Immune Checkpoint Inhibition in Early-Stage TNBC

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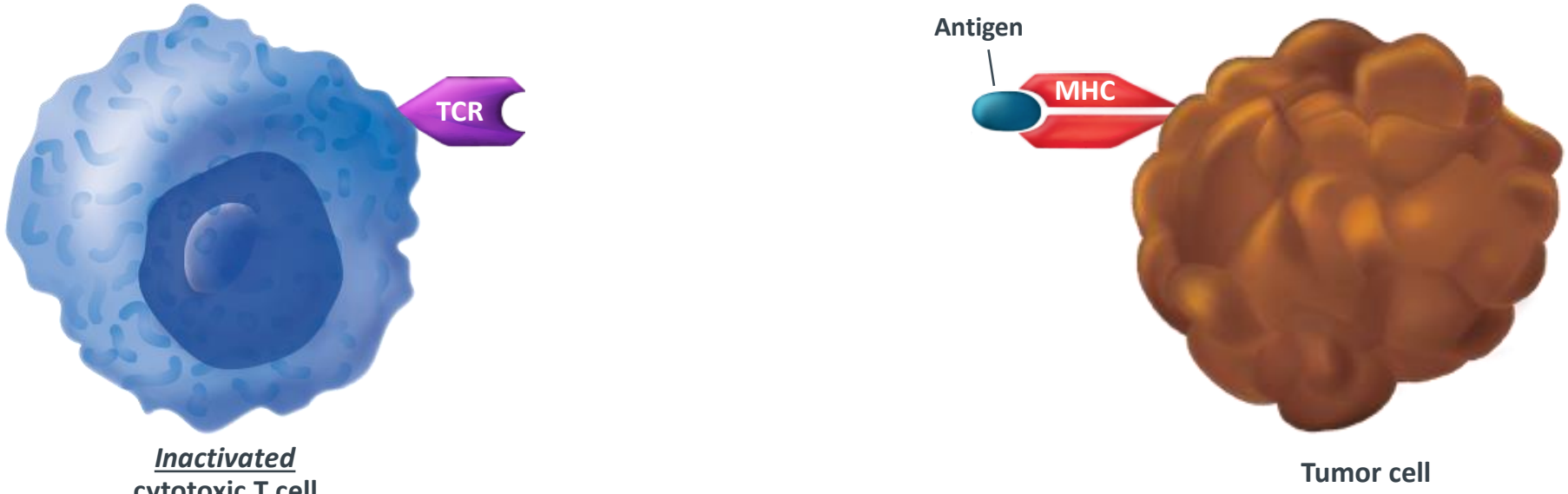
Mechanism of action of immune check point inhibitors

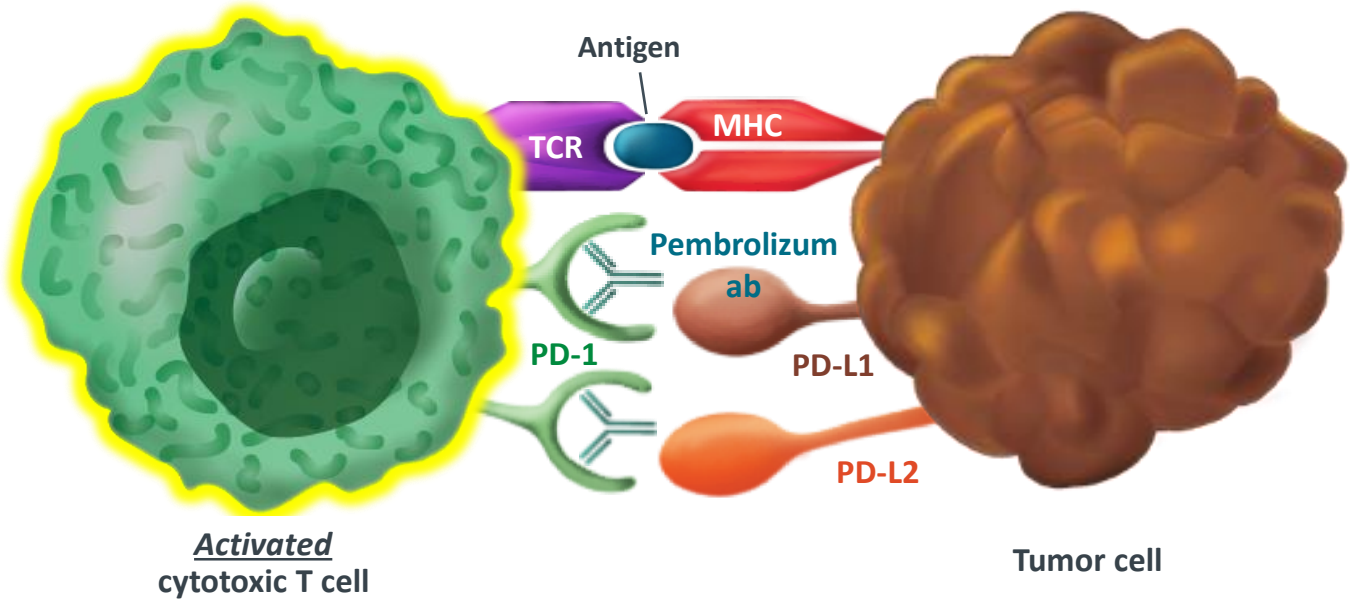


- The body's immune response can detect and destroy tumor cells through activated T cells and other mechanisms.[3]
- Emerging research has identified the programmed death receptor-1 (PD-1) as a key immune checkpoint pathway involved in inhibiting the T-cell–mediated immune response.[1]
- Tumor cells can downregulate T-cell activity by exploiting the PD-1 checkpoint pathway through expression of the PD-1 ligands, PD-L1 and PD-L2.[1]
- PD-L1 and PD-L2 engage the PD-1 receptor on T cells in order to inactivate them, which may allow tumor cells to evade the immune response.[1,2]

MHC = major histocompatibility complex; NSCLC = non–small cell lung cancer; PD-1 = programmed death receptor-1; PD-L1 = programmed death ligand 1; PD-L2 = programmed death ligand 2; TCR = T-cell receptor.

1. Pardoll DM. *Nat Rev Cancer*. 2012;12(4):252–264. **2.** Keytruda Prescribing Information. India, 2018 .**3.** Chen DS, Mellman I. *Immunity*. 2013;39(1):1–10.

Mechanism of action of immune check point inhibitors



- By inhibiting the PD-1 receptor from binding to its ligands, Pembrolizumab reactivates tumor-specific cytotoxic T lymphocytes in the tumor microenvironment and reactivates antitumor immunity.[2]

MHC = major histocompatibility complex; PD-1 = programmed death receptor-1; PD-L1 = programmed death ligand 1; PD-L2 = programmed death ligand 2; TCR = T-cell receptor.

1. Pardoll DM. *Nat Rev Cancer*. 2012;12(4):252–264.

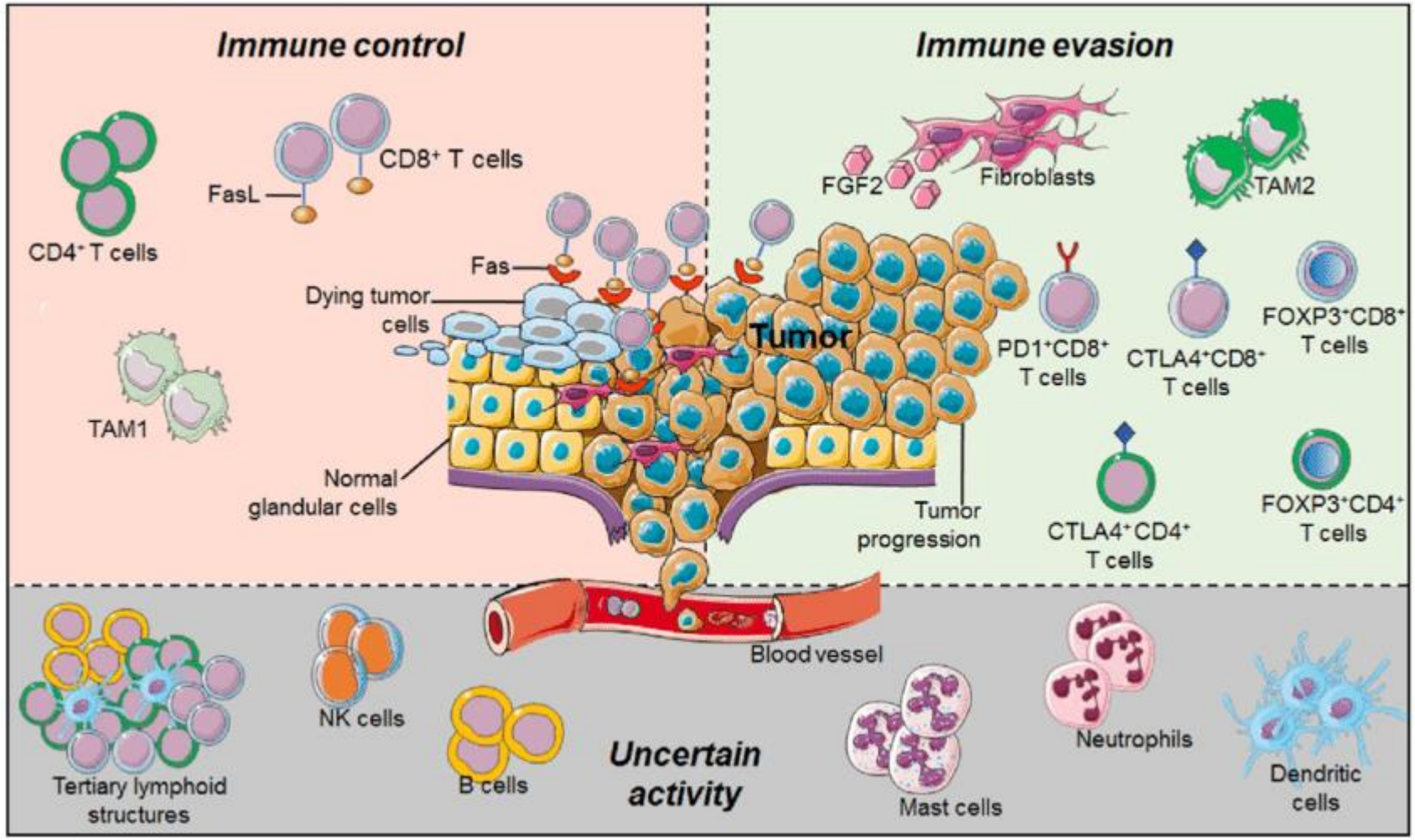
2. Keytruda Prescribing Information. India, 2018 .

Tumor microenvironment of Breast cancer

- Breast cancer has traditionally been considered an immunologically “cold” tumor with a low tumor mutational burden (TMB)
- HER2+ breast cancers and
- TNBCs share similarities in TMB, TILs and PD-L1 expression;
- (HR+) breast cancer
  - is characterized by low TIL infiltration and minimal response to ICB.
  - HR+ breast tumors establish a TME devoid of TILs, have low HLA class I expression, and recruit immune cells, other than T cells, which impact response to therapy

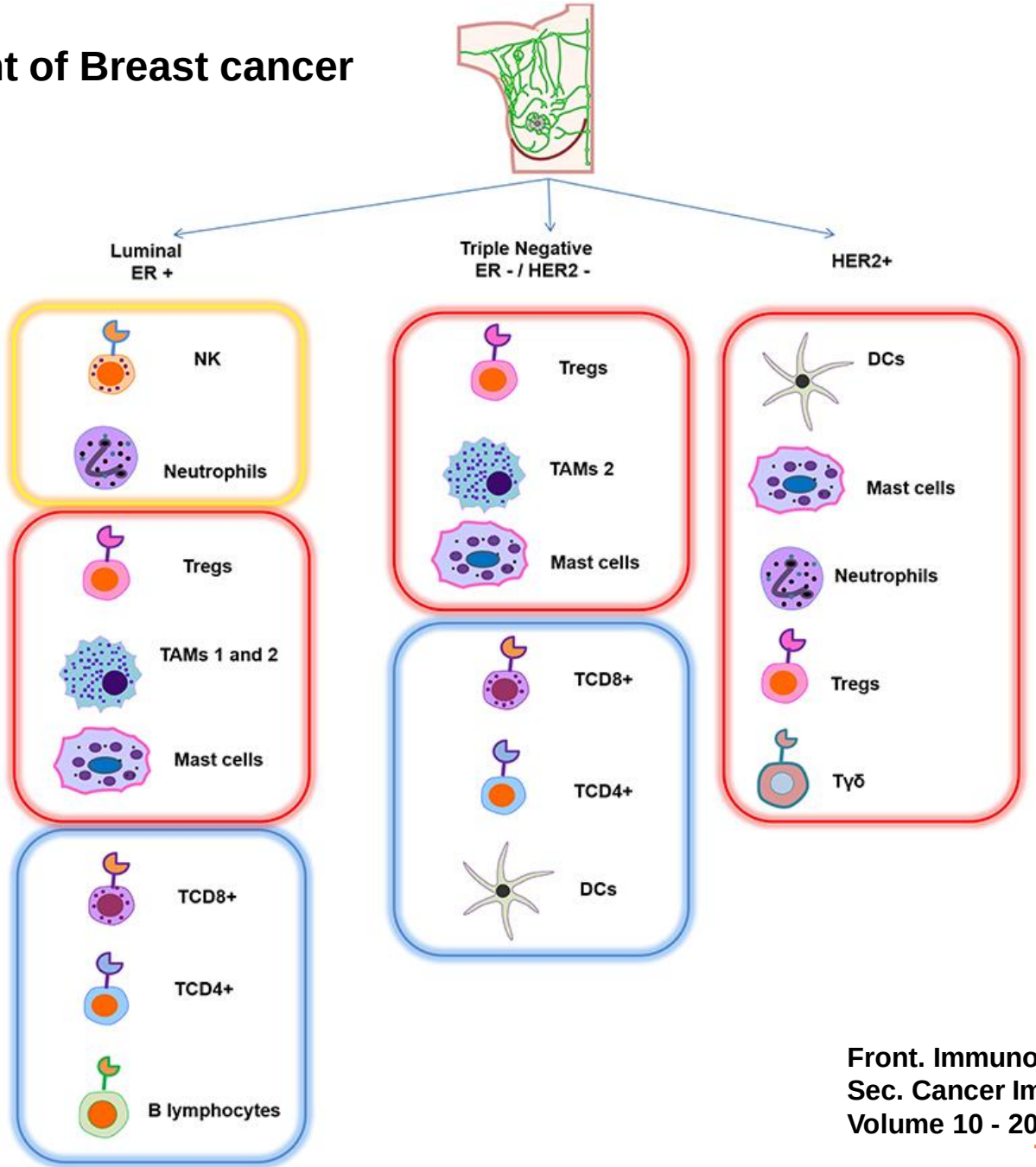
Tumor microenvironment of Breast cancer

- even higher TILS in HR-positive Breast cancer has a worse prognosis



Molecular Diagnosis & Therapy
https://doi.org/10.1007/s40291-021-00525-7

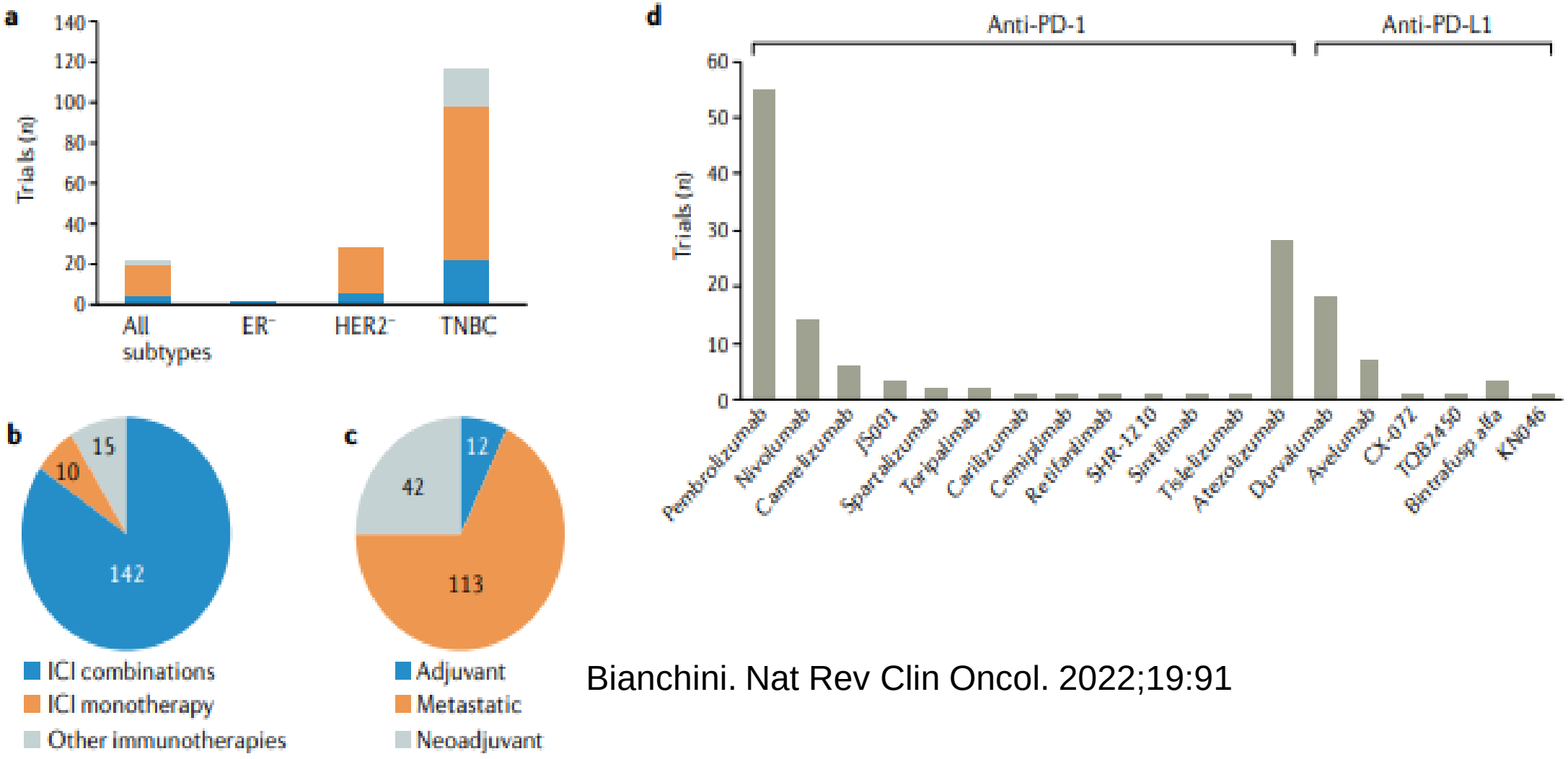
Tumor microenvironment of Breast cancer



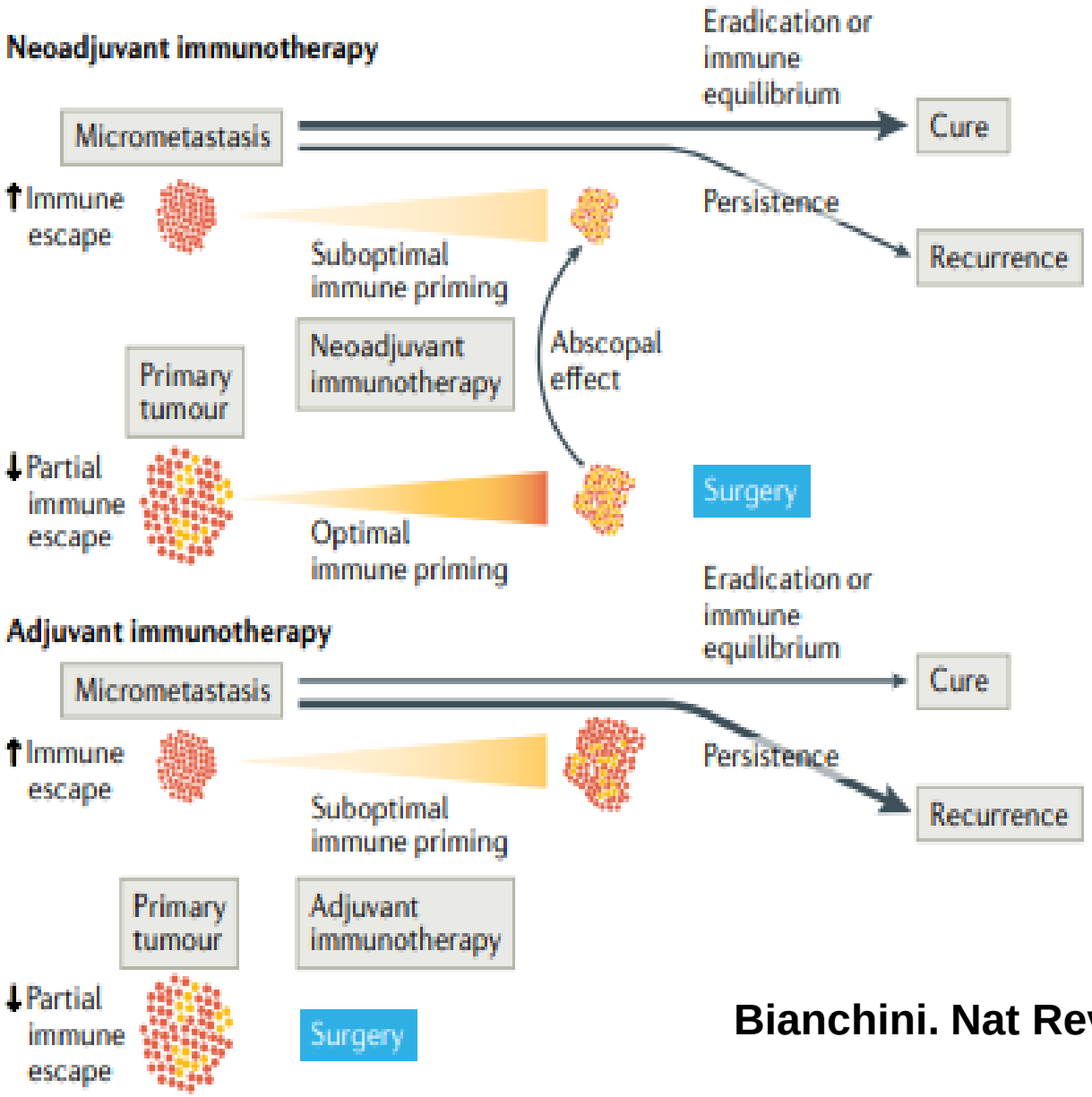
Infiltrating immune cell patterns in different cancer subtypes

TAMs are abundant in HR+ cancer, are highly immune-suppressive, and are associated with tumor progression, chemotherapy and ICB resistance, metastasis, and poor survival.

Front. Immunol., 01 March 2019
Sec. Cancer Immunity and Immunotherapy
Volume 10 - 2019 | https://doi.org/10.3389/fimmu.2019.00348



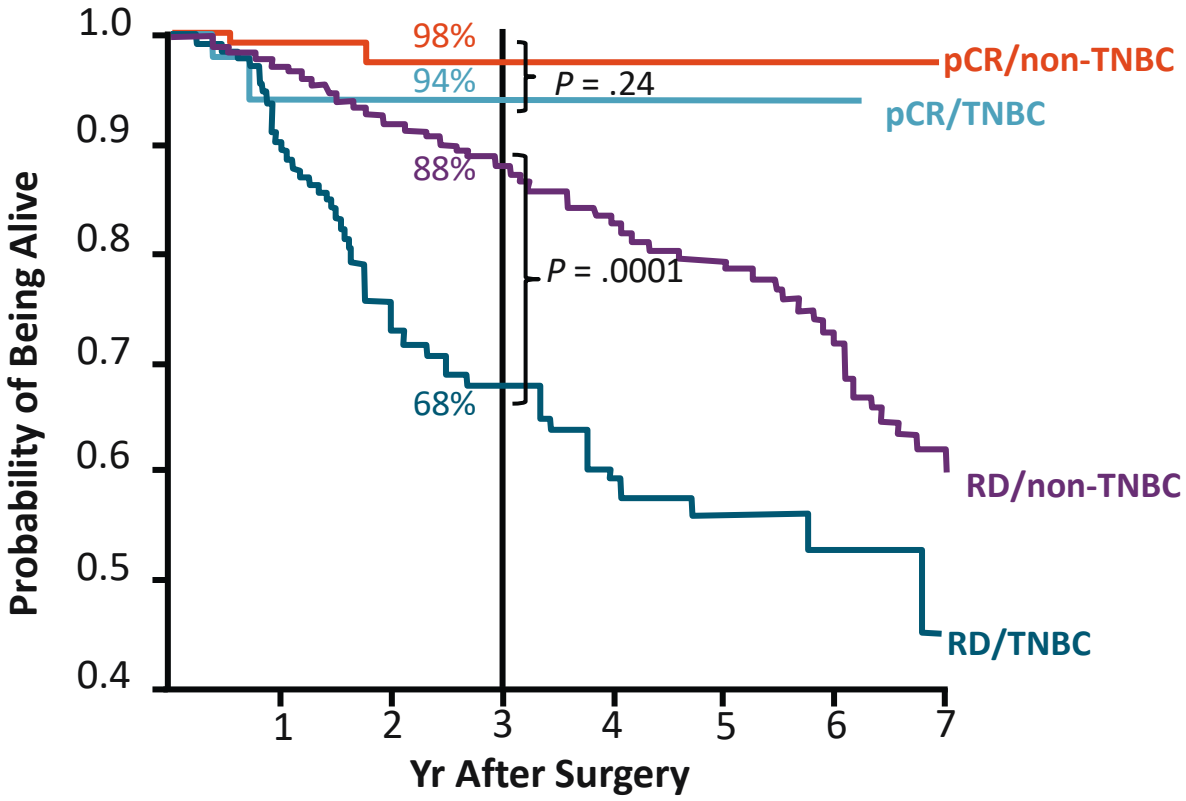
Bianchini. Nat Rev Clin Oncol. 2022;19:91



Bianchini. Nat Rev Clin Oncol. 2022;19:91

TNBC is Responsive to NAC With Outcomes Similar to Non-TNBC

Residual Cancer Burden and Outcomes[1]



Therapy options in TNBC to improve outcomes:

- Neoadjuvant chemotherapy[2]
  - Downstages tumors
  - Allows additional time for germline mutation testing
- Neoadjuvant approaches to increase pCR[2]
  - Drugs: platinums, sacituzumab govitecan[3]
  - Biologics: checkpoint inhibitors[4]
- Residual disease treatment options
  - CREATE X: adjuvant capecitabine[5]
  - Olaparib[6]

1. Liedtke. JCO. 2008;26:1275. 2. Furlanetto. Breast Care (Basel). 2020;15:217. 3. Spring. SABCS 2020. Abstr OT-03-06.
4. Schmid. NEJM. 2022;386:556. 5. Masuda. NEJM. 2017;376:2147. 6. Tutt. NEJM. 2021;384.2394.

Immunotherapy in Breast Cancer: Early-Stage vs Metastatic Breast Cancer

Chemotherapy is a rational partner for immunotherapy

- Disrupts tumor architecture
- Results in antigen shedding
- Induces rapid disease control

Parameter	EBC	MBC
Antigen presentation	↑	↓
Tumor clonality	↓	↑
Intratumor heterogeneity	↓	↑
TILs, CD8+ T-cells, DCs	↑	↓
PD-L1 positivity	↑	↓
Chemoattractants	↑	↓
Interferon signaling	↑	↓

Bianchini. Nat Rev Clin Oncol. 2022;19:91.

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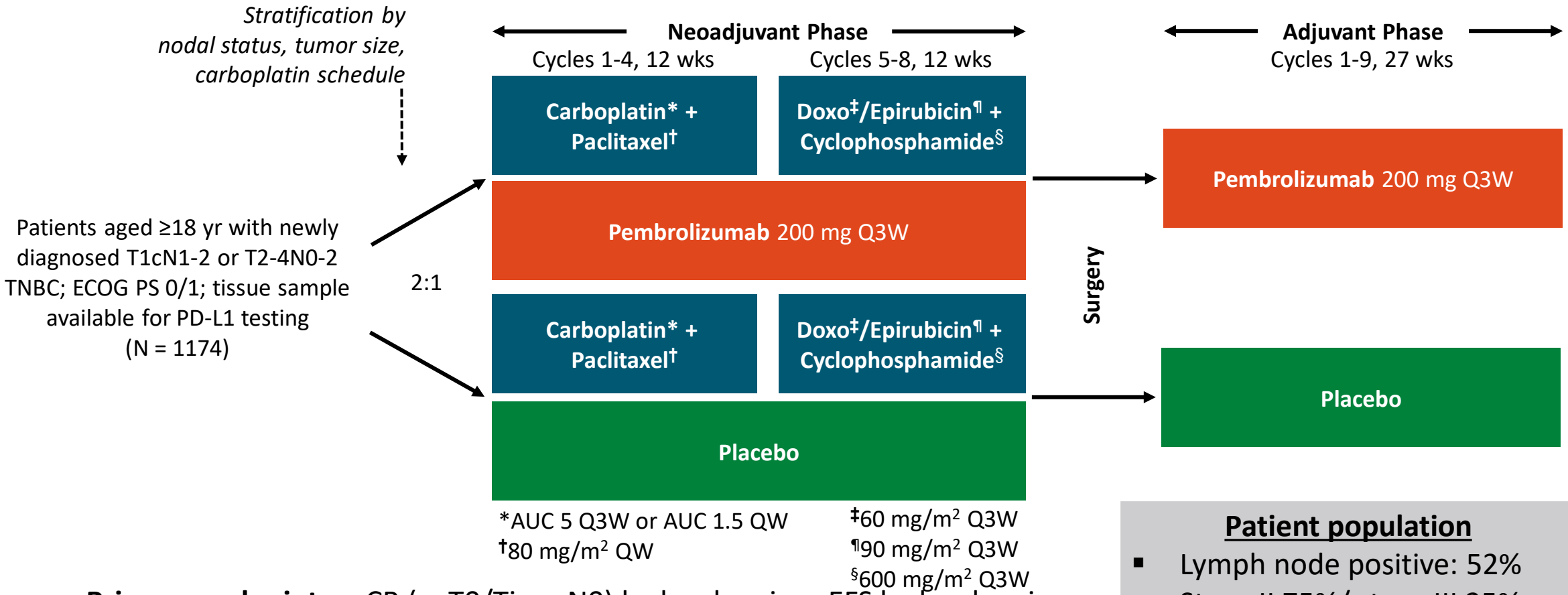
KEYNOTE-522: Neoadjuvant Pembrolizumab or Placebo + CT Followed by Adjuvant Pembrolizumab or Placebo



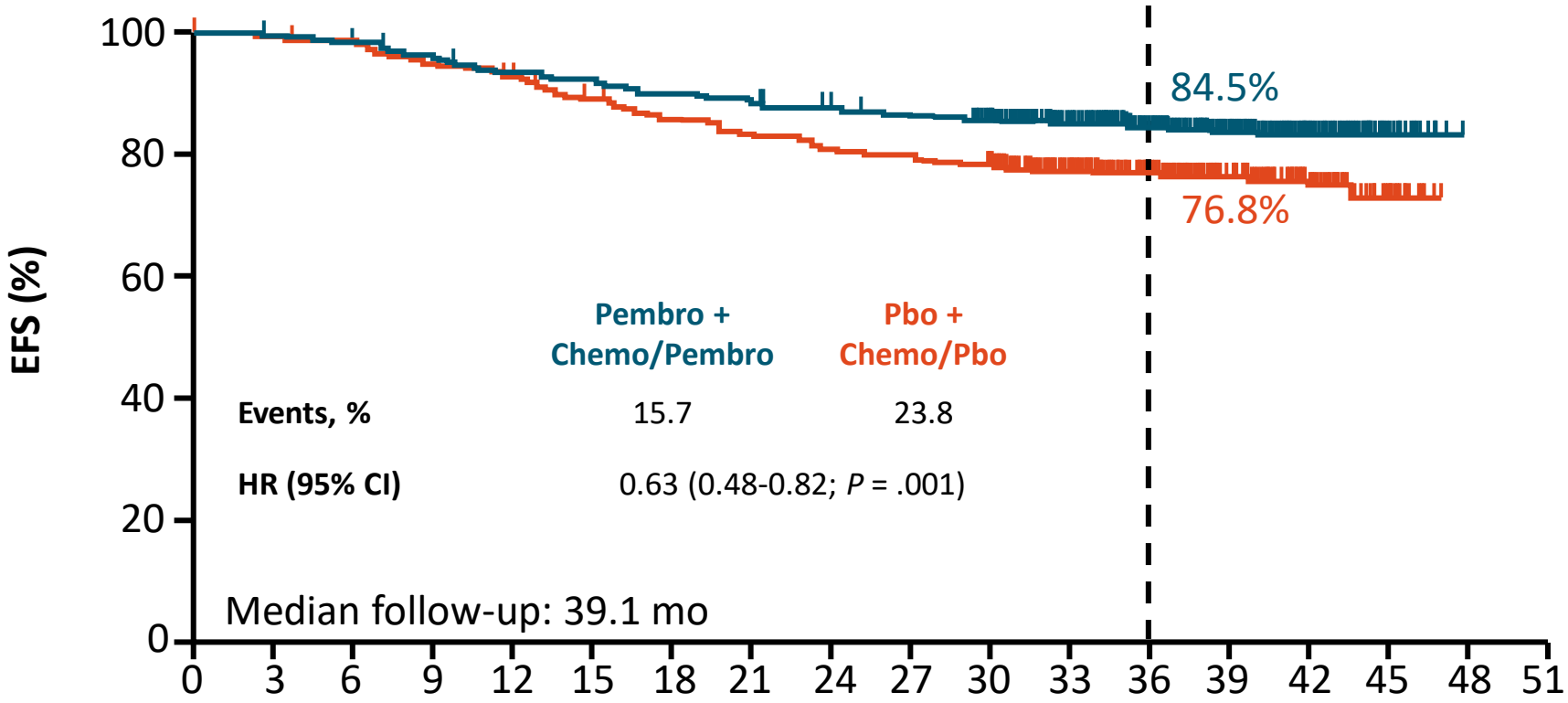
Patient population

- Lymph node positive: 52%
- Stage II 75%/ stage III 25%
- Premenopausal: 56%

- **Primary endpoints:** pCR (ypT0/Tis ypN0) by local review, EFS by local review
- **Secondary endpoints:** pCR (ypT0 ypN0 and ypT0/Tis), OS, safety
- **Exploratory endpoints:** EFS by subgroups, EFS by pCR, DPFS, DRFS

Schmid. N Engl J Med. 2020;382.810. Schmid. N Engl J Med. 2022;386:556.

KEYNOTE-522: EFS at Interim Analysis 4



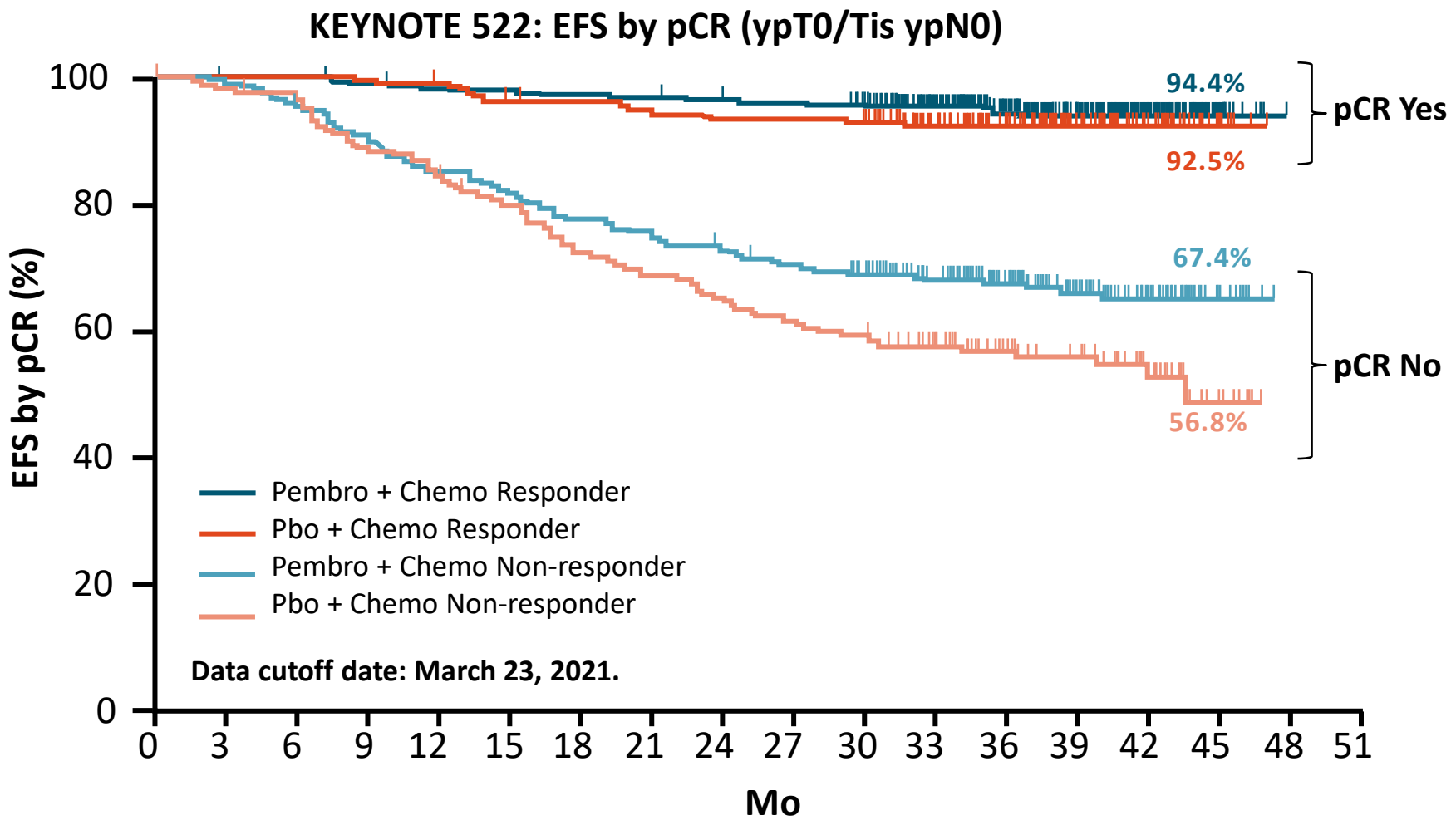
Patients at risk, n																		
Pembro + chemo	784	781	769	751	728	718	702	692	681	671	652	551	433	303	165	28	0	0
Pbo + chemo	390	386	382	368	358	342	328	319	310	304	297	250	195	140	83	17	0	0

- 6.3% increase in DRFS: 87% to 80.7%; HR: 0.61; 95% CI: 0.46-0.82.

Schmid. ESMO 2021. Abstr VP7-2021. Schmid. N Engl J Med. 2022;386:556.

Slide credit: clinicaloptions.com

KEYNOTE-522: EFS by pCR



Schmid. ESMO 2021. Abstr VP7-2021. Schmid. N Engl J Med. 2022;386:556.

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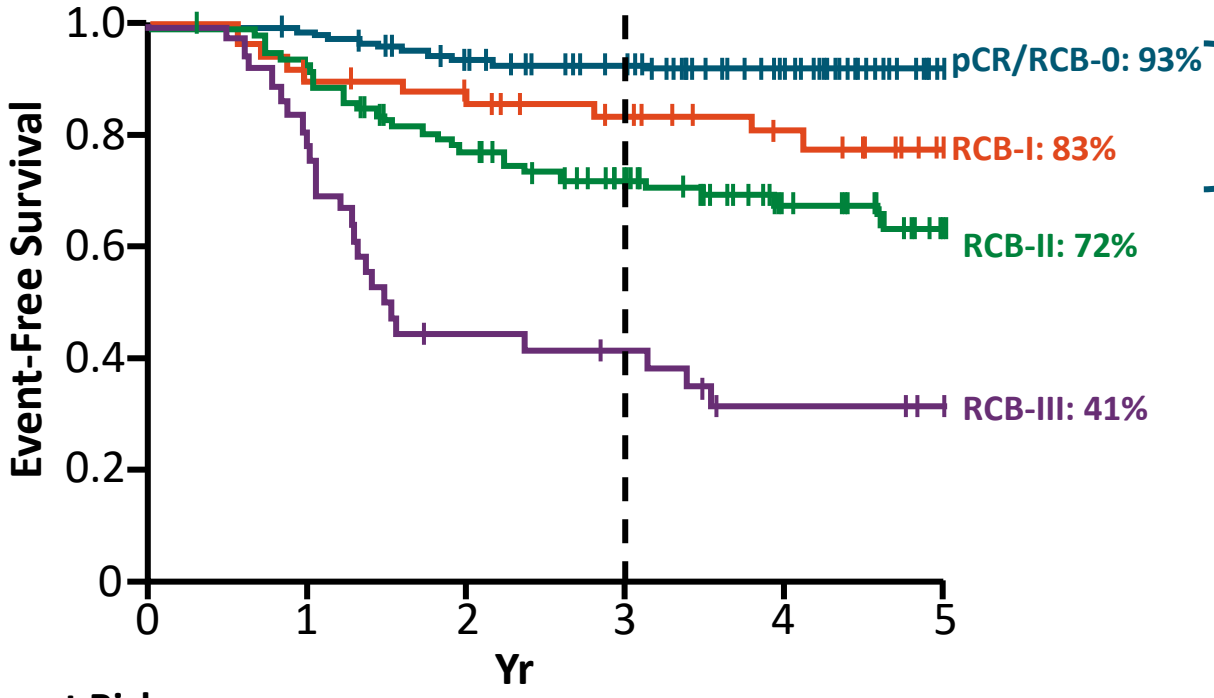
Residual Cancer Burden and EFS After Neoadjuvant/Adjuvant Therapy in TNBC

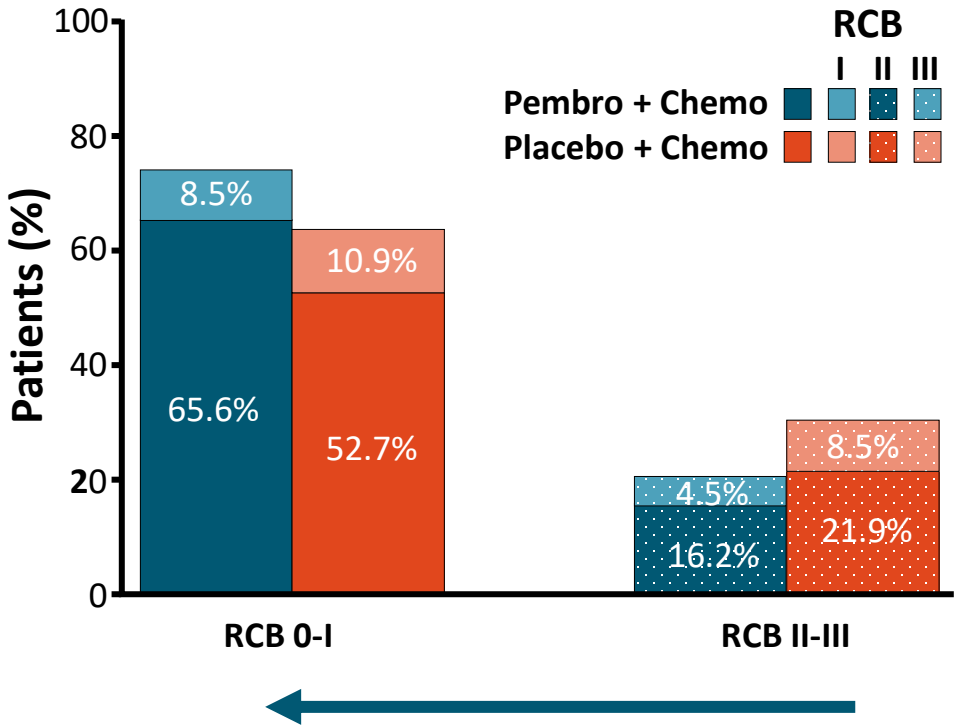
I-SPY2 3-year EFS by RCB for TNBC[1,2]



No. at Risk

0	140	138	126	109	86	52
I	50	44	42	35	26	15
II	93	85	68	54	36	24
III	36	28	15	13	8	6

KEYNOTE-522: RCB Shift With Pembrolizumab[3]



1. Symmans. JAMA Oncol. 2021;7:1654. 2. Nanda. JAMA Oncol. 2020;6:1. 3. Schmid. SABCS 2019. Abstr GS3-03.

Slide credit: clinicaloptions.com

Immune Checkpoint Inhibitors in Early-Stage TNBC

Variable	I-SPY2[1]	KEYNOTE-522[2,3]	IMpassion031[4]	NeoTRIPaPDL1[5]	GeparNuevo[6,7]
N	250	1174	333	280	174
ICI and # Cycles	Pembro x 4	Pembro x 17†	Atezo x 1 year	Atezo x 8	Durva x 8
Stage	Stage II/III	Stage II/III	Stage II/III	T1cN1, T2N1, T3N0 and locally advanced	36.4% <Stage IIA
Chemo use pre-op	Taxane and anthracycline	Paclitaxel, carboplatin; → doxorubicin or epirubicin plus cyclophosphamide	nab-paclitaxel, doxorubicin, and cyclophosphamide	No anthracyclines; received carboplatin and nab-paclitaxel	Nab-paclitaxel, epirubicin/cyclophosphamide
Carboplatin use	Could be added	Included in regimen	No	Included in regimen	No
pCR ICI vs control, % *P*-value	60 vs 22 NR	64.8 vs 51.2 *P* <.001*	57.6 vs 41.1 *P* = .0044	48.6 vs 44.4 *P* = .48	53.4 vs 44.2 *P* = .287
EFS	Similar (descriptive)	3-yr 84.5% vs 76.8%	NR	NR	3-yr 85.6% vs 77.2%

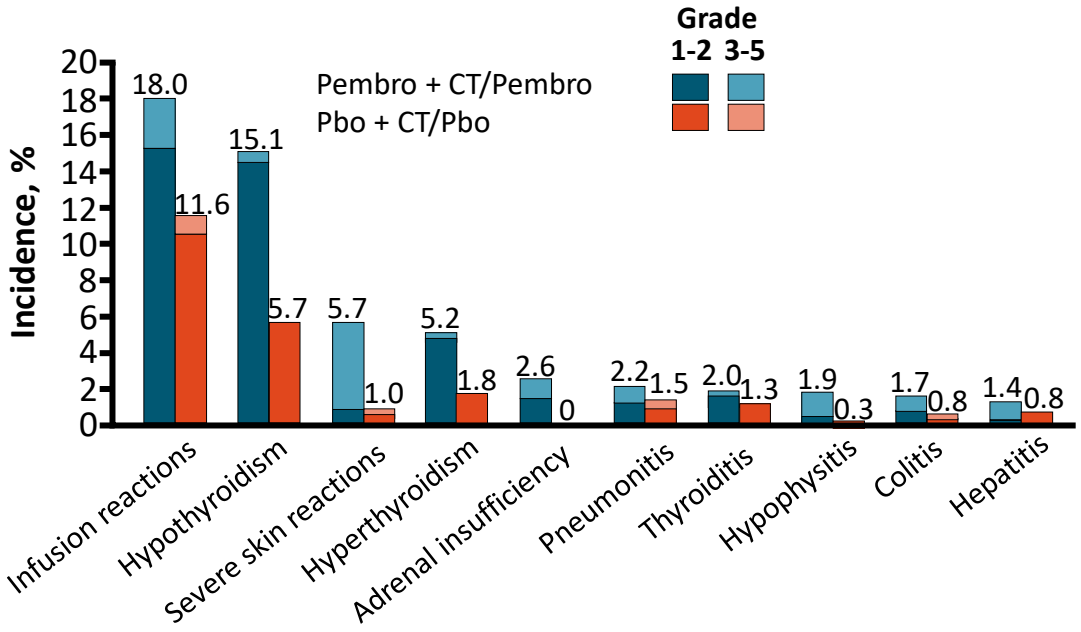
*Data for n = 602 presented.

†8 cycles neoadjuvant; 9 cycles adjuvant.

1. Nanda. JAMA Oncol. 2020;6:676. 2. Schmid. NEJM. 2020;382:810. 3. Schmid. N Engl J Med. 2022;386:556. 4. Mittendorf. Lancet. 2020;396:1090. 5. Gianni. Ann Oncol. 2022;33:534. 6. Loibl. Ann Oncol. 2019;30:1279. 7. Loibl. ASCO 2021. Abstr 506.

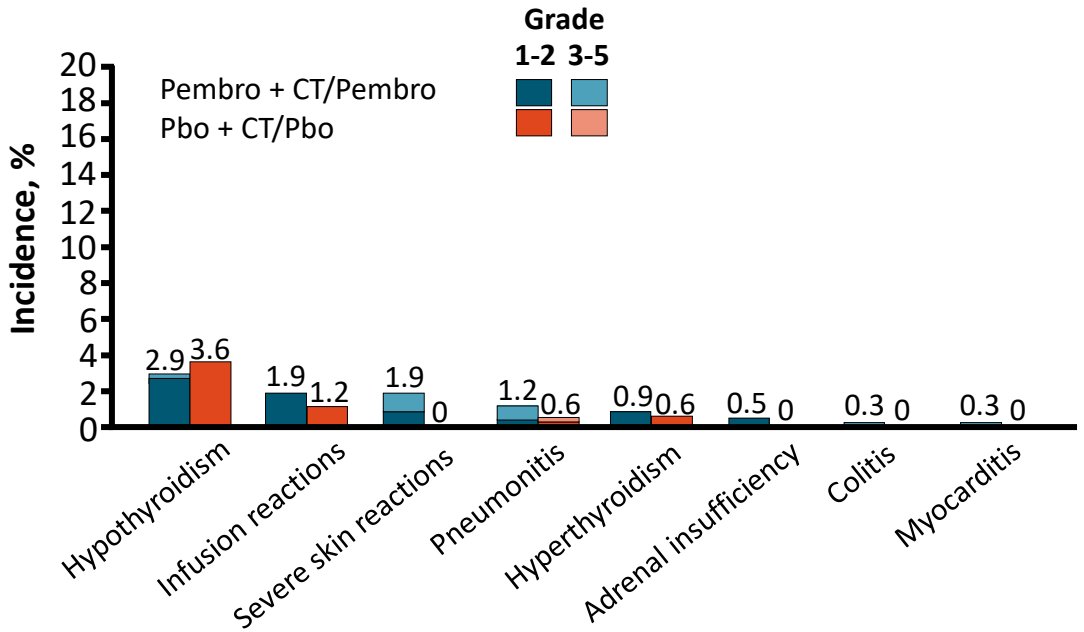
KEYNOTE-522: Immune-Mediated AEs

Immune-Mediated AEs and Infusion Reactions (≥10% Patients) Across Both Phases



Adverse Event, %	Pembro + CT/Pembro (n = 783)	Pbo + CT/Pbo (n = 389)
Any grade	43.6	21.9
Grade 3-5	14.9	2.1
Led to death	0.3	0
Discontinuation any drug	10.9	2.6

Immune-Mediated AEs in the Adjuvant Phase (≥2% of Patients)



Adverse Event, %	Pembro + CT/Pembro (n = 588)	Pbo + CT/Pbo (n = 331)
Any grade	10.2	6.0
Grade 3-5	2.9	0.3
Led to death	0.2	0
Discontinuation any drug	1.4	0.3

Schmid. N Engl J Med. 2020;382.810. Schmid. ESMO 2021. Abstr VP7-2021. Schmid. N Engl J Med. 2022;386:556.

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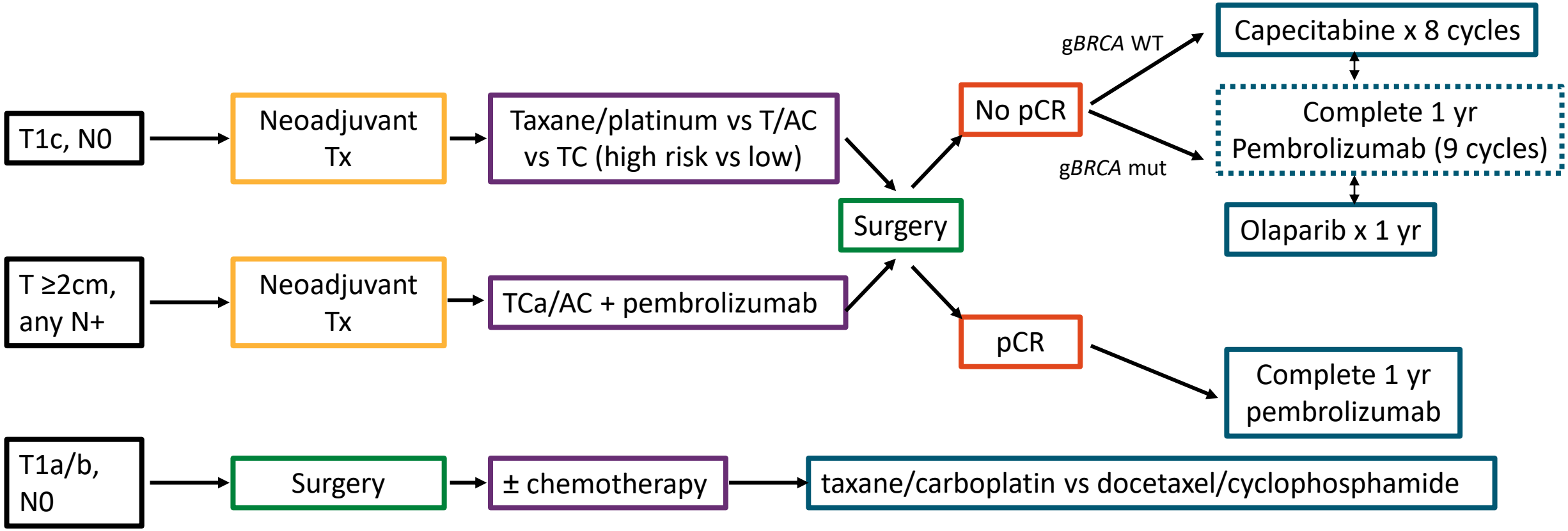
Considerations in the Treatment of Early-Stage TNBC



- **Ongoing trials:** Tailoring neoadjuvant therapy to response; optimizing post-neoadjuvant therapy – ADCs, checkpoint inhibitor?
- ***gBRCA* mutation:** neoadjuvant in addition to adjuvant PARP inhibitors?

Slide credit: clinicaloptions.com

Clinical Questions That Remain for Early-Stage TNBC: More Questions Than Answers?

Neoadjuvant Immunotherapy	Immunotherapy	CT Backbone	ADCs	Post Neoadjuvant Therapy
▪ Does everyone benefit? ▪ Biomarker selection ▪ Balance risk and cost: who will benefit from CT alone ▪ Balance risk and toxicity: who can avoid immunotherapy?	▪ Combining immunotherapy with AKT or PARP inhibitors? ▪ Optimal duration of immunotherapy in patients who achieve pCR vs non-pCR ▪ Impact of adjuvant immunotherapy?	▪ Optimal CT backbone? ▪ Platinum improves pCR (CALGB 40603, BrighTNess) and EFS (BrighTNess), but not OS; increase toxicity ▪ Anthracyclines modulate tumor microenvironment ?	▪ Role for ADCs? ▪ Sacituzumab govitecan ▪ Trastuzumab deruxtecan	▪ Optimal post-neoadjuvant therapy? ▪ Pembrolizumab plus other post-neoadjuvant therapies? ▪ Capecitabine still relevant?

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KEYNOTE-355: Randomized, Placebo-Controlled Phase III Trial of Pembrolizumab + Chemotherapy in Previously Untreated Metastatic TNBC (Final Results)

CCO Independent Conference Highlights*

of the *ESMO 2021 Conference,*
September 17-20, 2021, Virtual

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KEYNOTE-355 Final Analysis: Background

- Phase III KEYNOTE-355 trial evaluated pembrolizumab + chemotherapy vs chemotherapy alone as first-line treatment for locally recurrent inoperable or metastatic TNBC
- At prespecified interim analysis, pembrolizumab + chemotherapy showed a significant and clinically meaningful PFS benefit vs chemotherapy alone in patients whose tumors expressed PD-L1 (CPS ≥10)[1]
  - Based on these results, pembrolizumab + chemotherapy received FDA approval in PD-L1–positive (CPS ≥10), locally recurrent unresectable or metastatic TNBC[2]
- Final KEYNOTE-355 analysis evaluated OS outcomes (second primary endpoint)[3]

1. Cortes. Lancet. 2020;396:1817. 2. Pembrolizumab PI. 3. Rugo. ESMO 2021. Abstr LBA16.

KEYNOTE-355: Study Design

- Randomized, double-blind, multicenter phase III trial

Stratified by chemotherapy (taxane vs gem/carbo); PD-L1 tumor expression (CPS ≥1 vs <1); previous Tx with same class of chemotherapy for EBC (Y vs N)

*Investigator's choice of chemotherapy
- Nab-paclitaxel 100 mg/m^2 IV on D 1, 8, 15 of 28-day cycle
- Paclitaxel 90 mg/m^2 IV on D 1, 8, 15 of 28-day cycle
- Gem 1000 mg/m^2 + carbo AUC 2 on D 1, 8 of 21-day cycle

Adult patients with previously untreated locally recurrent inoperable or metastatic TNBC; completed curative intent treatment ≥6 mo before first recurrence; ECOG PS 0/1 (N = 847)

Pembrolizumab 200 mg IV Q3W **+ Chemotherapy*** (n = 566)

Placebo + Chemotherapy* (n = 281)

Until progression, toxicity, or completion of 35 cycles of pembrolizumab/placebo

- Primary endpoints: PFS and OS (PD-L1 CPS ≥10, PD-L1 CPS ≥1, and ITT)
  - PFS benefit reported in interim analysis; current analysis evaluated OS outcomes
- Secondary endpoints: ORR, DoR, DCR, safety in full treated population
- Median follow-up: 44.0 mo (pembro + CT), 44.4 mo (CT)

Rugo. ESMO 2021. Abstr LBA16.

KEYNOTE-355: Baseline Characteristics (ITT)

Characteristics	Pembrolizumab + CT (n = 566)	Placebo + CT (n = 281)
Median age, yr (range)	53 (25-85)	53 (22-77)
ECOG PS 1, n (%)	232 (41.0)	108 (38.4)
PD-L1–positive CPS ≥1, n (%)	425 (75.1)	211 (75.1)
PD-L1–positive CPS ≥10, n (%)	220 (38.9)	103 (36.7)
CT on study, n (%)		
▪ Taxane	255 (45.1)	127 (45.2)
▪ Gem/carbo	311 (54.9)	154 (54.8)
Previous same-class CT, n (%)		
▪ Yes	124 (21.9)	62 (22.1)
▪ No	442 (78.1)	219 (77.9)
Disease-free interval, n (%)		
▪ de novo metastasis	168 (29.7)	84 (29.9)
▪ <12 mo	125 (22.1)	50 (17.8)
▪ ≥12 mo	270 (47.7)	147 (52.3)

Rugo. ESMO 2021. Abstr LBA16.

Slide credit: clinicaloptions.com

KEYNOTE-355 Final Analysis: OS (Coprimary Endpoint)

OS	Pembrolizumab + CT	Placebo + CT	HR (95% CI)
PD-L1 CPS ≥10	(n = 220)	(n = 103)	
▪ Median OS, mo	23.0	16.1	0.73 (0.55-0.95)
▪ 18-mo OS, %	58.3	44.7	1-sided *P* = .0093
▪ 24-mo OS, %	48.2	34.0	
PD-L1 CPS ≥1	(n = 425)	(n = 211)	
▪ Median OS, mo	17.6	16.0	0.86 (0.72-1.04)
▪ 18-mo OS, %	48.4	41.4	1-sided *P* = .0563
▪ 24-mo OS, %	37.7	29.5	
ITT population	(n = 566)	(n = 281)	
▪ Median OS, mo	17.2	15.5	0.89 (0.76-1.05)
▪ 18-mo OS, %	47.8	41.8	
▪ 24-mo OS, %	35.5	30.4	

Rugo. ESMO 2021. Abstr LBA16.

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KEYNOTE-355 Final Analysis: OS in PD-L1 CPS Subgroups

Median OS, mo	n	Pembrolizumab + CT	Placebo + CT	HR for Death (95% CI)
Overall	847	17.2	15.5	0.89 (0.76-1.05)
PD-L1 CPS cutoff of 1				
▪ CPS ≥1	636	17.6	16.0	0.86 (0.72-1.04)
▪ CPS <1	211	16.2	14.7	0.97 (0.72-1.32)
PD-L1 CPS cutoff of 10				
▪ CPS ≥10	323	23.0	16.1	0.71 (0.54-0.93)
▪ CPS <10	524	14.7	15.2	1.04 (0.85-1.26)
PD-L1 CPS cutoff of 20				
▪ CPS ≥20	204	24.0	15.6	0.72 (0.51-1.01)
▪ CPS <20	643	15.9	15.5	0.96 (0.80-1.14)

- OS outcomes were generally consistent across demographic and disease subgroups within CPS ≥10 and CPS ≥1 patient populations

Rugo. ESMO 2021. Abstr LBA16.

KEYNOTE-355 Final Analysis: PFS (Coprimary Endpoint)

PFS	Pembrolizumab + CT	Placebo + CT	HR (95% CI)
PD-L1 CPS ≥10	(n = 220)	(n = 103)	
▪ Median PFS, mo	9.7	5.6	0.66 (0.50-0.88)
▪ 12-mo PFS, %	39.1	23.0	
PD-L1 CPS ≥1	(n = 425)	(n = 211)	
▪ Median PFS, mo	7.6	5.6	0.75 (0.62-0.91)
▪ 12-mo PFS, %	31.7	19.4	
ITT population	(n = 566)	(n = 281)	
▪ Median PFS, mo	7.5	5.6	0.82 (0.70-0.98)
▪ 12-mo PFS, %	29.3	20.8	

Rugo. ESMO 2021. Abstr LBA16.

Slide credit: clinicaloptions.com

KEYNOTE-355 Final Analysis: Other Efficacy Outcomes

Outcome	Pembrolizumab + CT	Placebo + CT
ORR, %		
▪ PD-L1 CPS ≥10	52.7	40.8
▪ PD-L1 CPS ≥1	44.9	38.9
▪ ITT	40.8	37.0
Disease control rate, %		
▪ PD-L1 CPS ≥10	65.0	54.4
▪ PD-L1 CPS ≥1	58.6	53.6
▪ ITT	56.0	51.2
Median DoR, mo (range)		
▪ PD-L1 CPS ≥10	12.8 (1.6+ to 45.9+)	7.3 (1.5 to 46.6+)
▪ PD-L1 CPS ≥1	10.1 (1.0+ to 45.9 +)	6.8 (1.5 to 46.6+)
▪ ITT	10.1 (1.0+ to 45.9+)	6.5 (1.5 to 46.6+)
12-month DoR, %		
▪ PD-L1 CPS ≥10	55.5	37.9
▪ PD-L1 CPS ≥1	46.8	29.6
▪ ITT	46.1	33.3

Rugo. ESMO 2021. Abstr LBA16.

Slide credit: clinicaloptions.com

KEYNOTE-355 Final Analysis: Safety

Treatment-Related AE, %	Pembro + CT (n = 562)	Placebo + CT (n = 281)
Any grade	96.3	95.0
Grade ≥3	68.1	66.9
Led to death*	0.4	0
Led to discontinuation of any drug	18.3	11.0
Anemia	49.1	45.9
Neutropenia	41.1	38.1
Nausea	39.3	41.3
Alopecia	33.1	33.5
Fatigue	28.6	29.9
Neutrophils decreased	22.4	26.3
ALT increased	20.5	16.4

Immune-Mediated AE, %	Pembro + CT (n = 562)	Placebo + CT (n = 281)
Any grade	26.5	6.4
Grade ≥3	5.3	0
Led to death	0	0
Led to discontinuation of any drug	2.8	0
Hypothyroidism	15.8	3.2
Hyperthyroidism	4.3	1.1
Pneumonitis	2.5	0
Colitis	1.8	1.4
Severe skin reactions	1.8	0.4

*1 event each acute kidney injury and pneumonia.

Rugo. ESMO 2021. Abstr LBA16.

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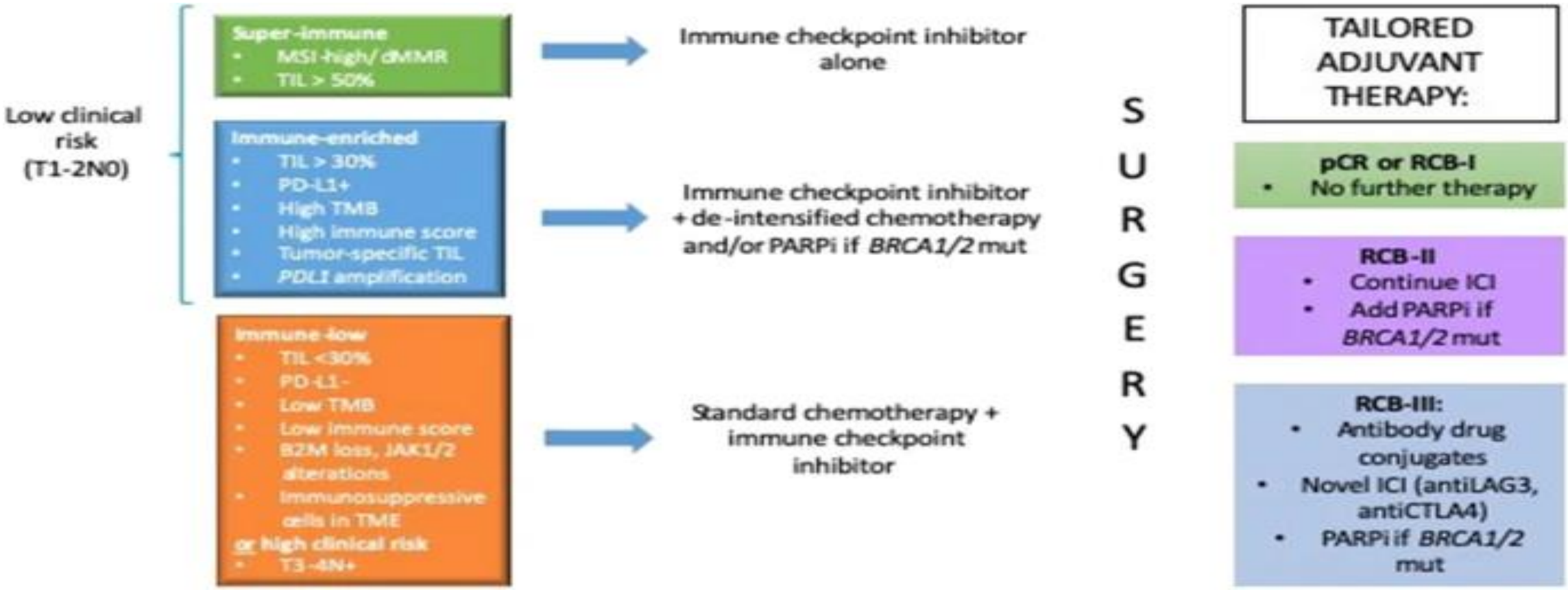
KEYNOTE-355 Final Analysis: Conclusions

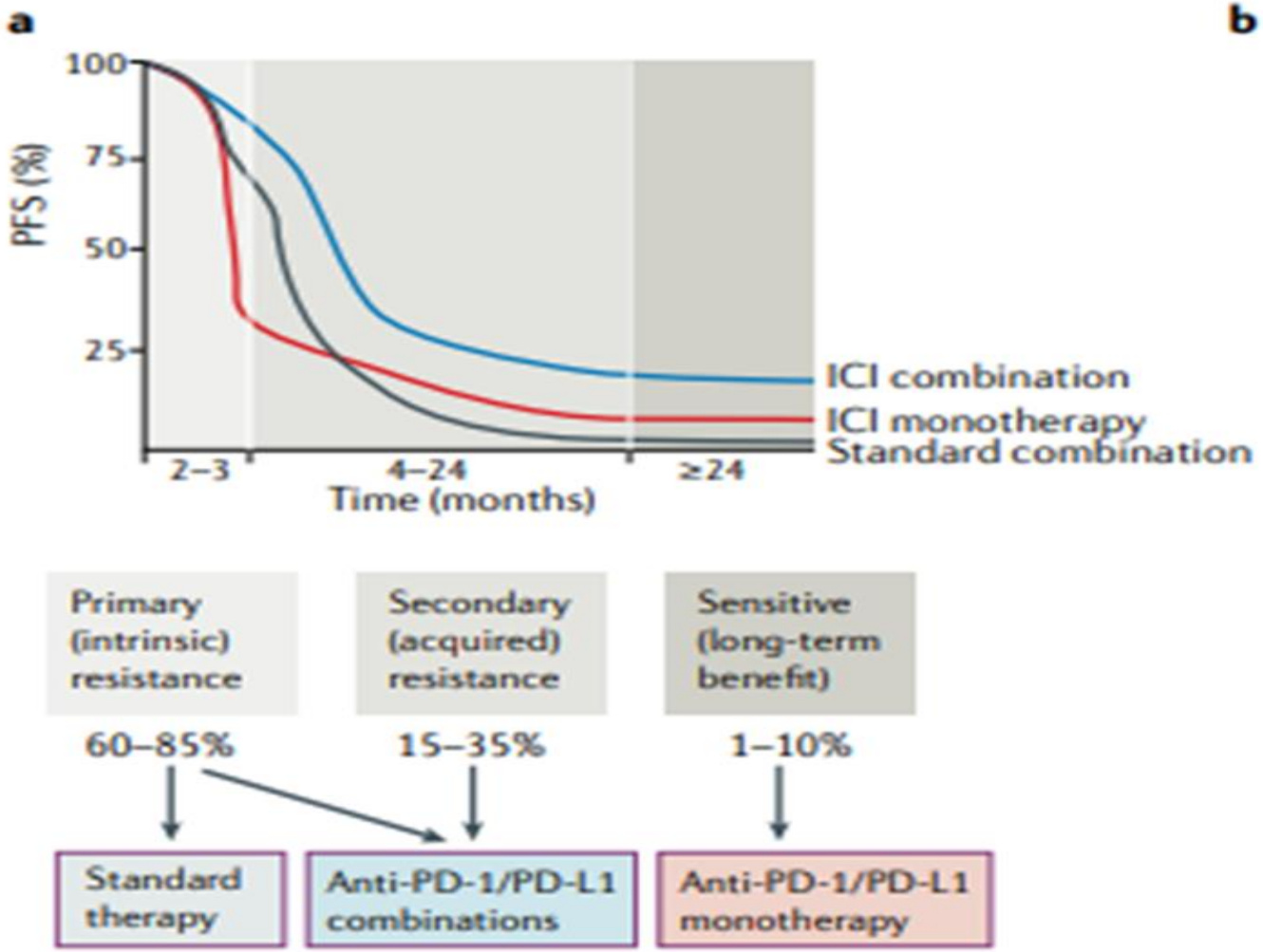
- In this phase III study, the addition of pembrolizumab to chemotherapy as first-line therapy significantly prolonged OS and PFS in patients with PD-L1–positive (CPS ≥10) metastatic TNBC
  - Median OS with PD-L1 CPS ≥10: 23.0 mo vs 16.1 mo without pembrolizumab
  - Median PFS with PD-L1 CPS ≥10: 9.7 mo vs 5.6 mo without pembrolizumab
- Safety outcomes consistent with profiles of each regimen and no new safety concerns emerged
- Investigators conclude results support pembrolizumab + chemotherapy as new standard of care for patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS ≥10)

Rugo. ESMO 2021. Abstr LBA16.

Future strategies in TNBC



Dixon-Douglas, J., Loi, S. Immunotherapy in Early-Stage Triple-Negative Breast Cancer: Where Are We Now and Where Are We Headed?. Curr. Treat. Options in Oncol. (2023). https://doi.org/10.1007/s11864-023-01087-y



Bianchini. Nat Rev Clin Oncol. 2022;19:91

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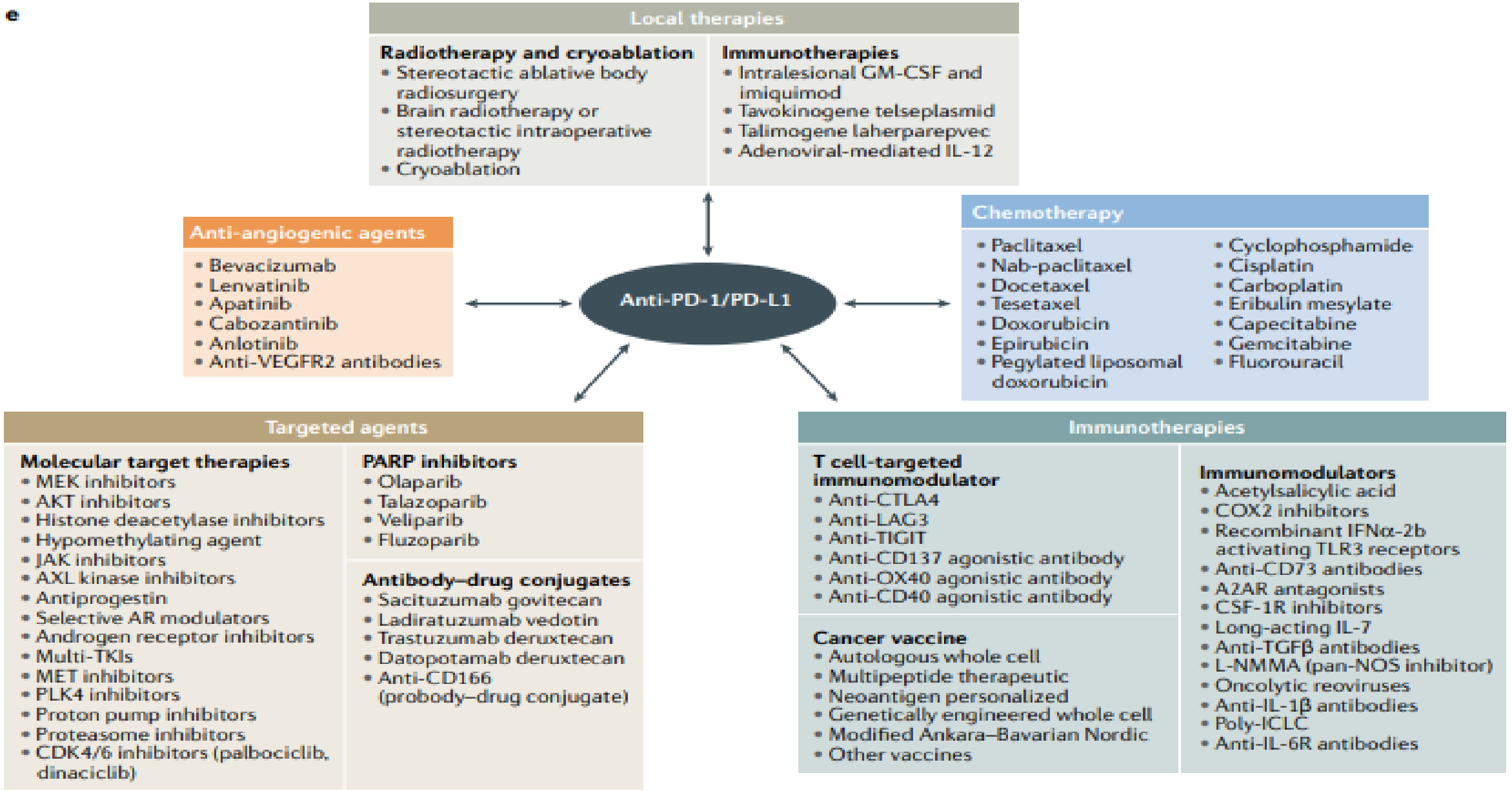

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Table 2 | **Trials of ICIs involving patients with metastatic TNBC**

Trial (NCT identifier)	Phase	Line of therapy	Patients with TNBC (*n*)	Treatment	Results in patients with TNBC	Refs
Single-agent ICIs						
KEYNOTE-012 (NCT01848834)[a]	Ib	All (first line in 15.6% of patients)	32	Pembrolizumab	ORR: 18.5%; mPFS: 1.9 mo; mOS: 11.2 mo	142
NCT01375842	I	All (first line in 18% of patients)	115	Atezolizumab	ORR in ITT: 10.0%; ORR in patients with PD-L1$^+$ tumours: 12.0%; ORR in patients with PD-L1$^-$ tumours: 0%; ORR in first-line setting: 26.0%; ORR in second-line setting or later: 7%; mPFS[b]: 1.4 mo; mOS[b]: 8.9 mo	141
JAVELIN (NCT01772004)	I	All (first or second line in 50% of patients)	58	Avelumab	ORR in ITT: 5.2%; ORR in patients with PD-L1$^+$ tumours: 44.0%; ORR in patients with PD-L1$^-$ tumours: 2.6%; mPFS[b]: 1.4 mo; mOS[b]: 9.2 mo	140
NCT02838823	I	First to sixth	20	JS001	ORR in ITT: 5.0%; ORR in patients with PD-L1$^+$ tumours: 11.1%; ORR in patients with PD-L1$^-$ tumours: 0%; mPFS[b]: 1.8 mo	139
ENCORE 602/TRIO025 (NCT02708680)	II	Second or later (second line in 69% of patients)	41	Atezolizumab[c]	ORR: 2.0%; mPFS: 1.51 mo; mOS: 12.4 mo	143
KEYNOTE-086 (cohort A; NCT02447003)	II	Second or later (second in 31% of patients)	170	Pembrolizumab	ORR in ITT: 5.3%; ORR in patients with PD-L1$^+$ tumours: 5.7%; ORR in patients with PD-L1$^-$ tumours: 4.7%; mPFS[b]: 2.0 mo; mOS[b]: 9.0 mo	138
KEYNOTE-086 (cohort B; NCT02447003)[a]	II	First	84	Pembrolizumab	ORR: 21.4%; mPFS: 2.1 mo; mOS: 18 mo	137
TONIC (NCT02499367)	II	First to fourth (first line in 24% of patients)	67	Nivolumab	ORR: 20.0%; mPFS: 1.9 mo	144
SAFIR02-BREAST IMMUNO	II	First or second	82	Durvalumab vs chemotherapy[d]	mOS in all patients with TNBC: 21.2 mo vs 14 mo ($P = 0.04$); mOS in patients with	25

Table 2 (cont.) | **Trials of ICIs involving patients with metastatic TNBC**

Trial (NCT identifier)	Phase	Line of therapy	Patients with TNBC (*n*)	Treatment	Results in patients with TNBC	Refs
Combinations (cont.)						
MEDIOLA (NCT02734004)[f]	I/II	First to fifth	17	Olaparib plus durvalumab	ORR: 58.8%; mPFS: 4.9 mo; mOS: 20.5 mo	168
TOPACIO/ KEYNOTE-162 (NCT02657889)	I/II	First to fourth	45	Niraparib plus pembrolizumab	ORR in ITT: 29.0%; ORR in patients with PD-L1$^+$ tumours 32%; ORR in patients with PD-L1$^-$ tumours: 8%; ORR in first-line and second-line setting: 27.0%; ORR in third-line setting or later: 7.0%; mPFS[b]: 2.3 mo	169
KEYNOTE-899 (NCT03752723)	Ib/II	Second to sixth (second line in 50% of patients)	30	GX-I7 plus pembrolizumab	ORR: 13.3%	164
COLET (NCT02322814)	II	First	63	Cobimetinib and atezolizumab plus either nab-paclitaxel or paclitaxel	ORR overall: 31.7%; ORR in patients with PD-L1$^+$ tumours: 44% with paclitaxel, 33% with nab-paclitaxel; ORR in patients with PD-L1$^-$ tumours: 11% with paclitaxel, 27% with nab-paclitaxel	162
ENCORE 602/TRIO025 (NCT02708680)	II	Second or later (second line in 69% of patients)	40	Entinostat plus atezolizumab[c]	ORR: 10.0%; mPFS: 1.68 mo; mOS: 9.4 mo	143
LEAP-005 (NCT03797326)	II	Second or third	31	Lenvatinib plus pembrolizumab	ORR: 29.0%	166
IMpassion130 (NCT02425891)	III	First	902	Nab-paclitaxel plus either atezolizumab or placebo	ORR in ITT: 56.0% vs 45.9% ($P = 0.002$); ORR in patients with PD-L1$^+$ tumours: 58.9% vs 42.6% ($P = 0.002$); PFS in ITT: HR 0.80, 95% CI 0.69–0.92; PFS in patients with PD-L1$^+$ tumours: HR 0.62, 95% CI 0.49–0.78; mPFS in ITT: 7.2 mo vs 5.5 mo ($P = 0.002$); mPFS in patients with PD-L1$^+$ tumours: 7.5 mo vs 5.3 mo ($P < 0.0001$); OS in ITT: HR 0.87, 95% CI 0.75–1.02; OS in patients with PD-L1$^+$ tumours: HR 0.67, 95% CI 0.53–0.86; mOS in ITT: 21.0 mo vs 18.7 mo ($P = 0.08$); mOS in patients with PD-L1$^+$ tumours: 25.4 mo vs 17.9 mo (*P* not formally tested)	151,152

Thank you