Nové trendy v imunoterapii (triple negativního) karcinomu prsu

Zuzana Bielčiková

Onkologická klinika VFN a 1.LF UK v Praze

Prague ONCO 2021

Osnova

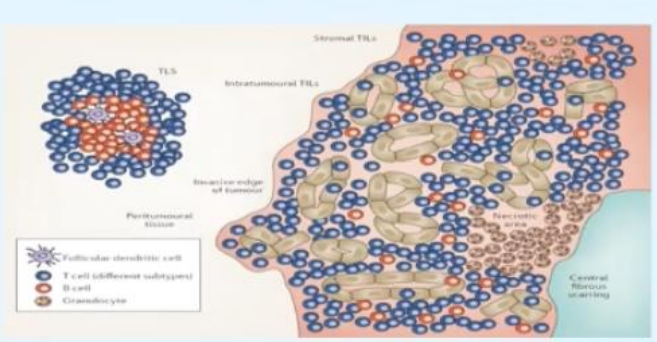
- Subtypizace TNBC ve vztahu k IO
- Biomarkery
- Klinická data o efektu IO
- IO a klinická praxe

BC: karcinom prsu, IO: imunoterapie

Proč je TNBC vhodný pro IO?

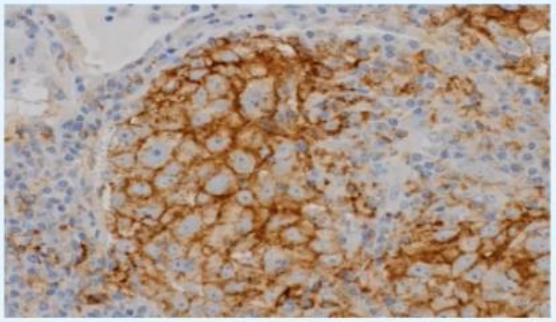
1. High mutation rate vs other BCs[1,2]

2. T-cell infiltration[3-6]



8

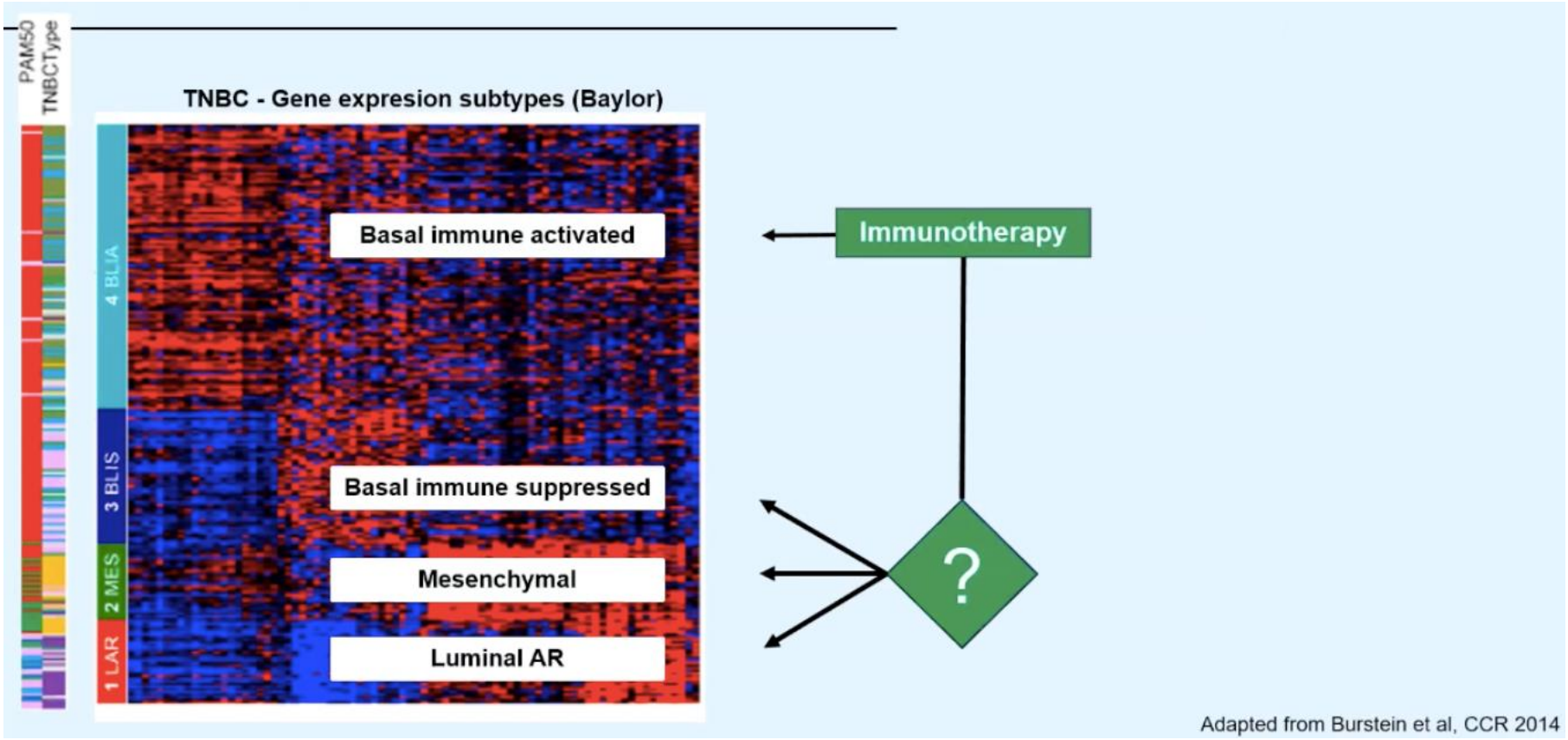
3. PD-L1 expression[7]



1. Wang, et al. Nature 2014; 2. The Cancer Genome Atlas Network, Nature 2012; 3. Lehmann, et al. J Clin Invest 2011; 4. Cimino-Matthews, et al. Hum Pathol 2013
5. Loi, et al. Ann Oncol 2014; 6. Chen and Mellman. Immunity 2013; 7. Mittendorf, et al. Cancer Immunol Res 2014; 8. Savas P, et al. Nat Rev Clin Oncol 2016

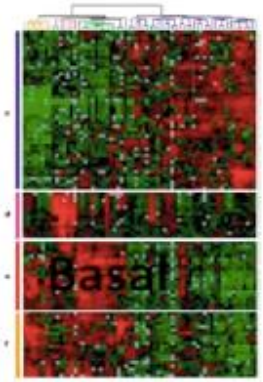
Dle J. Cortes, SABCS 2020

Heterogenita TNBC a IO



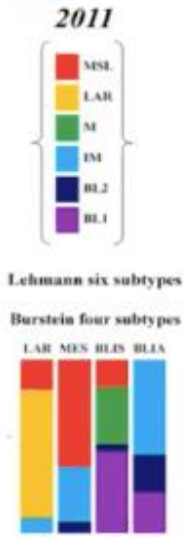
Evoluce v hledání biomarkerů

Hierarchical Clustering



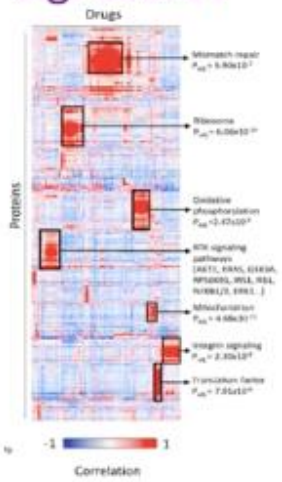
2000 Perou

Transcriptional signature



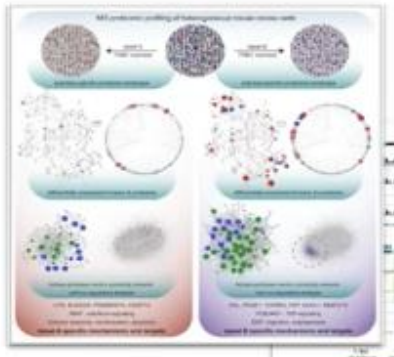
2015

Proteomic signatures

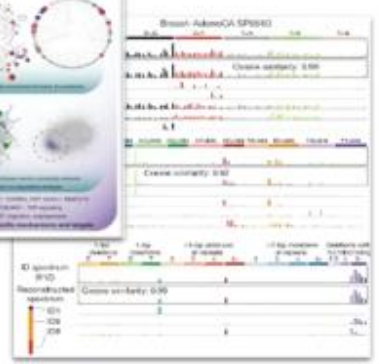


2015 Lawrence

Proteogenomic signatures



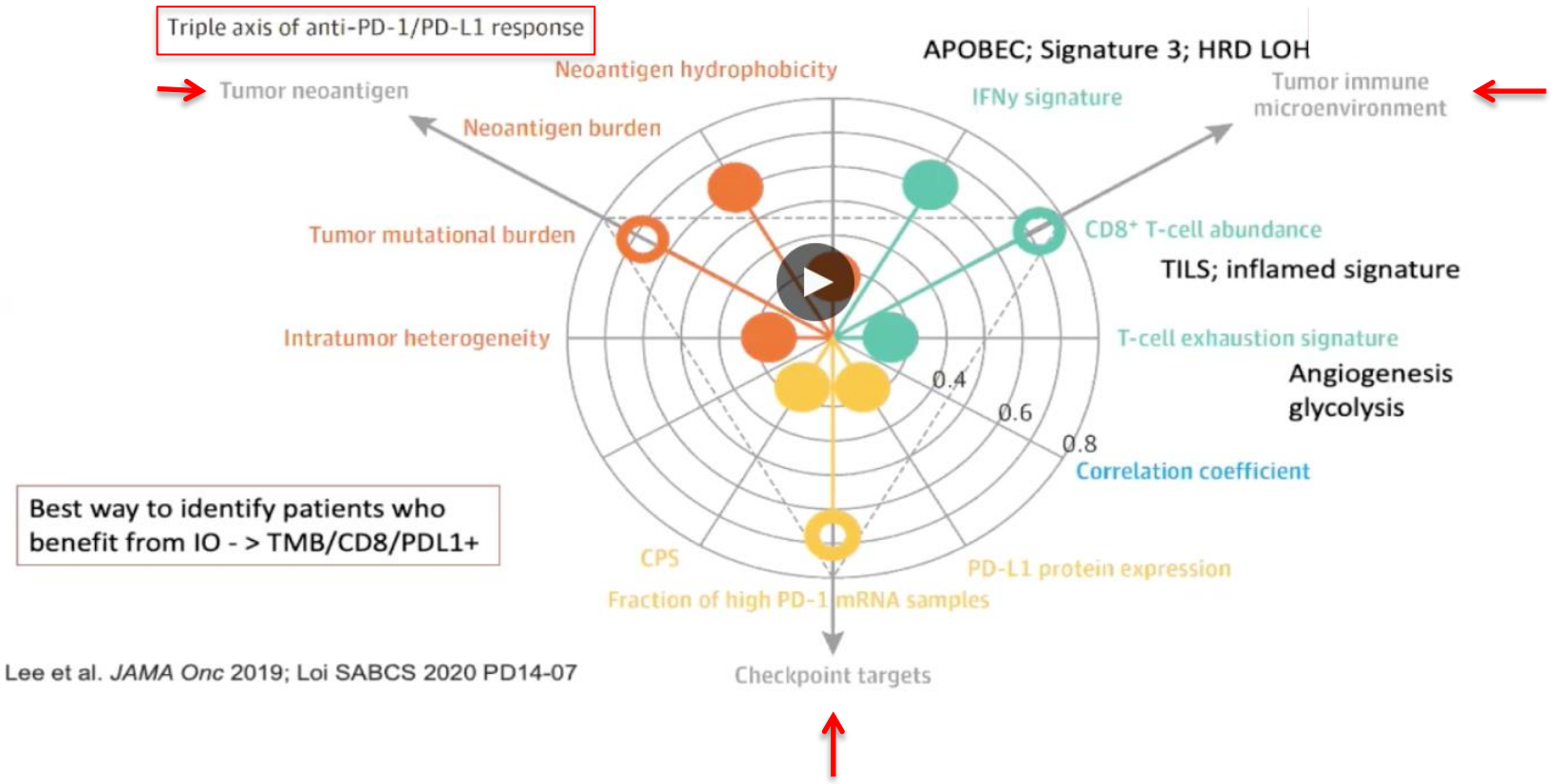
2020 Kosok



2020 Alexandrov

dle R. Dent, SABCS 2020

Odpověď na IO je výsledkem komplexní interakce



dle R. Dent, SABCS 2020

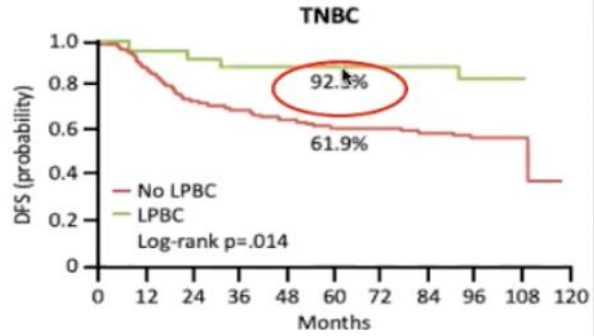
BIOMARKERY

Přítomnost TILs zlepšuje prognosu a predikuje chemosenzitivitu nemoci

EARLY

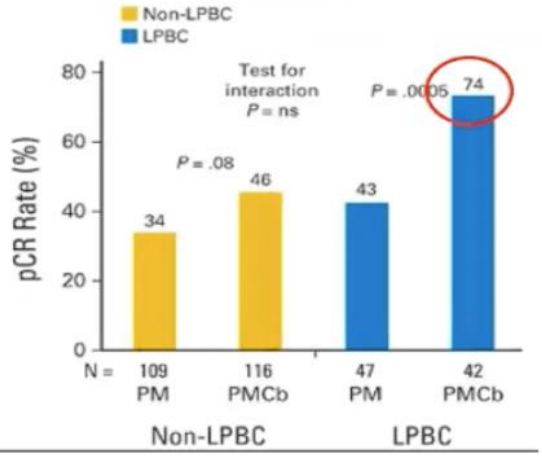
- No longer a death sentence, 5 year DFS > 80%
- More preoperative treatment, increasing pCR rates
- Aim now to de-escalate/escalate therapy and tailoring treatment better

Loi S et al, JCO 2013
BIG 02-98



Strongest link of TILs and outcome in TNBC

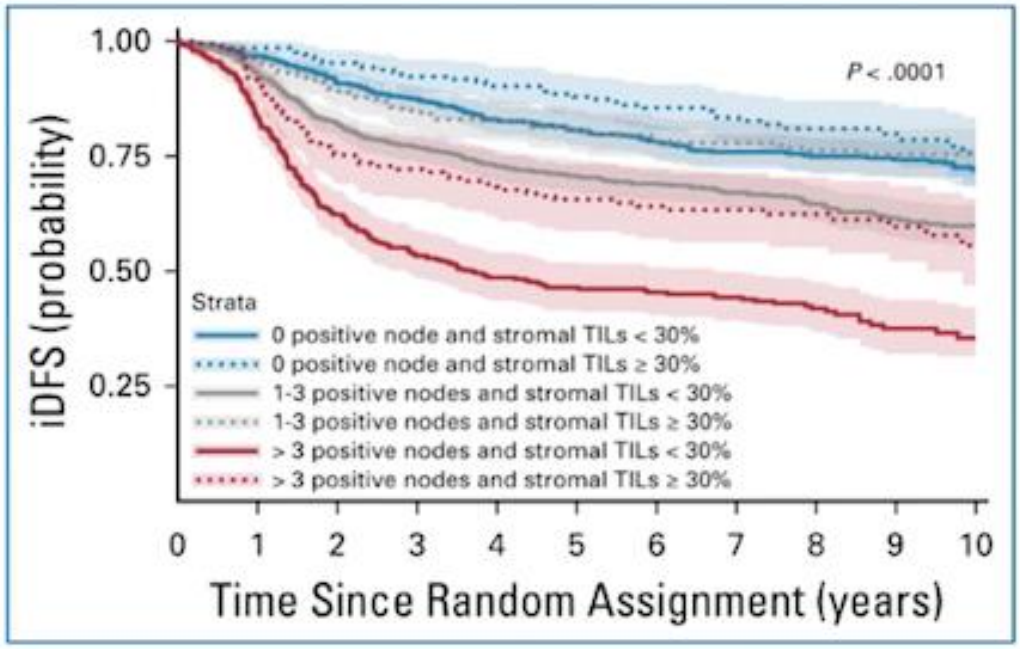
Denkert C et al, JCO 2015
GeparSixto



dle R. Dent, SABCS 2020

Prognostický přínos TILs

Adjuvant
(n=2148, TNBC)



5y- DDFS

N0: 91 → 97%
N1-3: 81 → 89%

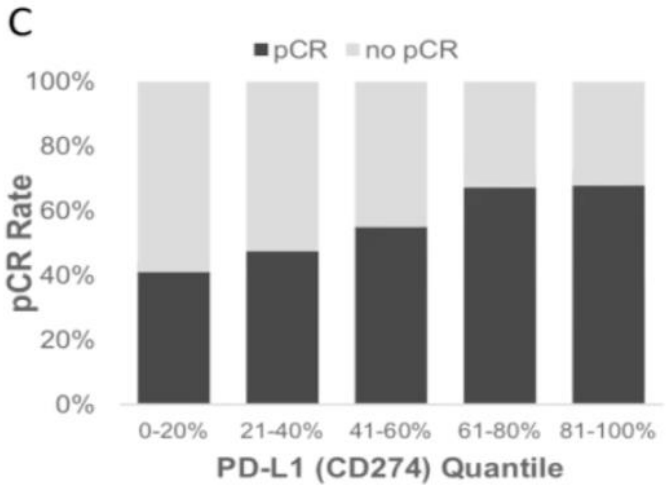
N4+: 50 → 67%

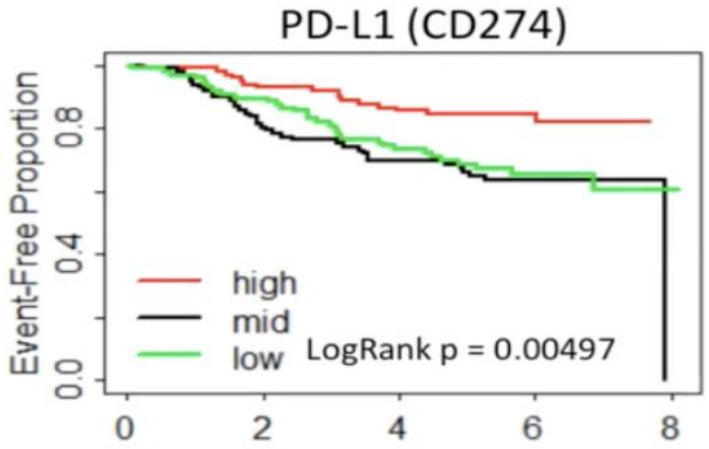
Loi et al, J Clin Oncol. 2019, Mar 1

www.tilsinbreastcancer.org

Prognostický význam PD-L1

Immune Activation, pCR and EFS in CALGB 40603





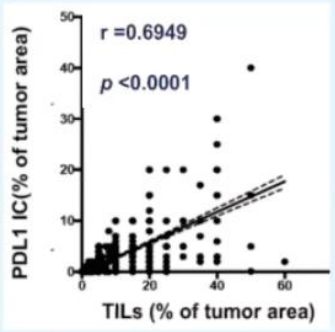
Immune activation (variety of RNA signatures and genes) = better pCR and better EFS. De-escalate chemo?

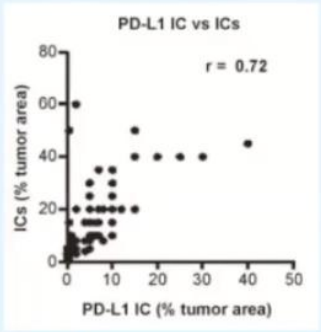
Shepherd et al, manuscript submitted

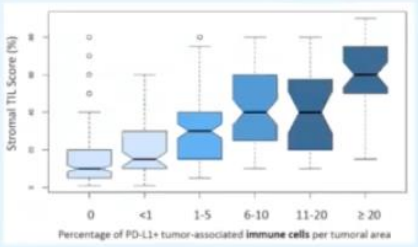
Dle LA Carey, SABCS 2020

Korelace PD-L1 a TILs u časného i metastatického TNBC

PD-L1 (SP142 IC) and TILs





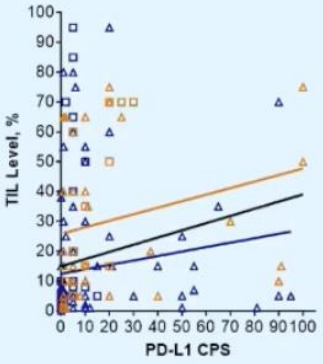


PDL1 IC vs sTILs
r = 0.60

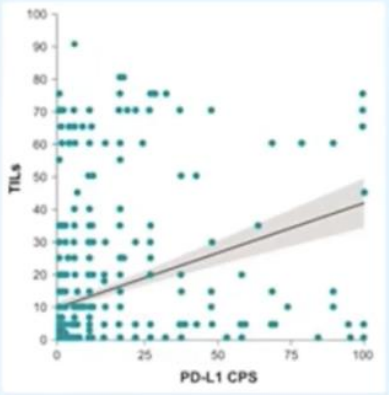
PD-L1 (22C3 CPS) and TILs

Combined cohorts
ρ = 0.496; *P* < 0.001

PD-L1 CPS vs sTIL Level



PDL1 CPS vs sTILs
r = 0.46



Li Y, et al. SABCS 2017; Emens LA, et al. Jama Oncol 2018; Carter JM, et al. SABCS 2019; Loi S, et al. Lancet Oncol 2019; Loi S, et al. SABCS 2019

Dle J. Cortes, SABCS 2020

PD-L1 a TILS mají nezávislý prediktivní význam pro efekt IO u mTNBC

KEYNOTE-086[1]
(TNBC, pembrolizumab)

	$\Delta\chi^{2a}$	P^a
sTIL level vs none	5.571	0.018
sTIL level + PD-L1 CPS vs sTIL level	0.003	0.958
sTIL level + LDH concentration vs sTIL level	6.684	0.010

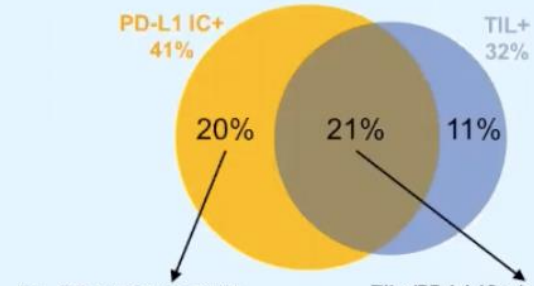
Loi S ESMO 2017

KEYNOTE-119[2]
(TNBC, pembrolizumab)

Treatment Arm	Variable	P^b			
		BOR	DCR	PFS	OS
Pembrolizumab	TILs[a]	0.011	0.032	0.003	0.004
	CPS[a]	0.040	0.061	0.038	0.090
Chemotherapy	TILs[a]	0.150	0.132	0.051	0.286
	CPS[a]	0.652	0.238	0.027	0.264

Loi S SABCS 2019 (PD5-03)

IMpassion130[3]
(TNBC, atezolizumab/nab-paclitaxel)



TIL–/PD-L1 IC+ (n = 176)	HR (95% CI)	*P* Value
PFS	**0.74** (0.54, 1.03)	0.07
OS	**0.65** (0.41, 1.02)	0.06

TIL+/PD-L1 IC+ (n = 190)	HR (95% CI)	*P* Value
PFS	**0.53** (0.38, 0.74)	≤ 0.005
OS	**0.57** (0.35, 0.92)	0.02

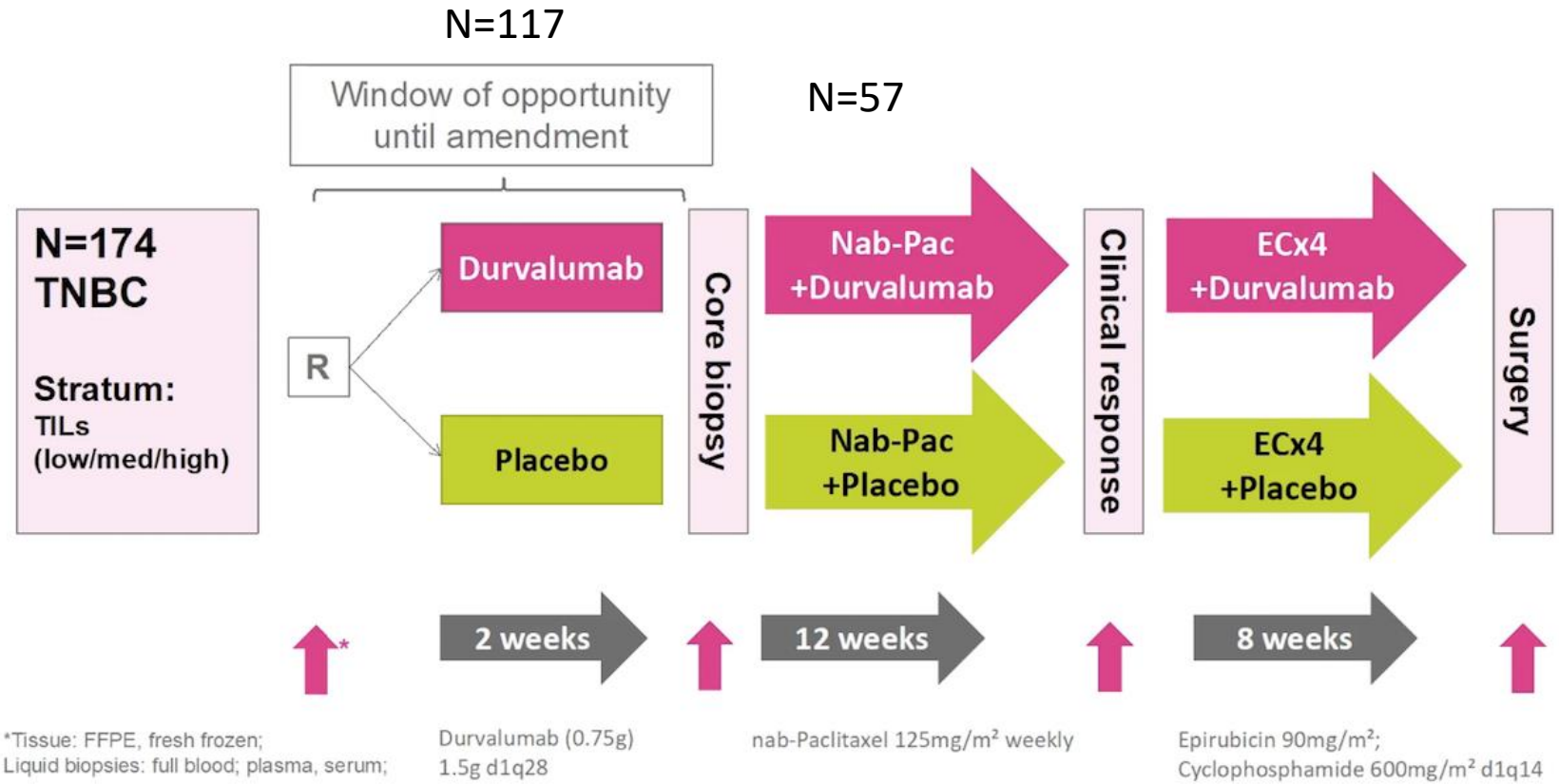
Emens L SABCS 2018

1. Loi S, et al. ESMO 2017; 2. Loi S, et al. SABCS 2019; 3. Emens L, et al. SABCS 2018

Dle J. Cortes, SABCS 2020

KLINICKÁ DATA O EFEKTU IO

GeparNUEVO (ph. II)

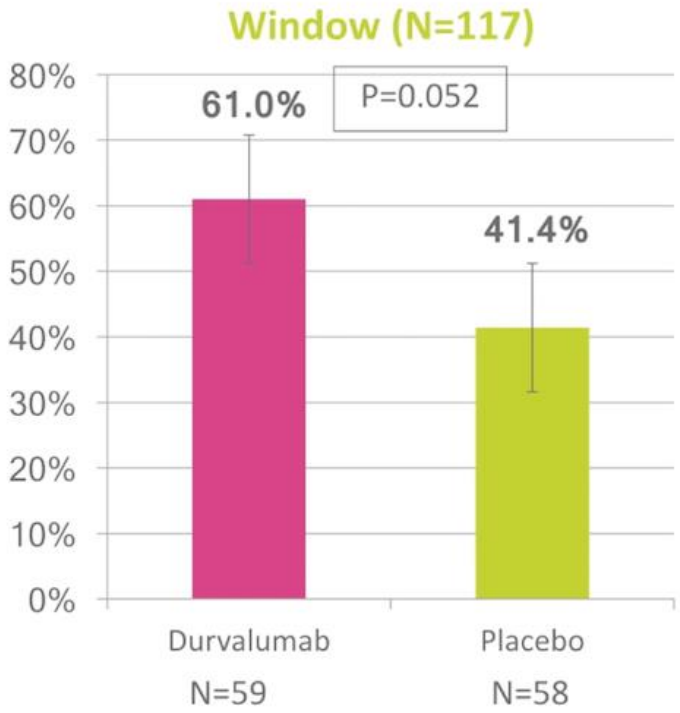


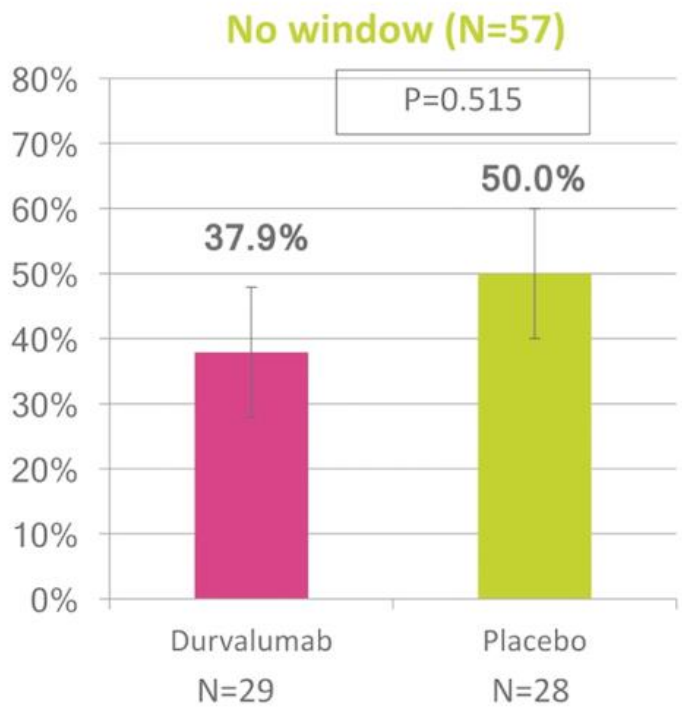
PD-L1+ = 88%, Low TILs= 39%, Midle TILs = 48%, **High TILs = 14%**

1/3 pts ve stadiu 0-I, **stadium II-III > 60%**

G3= 84%, Ki67 > 20% = 94%, median age 49.5, premeno = 60%

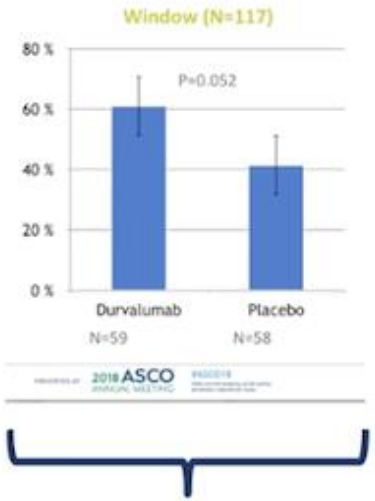
Pacientky předléčené ve window fázi IO dosáhli sign. více pCR

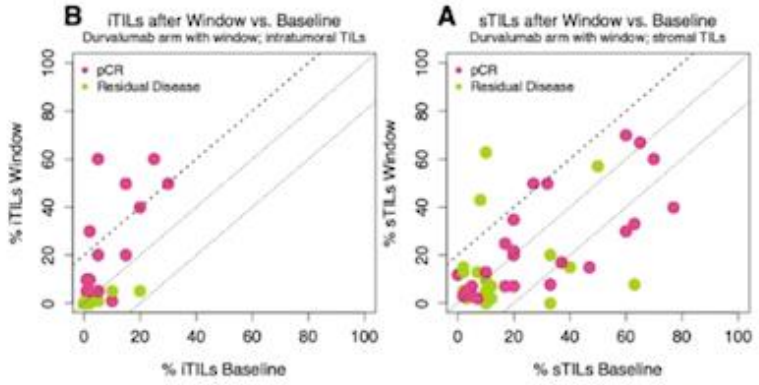


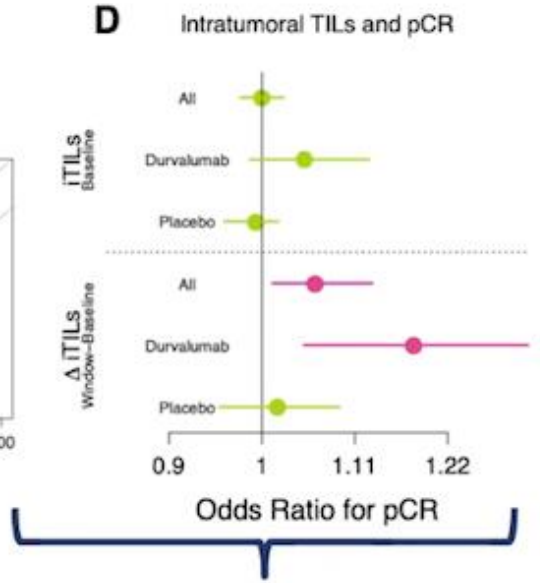


Prediktivní význam durvalumabu pouze ve window fázi
Z léčby signifikantně profitovali pacientky ve stadiu II-III

Imunitní aktivace ve window fázi







Zvýšení počtu pCR po 1 dávce DURVA před zahájením CHT

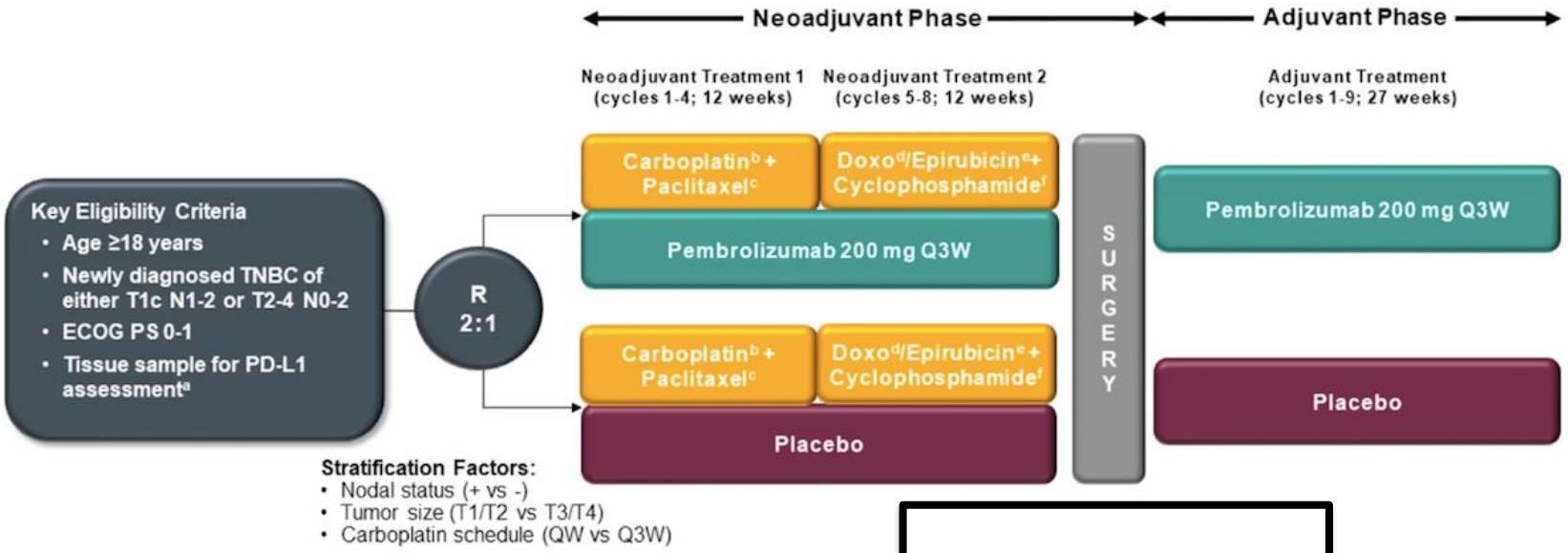
Zvýšení intratumorálních a stromálních TILs po 1 dávce DURVA

Zvýšení iTILs po 1 dávce DURVA prediktivní pro pCR

Sinn BV et al. SABCS 2018 PD5-05

Loibl et al. Ann. Oncol 2019

KEYNOTE-522



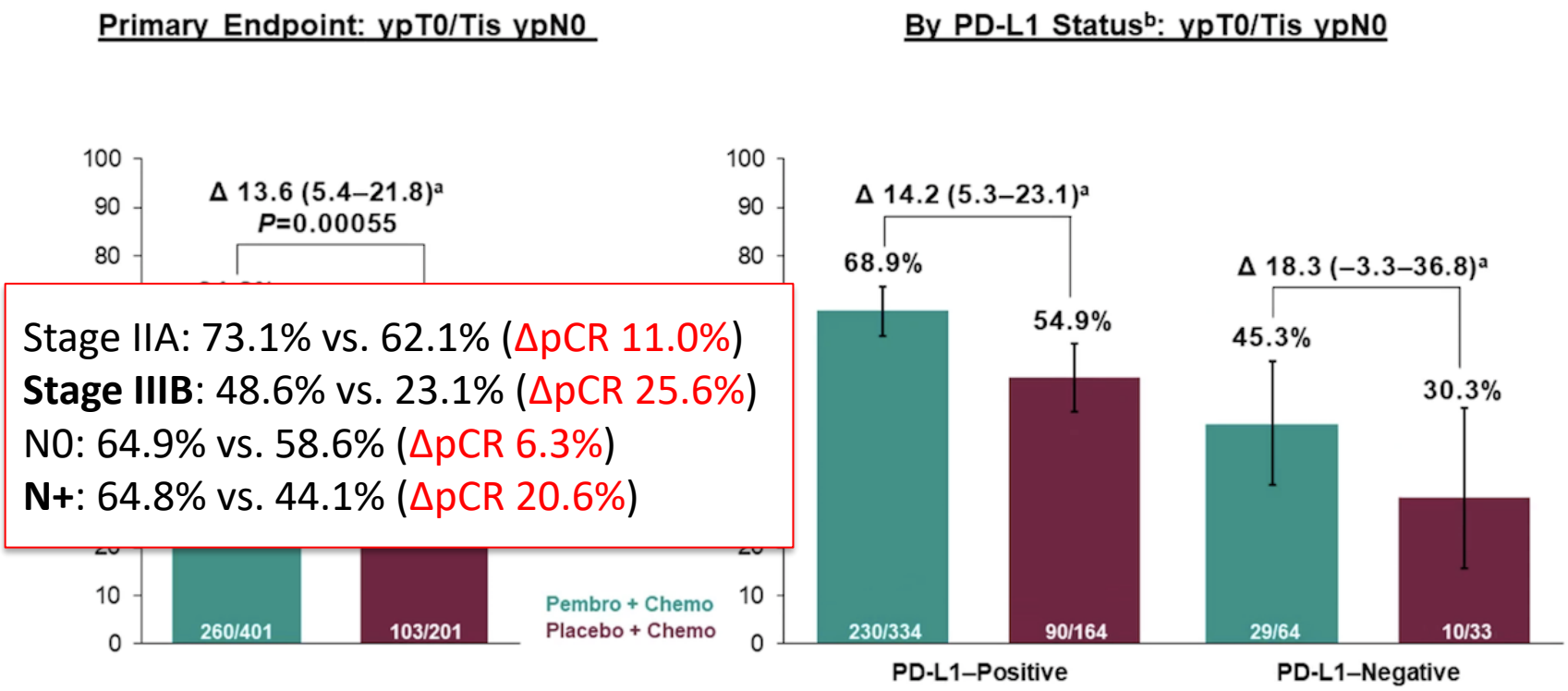
1. cíl = EFS + pCR

Median age= 49 let, premeno = 56%
Stage II = 75%, stage III = 25%
PD-L1+ = 83%
3week Pt = 43%, weekly Pt = 57%

[d]Doxorubicin dose was 60 mg/m² Q3W.
[e]Epirubicin dose was 90 mg/m² Q3W.
[f]Cyclophosphamide dose was 600 mg/m² Q3W.

Schmid P, et al. ESMO 2019, Abstr. LBA8

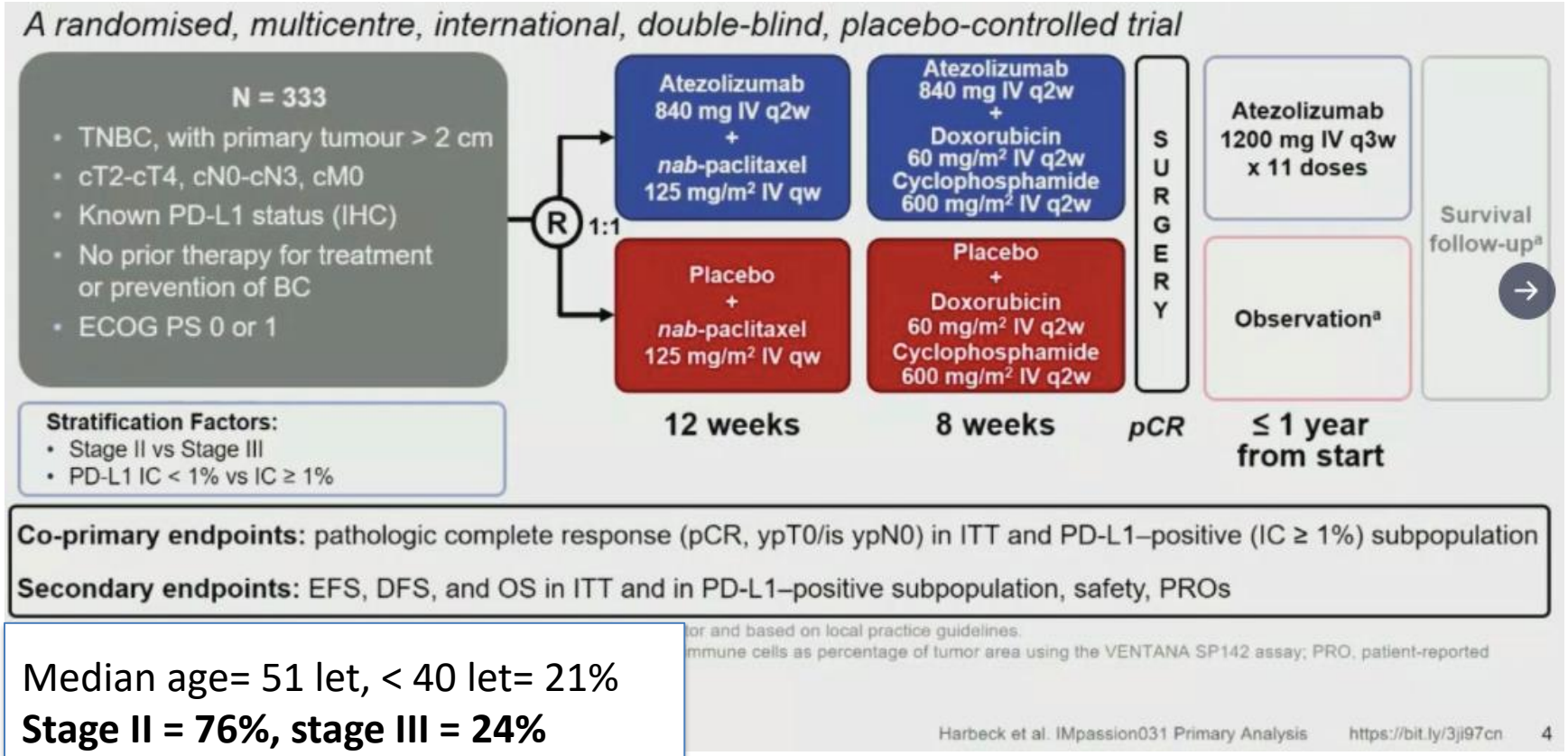
Potvrzen přínos PEMBRO, prediktivní význam PD-L1 pro efekt IO neprokázán



Stage IIA: 73.1% vs. 62.1% (ΔpCR 11.0%)
Stage IIIB: 48.6% vs. 23.1% (ΔpCR 25.6%)
N0: 64.9% vs. 58.6% (ΔpCR 6.3%)
N+: 64.8% vs. 44.1% (ΔpCR 20.6%)

Schmid P, et al. ESMO 2019, Abstr. LBA8

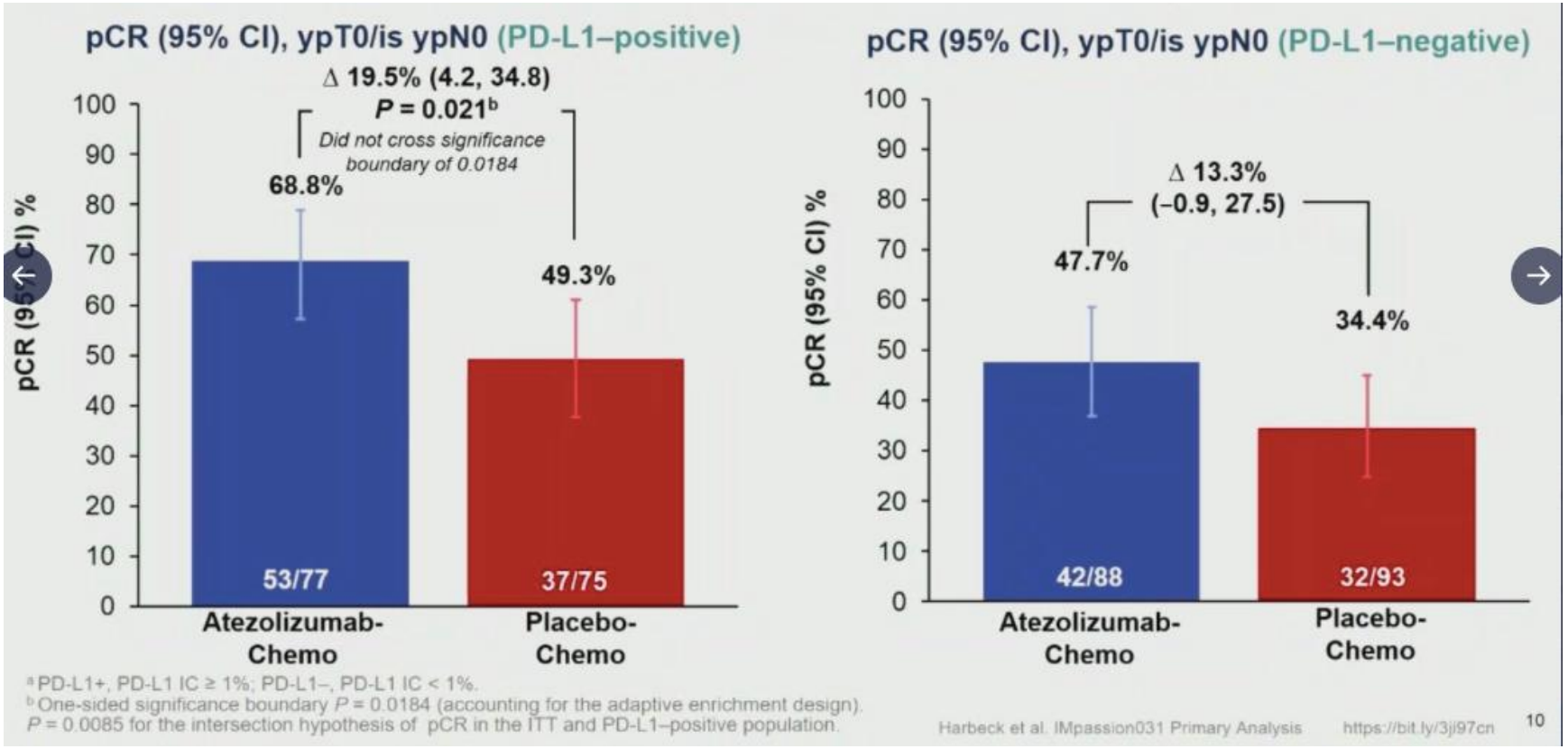
IMpassion031 (ph. III)



Median age= 51 let, < 40 let= 21%
Stage II = 76%, stage III = 24%
PD-L1+ = 47%

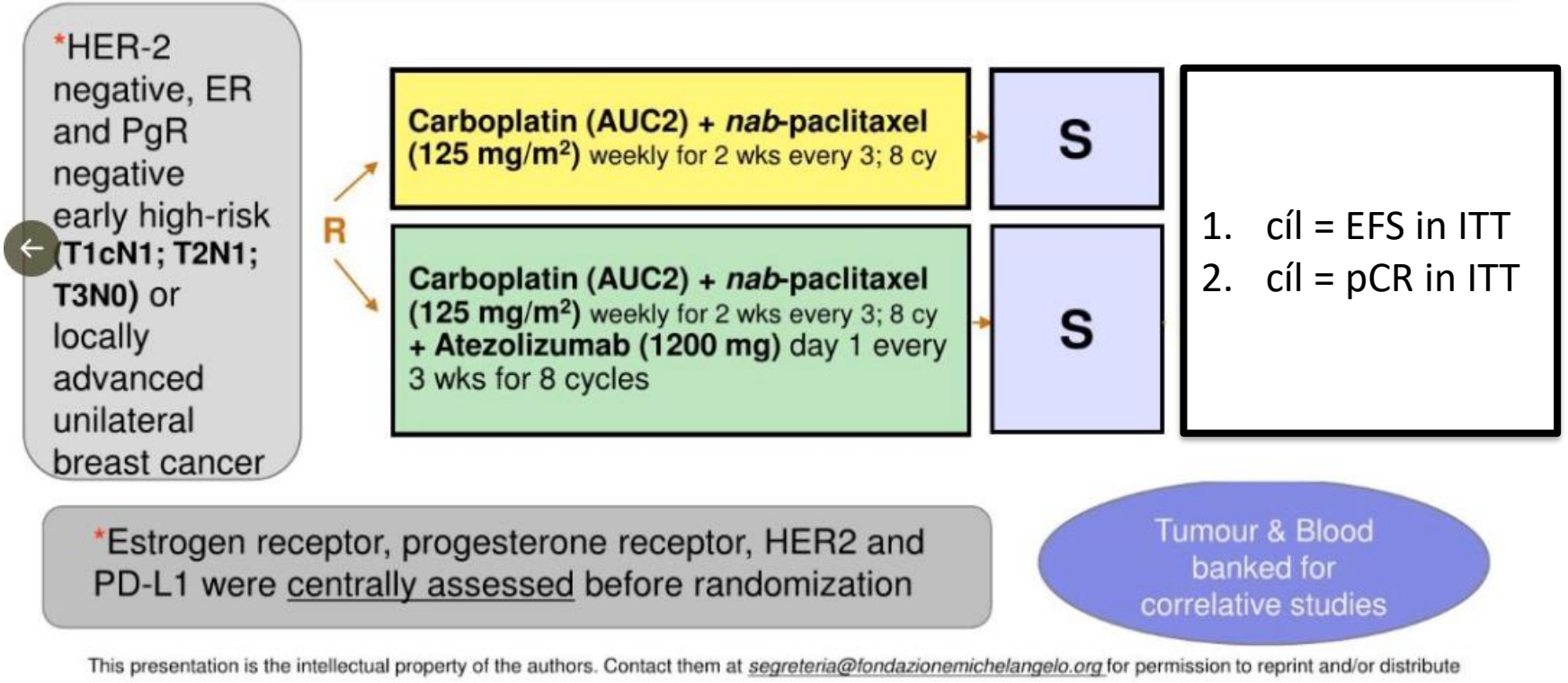
N.Harbeck, ESMO 2020

Potvrzen přínos ATEZO, prediktivní význam PD-L1 pro efekt IO neprokázán



N.Harbeck, ESMO 2020

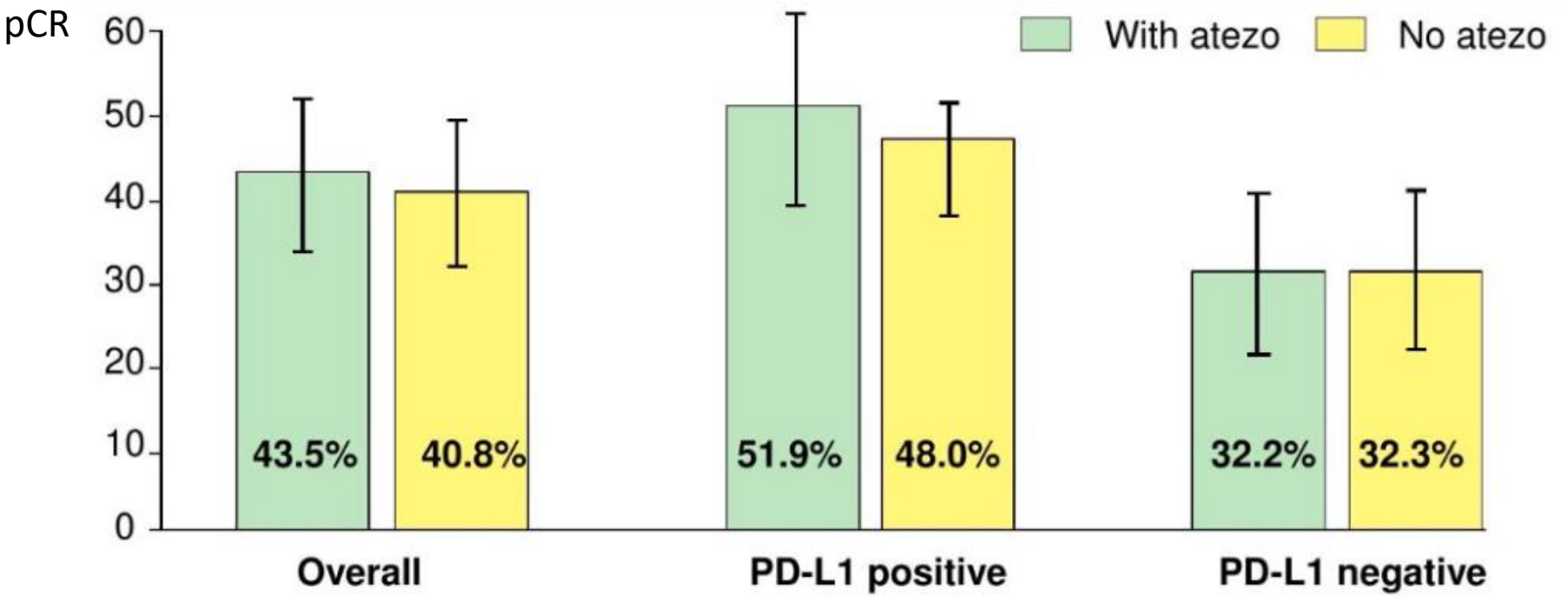
NeoTRIP (ph. III)



Median age= 50 let
N0= 13%, **LA TNBC = 49%**
PD-L1+ = 56%

Gianni, SABCS 2019

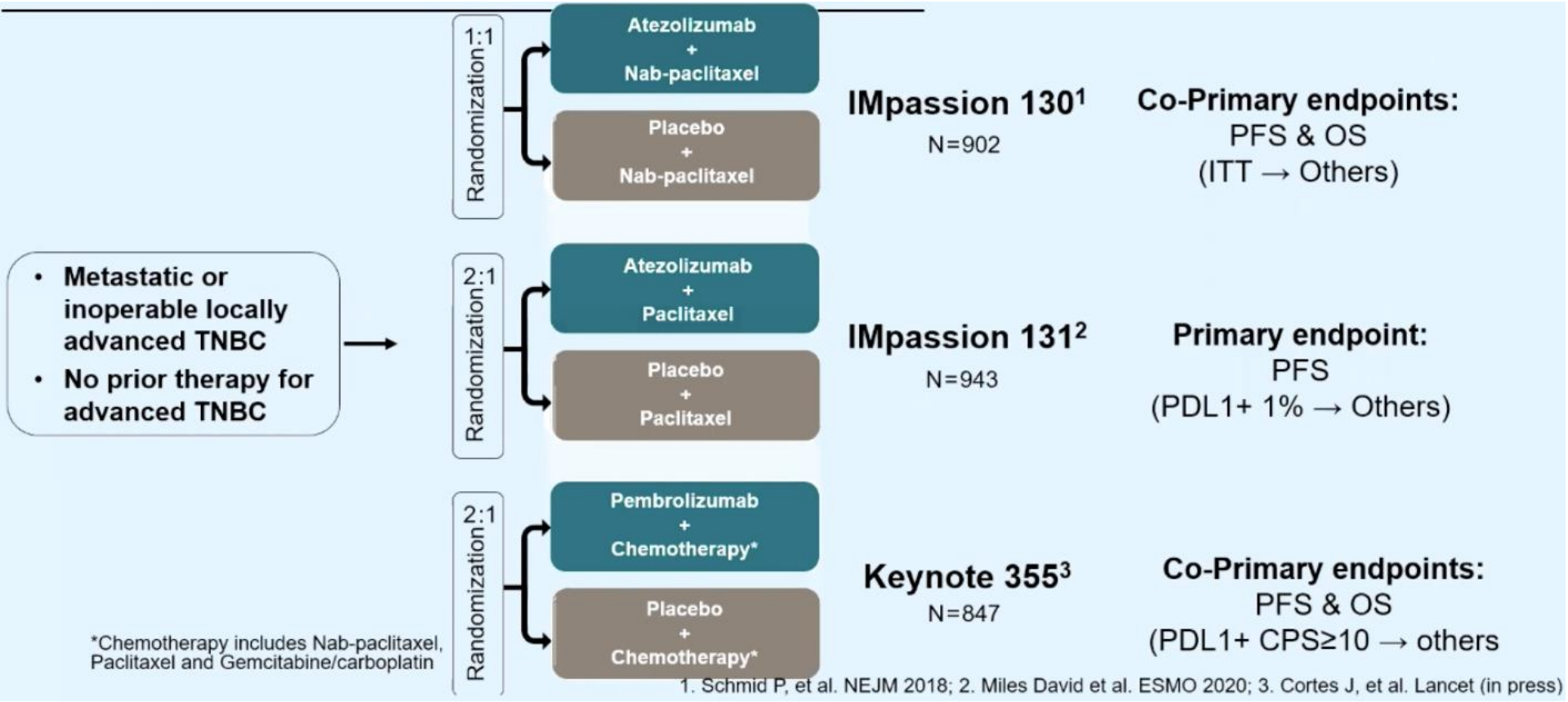
Negativní studie: IO bez efektu



P < 0.0001

Gianni, SABCS 2019

mTNBC: IO+CHT v I.linii



1. Schmid P, et al. NEJM 2018; 2. Miles David et al. ESMO 2020; 3. Cortes J, et al. Lancet (in press)

Výsledky studií ph. III, I.linie paliace

Trial	Target	Chemo	N	Open (Estimated Completion)	PD-L1+	Primary endpoints (Hierarchical testing)	Secondary endpoints	De novo, DFI (mos)	
IMpassion130 (NCT02425891) FDA approval 3/2019	**PD-L1**	**Nab-Paclitaxel**	900	June 2015 (April 2020)	IC≥1 41%	PFS ITT **7.2 vs 5.5 mos** PFS PD-L1+ **7.5 vs 5 mos** OS ITT 21 vs 18.7 mos n.s.* OS PD-L1+ 25.4 vs 17.9 mos n.t.*	ITT | PD-L1+ **ORR (%):** 56 vs 46% | 59 vs 43% **DOR (mos):** 7.4 vs 5.6 | 8.5 vs 5.5 **PRO** (no detriment to HRQoL with added IO)	37%, ≥ 12	✚
IMpassion131 (NCT03125902) FDA warning	**PD-L1**	**Paclitaxel**	651	Aug 2017 (June 2021)	IC≥1 45%	PFS PD-L1+ 6 vs 5.7 mos n.s. PFS ITT 5.7 vs 5.6 mos n.t.*	PD-L1+ | ITT **OS (mos):** 22.1 vs 28.3 | 19.2 vs 22.8 ORR, PFS by IRC and PRO (pending)	30%, ≥ 12	✖
KEYNOTE-355 (NCT02819518) FDA approval 11/2020	**PD-1**	**Nab-Paclitaxel** Or **paclitaxel** Or **gem/carbo**	847	July 2016 (Dec 2019)	CPS≥10 37% CPS≥1 75%	PFS CPS≥10 **9.7 vs 5.6 mos** PFS CPS≥1 7.6 vs 5.6 n.s.* PFS ITT 7.5 vs 5.6 n.t.* OS in PD-L1+ (pending) OS ITT (pending)	CPS≥10 | CPS≥1 | ITT **ORR (%):** 53 vs 40 | 45 vs 38 | 41 vs 36 **DCR (%):** 65 vs 54 | 59 vs 54 | 56 vs 52 **DOR (mos):** 19 vs 7 | 10 vs 7 | 10 vs 6 Consistency of efficacy per chemo regimen^ **PFS HR nab-Pac:** 0.57 | 0.66 | 0.69 **PFS HR Pac:** 0.33 | 0.46 | 0.57 **PFS HR Gem/Carbo:** 0.77 | 0.86 | 0.93	29%, ≥ 6	✚

IMpassion130: Atezolizumab 840/PLA q2w + Nab-Paclitaxel 100 D1, 8, 15 of 28 days
IMpassion131: Atezolizumab 840/PLA q2w + Paclitaxel 90 D1, 8, 15 of 28 days, 8–10 mg dexamethasone x at least 2 infusions. Stratifier prior taxane, PD-L1 status, liver mets, geographic location. 49% prior taxane, 50% prior anthracycline
IMpassion132: Atezolizumab 1200/PLA d1 q 3w + chemo (Gemcitabine 1000/carboplatin AUC 2 d 1, 8 of 21 days or Capecitabine 1000 mg/m2, BID d1 to 14 q21d)
KN-355: Pembro 200/PLA q3w + Chemo (Nab-Pac 100 D1, 8, 15 of 28 days Or Pac 90 D1, 8, 15 of 28 days Or Gem/ Carbo D1, 8 of 21 days). Stratified by taxane (45%) vs not (55%), PD-L1, prior expos to chemo class (same 22%).

* By hierarchical testing (n.s. not significant, n.t. not tested)
^ exploratory, not powered

Schmid et al, NEJM 2018, Adams et al, Ann Oncol 2020, Miles et al, ESMO 2020, Cortes et al, ASCO 2020, Rugo et al, SABCS 2020

IO A KLINICKÁ PRAXE

Aktuální standardy v indikaci IO

Typ nádoru	IO schválena FDA	IO schválena EMA	Dostupnost IO v ČR
HER2+ MBC	X	X	X
ER+ MBC	X	X	X
mTNBC	ATEZO 03/2019 PEMBRO 11/2020	ATEZO 08/2019 X	Paragraf 16 Paragraf 16*
Časný TNBC	PEMBRO 03/2021?	X	Paragraf 16*
MSI-H nádory st. IV	PEMBRO 05/2017	PEMBRO 12/2017	Paragraf 16

* off label indikace

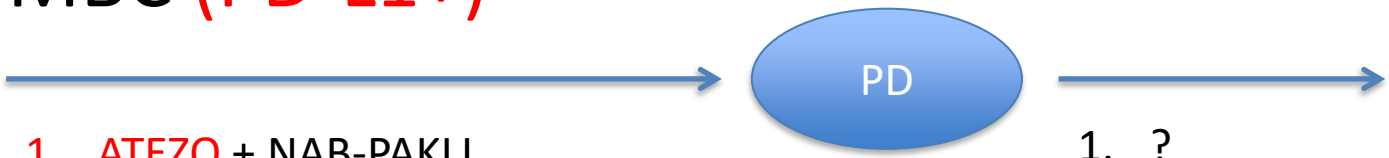
Schemata léčby

- EBC

1. ANTRA+TAX
2. ANTRA+TAX+CBDCA
3. TAX+CBDCA
4. ANTRA+TAX+/-CBDCA+IO

1. F-U or CAPE
2. F-U or CAPE?
3. F-U or CAPE?
4. F-U or IO?

- MBC (PD-L1+)

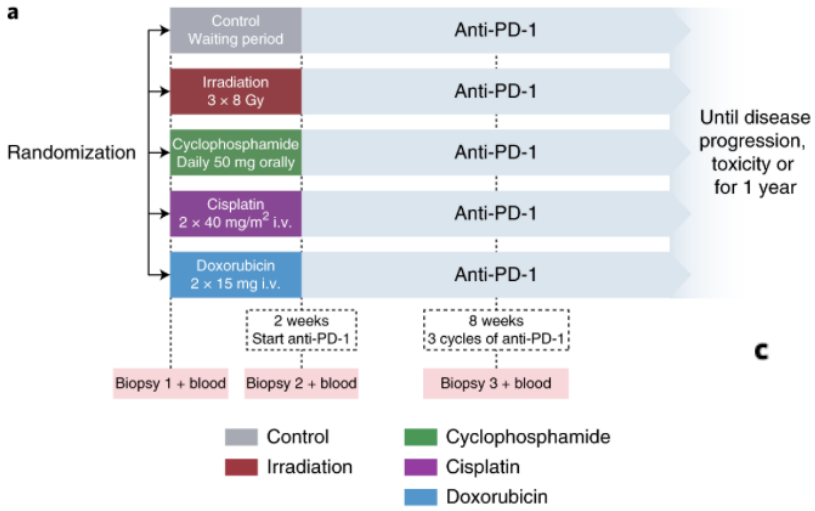


1. ATEZO + NAB-PAKLI
2. PEMBRO+pakli/nab-pakli/CBDCA+GEM
3. PARPi in BRCA+
4. cisPt + GEM

1. ?
2. ?
3. ?
4. ?

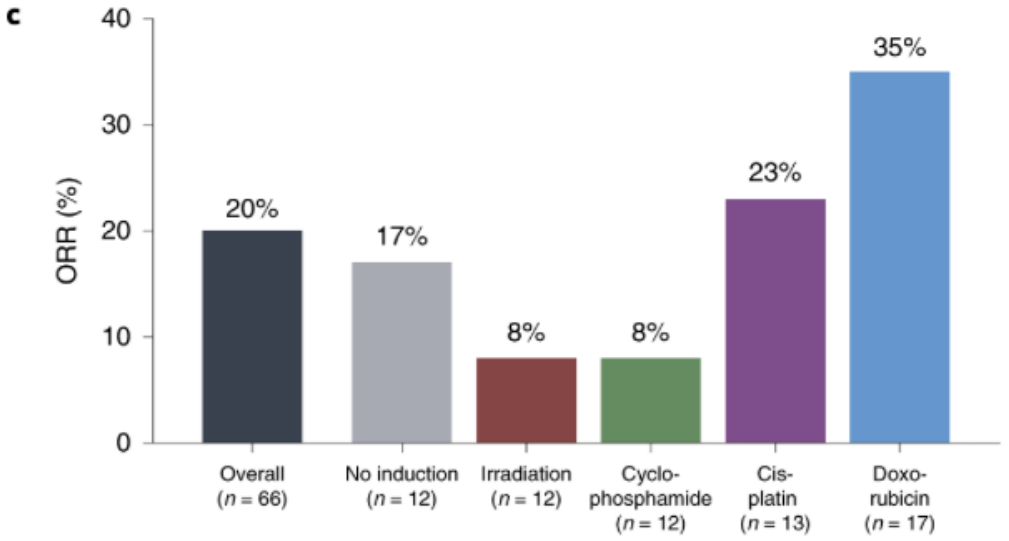
OTÁZKY

Otázka vhodného partnera pro IO



TONIC trial
non-comparative phase 2 trial
67 patients with mTNBC

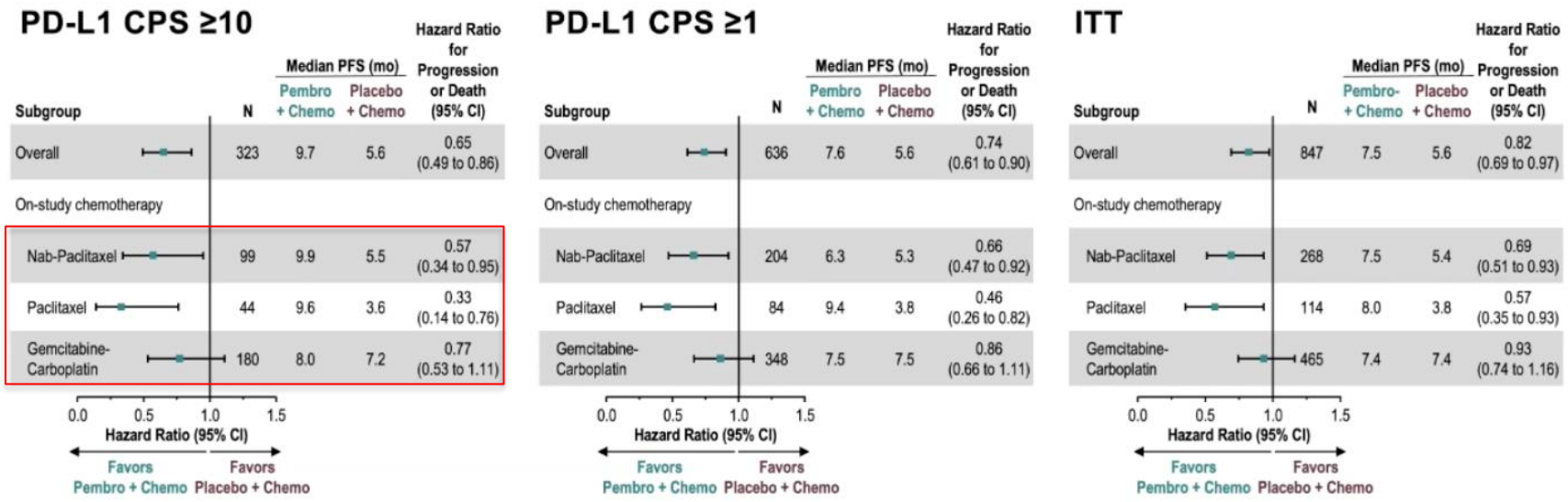
DOXO a cisPT mohou indukovat odpověď na IO



Voorwerk, Nature Medicine 2019

Selhal paklitaxel v kombinaci s IO v léčbě mTNBC?

Keynote 355

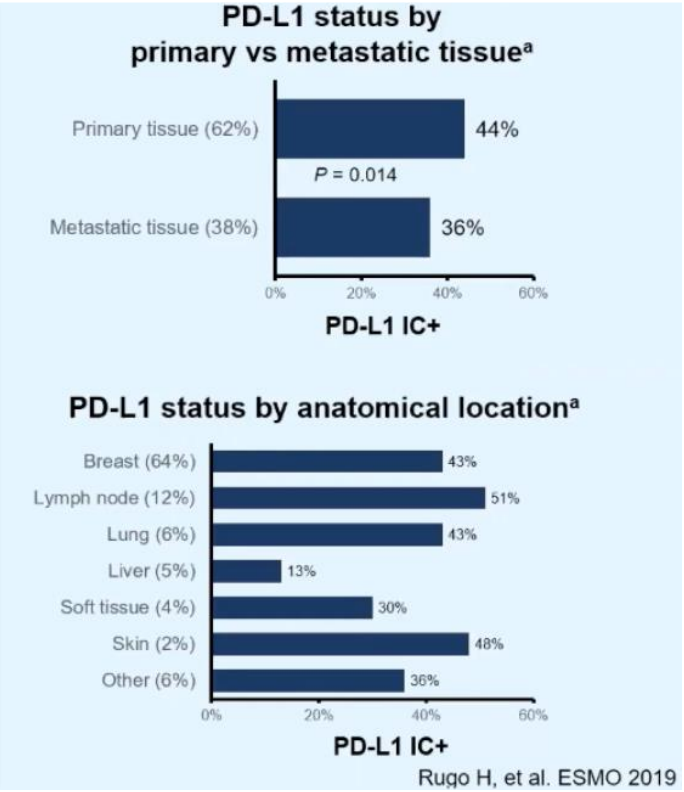


ıe PFS treatment effect was assessed in subgroups descriptively using hazard ratios and 95% CIs; although subgroup analyses by on-study chemotherapy were pre-specified, the trial ıs not powered to compare efficacy among treatment groups by different chemotherapy regimens. Steroid premedication for paclitaxel was given according to local guidelines and actices and was not restricted by the protocol. Steroid use was also allowed for the management of immune-mediated AEs across the study. Data cutoff December 11, 2019.

Proč má PD-L1 prediktivní význam (pro IO) v paliaci, ale ne u časného TNBC?

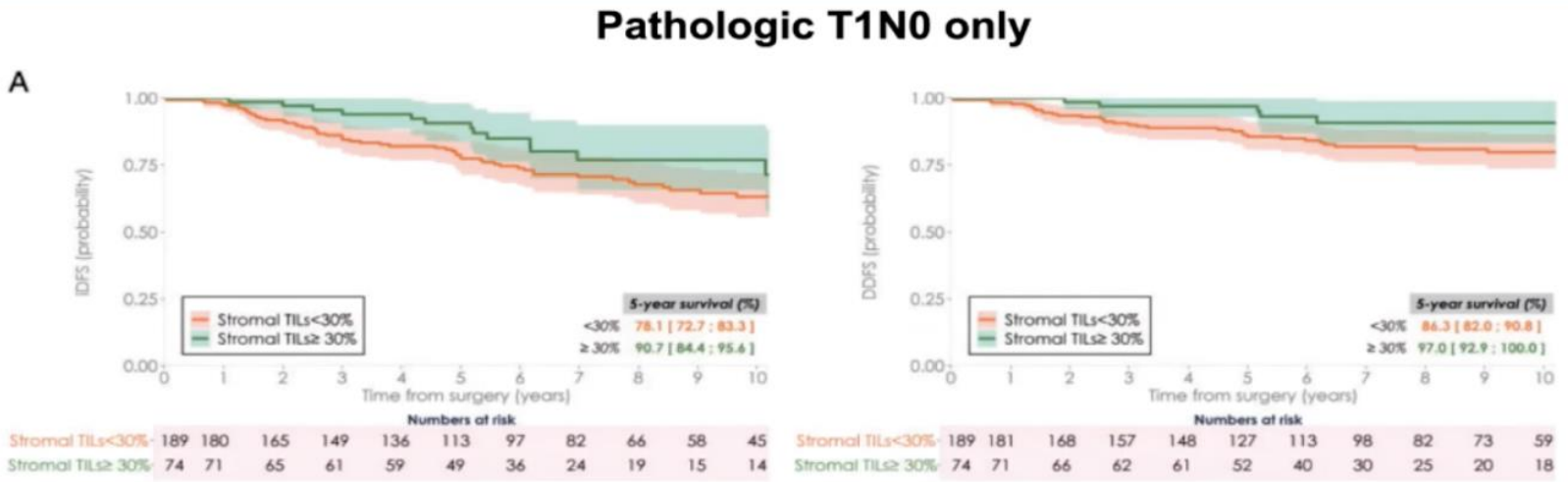
Comprehensive Profiling of Poor-Risk Paired Primary and Recurrent Triple-Negative Breast Cancers Reveals Immune Phenotype Shifts

Results: We observed a typical TNBC mutational landscape with minimal shifts in copy number or TMB over time. However, there were notable TNBC molecular subtype shifts, including increases in the Lehmann/Pietenpol-defined basal-like 1 (BL1, 11.4%–22.6%) and mesenchymal (M, 11.4%–22.6%) phenotypes, and a decrease in the immunomodulatory phenotype (IM, 31.4%–3.2%). The Burstein-defined basal-like immune-activated phenotype was also decreased (BLIA, 42.2%–17.2%). Among downregulated genes from metastases, we saw enrichment of immune-related Kyoto Encyclopedia of Genes and Genomes pathways and gene ontology (GO) terms, and decreased expression of immunomodulatory gene signatures ($P < 0.03$) and percent stromal TILs ($P = 0.03$). There was no clear association between stromal TILs and survival.



Hutchinson, Clin Cancer Res 2020

Může imuno-aktivace identifikovat low risk TNBC s možností vynechat CHT?



Convenience cohort of systemically untreated TNBC
In stage I TILs-High, 5y iDFS 91%, DDFS 97%

Park JH et al, Ann Oncol 2019

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

TILs: jak je použít v praxi?

Current guidelines

St. Gallen consensus 2019

„...the panel recommended that tumor infiltrating lymphocytes (TILs) be routinely characterized in triple negative breast cancer (TNBC) because of their prognostic value."

New WHO classification of breast tumors 2019

TILs are a new standard biomarker in TNBC

Prediktivní význam ve smyslu chemosenzitivity TNBC a HER2+ BC:
- Které cytostatika použít?
- Přidat k CHT imunoterapii?

Prognostický význam u TNBC a HER2+ BC:
- Možné CHT úplně vynechat?
- Možné dle TILs navigovat adjuvanci po NACT?

Závěry (eTNBC)

- Léčebným standardem high risk TNBC zůstávají ANTRA+TAX a CAPE v postneoadjuvantní indikaci v případě reziduální nemoci

- **Role a typ IO v neo/adjuvanci musí být potvrzena dalšími daty (EFS)**, prognostický význam pCR může být ale důvodem pro indikaci IO u high risk nemocných

- Potřeba biomarkerů kopíruje potřebu cílené eskalace/deeskalace neo/adjuvantní léčby, v praxi se ale zatím uplatňují pouze ER, PR, HER2, BRCA a PD-L1

Závěry (mTNBC)

- ATEZO a PEMBRO prodlužují PFS u PD-L1+ mTNBC
- Předpoklad rostoucího efektu PEMBRO s rostoucím CPS. Data pro OS zatím chybí.
- ATEZO prodlužuje přežívání pacientek s mTNBC
- Efekt IO lze očekávat zejména v I.linii paliace a při kombinaci s CHT
- Volba nejvhodnějšího partnera z řad cytostatik není zcela jasná, ale pravděpodobně predikovatelná

Biomarkery

- PD-L1 je jediným markerem rutinně použitelným v klinické praxi
- PD-L1 má prediktivní význam pro dosažení pCR před zahájením NACT, nemá ale prediktivní význam pro efekt IO. V paliaci je kruciálním markerem pro indikaci IO.
- PD-L1 eseje nejsou zaměnitelné
- Pro klinickou praxi genomové profilování nemá prakticky význam

Nové trendy v imunoterapii (triple negativního) karcinomu prsu

Zuzana Bielčiková

Onkologická klinika VFN a 1.LF UK v Praze

Prague ONCO 2021