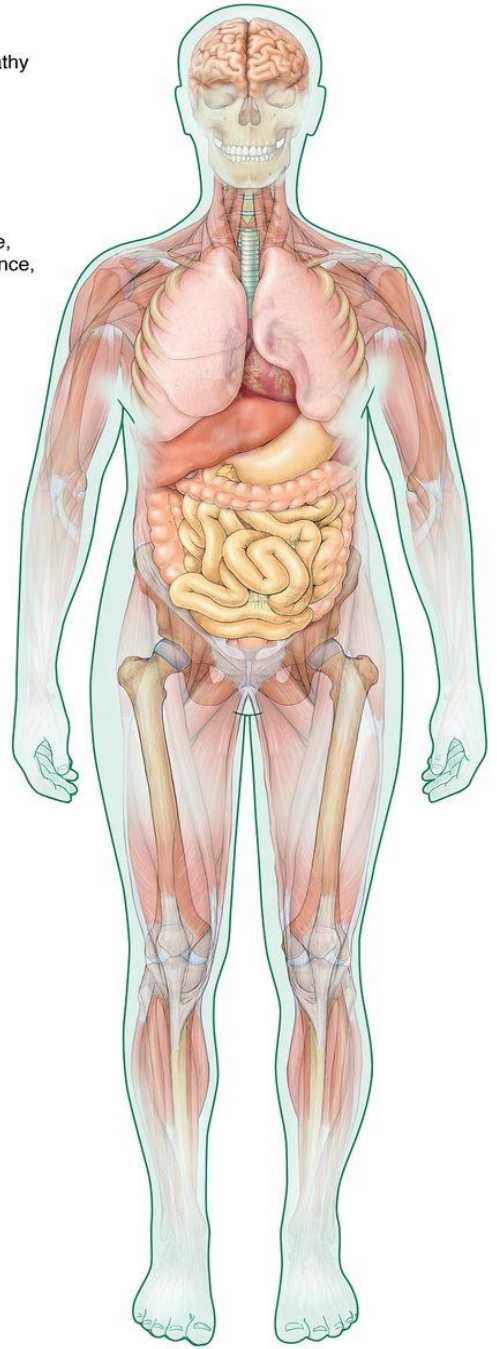
- Tubulointerstitial nephritis
- Acute renal failure
- Lupus nephritis
- Granulomatous lesions
- Thrombotic microangiopathy

HEMATOLOGIC

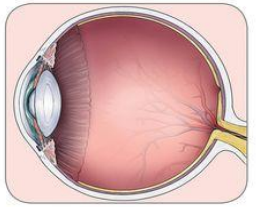
- Autoimmune hemolytic anemia
- Red cell aplasia
- Thombocytopenia
- Leukopenia/Neutropenia
- Acquired hemophilia
- Myelodysplasia

DERMATOLOGIC

- Rash/Pruritis
- Mucositis
- Psoriasis
- Vitiligo
- Bullous pemphigoid
- Steven-Johnson syndrome
- DRESS syndrome



OCULAR



- Uveitis
- Conjunctivitis
- Scleritis, episcleritis
- Optic neuritis
- Blepharitis
- Retinitis
- Peripheral ulcerative keratitis
- Vogt-Koyanogi-Harada

CARDIOVASCULAR

- Myocarditis
- Pericarditis
- Pericardial effusion
- Arrhythmia
- Hypertension
- Congestive heart failure

ENDOCRINE

- Hyper or hypothyroidism
- Hypophysitis
- Adrenal insufficiency
- Diabetes

GASTROINTERSTINAL

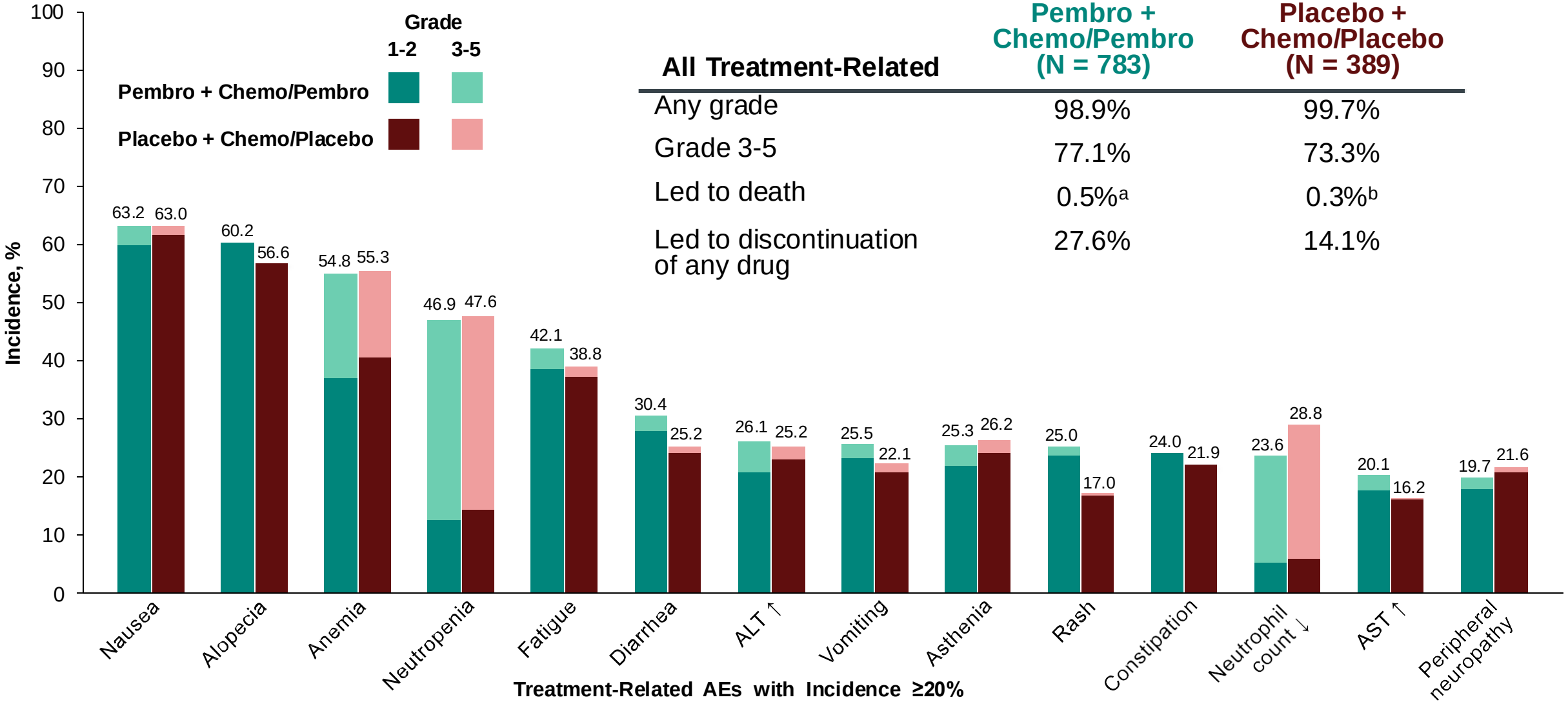
- Diarrhea
- Gastritis
- Colitis
- Ileitis
- Pancreatitis
- Hepatitis

RHEUMATOLOGIC

- Arthralgias/Myalgias
- Inflammatory Polyarthritis
- PMR-like
- Psoriatic Arthritis
- Oligoarthritis
- Vasculitis
- Sicca Syndrome
- Sarcoidosis
- Inflammatory myositis
- Resorptive bone lesions and fractures

The Journal of Rheumatology February 2020, 47 (2) 166-175; DOI: https://doi.org/10.3899/jrheum.190084

Keynote-522 Treatment-Related Adverse Events



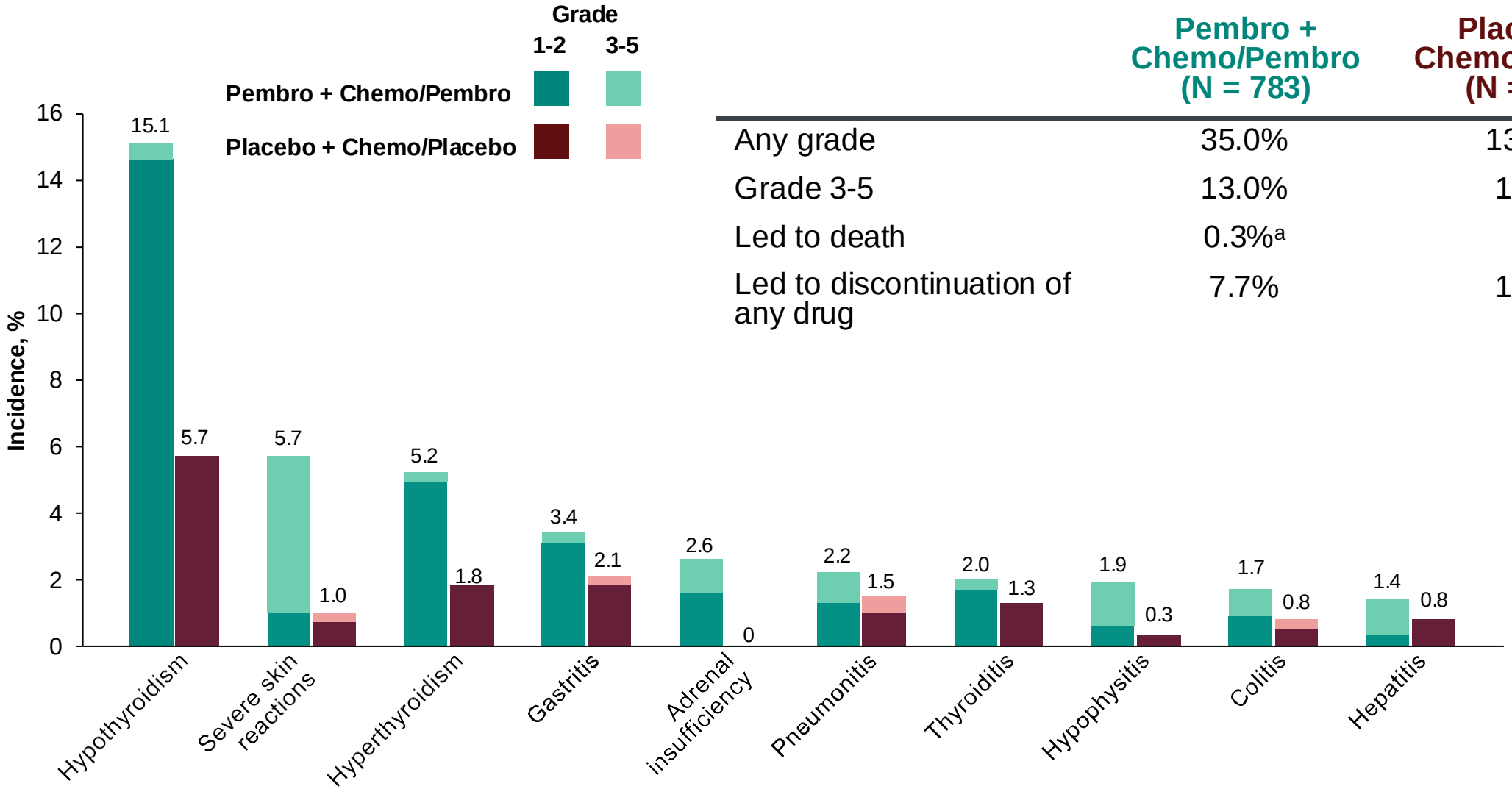
All Treatment-Related	Pembro + Chemo/Pembro (N = 783)	Placebo + Chemo/Placebo (N = 389)
Any grade	98.9%	99.7%
Grade 3-5	77.1%	73.3%
Led to death	0.5%[a]	0.3%[b]
Led to discontinuation of any drug	27.6%	14.1%

[a]1 patient from sepsis and multiple organ dysfunction syndrome; 1 patient from pneumonitis; 1 patient from pulmonary embolism; 1 patient from autoimmune encephalitis. [b]1 patient from septic shock.

Data cutoff date: March 22, 2024.

Peter Schmid

Keynote-522 Immune-Mediated Adverse Events

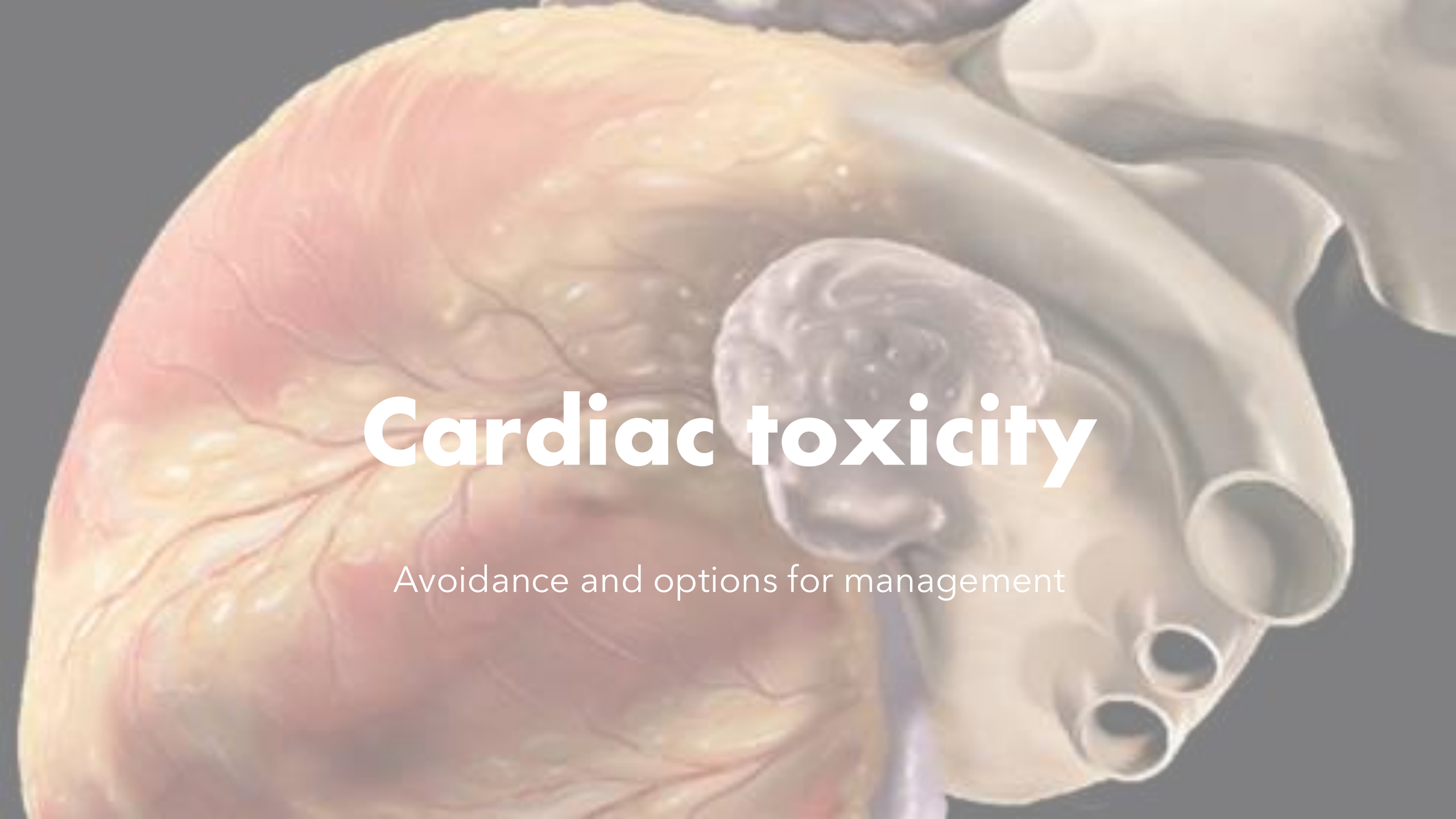


	Pembro + Chemo/Pembro (N = 783)	Placebo + Chemo/Placebo (N = 389)
Any grade	35.0%	13.1%
Grade 3-5	13.0%	1.5%
Led to death	0.3%[a]	0
Led to discontinuation of any drug	7.7%	1.0%

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.

Peter Schmid



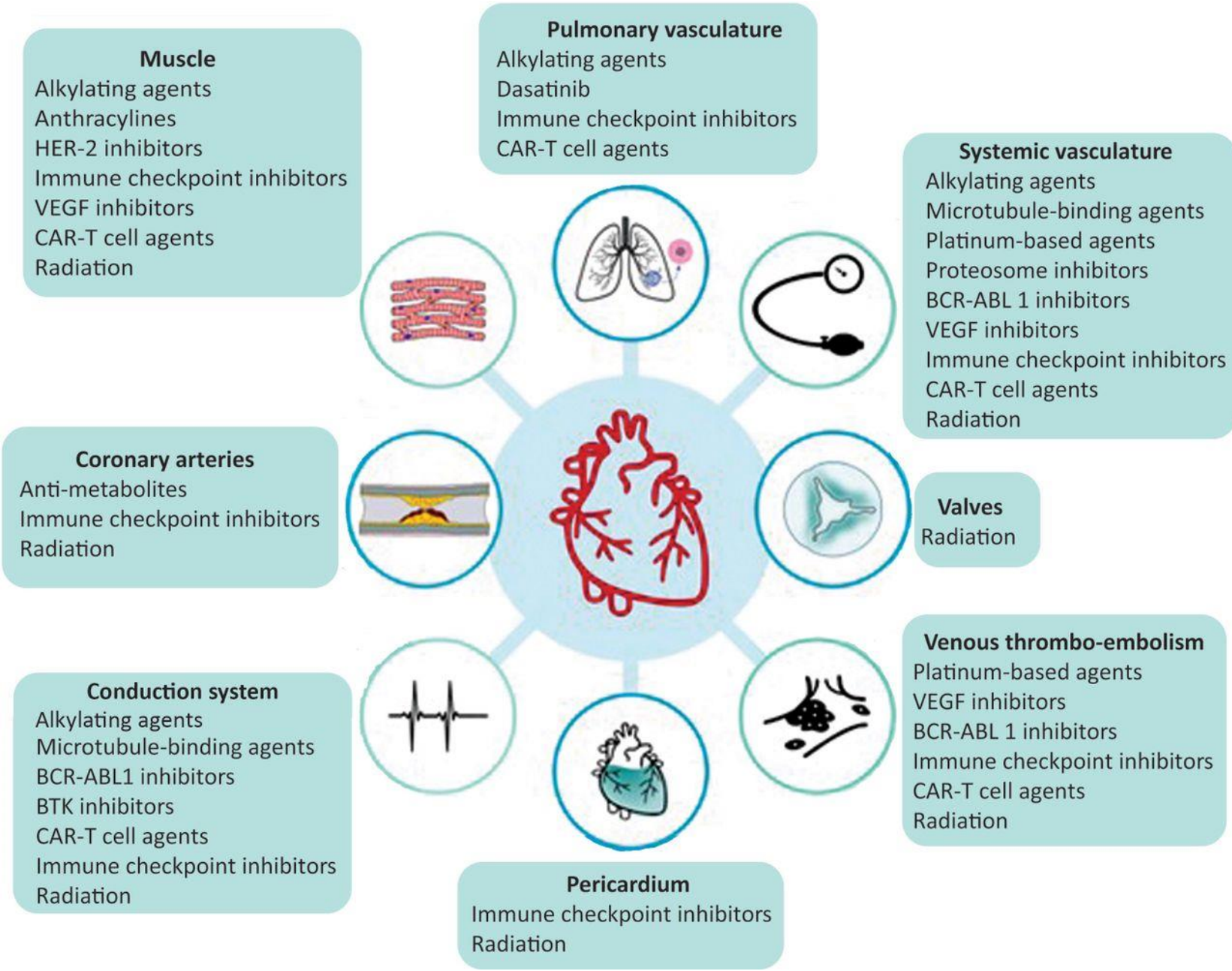
Cardiac toxicity

Avoidance and options for management

Essentials of cardio-oncology

Vera Vaz Ferreira and Arjun K Ghosh

DOI: https://doi.org/10.7861/clinmed.2022-0588
Clin Med January 2023



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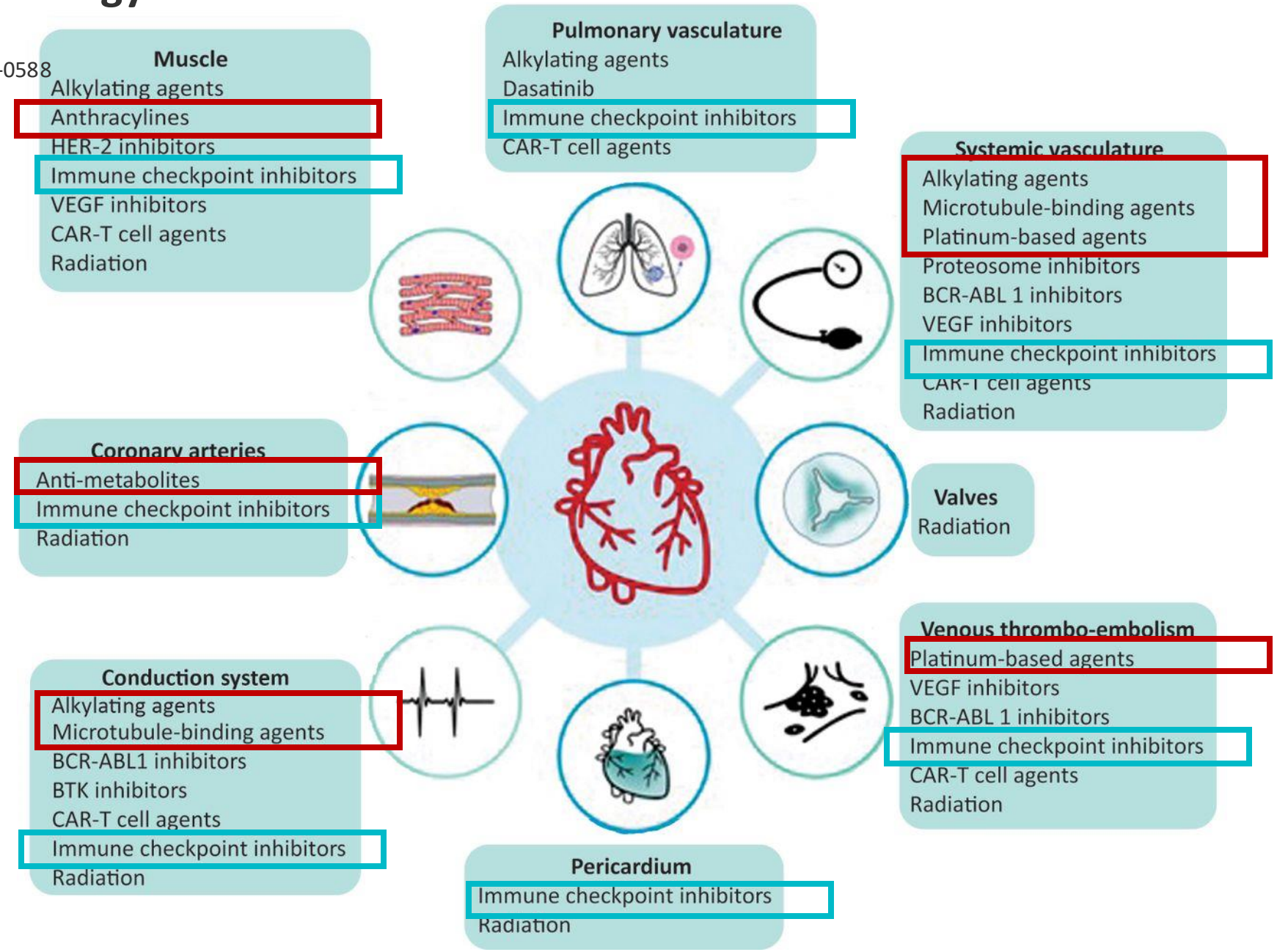

Fertility Issues with chemo-immunotherapy

- If a women has never been pregnant, her fertility status is an unknown
  - Fertility declines after ~age 35, normally
- Anthracycline/alkylating chemotherapy regimens significantly impair fertility in an age-dependent manner, ***so refer to Oncofertility.***
  - *STRONG consideration to ovarian protection (POEMS trial).*
- *Contribution of check-point block inhibition on fertility*
  - Secondary hypogonadism if endocrinopathy occurs
  - Can affect sex hormone regulation
- Post treatment pregnancy does NOT increase breast cancer recurrence risk, even if BRCA+ and IVF needed [POSITIVE trial data, NEJM 2023]
  - *Wash out from pembrolizumab prior to conception is 5 months*
- Right now, is a REALLY BAD TIME for pregnancy, so fertility must be controlled in a definitive manner.
  - *Timing of pembro exposure in utero matters*

Thank you!

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