Neoadjuverende behandling

Biomarkører

Anne-Vibeke Lænkholm

Patologiudvalget

NACT seminar 4-5 november 2019

Kapitel 16 NACT

- NACT kan tilbydes patienter, der vurderes at være kandidater til adjuverende kemoterapi, og som har klinisk tumorstadie klassificeret som T2: (2,0 cm < tumor <= 5.0 cm), N0-N1 og histologisk påvist invasivt c. mammae af ikke-lobulær type.

- Bestemmelse af biomarkører (på nålebiopsi og operationspræparat)
  - ER
  - HER2
  - (Ki67)

- Malignitetsgradering (på nålebiopsi?)

Eksempel biomarkør

Klinisk validitet og klinisk anvendelighed

Behandling

Patologi rapport

Evidensgrundlag/Biomarkører
- analytisk validitet
- klinisk validitet
- klinisk anvendelighed

- Vævshåndtering
- nålebiopsi/kirurgisk præparat
- fiksering

Præ-analytisk

Analyseplatfom
- Assay/ antistof

Analyse

Aflæsning (scoring)

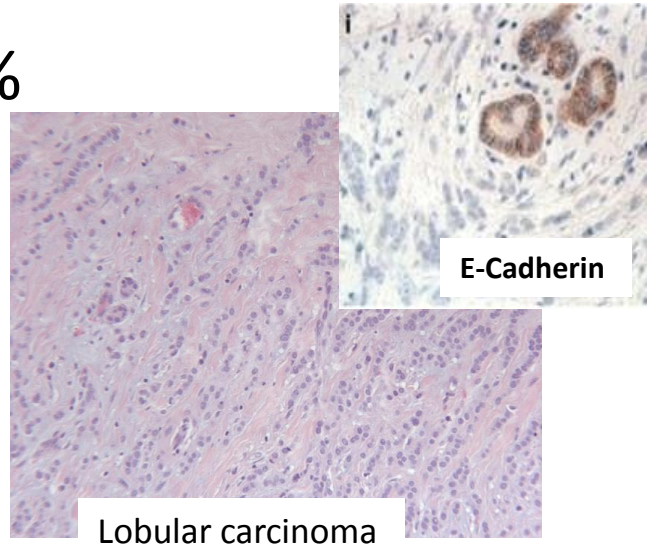
Post-analytisk

Kold iskæmitid – 1 time
Fiksering –
underfiksering (mængde formalin/formalin diffusion: 1mm/time)
overfiksering

Classification of malignant tumors of the breast
WHO blue books series

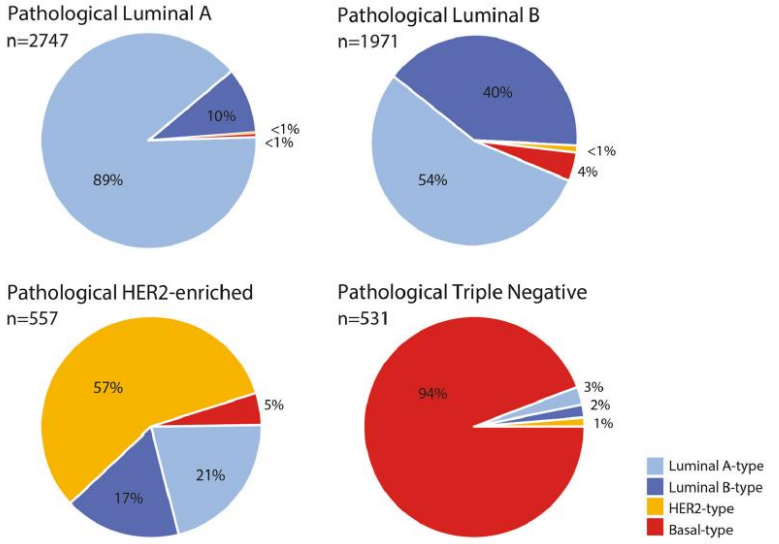
Histological subtypes

- Ductal : up to 80%
- Lobular: 5 - 14%
- Tubular: 2 - 8%
- Mucinous: 2 - 4 %
- Apocrine: 1 – 4%
- Papillary 1 – 2%
- Other



Intrinsic molecular subtypes

- **Luminal A**: ER+, low proliferative
- **Luminal B**: ER+, high(er) proliferative, (HER2+)
- **HER2 Enriched:** (HER2 positive)
- **Basallike:** (ER-, HER2-)



Breast Cancer Research and Treatment
January 2018, Volume 167, Issue 1, pp 123–131

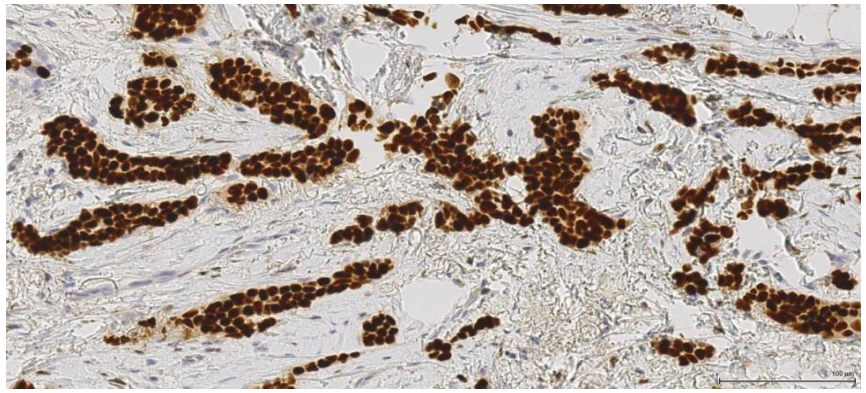
Immunhistokemisk fænotype
Receptorstatus DK

2017
Indikatorrapport

ER+:
1-9%, N= 75 (2%)
≥10%, N= 3273 (86%)

HER2+:
N= 559 (15%)

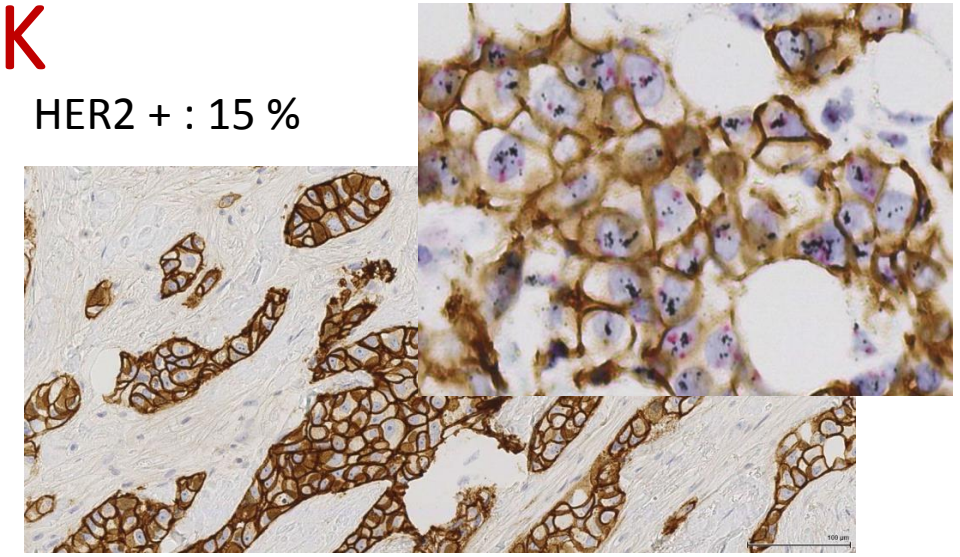
ER + : 88 % (cut-off 1%)



IHC

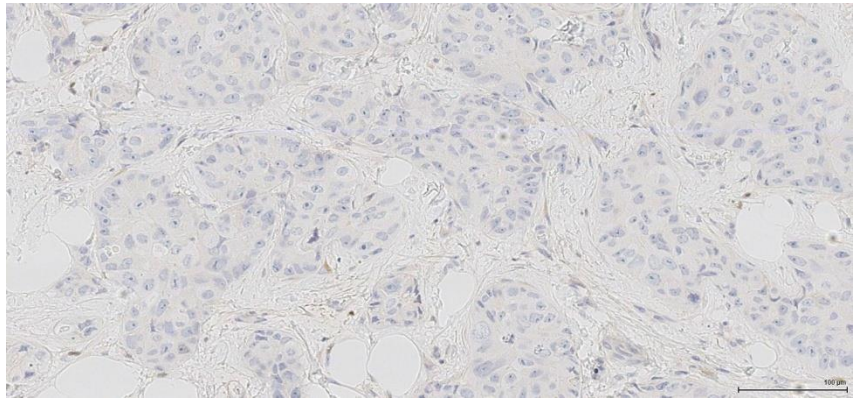
HER2 + : 15 %

In situ hybridisering



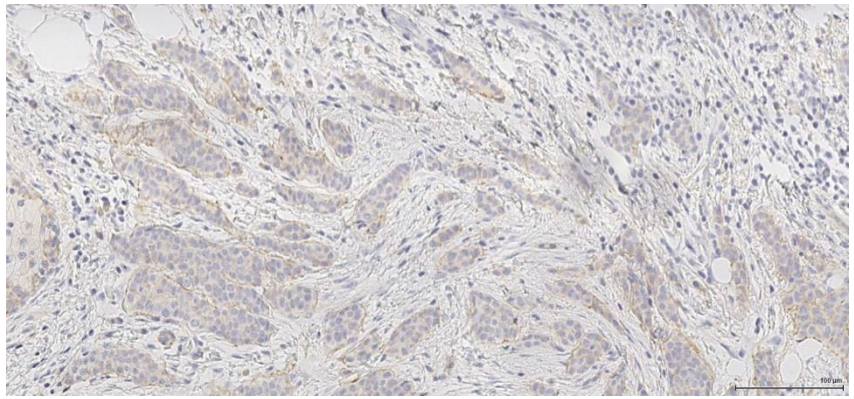
IHC

ER -



IHC

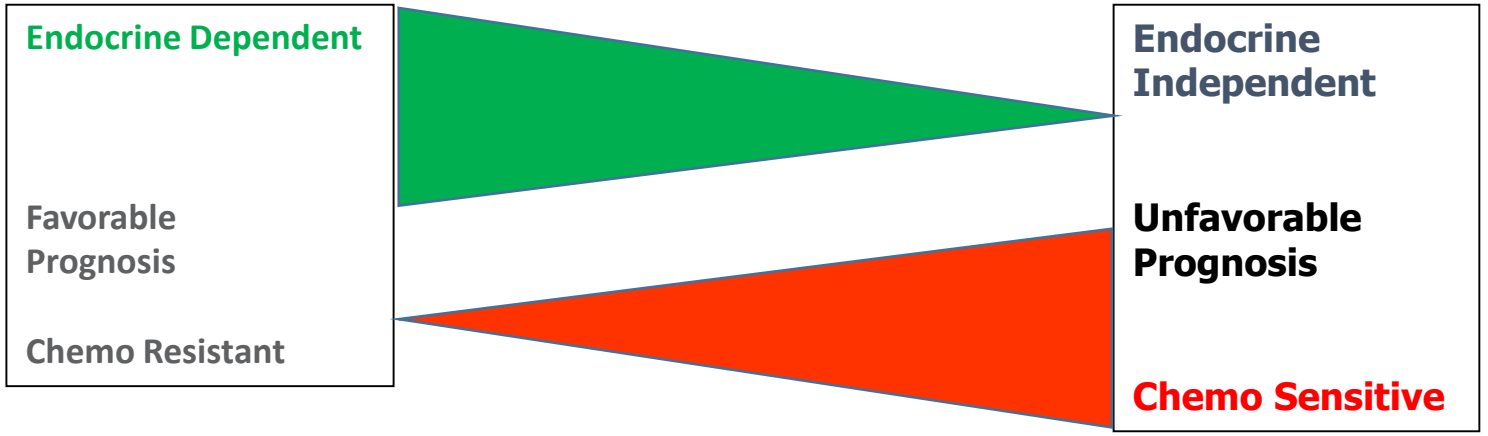
HER2 -

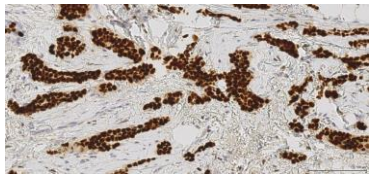
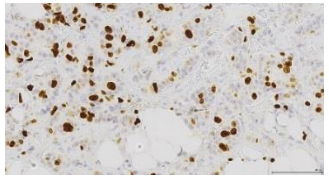
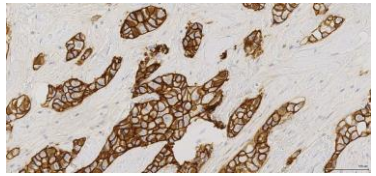
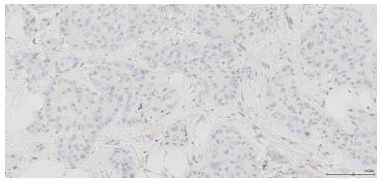
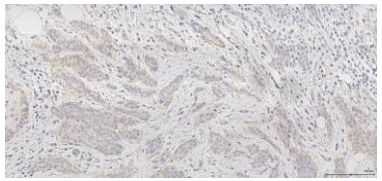


IHC

ER og HER2 negative: ca. 10%

Brystkræft – Molekylære subtyper



Luminal A	Luminal B	HER2-enriched	Basal-like	
				ER negative
ER positive Lum B har større aktivitet af proliferationsrelaterede gener		HER2 positive		HER2 negative

Overensstemmelse mellem lokal og central evaluering af:

- Histologisk subtype: 88%
- Malignitetsgrad: 68-72%, kappa 0.561
- ER: 96-97%
- PR: 88% kappa 0.721; cut-off 10%
- HER2: 94-96%, kappa 0.810
- Ki67 manglende analytisk validitet
    - *Polley et al. JNCI 2013, Polley et al. Mod Pathol 2015, Leung et al. npj Breast Cancer 2016, Leung et al. Histopathology 2019*

Annals of Oncology 21: 40–47, 2010

J Clin Oncol 34:2341-2349. 2016

Internationale guidelines biomarkøranalyser

- ASCO, Update 2019 (TAYLORx): use of biomarkers to guide systemic therapy

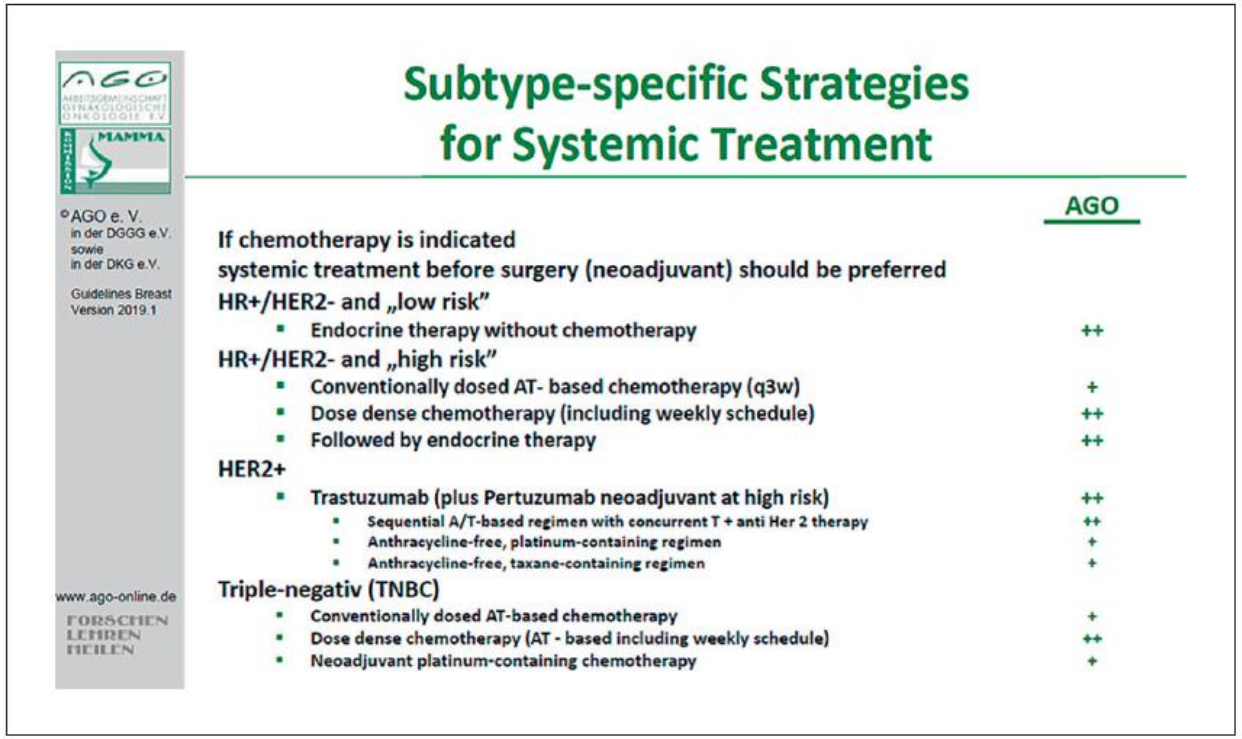
VOLUME 34 · NUMBER 10 · APRIL 1, 2016

JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline

Lyndsay N. Harris, Nofisat Ismaila, Lisa M. McShane, Fabrice Andre, Deborah E. Collyar, Ana M. Gonzalez-Angulo, Elizabeth H. Hammond, Nicole M. Kuderer, Minetta C. Liu, Robert G. Mennel, Catherine Van Poznak, Robert C. Bast, and Daniel F. Hayes

- The Breast Commitee of the German Gynecological Oncology group (AGO) update 2019
- NACT: Subtype-Specific Therapies



Review

Clinical use of biomarkers in breast cancer: Updated guidelines from the European Group on Tumor Markers (EGTM)

M.J. Duffy [a,*], N. Harbeck [b], M. Nap [c], R. Molina [d], A. Nicolini [e], E. Senkus [f], F. Cardoso [g]

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[d] *Laboratory of Biochemistry, Hospital Clinic, Barcelona, Spain*
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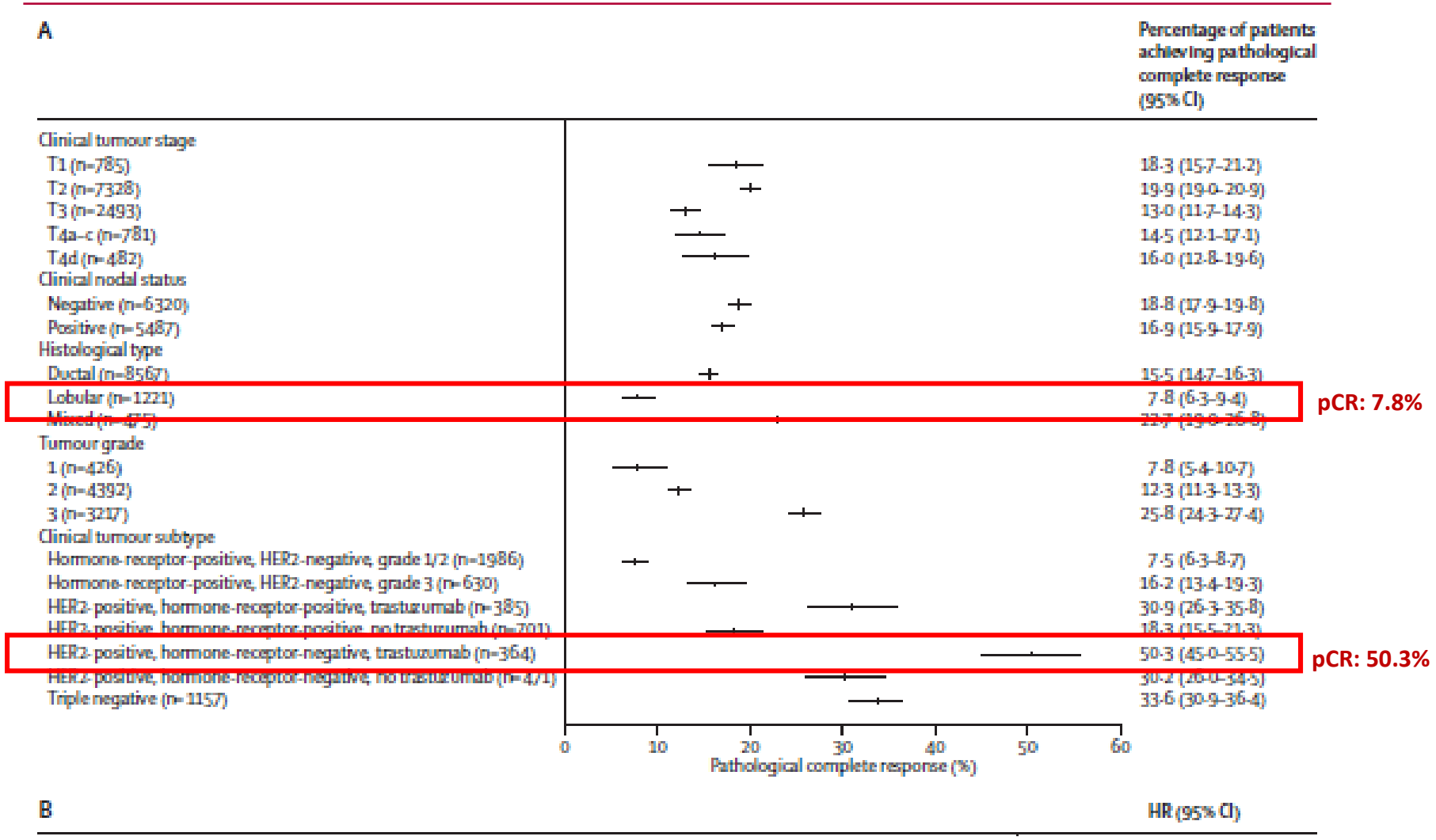
[f] *Department of Oncology and Radiotherapy, Medical University of Gdańsk, Gdańsk, Poland*
[g] *Breast Unit, Champalimaud Clinical Centre, Lisbon, Portugal*

Received 4 July 2016; received in revised form 12 October 2016; accepted 13 January 2017
Available online 28 February 2017

European Journal of Cancer 75 (2017) 284–298

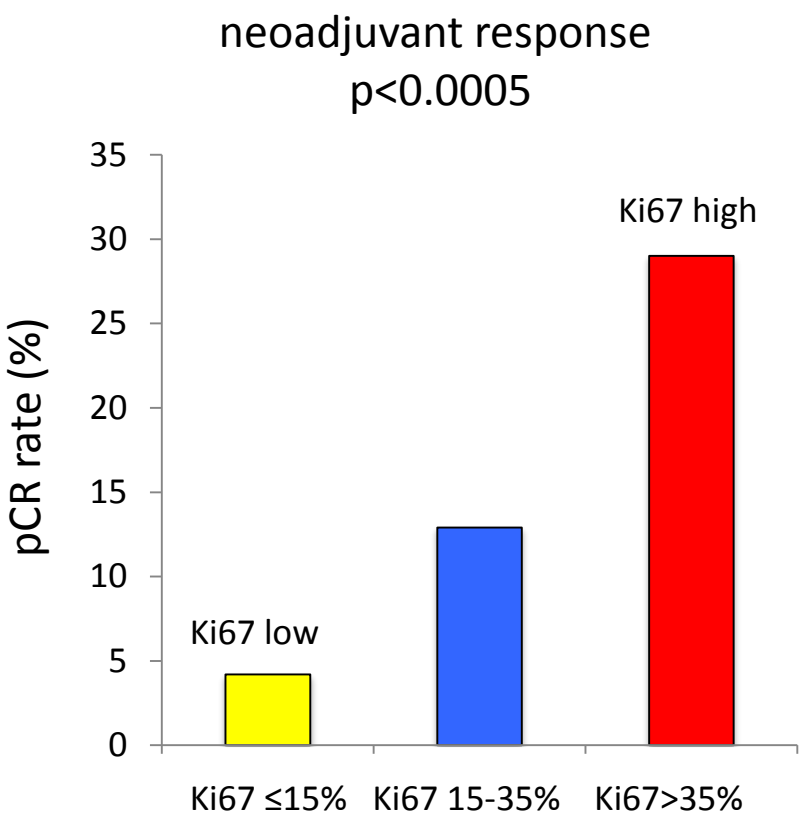
Breast Care 2019;14:224–245

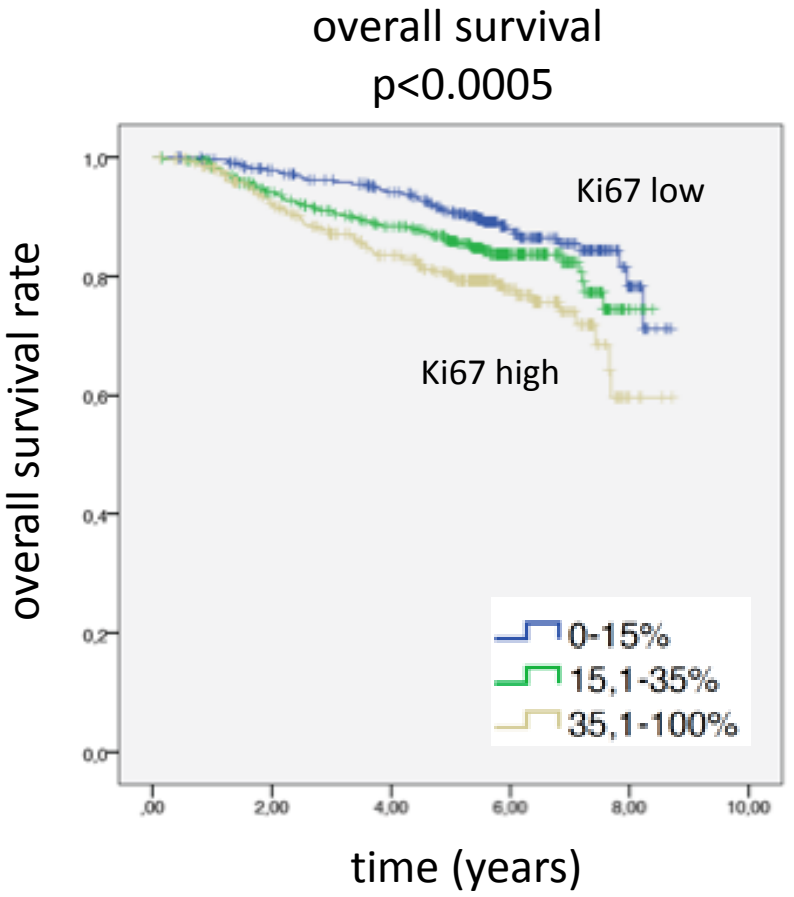
Tumor characteristics and association with pCR
Lobular carcinoma not recommended for neoadjuvant treatment



Cortazar et al. Lancet 2014; 384: 164-72

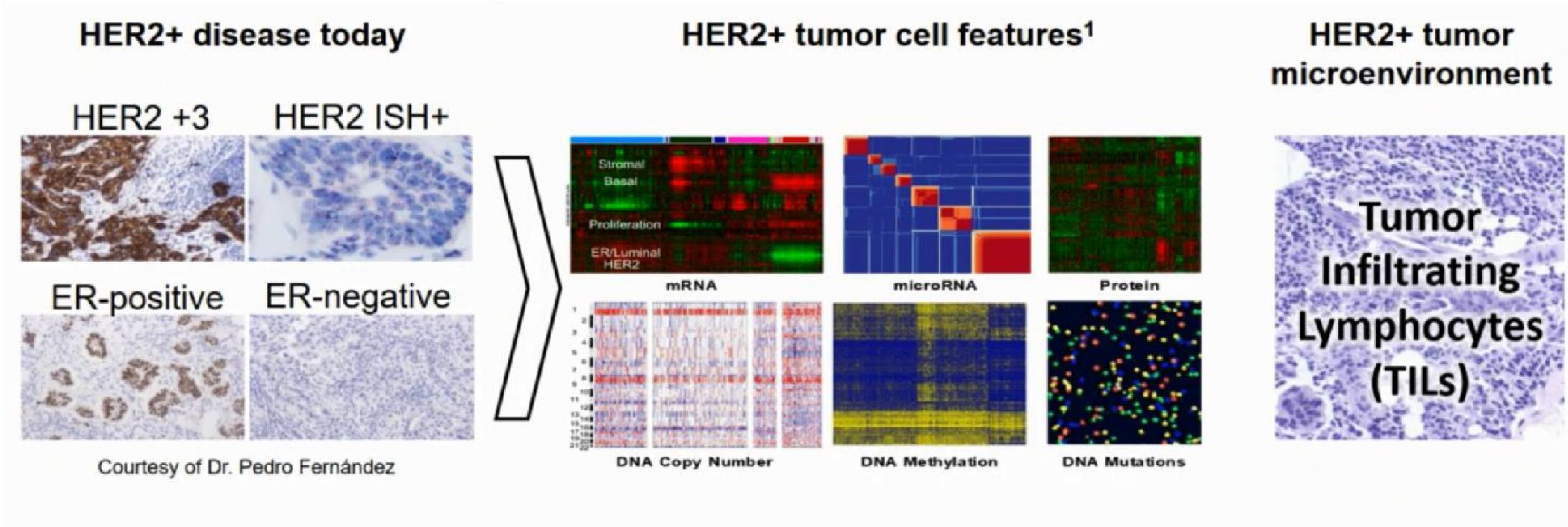
Ki67 – positive predictive and negative prognostic marker





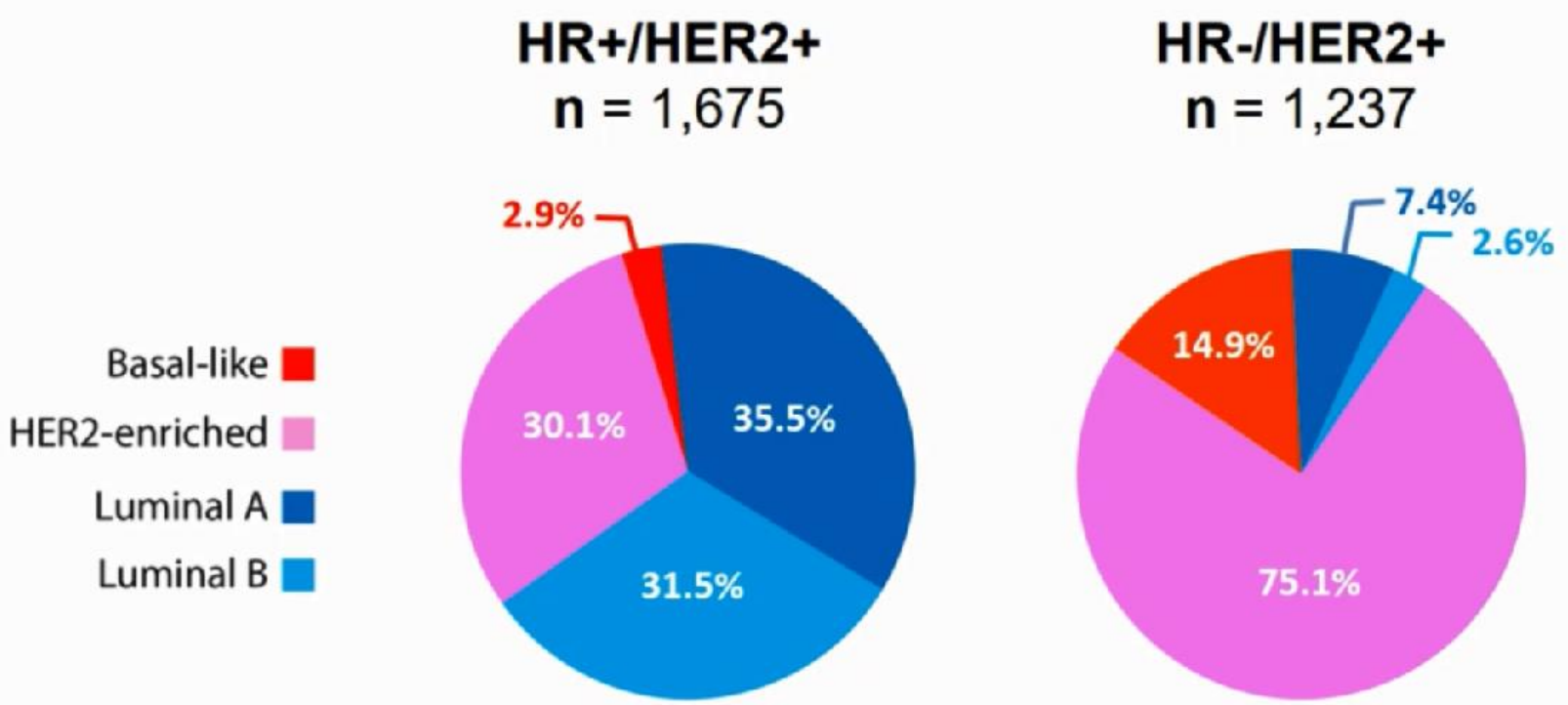
GeparTrio study, Denkert et al., Ann. Oncol, 2013

HER2 positiv brystkræft er en heterogen sygdom



Prat A. ESMO 2019

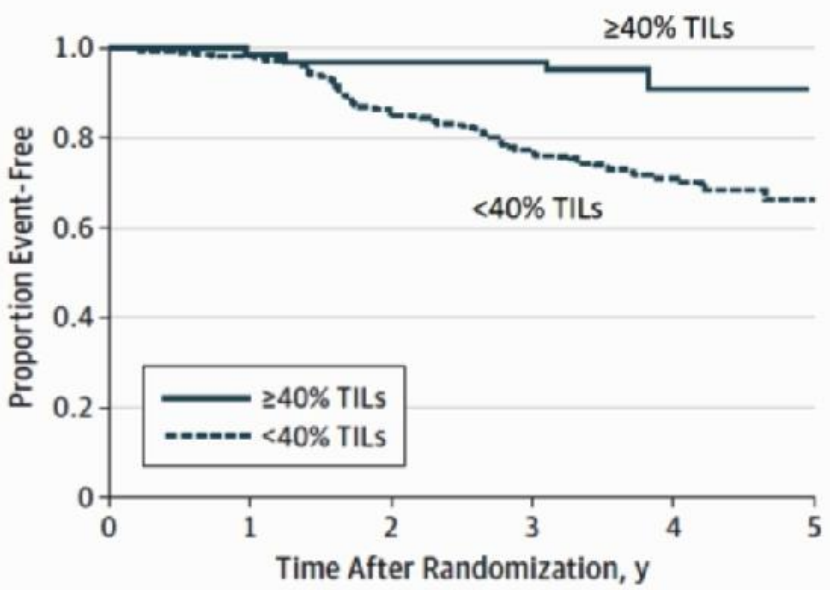
The intrinsic subtypes within HER2+ breast cancer

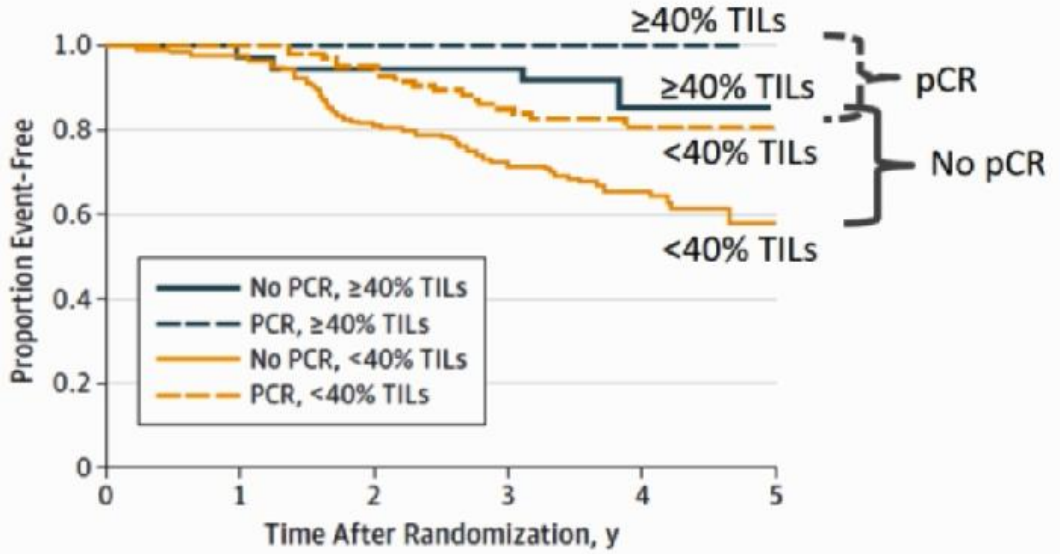


HER2-E subtype represents 50-60% of all HER2+ tumors

1. Cancer Genome Atlas Network Nature 2012; 490:61–70
2. Prat et al. J Natl Cancer Inst. 2014;106 (8)
3. Cejalvo et al. Cancer Treat Rev 2018
4. Cejalvo JM, et al. Ann Oncol. 2017 vol 28 suppl 5

TILs and outcome in NeoALTTO

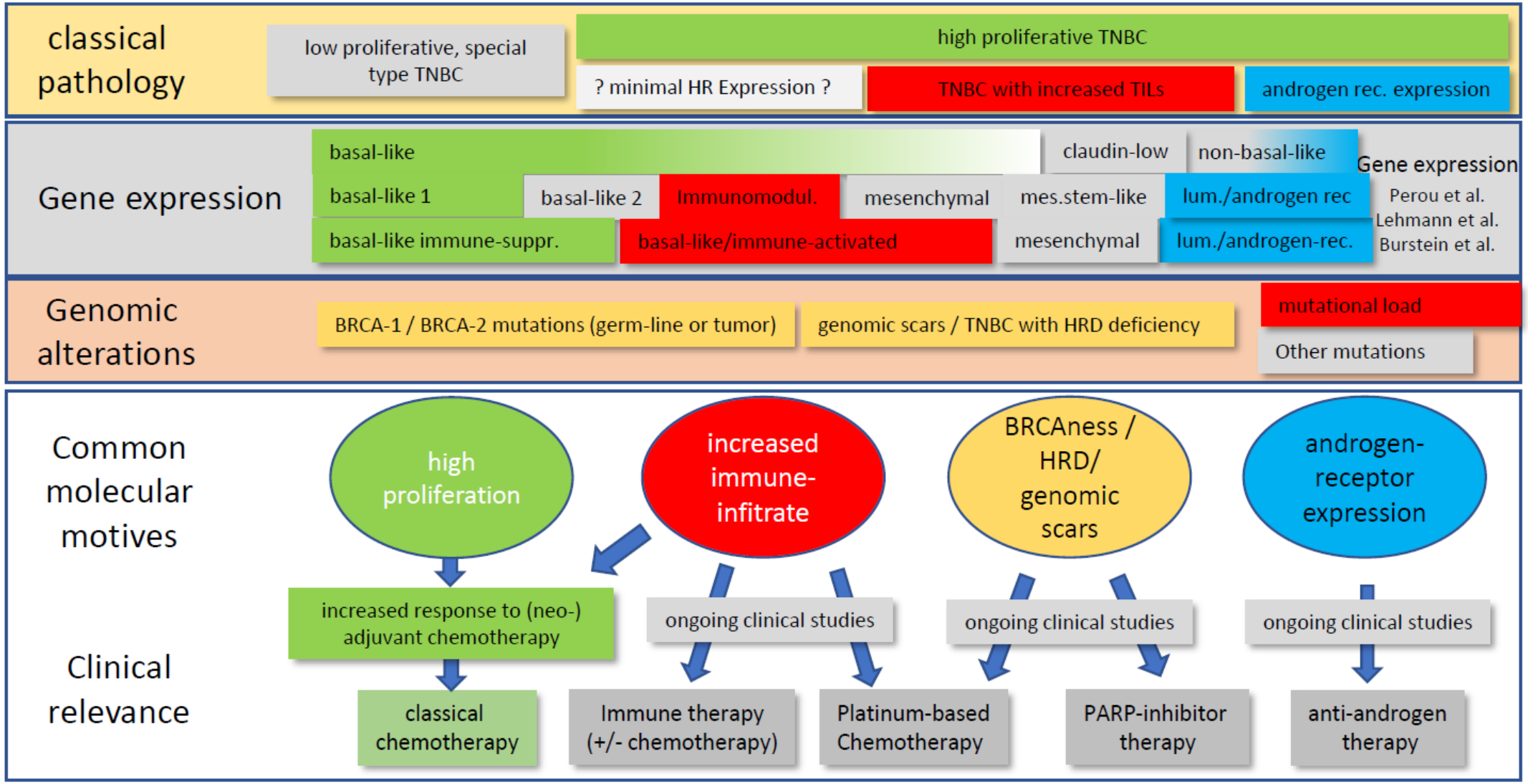




- **Every 1% ↑ in TILs was associated with a 3% ↓ in event rate.**
- **Independent of known clinical-pathological variables, including pCR status.**
- **No significant interaction between TILs and treatment arm.**

Salgado et al. JAMA Oncol 2015

Molecular characterization of TNBC



modified based on Denkert et al., Lancet 2017

ER 1-9%: non-luminal subtype kandidater til TNBC protokoller

- Karaktertræk som ER negative og HER2 negative tumorer (TNBC)
  - Molekylær subtype analyse - indtil videre ganske få data indberettet til DBCG – de registrerede indtil nu er basallike (N=10) eller HER2 enriched (N=5)
  - g*BRCA* mutation findes i samme omfang som ved ER-, HER2 negative tumorer 39.5% vs 36.1% (Cancer 2015 oct; 121 (19):3422-7).
  - Samme pCR rate som ER negative, (GBG neoadjuvant trials)

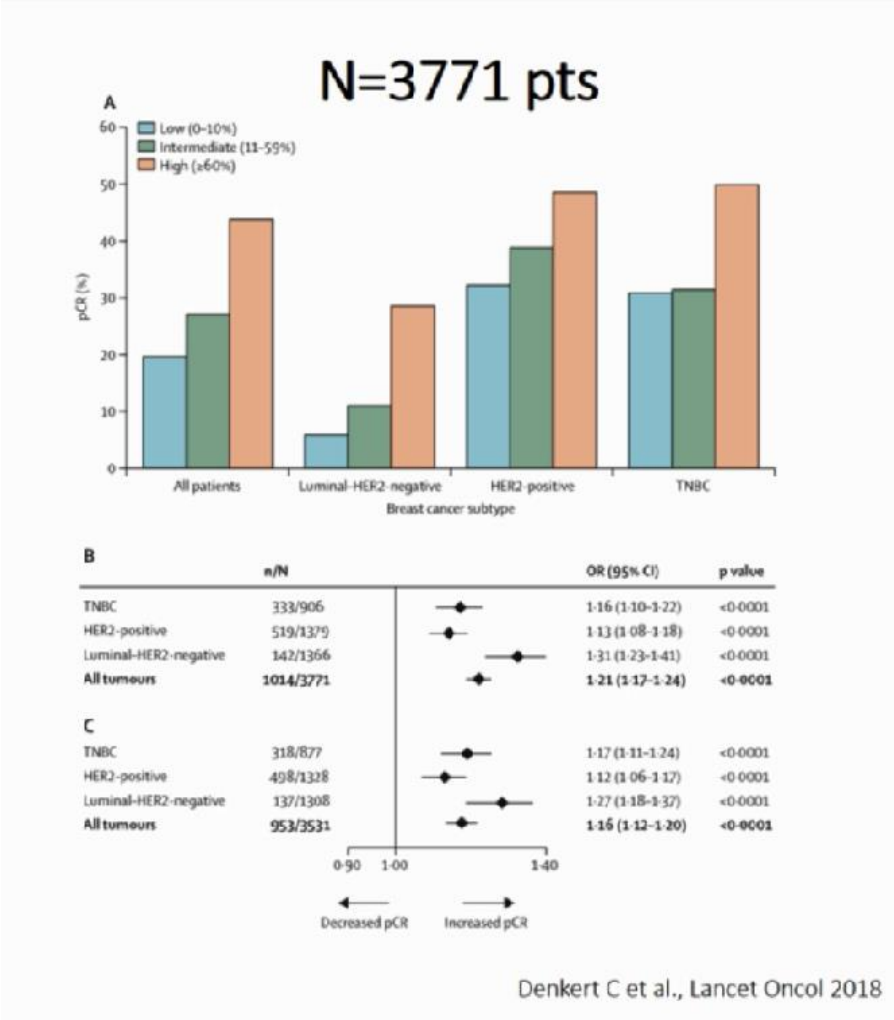
VOLUME 28 · NUMBER 16 · JUNE 1 2010
JOURNAL OF CLINICAL ONCOLOGY
ASCO SPECIAL ARTICLE

American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Immunohistochemical Testing of Estrogen and Progesterone Receptors in Breast Cancer

TILs as prognostic and predictive marker

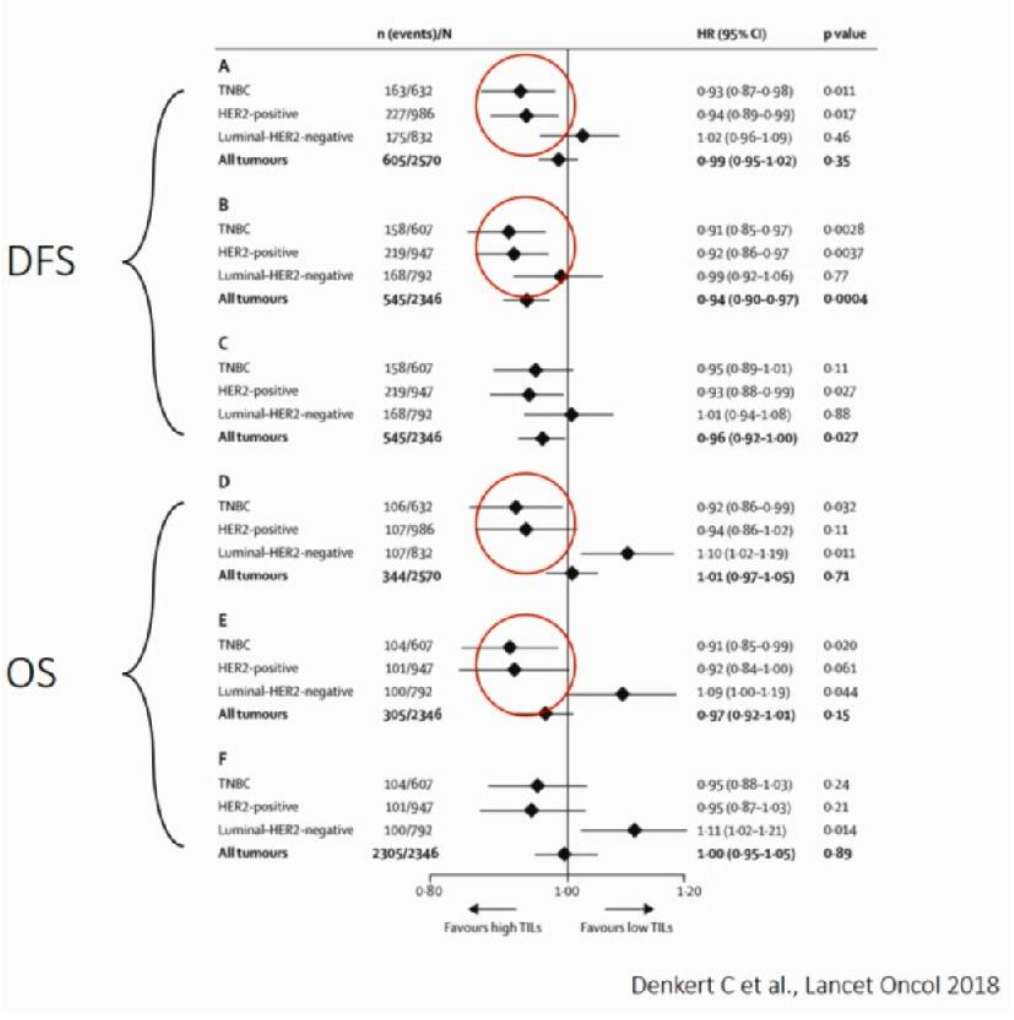
https://www.tilsinbreastcancer.org/

High TILs predict response to neoadjuvant treatment



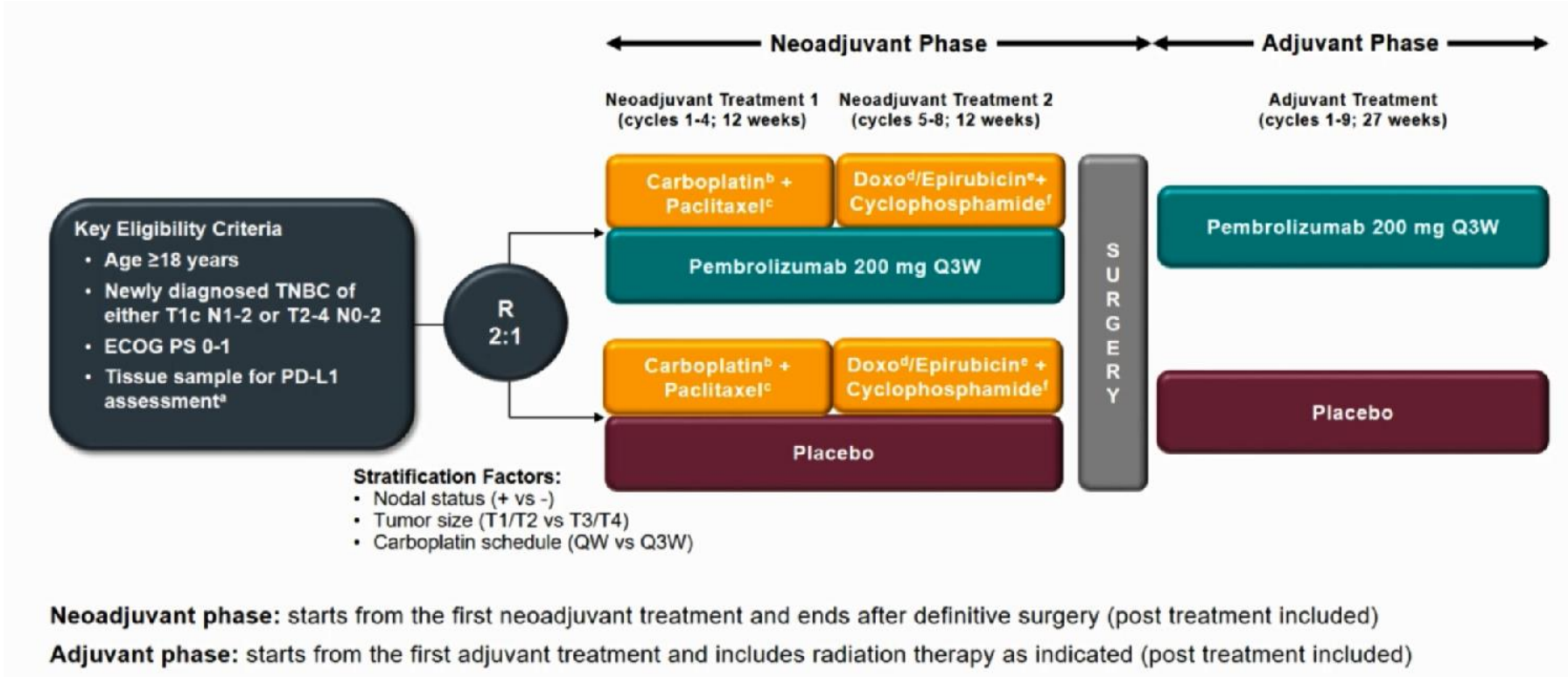
Denkert C et al., Lancet Oncol 2018

TILs are prognostic in early stage TNBC and HER2+ BC



Denkert C et al., Lancet Oncol 2018 Loi S. et al; JCO 2019

Immune check point inhibitor
Neoadjuvant trial. KEYNOTE-522 study design



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

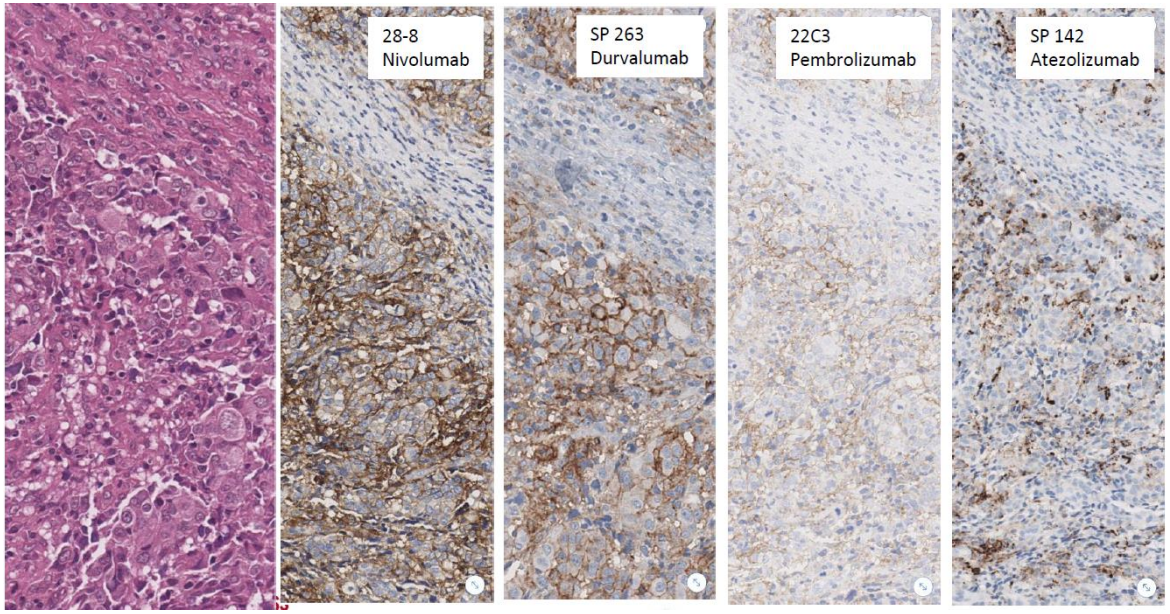
Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post treatment included)

- Median follow-up 15.8 mo, Pembro + chemo, N= 784, 80% PD-L1 positive.
- Analysis of data based on PD-L1 status showed that pCR defined as ypT0/Tis ypN0 was higher with the pembrolizumab regimen in both the PD-L1-positive and PD-L1-negative subgroups.
- The pCR rates were 68.9% versus 54.9% in the PD-L1-positive cohort and 45.3% versus 30.3% in the PD-L1-negative population in patients receiving chemotherapy plus pembrolizumab or placebo, respectively.
- A favorable trend for EFS in the pembrolizumab arm (HR 0.63)

ESMO 2019 Schmid P et al

Diagnostic assays for immune checkpoint inhibitor therapy

Comparison of different PD-L1 antibodies



Breast cancer

	IVD diagnostic antibodies used in clinical trials	
Drug	Pembro-lizumab **(MSD)**	Atezo-lizumab **(Roche)**
AB clone	22C3 Dako	SP-142 Ventana
Score	CPS	IC_A
cell type	Tumor Immune	Immune
Breast cancer trial	KN-012 KN-522	**Impassion -130**

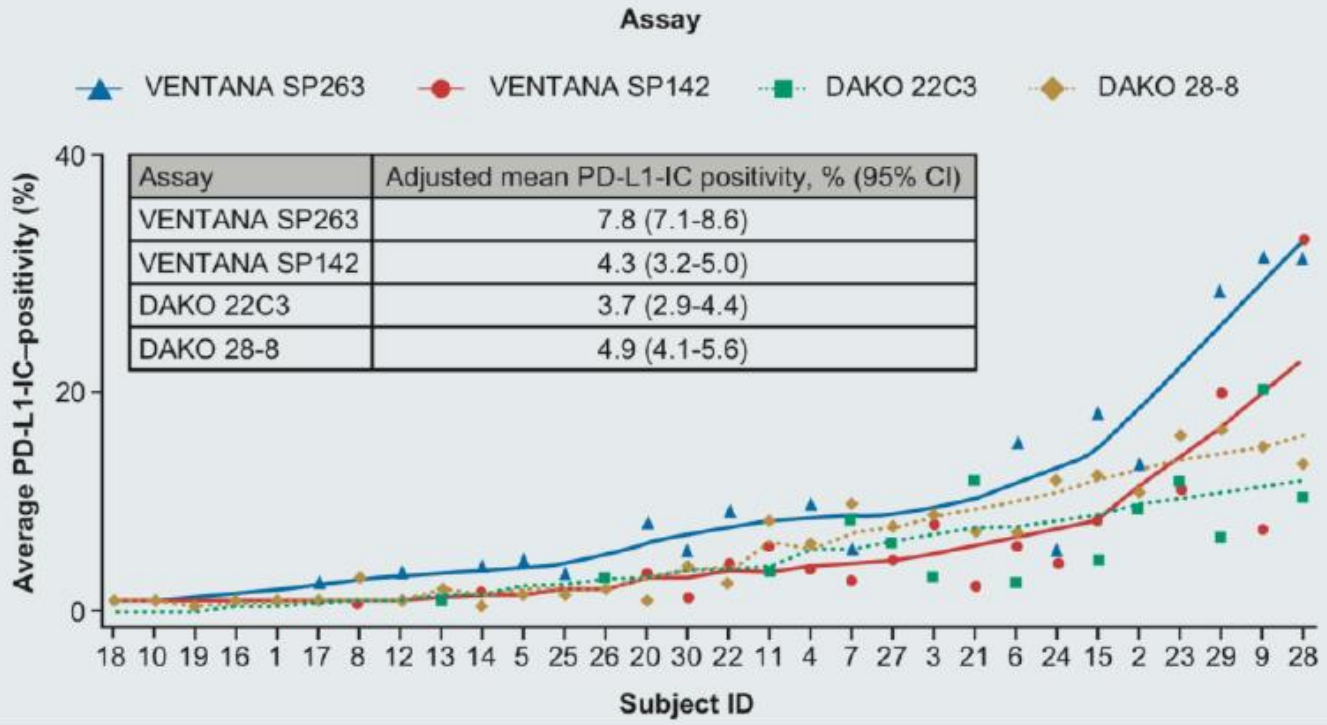
IC_A score: percentage of tumor area covered by PD-L1 positive immune cells (designed for Atezolizumab)

CPS score: positive tumor or immune cells as percentage of all tumor cells (designed for Pembrolizumab)

ESMO 2019, Denkert C

IC_A scoring is similar with most antibodies

Figure 1. Percentage of PD-L1-IC–positivity using each assay (averaged over the seven readers)



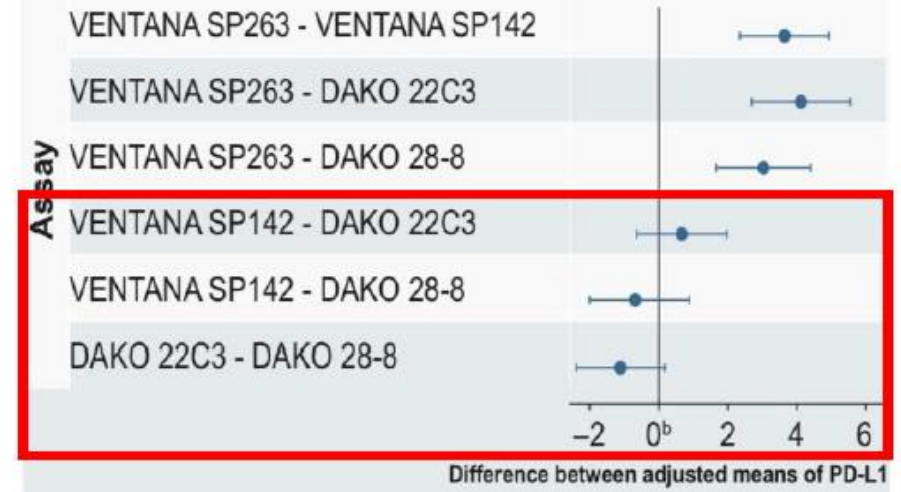
Assay	Adjusted mean PD-L1-IC positivity, % (95% CI)
VENTANA SP263	7.8 (7.1-8.6)
VENTANA SP142	4.3 (3.2-5.0)
DAKO 22C3	3.7 (2.9-4.4)
DAKO 28-8	4.9 (4.1-5.6)

CI, confidence interval; IC, tumour-infiltrating immune cell in the tumour area; PD-L1 programmed death-ligand 1.

SP263

SP142
22C3
28-8

Figure 2. Differences in adjusted means[a] each assay



ANOVA, analysis of variance; CI, confidence interval; IC, tumour-infiltrating im
programmed death-ligand 1.
[a]Differences between adjusted means (including 95% CIs) were based on an

ESMO poster 2019 Noske A, Denkert C et al.

Analyser som kan overvejes i forbindelse med allokering til neoadjuverende kemoterapi:

Supplement med henblik på prospektiv registrering:

- TILs på nålebiopsi og resttumor?

- Molekylær subtypebestemmelse?
  - ER + HER2 - (luminal A vs Luminal B – hvis luminal A primær kirurgi)
  - (HER2 positiv - HER2 enriched vs andre)

Analyser som med fordel kan inkluderes i fremtidige neoadjuverende protokoller afhængig af inklusionskriterier

- HE snit TILs
- Molekylær subtype
  - ER positive HER2 negative: Lum A vs Lum B
  - HER2 positive: HER2 enriched vs andre
- Mutations analyser
  - HER2 positive
    - PIK3CA mutation (app 30%)
  - Flere andre
- TNBC
  - PD-L1
  - TMB
  - Androgen receptor
  - Lehmann molecular subtypes
- g*BRCA* – PARP inhibitors
- Homologues Rekombination Deficiency – PARP inhibitors, selection of chemotherapy regimens
- Genekspressionsprofiler (ie immun-signatur)
- Multiplex analyser
  - IHC ex. målrettet immunrespons – subpopulationer af IC
  - Nanostring teknologi: Identifikation af multiple proteiner (protein quantification using oligonucleotide bar-coded antibodies – window of opportunity studies – cost effective for reseach protocols, tissue sparing)

TAK