POST-SABCS 2023

Neue Medikamente

Neoadjuvant

Adjuvant

Nebenwirkungen immunonkologischer Therapien

Cardio-Onkologie

Rudolf Weide
Praxis für Hämatologie und Onkologie
Neversstrasse 5
56068 Koblenz

Neue Medikamente

San Antonio Breast Cancer Symposium®,
December 5-9, 2023

U.S. FOOD & DRUG ADMINISTRATION

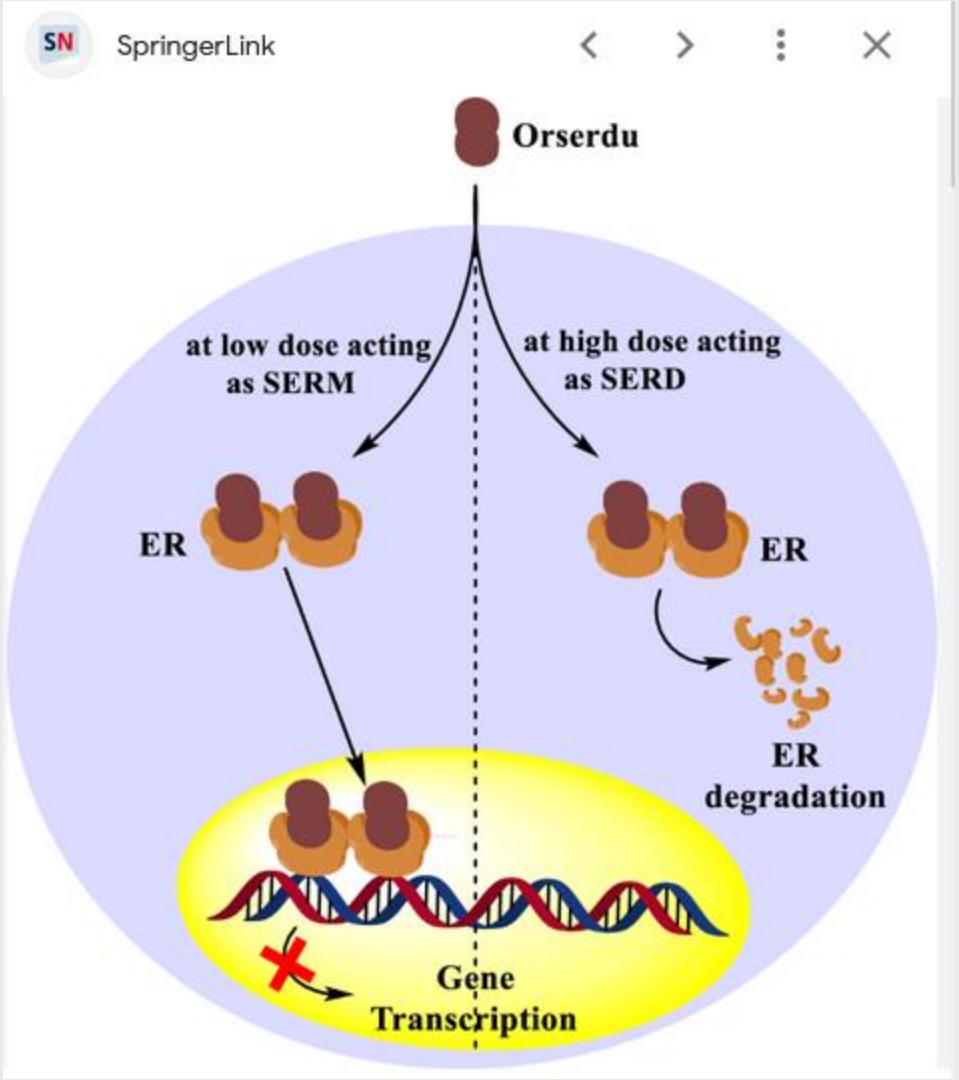
SABCS 2023

New Drug Approvals for Metastatic Breast Cancer

Elacestrant (ORSERDU®)

Mirat Shah, MD
Division of Oncology 1
FDA Office of Oncologic Diseases

December 5, 2023


SpringerLink
Orserdu
at low dose acting
as SERM
at high dose acting
as SERD
ER
ER
ER
degradation
Gene
Transcription

Elacestrant

Mechanism of Action

- Oral estrogen receptor antagonist

Approved Indication

- For the treatment of postmenopausal women and men with ER-positive, HER2-negative, ***ESR1*-mutated** advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy

Dosage and Administration

- 345 mg orally daily, with food

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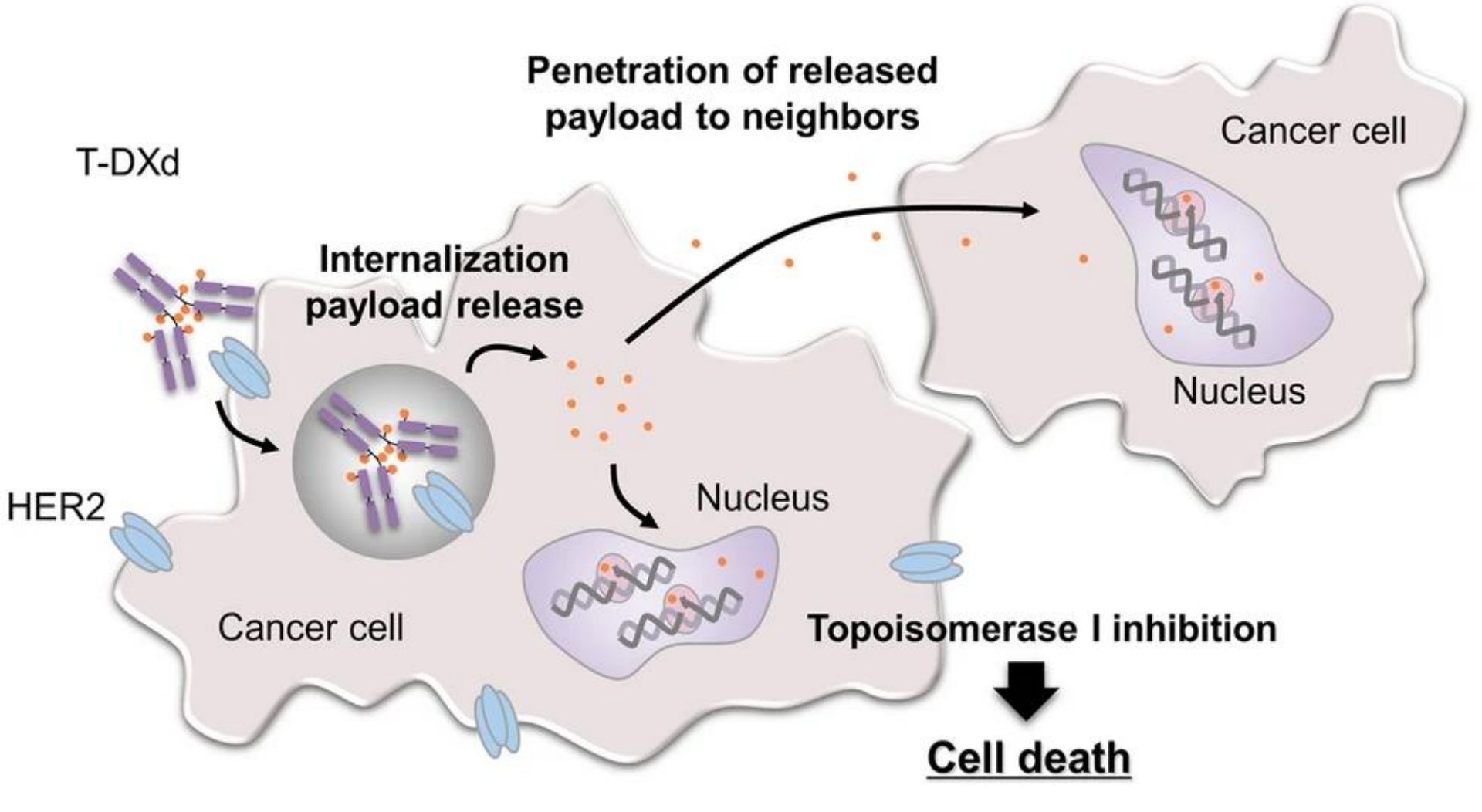
SABCS 2023

New Drug Approvals for Metastatic Breast Cancer

Fam-Trastuzumab Deruxtecan-nxki (T-DXd, ENHERTU®)

Preeti Narayan, MD
Division of Oncology 1
FDA Office of Oncologic Diseases

December 5, 2023


Penetration of released
payload to neighbors
T-DXd
Cancer cell
Internalization
payload release
Nucleus
HER2
Nucleus
Cancer cell
Topoisomerase I inhibition
Cell death

T-DXd

- Antibody drug conjugate: Anti-HER2 mAb linked to a topoisomerase I inhibitor payload
- Prior FDA approvals in metastatic HER2-positive BC, metastatic HER2-positive gastric/GEJ adenocarcinoma, metastatic NSCLC with activating HER2 mutations

Approved Indication

- Adult patients with unresectable or metastatic **HER2-low (IHC 1+ or IHC 2+/ISH-)** breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy

Dosage and Administration

- 5.4mg/kg given as an IV infusion once every 3 weeks

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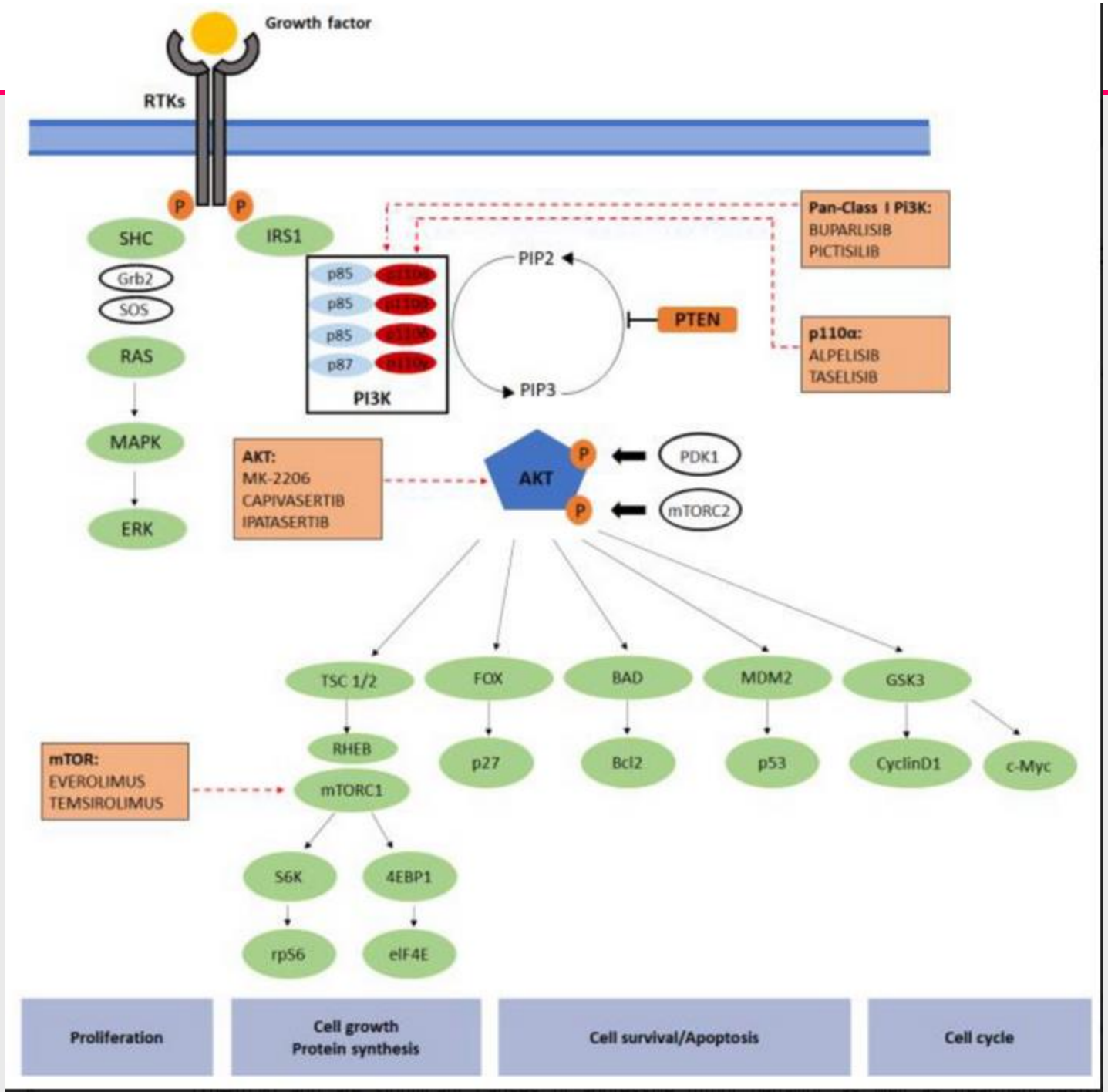
SABCS 2023

New Drug Approvals for Metastatic Breast Cancer

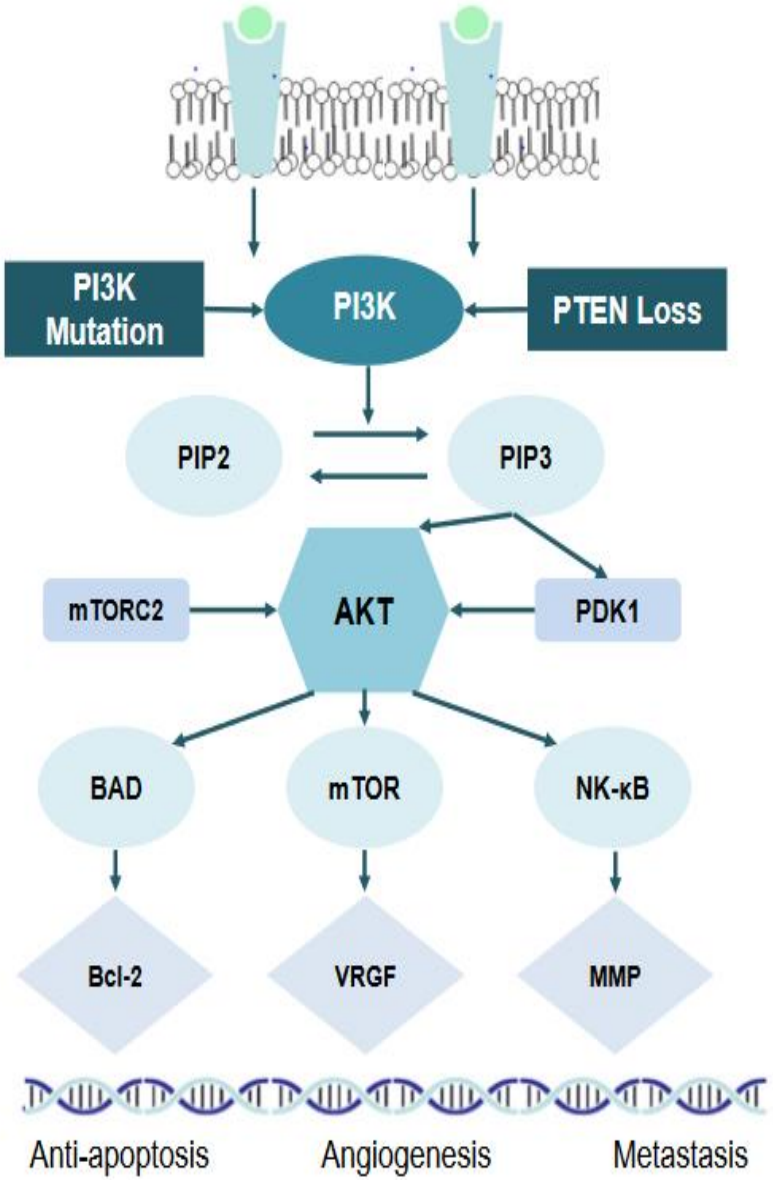
Capivasertib (TRUQAP®)

Christy Osgood, MD
Division of Oncology 1
FDA Office of Oncologic Diseases

December 5, 2023


Growth factor
RTKs
P
P
SHC
IRS1
Grb2
SOS
RAS
MAPK
ERK
p85
p85
p85
p87
PI3K
PIP2
PIP3
PTEN
Pan-Class I PI3K:
BUPARLISIB
PICTISILIB
p110α:
ALPELISIB
TASELISIB
AKT:
MK-2206
CAPIVASERTIB
IPATASERTIB
AKT
PDK1
mTORC2
TSC 1/2
FOX
BAD
MDM2
GSK3
RHEB
p27
Bcl2
p53
CyclinD1
c-Myc
mTOR:
EVEROLIMUS
TEMSIROLIMUS
mTORC1
S6K
4EBP1
rpS6
eIF4E
Proliferation
Cell growth
Protein synthesis
Cell survival/Apoptosis
Cell cycle

Biological Rationale



- PI3K gene commonly mutated
- AKT is key signal resulting in anti-apoptosis, angiogenesis, and metastasis
- Capivasertib
  - Serine/threonine kinase AKT inhibitor
  - Reduced in vivo and in vitro cell and tumor growth

Capivasertib

Approved Indication

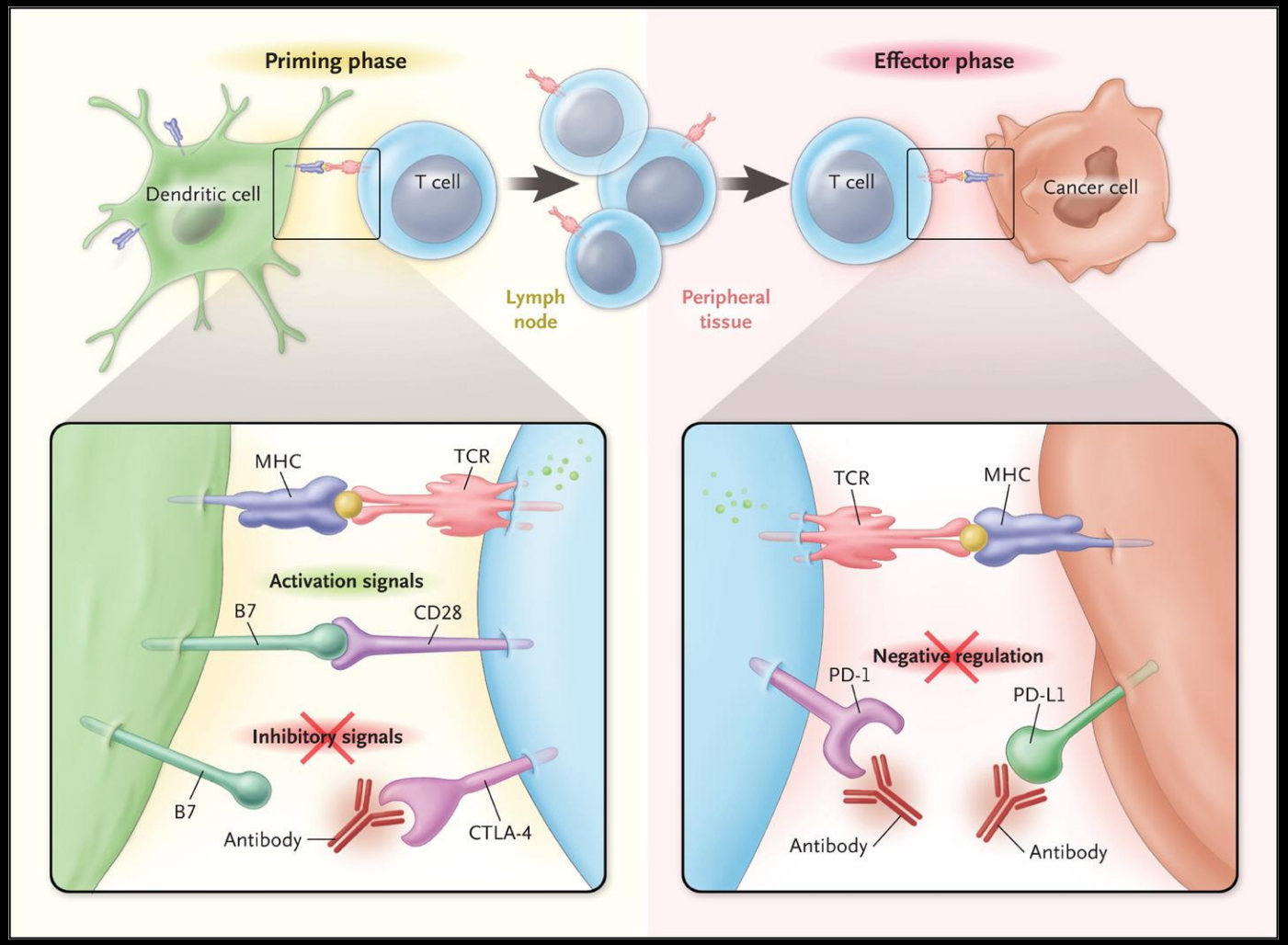
- In combination with fulvestrant for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alteration as detected by an FDA approved test following progression on at least one endocrine based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.

Approved Dose and Schedule

- Capivasertib 400 mg orally twice daily for 4 days followed by 3 days off in combination with
- Fulvestrant 500 mg IM on days 1,15, and 29 and once monthly thereafter

Neoadjuvant

Blockade of PD-1 or CTLA-4 Signaling in Tumor Immunotherapy.



Ribas A. N Engl J Med 2012;366:2517-2519.

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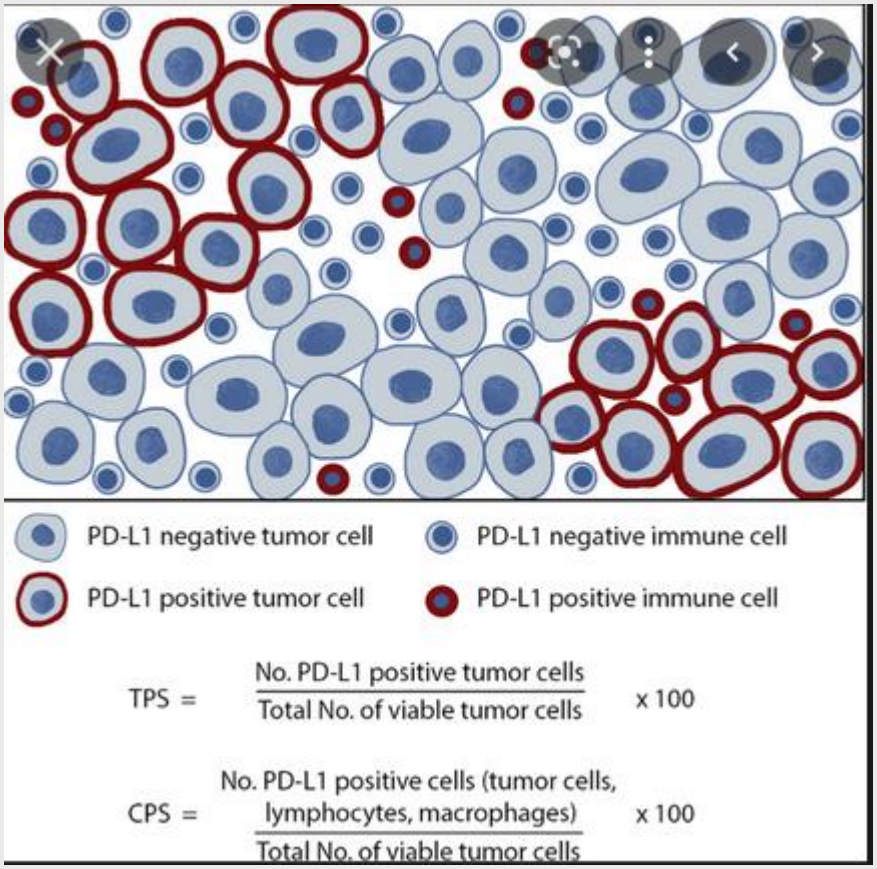

IC: Immune Cells
TPS: Tissue Positive Score
CPS: Combined Positive Score

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Biomarker results in high-risk estrogen receptor-positive, human epidermal growth factor receptor 2-negative primary breast cancer following neoadjuvant chemotherapy ± nivolumab: an exploratory analysis of CheckMate 7FL

Sherene Loi,[1] Giuseppe Curigliano,[2,3] Roberto Salgado,[1,4] Roberto Iván Romero Díaz,[5] Suzette Delaloge,[6] Carlos Ignacio Rojas García,[7] Marleen Kok,[8] Cristina Saura,[9] Nadia Harbeck,[10] Elizabeth A. Mittendorf,[11] Denise A. Yardley,[12] Lajos Pusztai,[13] Alberto Suárez Zaizar,[14] Andrei Ungureanu,[15] Felipe Ades,[16] Rajalakshmi Chandra,[16] Raheel Nathani,[16] Misena Pacius,[16] Thomas Spires,[16] Jenny Qun Wu,[16] Heather McArthur[17]

[1]Peter McCallum Cancer Center, Melbourne, Australia; [2]European Institute of Oncology, IRCCS, Milan, Italy; [3]University of Milan, Milan, Italy; [4]GZA-ZNA Hospitals, Antwerp, Belgium; [5]Consultorio de Oncólogo Médico, Oaxaca, Mexico; [6]Institut Gustave Roussy, Villejuif, France; [7]Bradford Hill Investigación Clinica, Región Metropolitana, Santiago, Chile; [8]Netherlands Cancer Institute, Amsterdam, The Netherlands; [9]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [10]Ludwig Maximilians University Hospital, Munich, Germany; [11]Dana Farber Cancer Institute, Boston, MA, USA; [12]Sarah Cannon Research Institute and Tennessee Oncology PLLC, Nashville, TN, USA; [13]Smilow Cancer Hospital at Yale, New Haven, CT, USA; [14]CENEIT Oncológicos, Mexico City, Mexico; [15]Radiotherapy Center CLUJ S.R.L., Florești, Romania; [16]Bristol Myers Squibb, Princeton, NJ, USA; [17]University of Texas Southwestern Medical Center, Dallas, TX, USA

Presentation number GS01-01

CA209-7FL study design

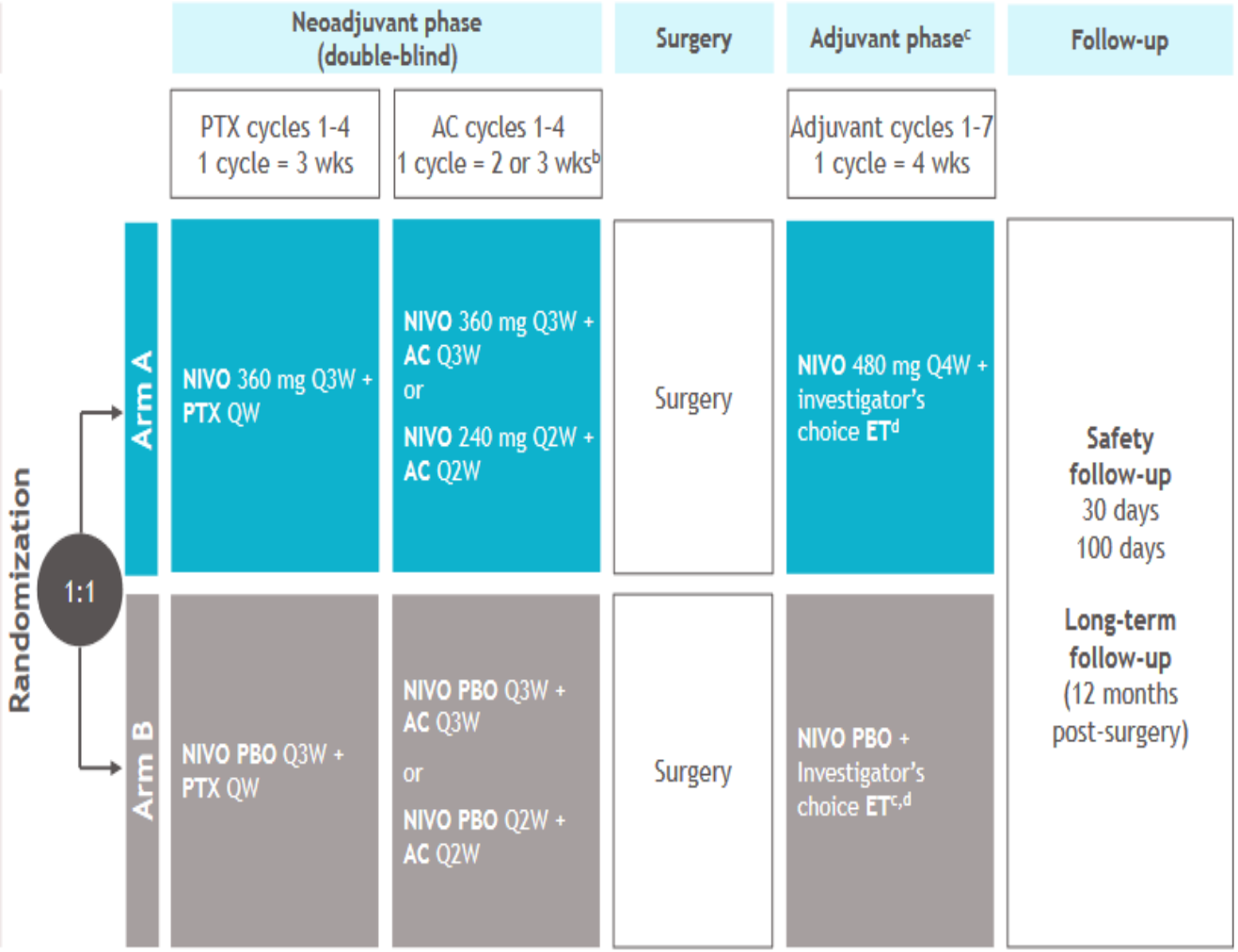
Screening

Key inclusion criteria

- Newly diagnosed ER+ HER2− breast cancer
- Confirmed ER+ breast cancer
- T1c (tumor size 2 cm only)-T2, cN1-cN2 or T3-T4, cN0-cN2
- Grade 3 with ER ≥ 1% or grade 2 with ER 1-10%[a]
- Adequate organ function
- Tissue available for biomarker assessment
- ECOG PS 0-1

Stratification factors

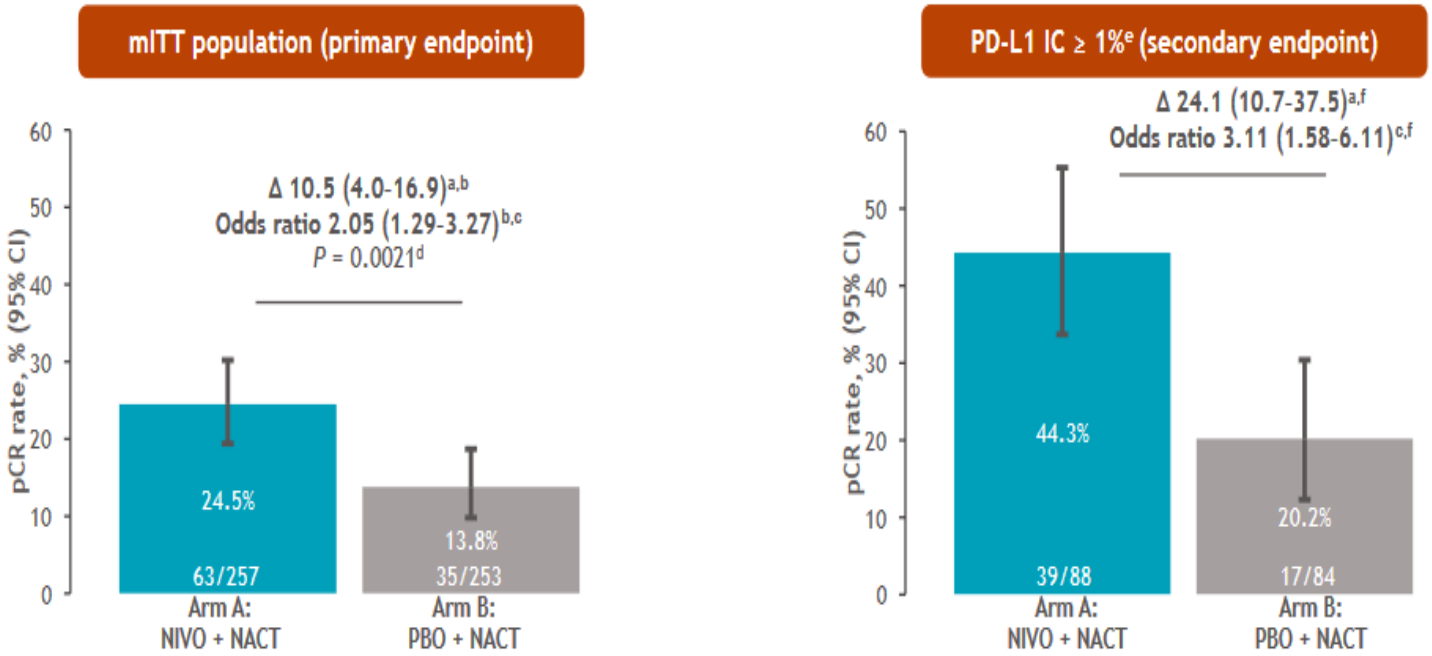
- PD-L1 IC (≥ 1% or < 1%) by SP142
- Tumor grade (3 or 2)
- Axillary nodal status (positive or negative)
- AC frequency (Q3W or Q2W)



[a]Grade was determined locally by investigator. [b]Investigator's choice: anthracycline dosing frequency of Q2W or Q3W for AC cycles determined by the investigator. [c]After protocol amendment 3, the study was unblinded in the adjuvant phase; participants in arm B did not receive NIVO PBO. [d]Available ET agents included tamoxifen, letrozole, anastrozole, and exemestane.
AC, anthracycline + cyclophosphamide; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; ET, endocrine therapy; HER2−, human epidermal growth factor receptor 2-negative; IC, immune cell; N, lymph node involvement; NIVO, nivolumab; PBO, placebo; PD-L1, programmed death ligand 1; PTX, paclitaxel; QXW, every X weeks; SP142, Ventana PD-L1 SP142 assay; T, size and extent of primary tumor; wk, week.

Introduction

- CheckMate 7FL (NCT04109066) is a prospective, randomized, multicenter, double-blind, placebo-controlled trial investigating the benefit of NIVO in combination with NACT and adjuvant ET in patients with high-risk, high-grade ER+ HER2− primary BC
- The addition of NIVO to NACT resulted in a statistically significant improvement in pCR (the primary endpoint) in the overall population (mITT: n = 510); RCB 0-1 rate was also meaningfully improved[1]
- Benefit of NIVO was greater in the PD-L1+ population (SP142 > 1%)



[a]Strata-adjusted difference in pCR (arm A−arm B) based on Cochran-Mantel-Haenszel method of weighting. [b]Stratified by PD-L1 by SP142 (< 1% vs ≥ 1%) and AC dose-frequency chemotherapy regimen (Q2W vs Q3W) per IRT. [c]Strata-adjusted odds ratio (arm A over arm B) using Mantel-Haenszel method. [d]Two-sided *P* value from stratified Cochran-Mantel-Haenszel test. [e]PD-L1 ICs and PD-L1-expressing tumor-infiltrating ICs as percentage of tumor area using the VENTANA SP142 assay. [f]Stratified by AC dose-frequency chemotherapy regimen.

AC, anthracycline + cyclophosphamide; CI, confidence interval; BC, breast cancer; ER, estrogen receptor; ET, endocrine therapy; HER2−, human epidermal growth factor receptor 2-negative; IC, immune cell; IRT, interactive response technology; mITT, modified intent-to-treat; NACT, neoadjuvant chemotherapy; NIVO, nivolumab; PBO, placebo; pCR, pathological complete response; PD-L1+, programmed death ligand 1-positive; QXW, every X weeks; RCB, residual cancer burden; SP142, Ventana PD-L1 SP142 assay.

1. Loi S, et al. Oral presentation at ESMO; October 20-24, 2023; Madrid, Spain. Abstract LBA20.

Summary

- CheckMate 7FL met its primary endpoint showing a statistically significant improvement in pCR with NIVO added to NACT in the mITT population[1]
  - Higher magnitude of benefit was observed in patients with PD-L1+ tumors defined by SP142 IC (≥ 1%)
- NIVO benefit on pCR and RCB 0-1 rates was the highest in patients with tumors with higher CPS, sTIL ≥ 5%, low ER (≤ 50%) and/or PR expression (≤ 10% in ER ≥ 10%)
  - Increased pCR was seen with any sTIL (>1%)
  - High pCR rates were observed in patients with CPS ≥10, 20
- No association between NIVO benefit and Ki67 was observed
- Moderate (~70-80%) overlap between the SP142 IC (≥ 1%), 28-8 CPS assays and sTIL was observed
- Additional exploratory and correlative analyses are ongoing to further refine the patient subpopulation with primary ER+/HER2– breast cancer who could benefit from the addition of NIVO to NACT

28-8 CPS, Dako 28-8 assay using CPS algorithm; CPS, combined positive score; ER(+), estrogen receptor(-positive); HER2–, human epidermal growth factor receptor 2-negative; IC, immune cell; NACT, neoadjuvant chemotherapy; NIVO, nivolumab; pCR, pathological complete response; PD-L1(+), programmed death ligand 1(-positive); PR, progesterone receptor; RCB, residual cancer burden; SP142, Ventana PD-L1 SP142 assay; sTIL, stromal tumor-infiltrating lymphocyte.

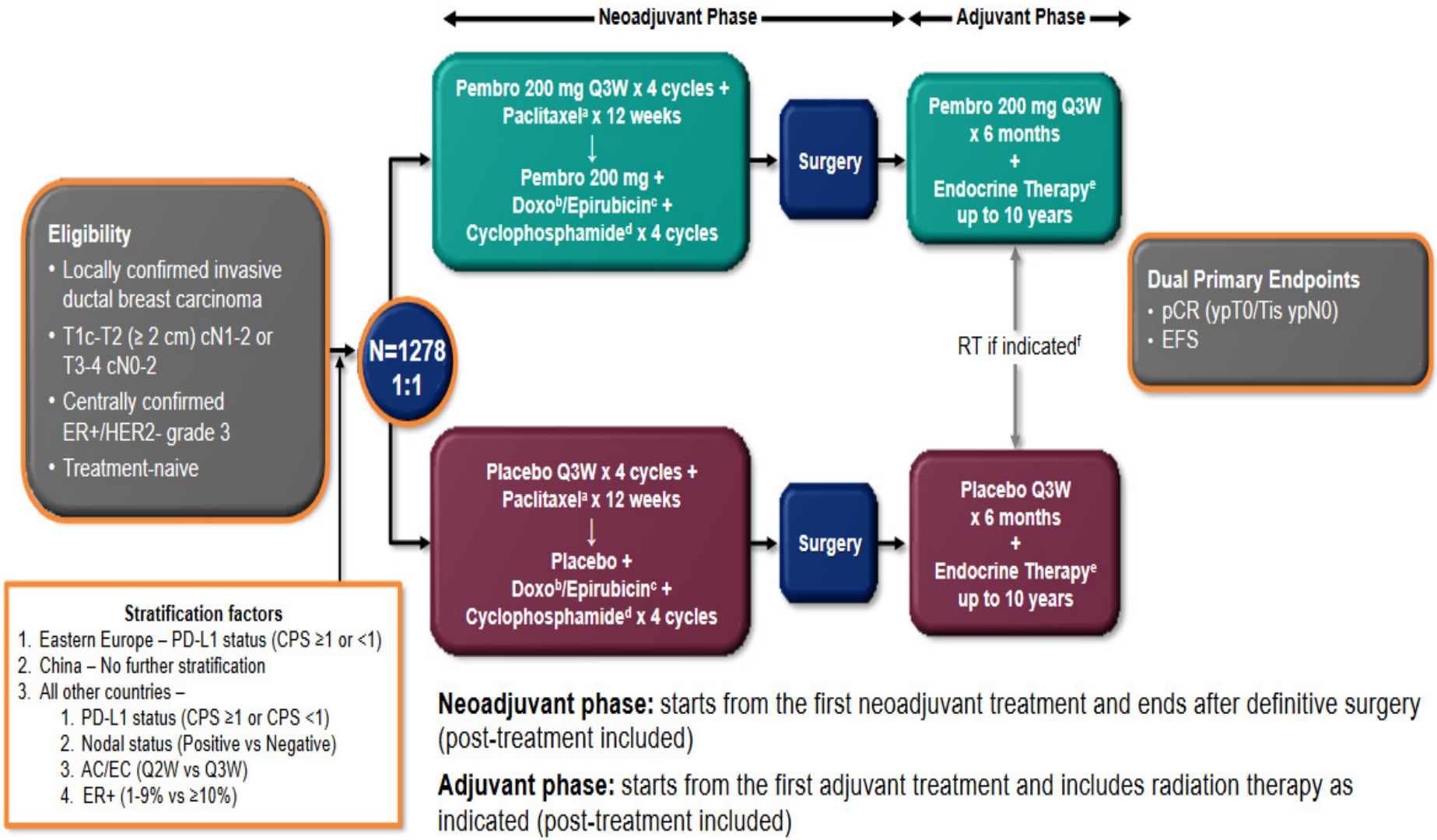
1. Loi S, et al. Oral presentation at ESMO; October 20-24, 2023; Madrid, Spain. Abstract LBA20.

Phase 3 Study of Neoadjuvant Pembrolizumab or Placebo Plus Chemotherapy, Followed by Adjuvant Pembrolizumab or Placebo Plus Endocrine Therapy for Early-Stage High-Risk ER+/HER2– Breast Cancer: KEYNOTE-756

Fatima Cardoso[1]; Joyce O'Shaughnessy[2]; Heather McArthur[3]; Peter Schmid[4]; Javier Cortes[5]; Nadia Harbeck[6]; Melinda L. Telli[7]; David W. Cescon[8]; Peter A. Fasching[9]; Zhimin Shao[10]; Delphine Loirat[11]; Yeon Hee Park[12]; Manuel Gonzalez Fernandez[13]; Gábor Rubovszky[14]; Seock-Ah Im[15]; Rina Hui[16,17]; Toshimi Takano [18]; Fabrice André[19]; Hiroyuki Yasojima[20]; Zhenzhen Liu[21]; Yu Ding[22]; Liyi Jia[22]; Vassiliki Karantza[22]; Konstantinos Tryfonidis[22]; Aditya Bardia[23]

[1]Champalimaud Clinical Centre/Champalimaud Foundation, Lisbon, Portugal; [2]Baylor University Medical Center, Texas Oncology, US Oncology Network, Dallas, TX, USA; [3]University of Texas Southwestern Medical Center, Dallas, TX, USA; [4]Centre for Experimental Cancer Medicine, Barts Cancer Institute, Queen Mary University London, London, UK; [5]International Breast Cancer Center, Quironsalud Group, Barcelona, Spain and Universidad Europea de Madrid, Faculty of Biomedical and Health Sciences, Department of Medicine, Madrid, Spain; [6]Breast Center, Dept. OB&GYN, LMU University Hospital, Munich, Germany; [7]Stanford University School of Medicine, Stanford, CA, USA; [8]Princess Margaret Cancer Centre, Toronto, Ontario, Canada; [9]University Hospital Erlangen, Comprehensive Cancer Center Erlangen-EMN, Bavarian Cancer Research Center (BZKF), Erlangen, Germany; [10]Department of Breast Surgery, Fudan University Shanghai Cancer Center, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China; [11]Institut Curie, Paris, France; [12]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [13]Hemato Oncólogo, IMAT-Oncomedica, Montería, Colombia; [14]National Institute of Oncology, Budapest, Hungary; [15]Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea; [16]Westmead Breast Cancer Institute, Westmead Hospital and the University of Sydney, Sydney, NSW, Australia; [17]Centre of Cancer Medicine, the University of Hong Kong, Hong Kong; [18]The Cancer Institute Hospital of JFCR, Tokyo, Japan; [19]Faculté de Medicine Paris-Sud XI, Gustave Roussy, Villejuif, France; [20]NHO Osaka National Hospital, Osaka, Japan; [21]Henan Breast Cancer Center, Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, Henan, China; [22]Merck & Co., Inc., Rahway, NJ, USA; [23]Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

KEYNOTE-756 Study Design (NCT03725059)

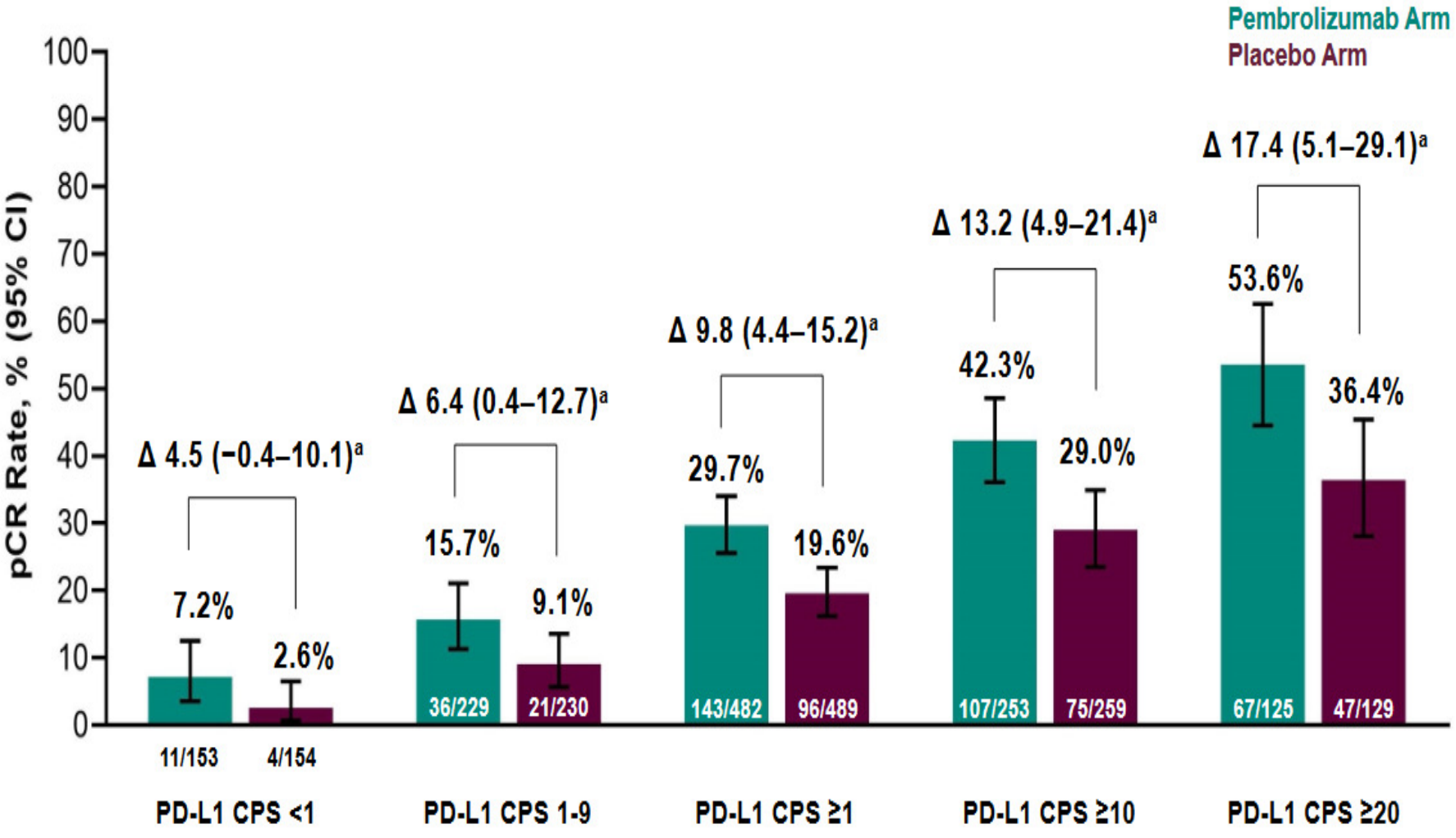


Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post-treatment included)

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

[a]Paclitaxel dose was 80 mg/m² QW. [b]Doxorubicin dose was 60 mg/m² Q3W. [c]Epirubicin dose was 100 mg/m² Q3W. [d]Cyclophosphamide dose was 600 mg/m² Q3W or Q2W.
[e]Endocrine therapy was administered according to institution guidelines. [f]Radiation therapy (concurrent or sequential) was administered according to institution guidelines.

Pathological Complete Response at IA1 by PD-L1 Expression Level



[a]Estimated treatment difference based on Miettinen & Nurminen method stratified by geographic region (China vs Eastern Europe vs all other countries). Data cutoff date: May 25, 2023.

Summary

- Addition of pembrolizumab to neoadjuvant chemotherapy led to a statistically significant increase in pCR in the ITT population
- Addition of pembrolizumab increased pCR rates in subgroups defined by geography, stage, baseline clinical lymph node involvement, and different levels of PD-L1 expression
- A larger magnitude of pCR benefit was observed in patients with node-positive disease, higher PD-L1 CPS thresholds, and ER-low tumors (<10%)
- Patients who received less than the planned chemotherapy doses had lower pCR rates, although pCR rates were improved with pembrolizumab regardless of chemotherapy exposure (ie, full exposure or less than full exposure)
- Addition of pembrolizumab to neoadjuvant chemotherapy shifted more patients to lower residual cancer burden categories (RCB 0–1)
- Immune-mediated AE rates were consistent with the known toxicity profile of pembrolizumab plus neoadjuvant chemotherapy and no new safety concerns were observed
- The study is powered to evaluate EFS as the dual primary endpoint; EFS results are immature and continue to be evaluated

Adjuvant

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Mays Cancer Center UT Health MD Anderson Cancer Center
AACR American Association for Cancer Research

Adding atezolizumab to adjuvant chemotherapy for stage II and III triple-negative breast cancer is unlikely to improve efficacy: interim analysis of the ALEXANDRA/IMpassion030 phase 3 trial

Michail Ignatiadis[1], MD, PhD, Andrew Bailey[2], Heather McArthur[3], MD, PhD Sarra El-Abed[4], Evandro De Azambuja[1], Otto Metzger[5], Stephen Y. Chui[6], Max Dieterich[7], Thomas Perretti[7], Guenther Steger[8], Jacek Jassem[9], Soo Chin Lee[10], Michaela Higgins[11], Jose Zarba[12], Marcus Schmidt[13], Henry Gomez[14], Angel Guerrero Zotano[15], Luca Moscetti[16], Joanne Chiu[17], Carter DuFrane[5], Vanessa Honvault[1], Rosa Altarcheh-Xifro[4], Luciana Molinero[6], Andrew Ellingson[2], Elisabetta Munzone[18], Noa Efrat Ben-Baruch[19], Emilio Bajetta[20], Shinji Ohno[21], Seock-Ah Im[22], Gustavo Werutsky[23], Einav Nili Gal-Yam[24], Xavier Gonzalez Farre[25], Ling-Ming Tseng[26], William Jacot[27], Oleg Gluz[28], Zhimin Shao[29], Yaroslav Shparyk[30], Ivan Sinielnikov[31], Anastasia Zimina[32], Vasiliev Aleksander[33], Esther Shearer-Kang[6], Eric Winer[5], Diogo Martins Branco[1], Shona Fielding[2], David Cameron[34], Giuseppe Viale[18], Shigehira Saji[35], Richard Gelber[2,5], Martine Piccart[1].

[1]Institut Bordet, Brussels, Belgium, [2]Frontier Science, [3]Simmons Cancer Center at UT Southwestern Medical Center, Dallas USA. [4]Breast International Group, Brussels, Belgium, [5]Dana-Farber Cancer Institute, Boston , USA , [6]Genentech Inc., South San Francisco, CA, USA, [7]F. Hoffmann-La Roche Ltd, Basel, Switzerland, [8]Medical University of Vienna, Austria, [9]Medical University of Gdansk, Poland, [10]National University Hospital Singapore, [11]Cancer Trials Ireland, [12]National University of Tucaman, Argentina, [13]Comprehensive Cancer Center University Medical Center Mainz, Germany, [14]National Institute of Neoplatic diseases, Lima, Peru, [15]Oncology Institute, Valencia, Spain, [16]Azienda University Hospital, Modena, Italy, [17]Queen Mary Hospital & Gleneagles Hospital Hong Kong, [18]IEO, European Institute of Oncology IRCCS, Milan, Italy, [19]Kaplan Medical Center, Israel, [20]Instituto Nationale Tumori, Milan, Italy, [21]The Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan, [22]Seoul National University college of Medicine, Korea, [23]Hospital São Lucas PUCRS, Porto Alegre, Brasil, [24]Breast Oncology Institute, Sheba MC, Israel, [25]International University of Catalonia, Barcelona, Spain, [26]Taipei Veterans General Hospital, Taiwan , [27]Institut Regional du Cancer, Montpellier, France, [28]Breast Center Niederrhein, Mönchengladbach, Germany, [29]Fudan University Cancer Institute, Shanghai, China, [30]Lviv National Medical University, Ukraine, [31]The Municipal Enterprise Volyn Regional Medical Oncology Centre of the Volyn Regional Council, Lutsk, Ukraine, [32]Omsk Clinical Oncological Dispensary, Omsk, Russian Federation, [33]Moscow State University of Medicine and Dentistry, Russian Federation, [34]The University of Edinburgh, UK, [35]Fukushima Medical University, Fukushima, Japan.

Alexandra/IMpassion030 phase 3 open-label study design

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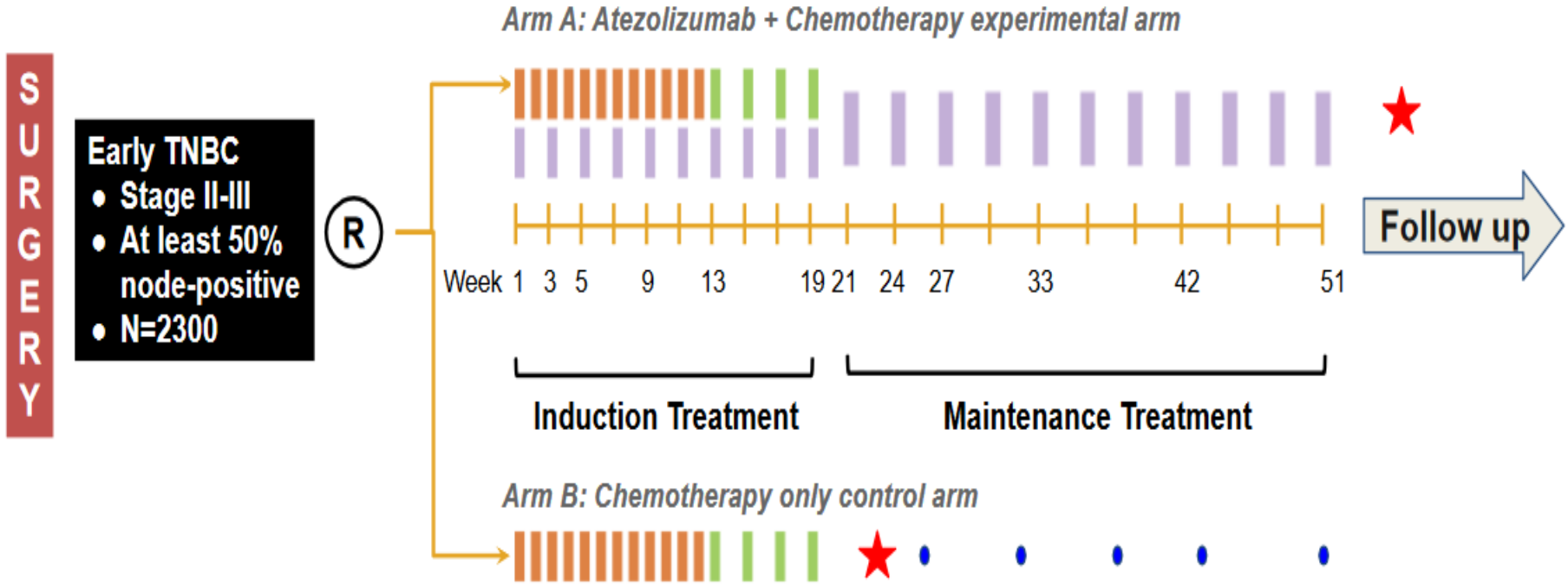

Stratification factors:

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)

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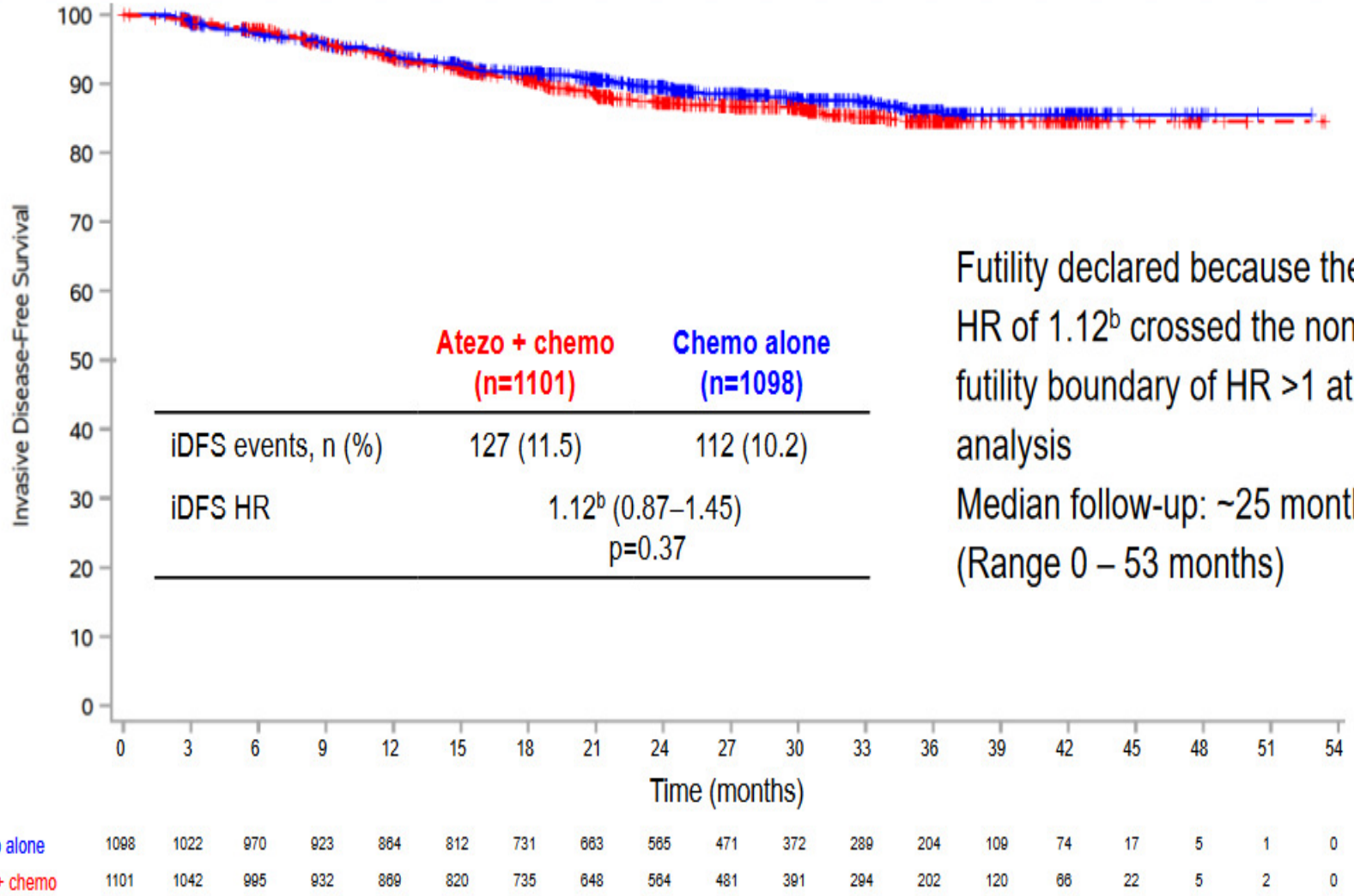


	Atezo + chemo (n=1101)	Chemo alone (n=1098)
iDFS events, n (%)	127 (11.5)	112 (10.2)
iDFS HR	1.12[b] (0.87–1.45) p=0.37	

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

Conclusions

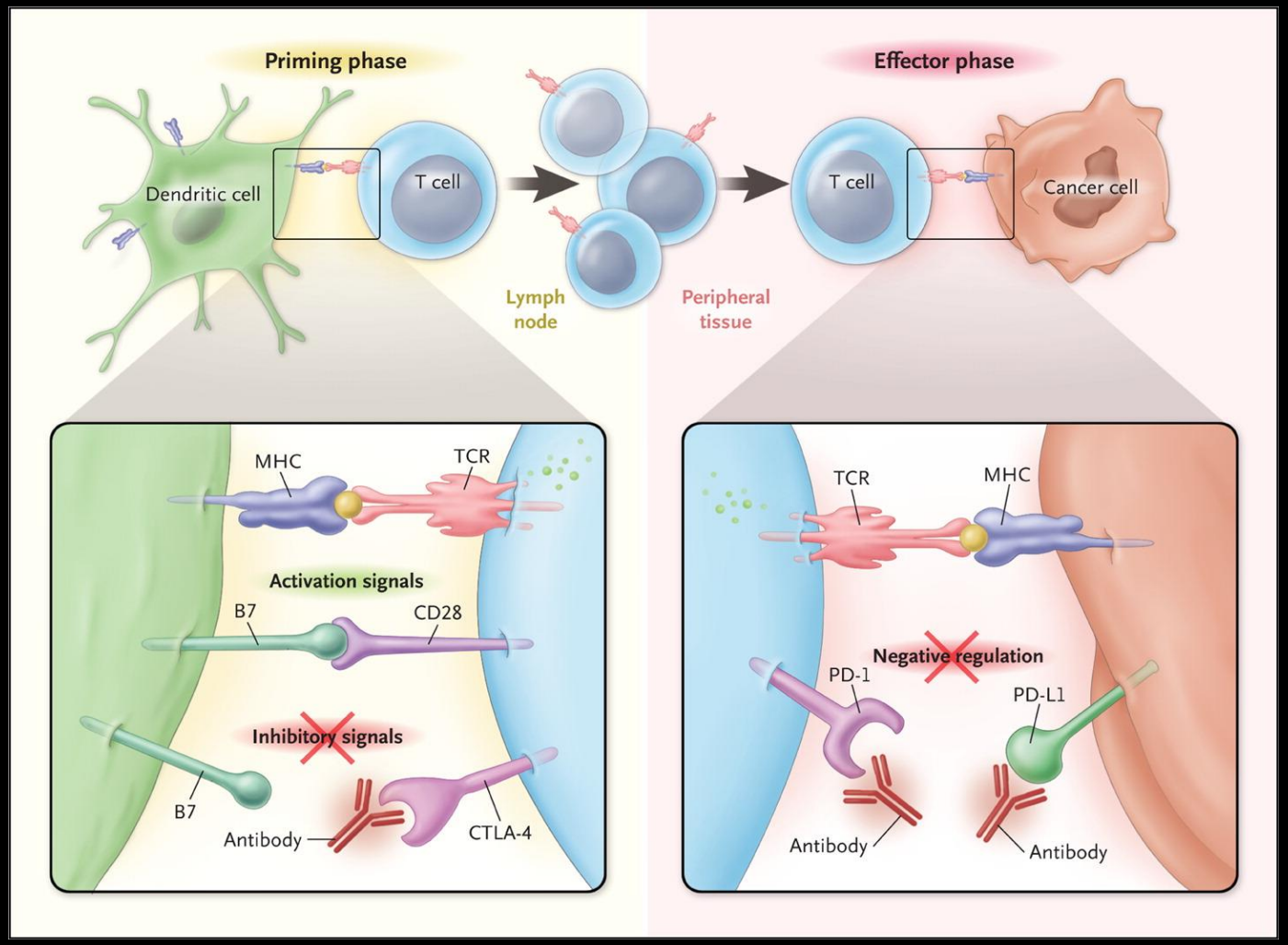
- At the requested interim analysis of the phase 3 ALEXANDRA/IMpassion030 trial, HR for iDFS in the ITT population (primary endpoint) crossed the pre-specified futility boundary (HR>1), HR 1.12 [0.87–1.45].
- The primary endpoint together with secondary efficacy endpoints do not support the addition of atezolizumab to adjuvant chemotherapy in patients who have undergone primary surgery for early TNBC.
- Safety data were consistent with the known safety profile of atezolizumab in early TNBC (IMpassion031)[1] and across indications with numerically more AEs, grade 3/4 AEs and SAEs in the atezolizumab arm.
- Addition of atezolizumab did not compromise delivery of the SoC chemotherapy backbone.
- Study data are being updated to a clinical cut-off of 17 November 2023, and results will be published based on the final database. Moreover, the study partners will conduct translational research in this unique dataset.
- The ALEXANDRA/IMpassion030 trial contributes to an improved understanding about the optimal use of immunotherapy in patients with early TNBC.

[1] E A Mittendorf et al, The Lancet 2020; 396: 1090–100

Checkpoint-Inhibitoren

Immunvermittelte Nebenwirkungen

Blockade of PD-1 or CTLA-4 Signaling in Tumor Immunotherapy.



Ribas A. N Engl J Med 2012;366:2517-2519.

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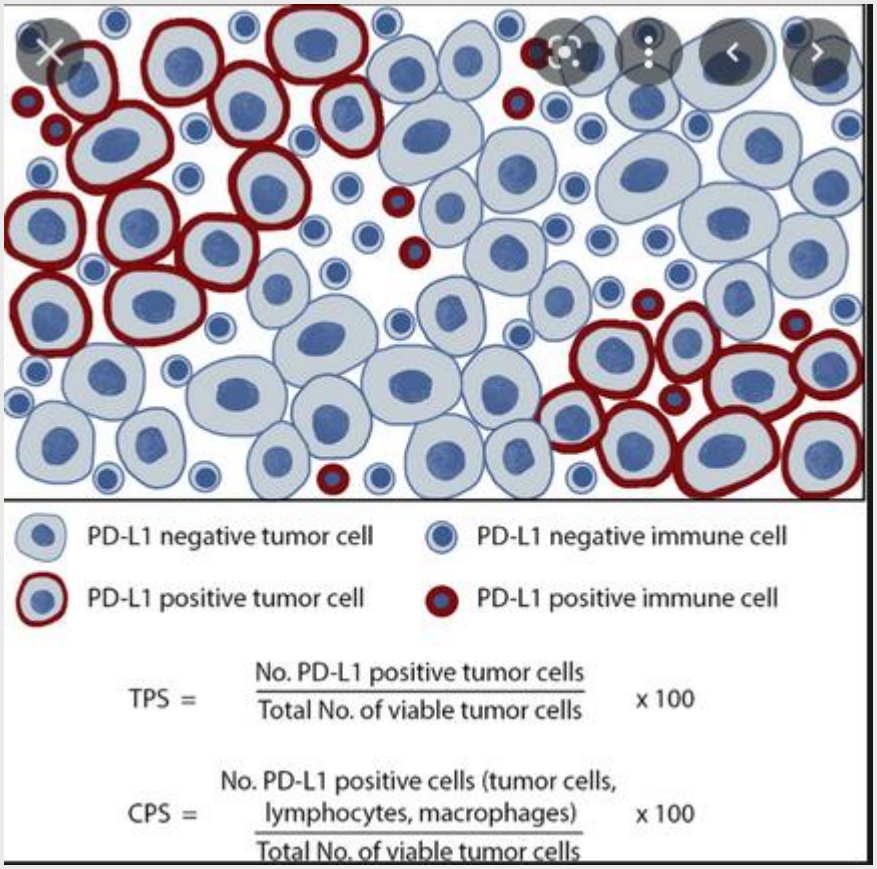
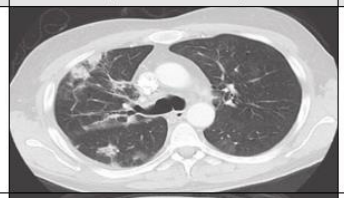
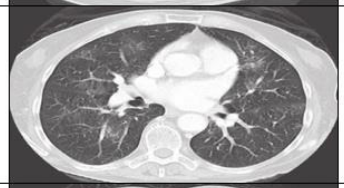
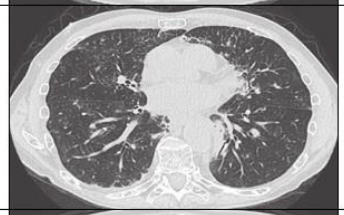
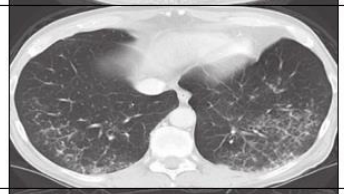
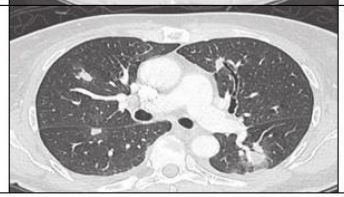


IC: Immune Cells
TPS: Tissue Positive Score
CPS: Combined Positive Score

Immune checkpoint inhibitors by mechanism

Drug mechanism	Drug name
Anti-PD-1	▪ Nivolumab ▪ Pembrolizumab ▪ Cemiplimab ▪ Dostarlimab ▪ Retifanlimab
Anti-PD-L1	▪ Atezolizumab ▪ Avelumab ▪ Durvalumab
Anti-CTLA-4	▪ Ipilimumab ▪ Tremelimumab
Anti-LAG-3/anti-PD-1	▪ Relatlimab and nivolumab

Pneumonitis with anti-PD-1/PD-L1 therapy

Radiologic subtypes	Representative image	Description
Cryptogenic organizing pneumonia-like (n = 5, 19%)		▪ Discrete patchy or confluent consolidation with or without air bronchograms ▪ Predominantly peripheral or subpleural distribution
Ground glass opacities (n = 10, 37%)		▪ Discrete focal areas of increased attenuation ▪ Preserved bronchovascular markings
Interstitial (n = 6, 22%)		▪ Increased interstitial markings, interlobular septal thickening ▪ Peribronchovascular infiltration, subpleural reticulation ▪ Honeycomb pattern in severe patient cases
Hypersensitivity (n = 2, 7%)		▪ Centrilobular nodules ▪ Bronchiolitis-like appearance ▪ Tree-in-bud micronodularity
Pneumonitis not otherwise specified (n = 4, 15%)		▪ Mixture of nodular and other subtypes ▪ Not clearly fitting into other subtype classifications

Radiologic features of pneumonitis associated with anti-PD-1/PD-L1 therapy stratified into five distinct phenotypes.

PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1.

From: Naidoo J, Wang X, Woo KM, et al. Pneumonitis in Patients Treated With Anti-Programmed Death-1/Programmed Death Ligand 1 Therapy. J Clin Oncol 2016; 35:709. DOI: 10.1200/JCO.2016.68.2005.

Management of lung irAEs in patients treated with immune checkpoint inhibitors*

3.1. Pneumonitis

Work-up and evaluation:

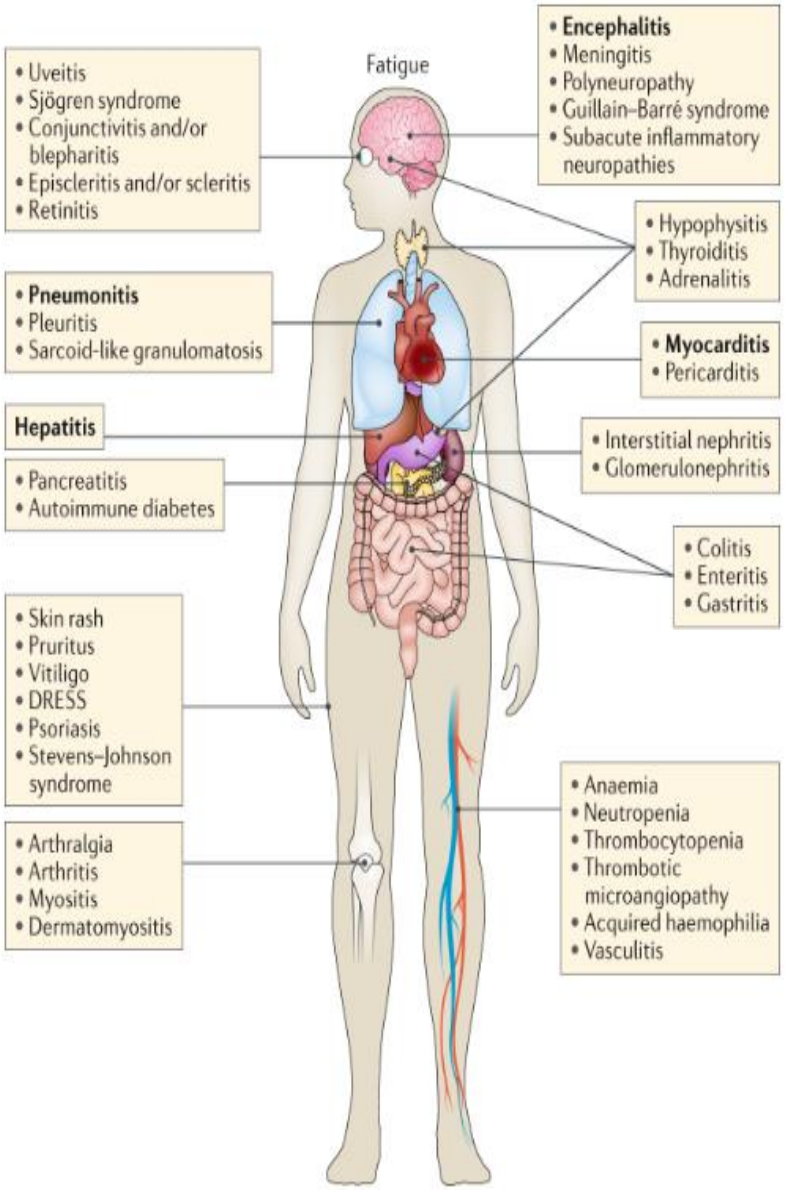
- Should include the following: Pulse oximetry and CT chest preferably with contrast if concerned for other etiologies such as pulmonary embolus.
- For G2 or higher, may include the following infectious work-up: nasal swab, sputum culture, and sensitivity, blood culture and sensitivity, urine culture, and sensitivity.
- COVID-19 evaluation – per institutional guidelines where relevant.

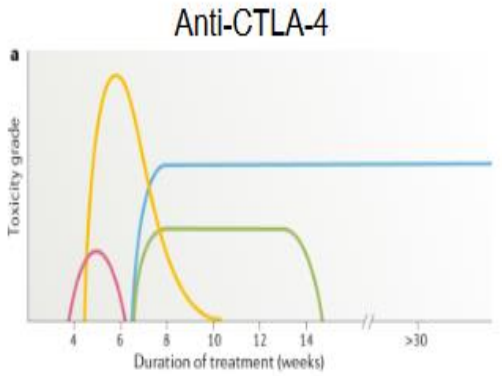
Grading	Management
G1: Asymptomatic; confined to one lobe of the lung or <25% of lung parenchyma; clinical or diagnostic observations only.	▪ Hold ICPi or proceed with close monitoring. ▪ Monitor patients weekly with history and physical examination, pulse oximetry; may also offer chest imaging (CXR, CT) if uncertain diagnosis and/or to follow progress. ▪ Repeat chest imaging in 3 to 4 weeks or sooner if patient becomes symptomatic. ▪ In patients who have had baseline testing, may offer a repeat spirometry or DLCO in 3 to 4 weeks. ▪ May resume ICPi with radiographic evidence of improvement or resolution if held. If no improvement, should treat as G2.
G2: Symptomatic; involves more than one lobe of the lung or 25 to 50% of lung parenchyma; medical intervention indicated; limiting instrumental ADL.	▪ Hold ICPi until clinical improvement to ≤G1. ▪ Prednisone 1 to 2 mg/kg/day and taper over 4 to 6 weeks. ▪ Consider bronchoscopy with BAL ± transbronchial biopsy. ▪ Consider empiric antibiotics if infection remains in the differential diagnosis after work-up. ▪ Monitor at least once per week with history and physical examination, pulse oximetry, consider radiologic imaging; if no clinical improvement after 48 to 72 hours of prednisone, treat as grade 3. ▪ Pulmonary and infectious disease consults if necessary.
G3: Severe symptoms; hospitalization required: involves all lung lobes or >50% of lung parenchyma; limiting self-care ADL; oxygen indicated. G4: Life-threatening respiratory compromise; urgent intervention indicated (intubation).	▪ Permanently discontinue ICPi. ▪ Empiric antibiotics may be considered. ▪ Methylprednisolone IV 1 to 2 mg/kg/day. ▪ If no improvement after 48 hours, may add immunosuppressive agent. Options include infliximab or mycophenolate mofetil IV or IVIG or cyclophosphamide. Taper corticosteroids over 4 to 6 weeks.* ▪ Pulmonary and infectious disease consults if necessary. ▪ May consider bronchoscopy with BAL ± transbronchial biopsy if patient can tolerate.

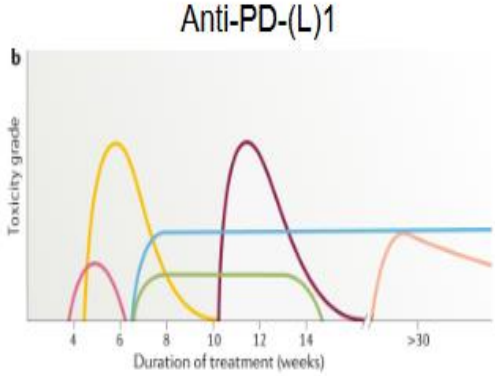
ADL: activity of daily living; BAL: bronchoalveolar lavage; CT: computed tomography; CXR: chest x-ray; DLCO: diffusing capacity of lung for carbon monoxide; ICPi: immune checkpoint inhibitor; IV: intravenous; IVIG: intravenous immune globulin.

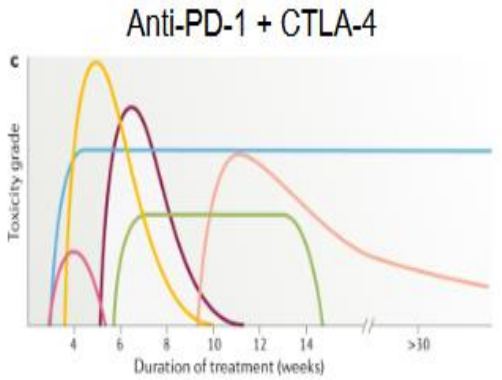
* Subset of patients may develop chronic pneumonitis and may require longer taper. Chronic pneumonitis is a described phenomenon where the incidence is not known, but <2%.

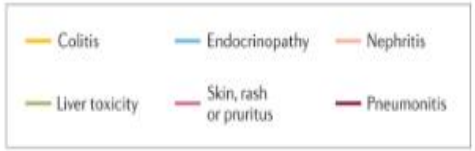
A new toxicity profile: immune related adverse events (irAEs)





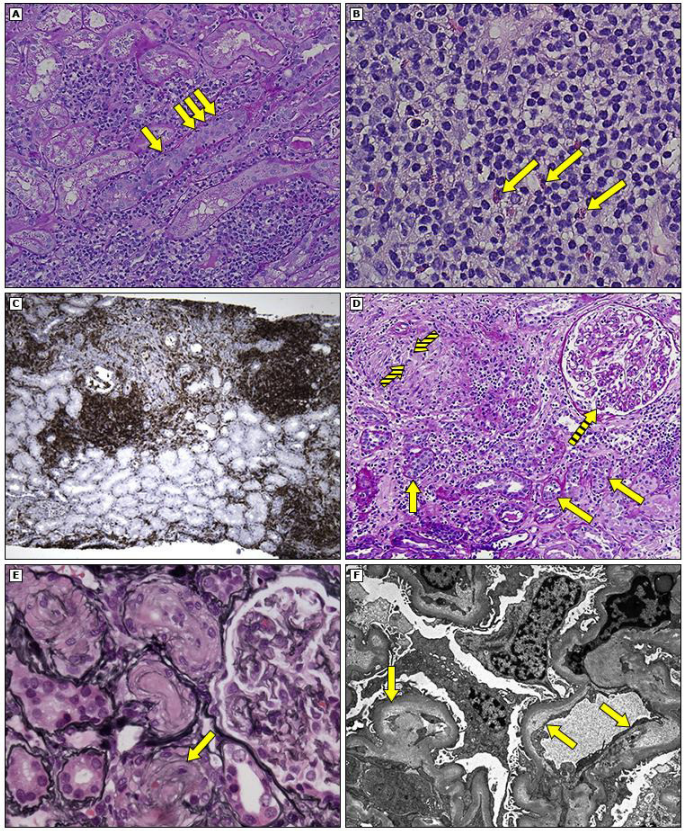






Martins et al., *Nature Reviews Clinical Oncology 2019*

Representative images of checkpoint inhibitor-induced acute kidney injury



Core needle biopsy specimens (A-C) from patient 9 show "typical" features of acute tubulointerstitial nephritis; (D) from patient 2 show granulomatous acute tubulointerstitial nephritis; (E,F) from patient 8 show acute thrombotic microangiopathy.

(A) Periodic acid-Schiff stain shows diffuse interstitial inflammation and focal severe tubulitis with infiltrating lymphocytes (arrows, times 200; bar = 50 mcg).

(B) Hematoxylin and eosin stain shows diffuse interstitial infiltrates predominantly composed of lymphocytes, with several eosinophils (arrows, times 400; bar = 25 mcg).

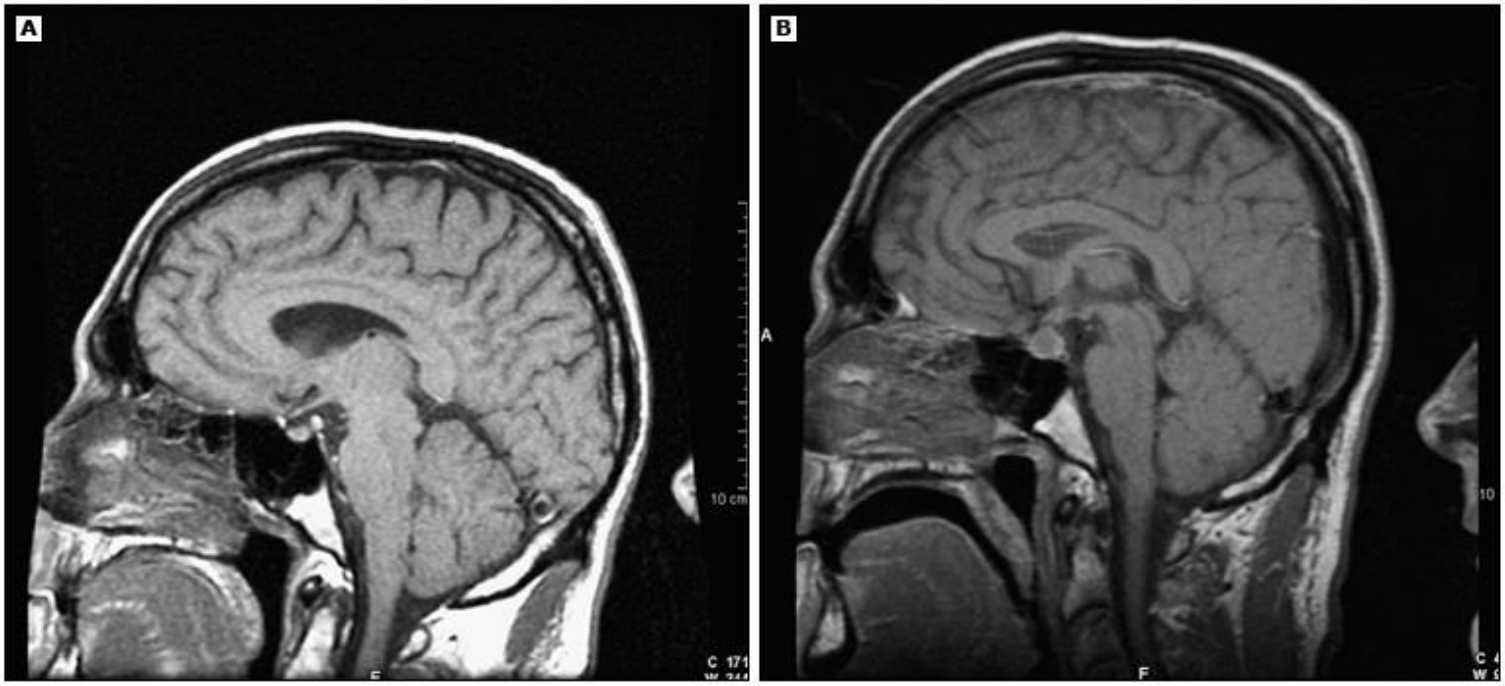
(C) Immunohistochemistry reveals the lymphocytic infiltrates in the interstitium to be predominantly CD4b T cells (times 40; bar = 100 mcg).

(D) Periodic acid-Schiff stain shows a noncaseating granuloma with multinucleated giant cells (striped arrows), severe interstitial inflammation and tubulitis (arrows), and severe glomerulitis (dashed arrow, times 200; bar = 50 mcg).

(E) Silver stain shows diffusely wrinkled glomerular basement membranes and "onion-skin" lesion of small arteries (arrow, times 200; bar = 50 mcg).

(F) Electron microscopy shows swollen endothelium and subintimal widening filled with electron-lucent "fluffy" material (arrows, times 1400; bar = 4 mcg).

Hypophysitis associated with checkpoint inhibition



06/30/04 - Baseline (4.5 mm) **12/03/04 - Headache/fatigue (10.8 mm)**

Sagittal MRI section from patient 7 before anti-CTLA-4 antibody treatment and after onset of clinical symptoms. Pituitary height is in parentheses.

MRI: magnetic resonance imaging.

Cardio-Onkologie

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Mays Cancer Center UT Health San Antonio MD Anderson Cancer Center
AACR American Association for Cancer Research

Debate: Anthracyclines...To give or not to give?

Moderator: Harold Burstein
Martine Piccart
Virginia Borges

Early signs of cardiac damage before ↓LVEF!

- New echocardiographic, more sensitive parameters
  - Diastolic function
  - Global longitudinal strain
- Cardiac biomarkers
  - Troponin I
  - Natriuretic peptides
  - Myeloperoxidase
- Novel circulating biomarkers
  - Circulating cardiomyocyte cell free DNA
  - Circulating microRNAS

ANTHRACYCLINE CARDIOTOXICITY

Early intervention with cardioprotective agents

Lisinopril (ACE inh) or Carvedilol (BB) Shown to prevent cardiotoxicity (HR≈ 0.50) in 184 patients receiving anthracyclines followed by trastuzumab (randomized, double blind, placebo controlled trial)

Ky JACC 2014, thevindina Nathan JACC 2014

Zhas JACC 2020, Lakhani Scient Reports 2021,

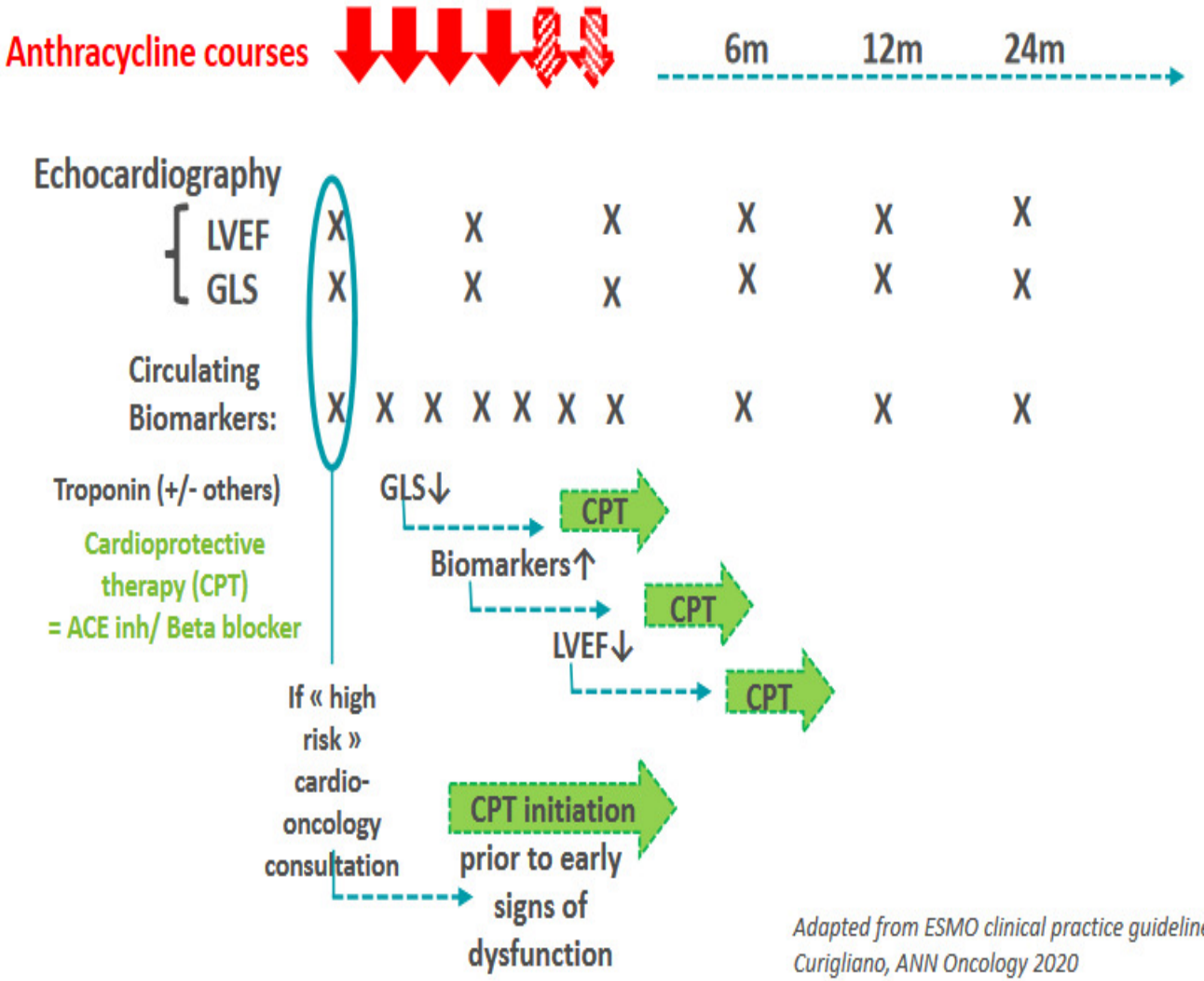
Yu Jana Candik 2023

Guglin, J Am Coll Cardiol 2019

IMPROVED « TOOLS » anthracycline +/- trastuzumab cardiotoxicity monitoring and management

Cardiovascular risk factors

- Age> 60
- Diabetes
- Hypertension
- Dyslipidemia
- Smoking
- Obesity
- Combined therapies
  - RT
  - Anti HER2
  - Cyclophosphamide
- Prior chest RT

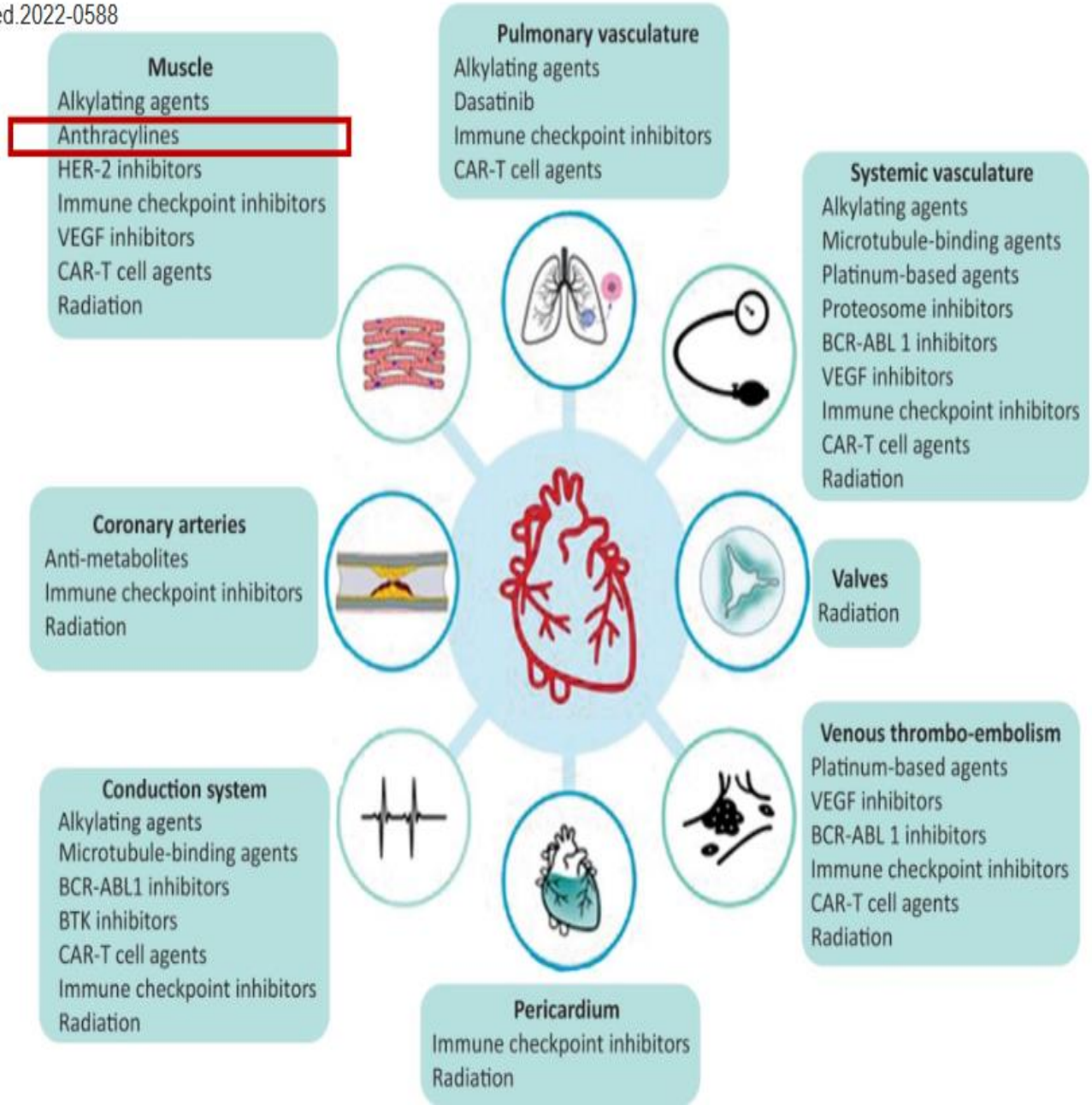


Adapted from ESMO clinical practice guidelines Curigliano, ANN Oncology 2020

Essentials of cardio-oncology

Vera Vaz Ferreira and Arjun K Ghosh

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



Zusammenfassung:

-Nivolumab und Pembrolizumab steigern die pCR-Rate in der Neoadjuvanz beim ER-positven Brustkrebs mit hohem Rezidivrisiko

-Atezolizumab steigert nicht das Überleben in der Adjuvanz beim triple negativen Brustkrebs

-Auf immunvermittelte Nebenwirkungen sollte während und -nach einer Immunonkologischen Therapie geachtet werden

-Die Indikationsstellung von Anthrazyklinen sollte gut überlegt sein

-Auf die Herzgesundheit ist vor, während und nach einer zytoreduktiven Therapie zu achten