Neoadjuvant immune checkpoint inhibitors for resectable cancer at high risk of recurrence

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Disclosures

- None

Pre-operative evaluation after treatment with neoadjuvant immunotherapy should include which of the following studies:

A. Cardiac stress test
B. Liver function tests
C. Thyroid function tests
D. Brain MRI

Which of the following patients with triple negative breast cancer would NOT qualify to receive immunotherapy:

A. 30-year-old woman with clinical T2N0 TNBC
B. 35-year-old woman s/p lumpectomy and sentinel node biopsy with T1cN1 TNBC
C. 60-year-old woman with clinical T3N2 TNBC
D. 40-year-old woman with clinical T2N1 TNBC and lupus

SITC at SSO

Neoadjuvant immune checkpoint inhibitors for resectable cancer at high risk of recurrence

- Review of checkpoint blockade
- Triple negative breast cancer
  - Clinical trials of neoadjuvant chemo-immunotherapy for triple negative breast cancer
  - Patient selection for pre-operative chemo-immunotherapy
  - Monitoring for immune-related adverse events
  - Immunotherapy and surgical complications
  - Expanding indications
- Non-small cell lung cancer
- Melanoma
- Summary & Future Directions

Two-Signal Hypothesis

Checkpoint molecules

-Second signal required to activate or suppress T cells

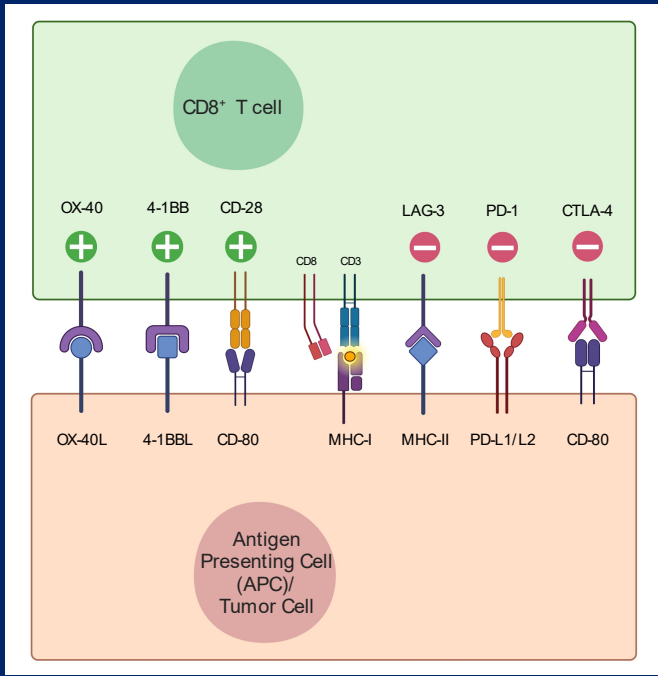
-Checkpoint molecules suppress T cell function

-Present on immune cells and cancer cells

-Prevent autoimmunity

-Prevent immune cells from killing cancer cells

Baldwin et al, Journal of Surgical Research, 2023



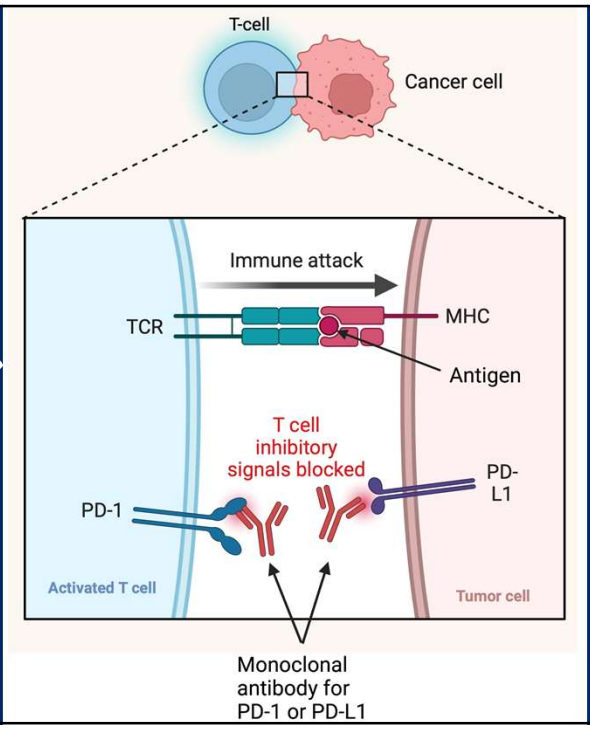
PD-1 and PDL-1

Checkpoint Molecules and Monoclonal Antibodies

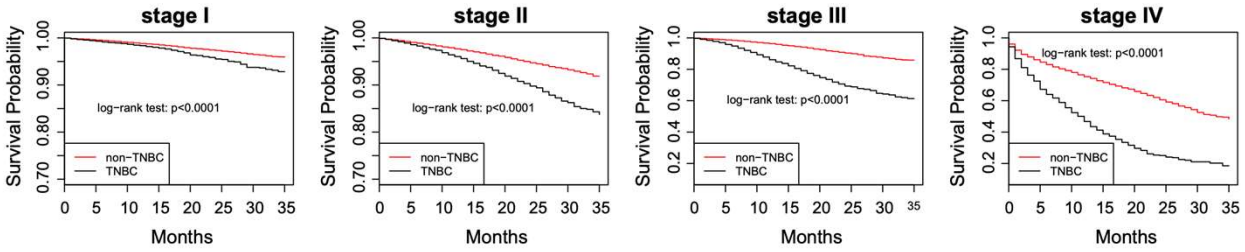
PD-1
-PD-1 upregulated with repetitive T-cell stimulation
-Present on T cells
-Suppress T-cell function when engaged
FDA approved Anti-PD-1 monoclonal antibodies: Nivolumab, Pemrolizumab, Cemiplimab, Dostarlimab

PDL-1
-PD-L1 is the ligand for PD-1
-On tumor cells and immune cells
-Engagement with receptor PD-1 suppressed T cell function
FDA approved Anti-PDL-1 monoclonal antibodies:
Atezolizumab, Avelumab, Durvalumab

Downs-Canner and Mittendorf, Surg Clin NA, 2023



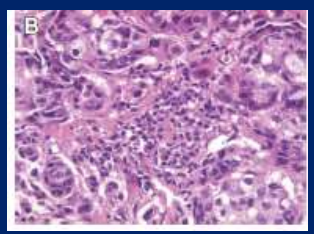
Triple Negative Breast Cancer has poorest prognosis

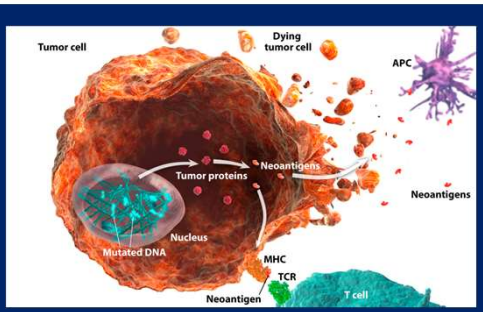


Hallmarks of TNBC

Tumor infiltrating lymphocytes (TILS)

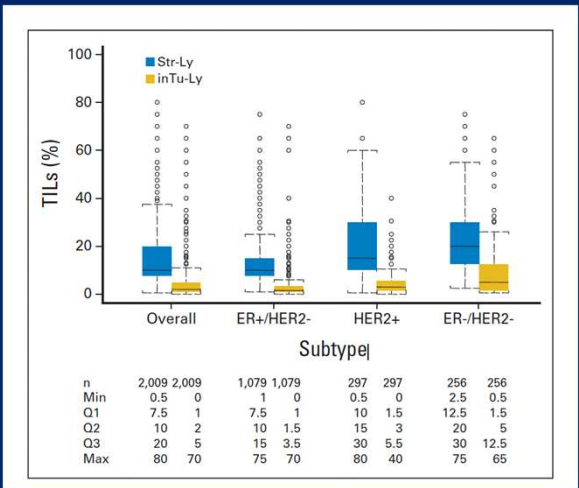
High tumor mutational burden





Li et al, Breast Cancer Res Treat 2017
Denkert et al, JCO 2010
Denkert et al, Lancet Oncol, 2018
Suranand Talla, 2018

TNBC: Higher infiltration of TILs



BIG 02-98 (addition of docetaxel to doxorubicin regimen in node + breast cancer)

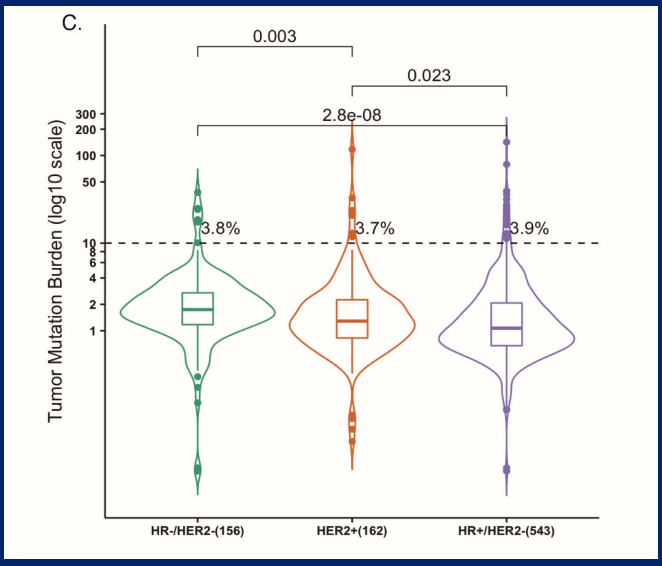
-Her2+ and TNBC TILS > ER+

Loi et al, JCO 2013

TNBC: Tumor mutational burden higher than other types

Breast cancer overall has low TMB

TNBC has highest TMB of all subtypes



Barroso-Sousa et al, Annals of Oncology 2020

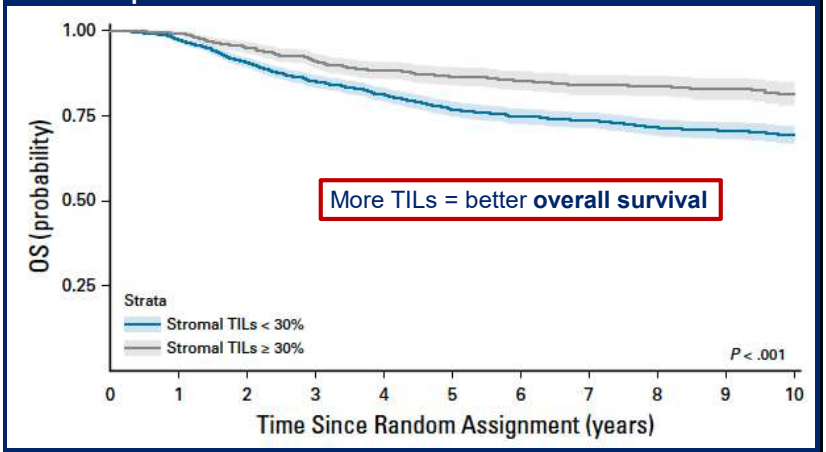
TILS and TNBC

Associated with better overall survival

*Based on individual patient data from 2148 patients from 9 separate studies

Loi et al, JCO 2019

OS in patients with >30% Stromal TILs vs <30% Stromal TILs



Keynote-355

Efficacy of pembrolizumab in metastatic setting

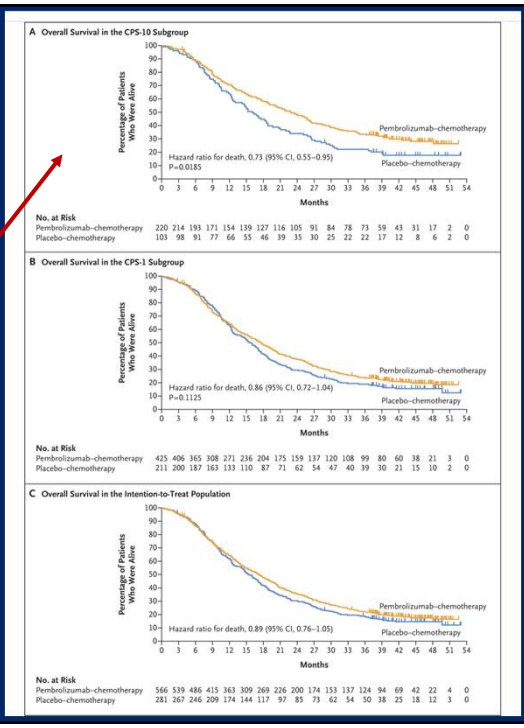
FDA approved
(with chemotherapy) Nov 2020

Locally recurrent unresectable or Metastatic TNBC

PDL-1 positive (CPS>10)

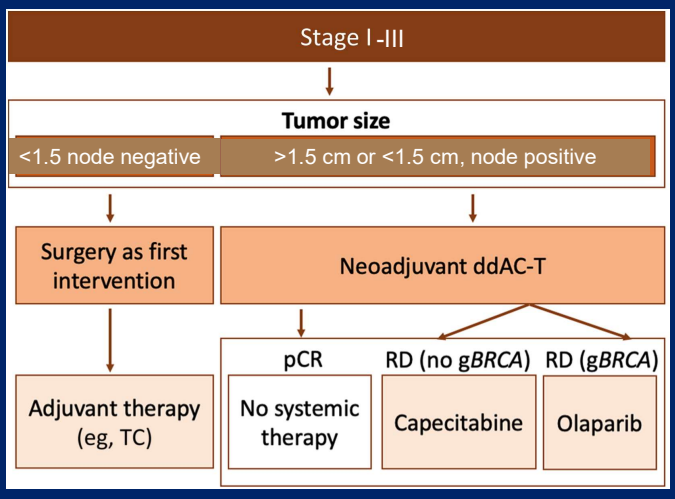
PFS 9.7 mos vs 5.6 mos (in CPS>10)

Cortes et al, NEJM, 2020



Immunotherapy plus chemotherapy in early TNBC

TNBC Treatment Paradigm Pre-KN522



Neoadjuvant therapy favored:

Tailor treatment based on residual disease
- CreateX
- Olympia

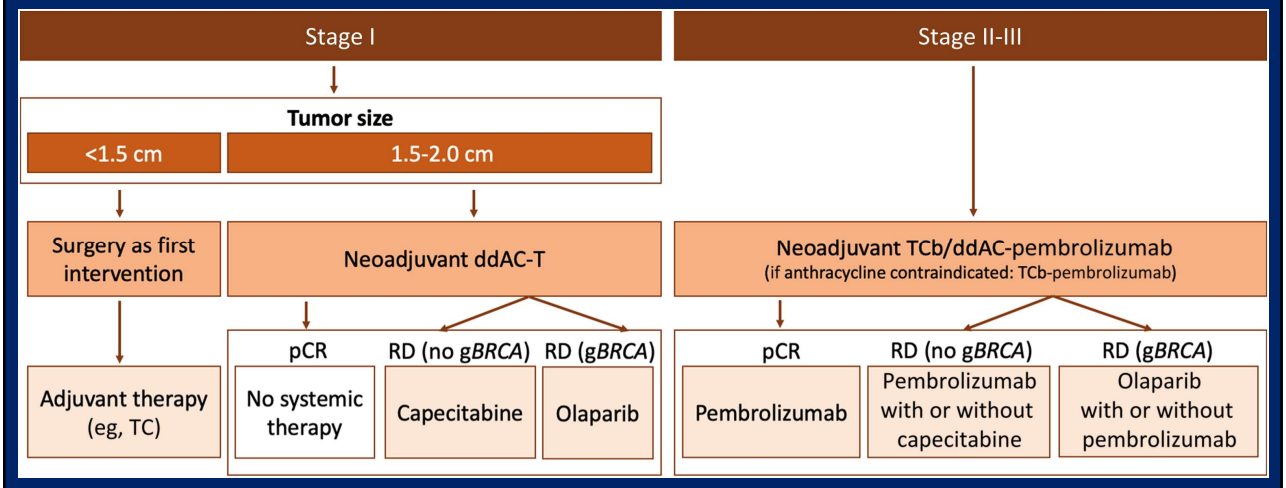
Nodal downstaging

Tumor downstaging

Metastatic → Adjuvant → Neoadjuvant clinical trial progression not relevant

Han et al, ASCO educational book

TNBC Treatment Paradigm Post-KN522

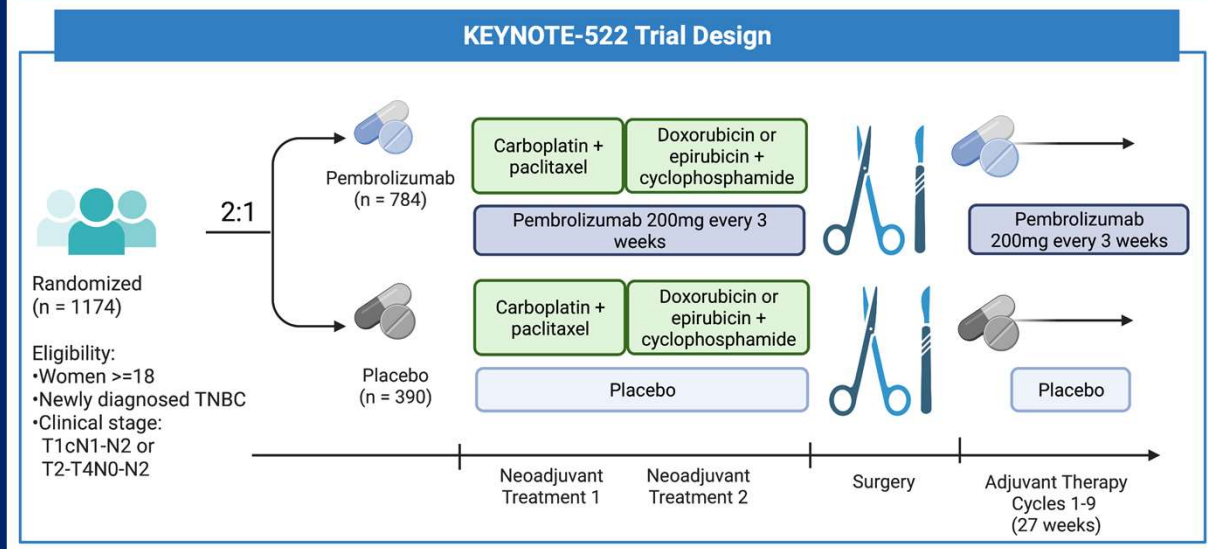


Han et al, ASCO educational book

Trials of checkpoint inhibitors + chemotherapy in the neoadjuvant setting

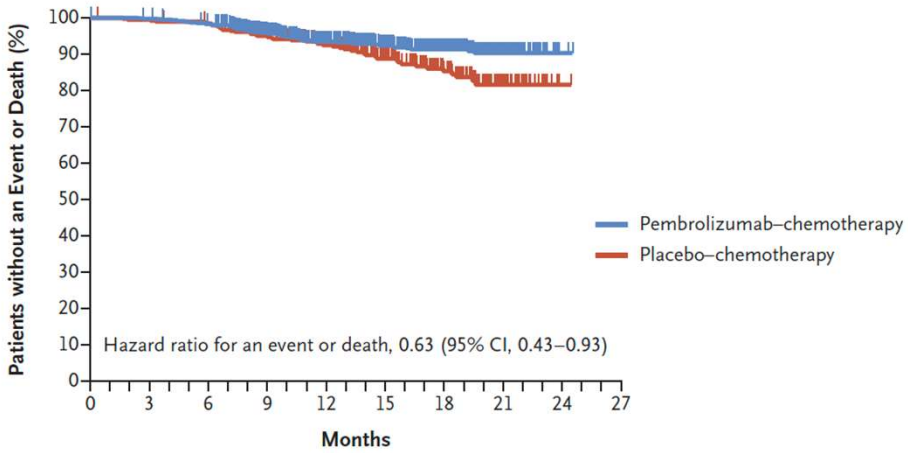
	GeparNuevo (Phase II)	IMpassion031 (Phase III)	KEYNOTE-522 (Phase III)	NeoTRIPaPDL1 (Phase III)	I-SPY2 (Phase II)*
N	174	333	1174	280	270
Primary endpoint(s)	pCR	pCR	pCR and EFS	pCR and EFS	pCR
Immunotherapy agent	Durvalumab	Atezolizumab	Pembrolizumab	Atezolizumab	Pembrolizumab
Duration immunotherapy	24-26 weeks	52 weeks	52 weeks	24 weeks	4 cycles
Chemotherapy backbone	Nab-paclitaxel →EC	Nab-paclitaxel →dd AC	Paclitaxel-carboplatin → AC	Nab-paclitaxel+carbo	Paclitaxel → AC
Change pCR (ITT)	9%	17%	14%	3%	38%
Immunotherapy arm	59%	58%	65%	44%	60%
Placebo arm	44%	41%	51%	41%	22%
EFS difference / Hazard ratio		20 months / 0.76 (ns)	15 months / 0.62 (p<0.001)		

Keynote-522 Trial Design



Schmid et al, NEJM, 2020

Keynote-522 Event Free Survival Benefit (15 months)



No. at Risk

Pembrolizumab–chemotherapy	784	780	765	666	519	376	242	73	2	0
Placebo–chemotherapy	390	386	380	337	264	186	116	35	1	0

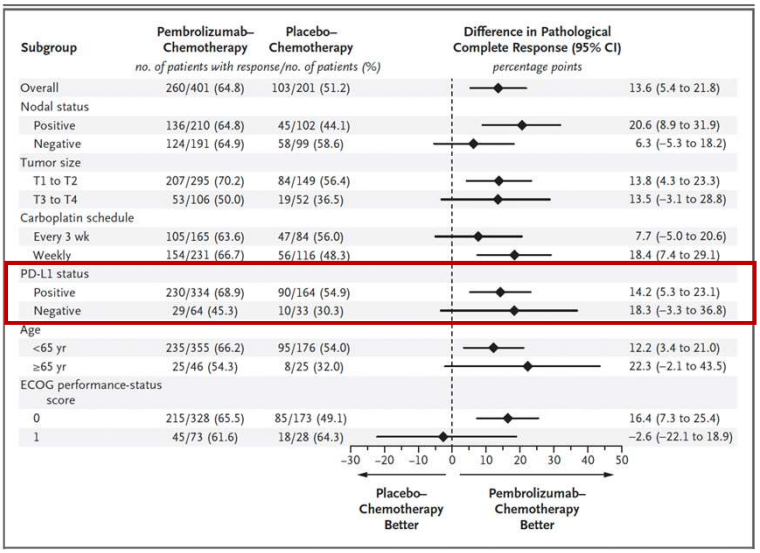
Schmid et al, NEJM, 2020

Keynote-522

Subgroup Analyses

Nearly all subgroups benefit

PD-L1 positive and negative **benefit**



Schmid et al, NEJM, 2020

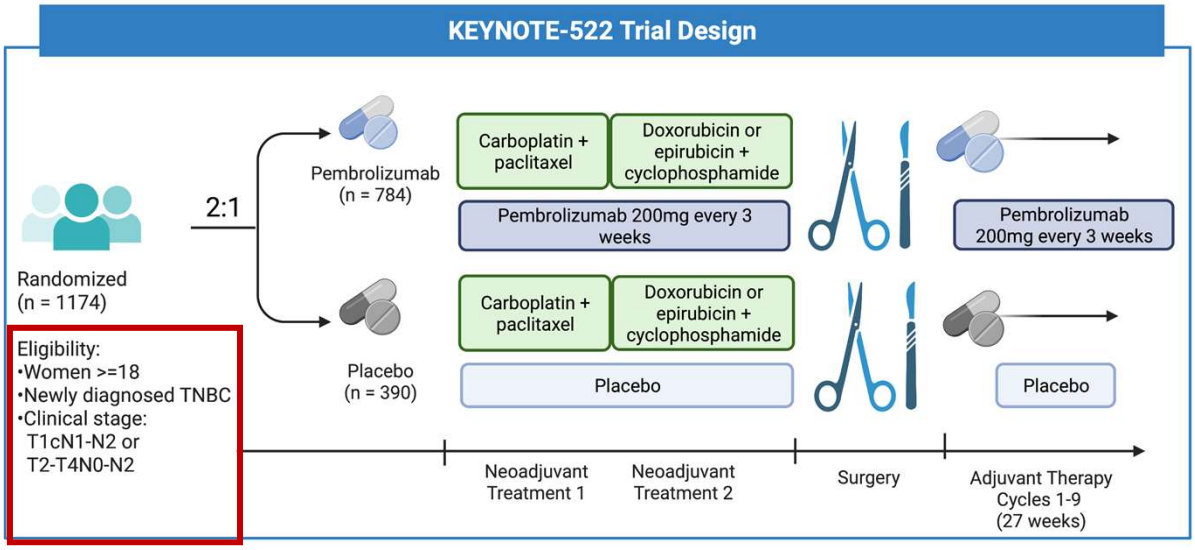
Adverse events of interest in Keynote-522

	PEMBROLIZUMAB + CHEMOTHERAPY (N=781)		CHEMOTHERAPY (N=389)	
	Any	**Grade >=3**	**Any**	**Grade >=3**
Adverse event of interest	304 (38.9)	101 (12.9)	71 (18.3)	7 (1.8)
Infusion reaction	132 (16.9)	20 (2.6)	43 (11.1)	4 (1.0)
Hypothyroidism	107 (13.7)	3 (0.4)	4 (1.0)	0
Hyperthyroidism	36 (4.6)	2 (0.3)	4 (1.0)	0
Severe skin reaction	34 (4.4)	30 (3.8)	4 (1.0)	1 (0.3)
Adrenal insufficiency	18 (2.3)	10 (1.3)	0	0

Schmid et al, NEJM, 2020

Patient Selection in the Real World

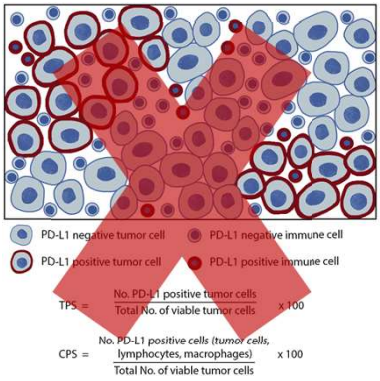
Keynote-522 Inclusion Criteria



Keynote-522 Patient Selection: No PDL-1 staining needed

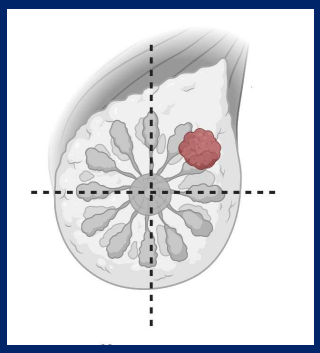
No additional immunohistochemical stains needed

No PDL-1 staining needed



deRuiter et al, Modern Pathology, 2020

Optimizing measurement for T stage in early TNBC



T stage can be based on any imaging modality:

MRI
Mammogram
Ultrasound

or physical exam

Optimizing nodal staging for patients with early TNBC

Rates of pathologic node-positivity in patients with cT1–2N0 triple–negative breast cancer undergoing surgery as their initial intervention

Clinical T Category	Dana-Farber Brigham Cancer Center (*n* = 343)		National Cancer Database (*n* = 46,015)	
	N	Number of pathologic node positive (%)	*N*	Number of pathologic node positive (%)
cT1a/b	96	9 (9.4%)	8171	399 (4.9%)
cT1c	175	26 (14.9%)	18,608	2121 (11.4%)
cT2	72	15 (20.8%)	19,236	3784 (19.7%)

Mittendorf et al, Ann Surg Onc, 2023

Optimizing nodal staging for patients with early TNBC

Axillary ultrasound use among patients with cT1–2 triple-negative breast cancer with a negative clinical axillary examination at presentation in the Dana-Farber Brigham Cancer Center Cohort (n = 499)

Clinical T category	Axillary ultrasound performed	Number/percentage with abnormal nodes on axillary ultrasound	Number/percentage with FNA/core biopsy-positive nodes
T1a (*n* = 18)	4/18 (22.2%)	0 (0%)	0 (0%)
T1b (*n* = 83)	10/83 (12.0%%)	1/10 (10.0%)	1/1 (100%)
T1c (*n* = 193)	53/193 (27.4%)	15/53 (28.3%)	4/15 (26.7%)
T2 (*n* = 205)	103/205 (50.2%)	30/103 (37.9%)	9/30 (30.0%)

FNA Fine needle aspiration

Consider ROUTINE AXILLARY ULTRASOUND in patients with clinical T1cN0 TNBC

Mittendorf et al, Ann Surg Onc, 2023

Special populations

Optimizing patient selection: safety considerations

Unique mechanism of action → consequences for pre-existing diseases mediated by the immune system

HIV: safe in other solid tumors

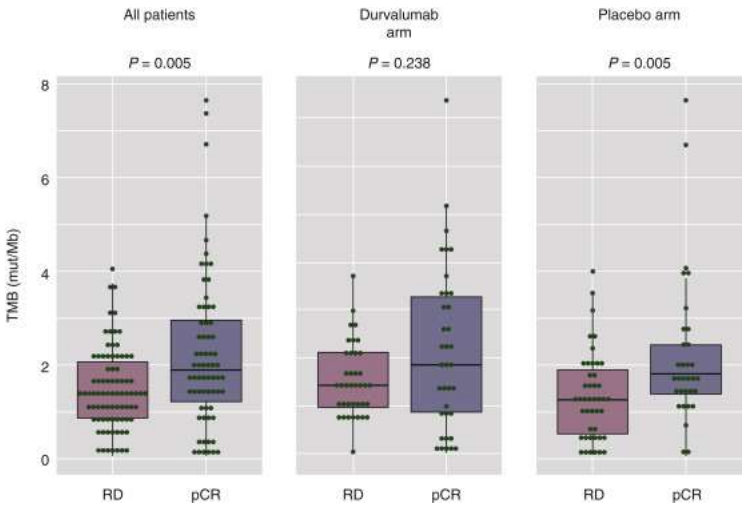
Autoimmune Disease: safe → may reactivate disease

Pregnancy: contraindicated

Solid Organ Transplant Recipients: clinical trial only → risk of rejection

Older Age: assess functional status first

Immunotherapy: Predictors of Response



Karn, Ann Oncol 2020

Tumor mutational burden and TILS predict Response to immunotherapy

BUT not any better than to chemotherapy

Biomarkers to predict response needed

Monitoring for Immune Related Adverse Events

Immunotherapy Toxicity

Immune-related adverse events (irAEs)

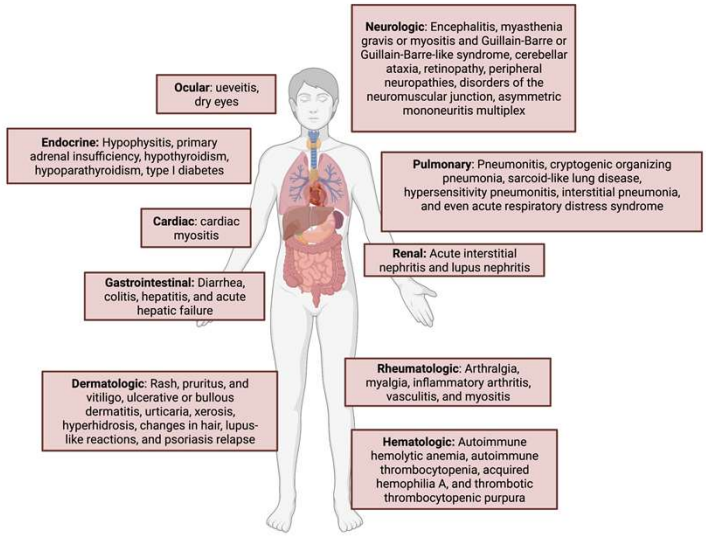
-Impact all organ systems

-Can be severe/life-threatening

-Many are permanent

-Different than toxicity from cytotoxic chemotherapy

-**Time course is highly variable**



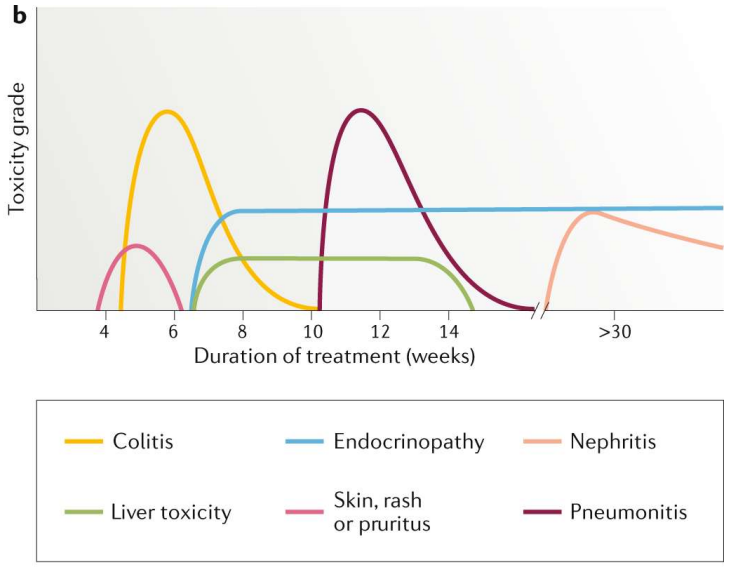
Baldwin et al, Journal Surg Res, 2023

Kinetics of Onset

Immune-Related Adverse Events

Onset of immune-related adverse events varies by type

Endocrinopathies can present very late



Martins et al, Nature Reviews, 2019

Monitoring for irAEs

Immune-Related Adverse Events in Real World Setting

142 consecutively treated patients (KN-522)

Median Age: 52

Self-Reported Race:
Black: 19%
Asian: 14%
Native American: 0.7%
White: 52%
Other: 4.5%

75% ASA 3

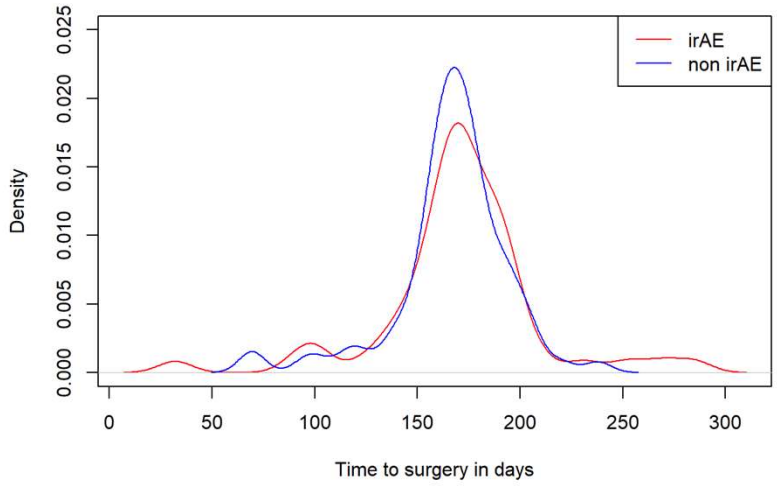
irAE type	Number of irAE experienced (N=82)*
Hypothyroidism	13 (15.9%)
Hepatitis/transaminitis	12 (14.6%)
Adrenal insufficiency	8 (9.8%)
Dermatitis	8 (9.8%)
Pneumonitis	7 (8.5%)
Arthritis/myositis	7 (8.5%)
Neurologic/opthalmologic	6 (7.3%)
Hyperthyroidism	4 (4.9%)
Colitis	4 (4.9%)
Nephritis	3 (3.7%)
Diabetes	2 (2.4%)
Myocarditis	1 (1.2%)
Other	2 (2.4%)

*82 adverse events were experienced by 59 patients

Myers et al, ASCO 2023

irAEs and adjuvant therapy

Immune-related adverse events are not associated with increased time to surgery



Myers et al, ASCO 2023

S Kümmel. ASBrS 2023

Time To and From Definitive Surgery

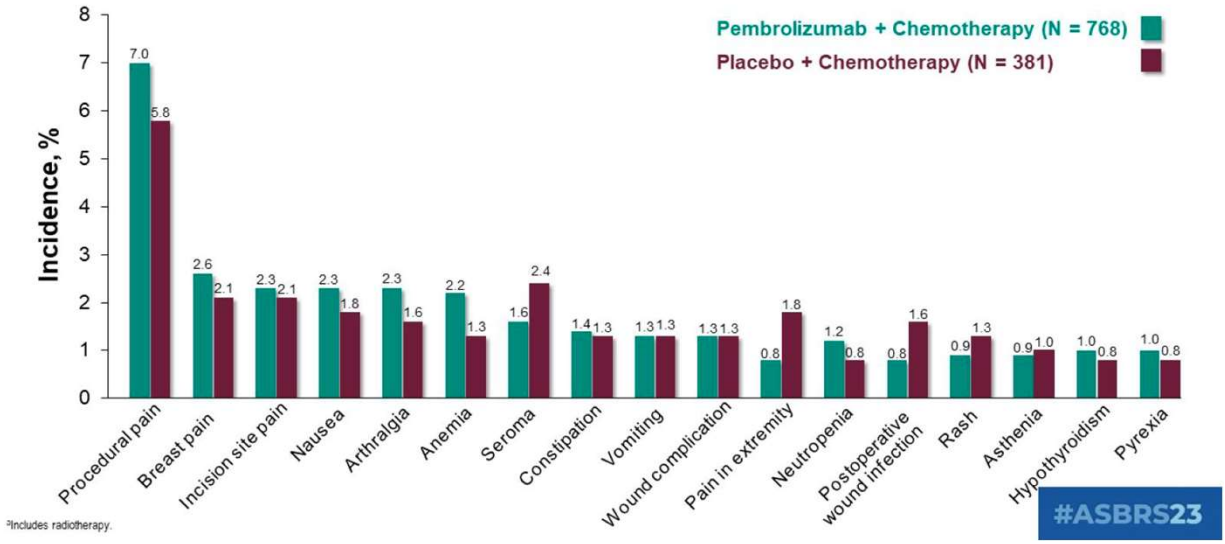
	Pembrolizumab + Chemotherapy	Placebo + Chemotherapy
	N = 763[a]	**N = 381**
Median (range) time from end of neoadjuvant treatment to surgery, mo	1.2 (0.4–6.7)	1.2 (0.5–9.3)
	N = 558[b]	**N = 320[b]**
Median (range) time from surgery to adjuvant treatment, mo	2.6 (0.4–7.6)	2.7 (0.8–7.1)

[a]5 patients in the pembrolizumab plus chemotherapy group did not receive neoadjuvant medication but had surgery later and are not included here.
[b]210 patients in the pembrolizumab plus chemotherapy group and 61 patients in the placebo plus chemotherapy group did not receive adjuvant treatment after surgery and are not included here.

#ASBRS23

S Kümmel. ASBrS 2023

New AEs Occurring in ≥1% of Patients From Day 0 (Surgery Day) to Day 30 After Definitive Surgery Before the Initiation of Adjuvant[a] Treatment



[a]Includes radiotherapy.

#ASBRS23

Clinical Pearl

Monitoring for immune-related adverse events

Should be standardized

**Surgeons should know symptoms of irAEs

**Surgeons are responsible to ensure thyroid and adrenal function are normal before surgery

Standard Monitoring for irAEs

Test	Frequency
On treatment	
CBC and CMP	Prior to every pembrolizumab dosing
Thyroid function tests, cortisol	Every other cycle or every 6 weeks
Echocardiogram	Baseline, completion of treatment, symptoms of cardiac dysfunction
Between end of neoadjuvant therapy and surgery	
Thyroid function tests, cortisol	Once
1 year following treatment	
Thyroid function tests, cortisol	Every 3 months

Clinical Pearl

Monitoring for immune-related adverse events

Appropriate testing and referrals necessary to prevent surgical/anesthetic complications

Standard Monitoring for irAEs

Between end of neoadjuvant therapy and surgery	
Thyroid function tests, cortisol	Once

-Time 2-3 weeks in advance of surgery

-Endocrinology consult if abnormalities

-Normalize thyroid function prior to surgery

-Stress dose steroids if necessary

Neoadjuvant chemo-immunotherapy versus neoadjuvant chemotherapy alone

No increased risk of surgical complications with KN-522

Complication*	KN-522, n (%) (N=139)	Non-KN-522, n (%) (N=287)
Cardiac arrest	0	1 (0.4%)
Hematoma	2 (1.4%)	3 (1.1%)
Implant loss	1 (0.7%)	0
Skin-flap ischemia	5 (3.6%)	8 (2.8%)
Pneumothorax	0	1 (0.4%)
Infection/abscess	3 (2.2%)	13 (4.6%)

No increased risk of surgical complications in patients treated with:

chemotherapy + immunotherapy

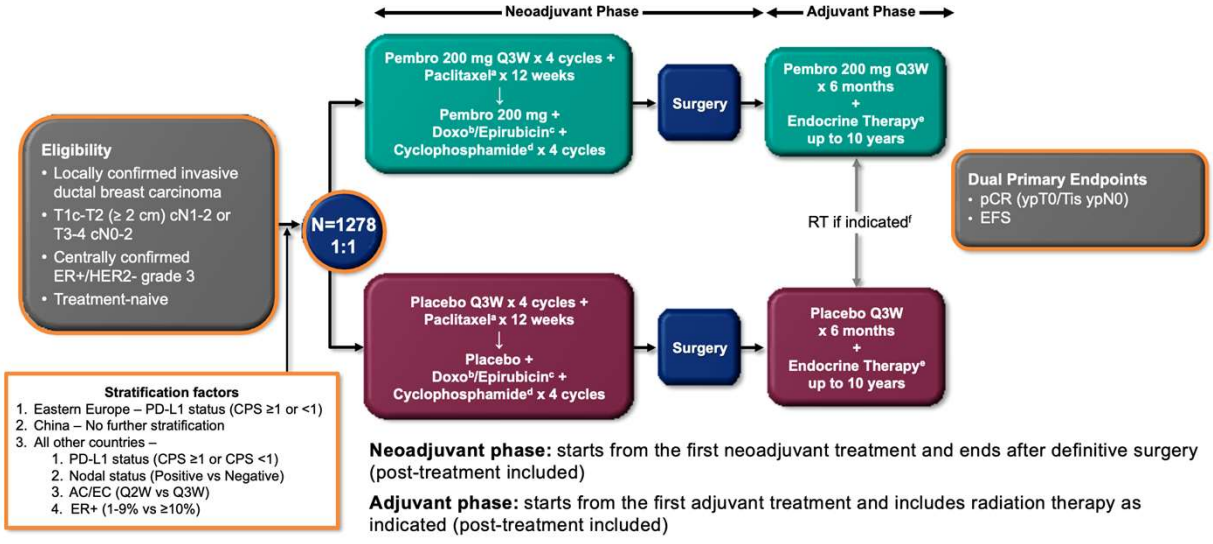
VS

Chemotherapy alone (historical controls)

Myers et al, ASCO 2023

Breast Cancer: Expanding Indications for neoadjuvant immunotherapy

KEYNOTE-756



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)

O'Shaughnessy J, SABCS 2023

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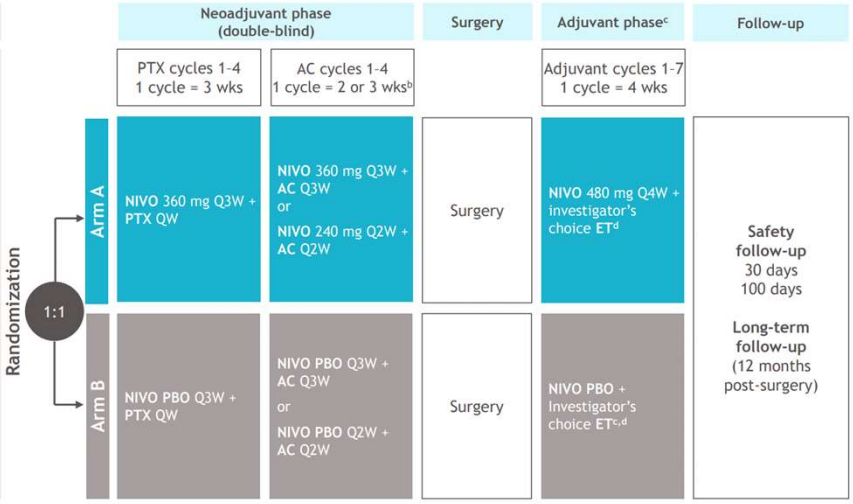
CHECKMATE 7FL

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)



Loi S. SABCS 2023

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Comparing the trial designs

Trial element	KEYNOTE-756 (N=1278) Similarities	CHECKMATE 7FL (N=510) Differences

Trial design	• Both phase III, placebo-controlled RCTs that evaluated neoadj/adj PD1 inhibitors in combination with the same NACT regimen for high-risk HR+/HER2- EBC	• Use of different PD1 inhibitors:
		  • KN756: Pembrolizumab
		  • 7FL: Nivolumab
		• Keynote-756 enrolled over twice as many pts

Eligibility criteria	• Overall similar: pts with high-risk HR+/HER2- EBC	• Slight differences in enrollment criteria:
		  • KN756: All grade 3, T1c-T2/ N1-2 or T3/T4
		  • 7FL: Gr 2/3, T1c-T2/N1-2 or T3/T4 N0-2

Stratification factors	• Similar: nodal status, AC/EC q2w/3w, PD-L1 status	• Use of different PD-L1 assays:
		  • KN756: 22C3 CPS
		  • 7FL: SP142 (and 28-8 CPS in biomarker analysis)

1º endpoint(s)	• Both powered to detect difference in pCR rates	• KN756 also powered to detect difference in EFS

Loi S, SABCS 2023 / O'Shaughnessy J, SABCS 2023 / Hupper L, SABCS 2023

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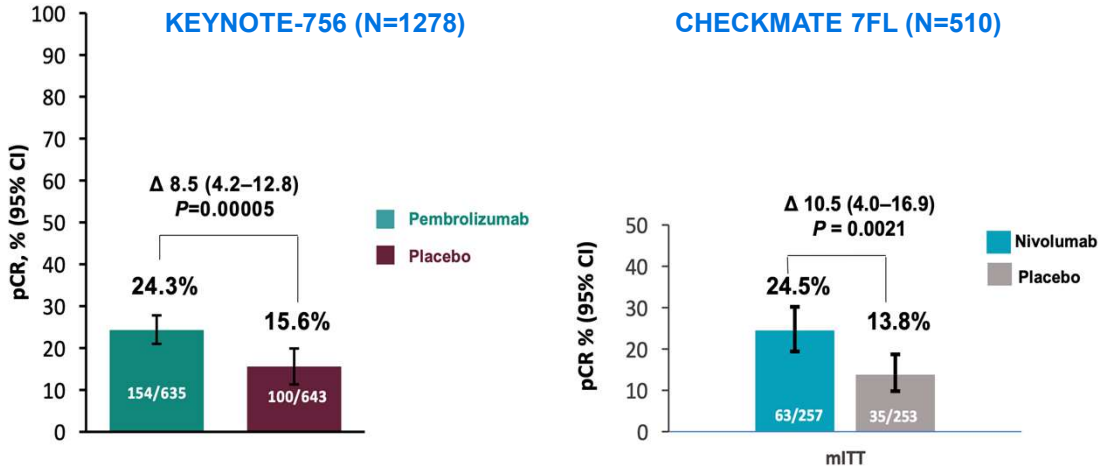
Comparing the trial results



Loi S, SABCS 2023 / O'Shaughnessy J, SABCS 2023 / Hupper L, SABCS 2023

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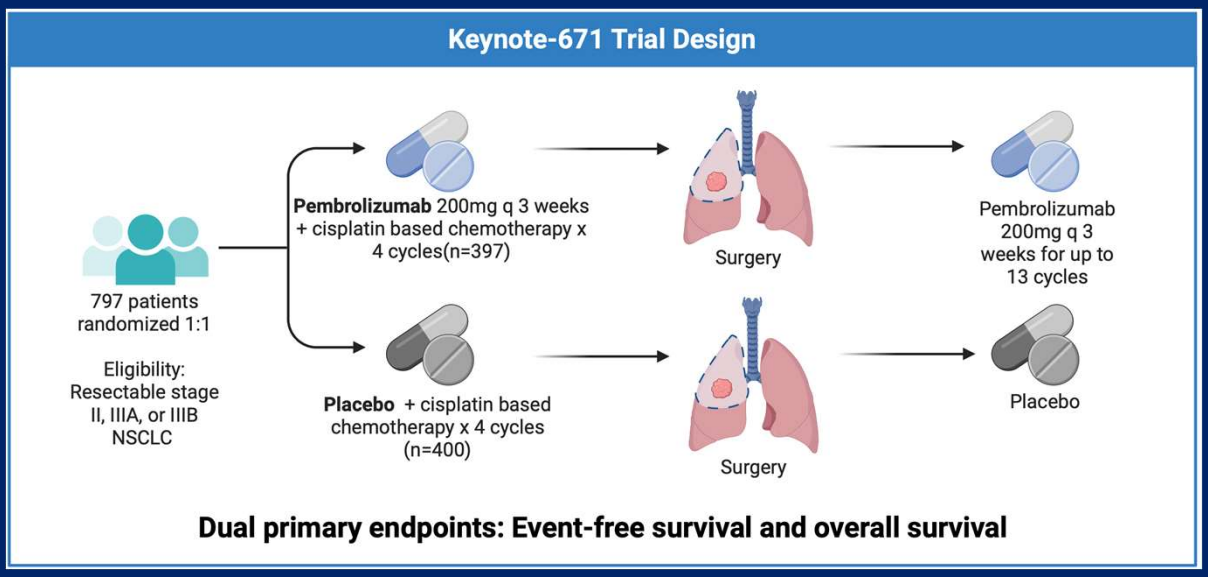
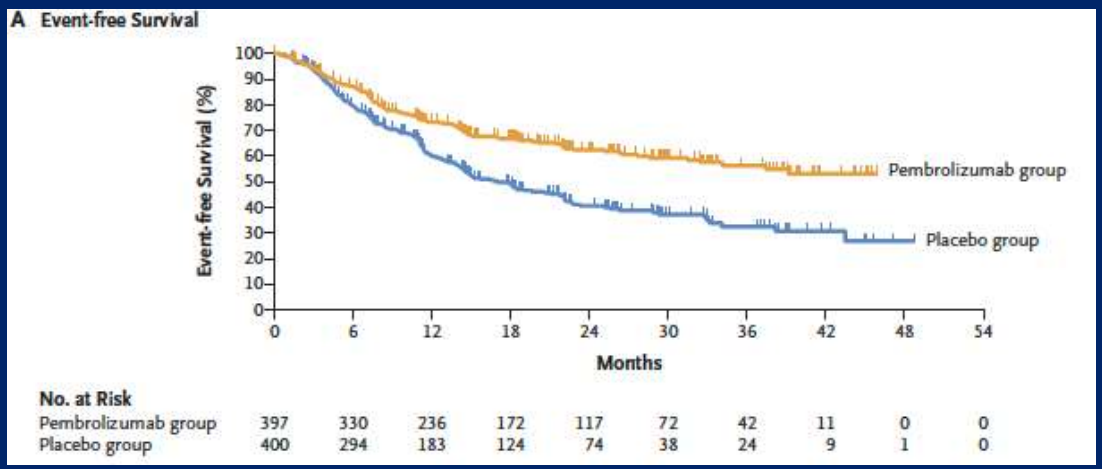
Neoadjuvant immunotherapy : Non-small cell lung cancer

Keynote-671



Wakalee et al, NEJM, 2023

Keynote-671:Event-free survival at first-interim analysis



→ FDA approval October 2023

Wakalee et al, NEJM, 2023

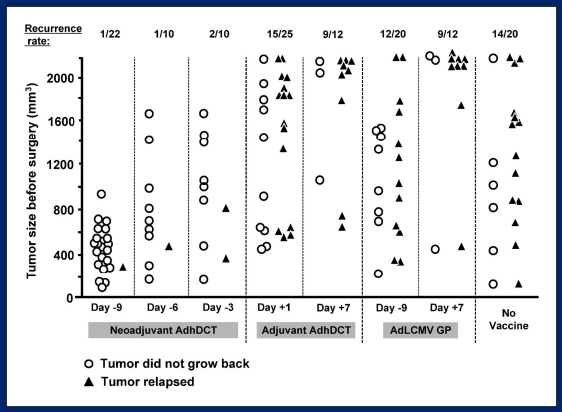
Neoadjuvant immunotherapy: Melanoma

Melanoma

Rationale for neoadjuvant versus adjuvant immunotherapy

Preclinical Data

Neoadjuvant (versus adjuvant) vaccination induces a better cure rate (and immune response) in mice with B16 melnaoma



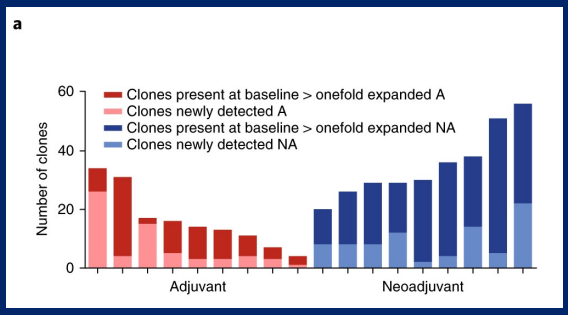
Grinshtein et al, Cancer Res 2009

Melanoma

Rationale for neoadjuvant versus adjuvant immunotherapy

Clinical Data

Better immune response with neoadjuvant vs adjuvant ipi + nivo in Stage III melanoma (Blank, Nat Med 2018)



Melanoma

Rationale for neoadjuvant versus adjuvant immunotherapy

- (OpACIN)-neo trial: Compared doses of ipilimumab + nivolumab (Rozeman et al, Lancet Oncol 2019)
  - PRADO trial: test omission of TLDN based on response and personalization of adjuvant therapy (Blank et al, JCO 2022)
- Nivolumab-relatlimab for unresectable melanoma based on RELATIVITY-047 (Amaria et al, Nature 2022)

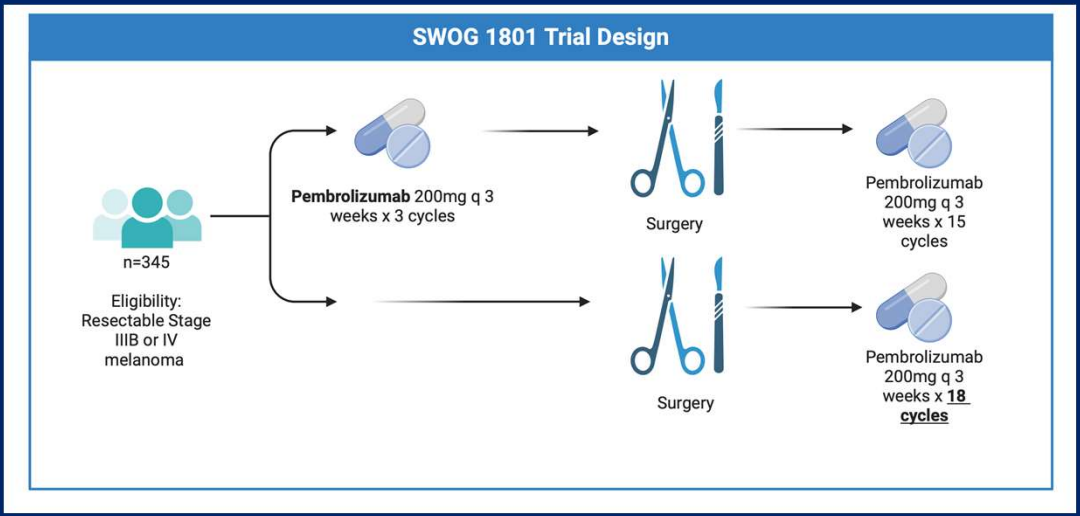
Phase II Trial Neoadjuvant VERSUS adjuvant

Southwest Oncology Group (SWOG) S1801

Adjuvant versus neoadjuvant pembrolizumab

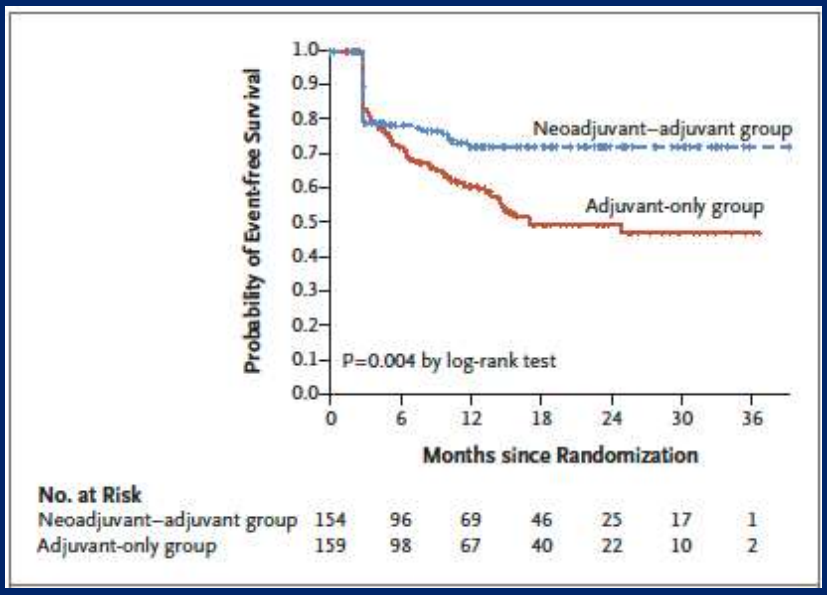
clinical stage III or oligometastatic, resectable stage IV melanoma (Patel et al, NEJM 2023)

SWOG-1801



Patel et al, NEJM, 2023

SWOG 1801:Event-free survival



EFS at 2 years: 72% versus 49%

More Grade 3 events in the neoadjuvant group

Patel et al, NEJM, 2023

Summary

- Neoadjuvant chemo-immunotherapy improves pCR and event-free survival in early triple negative breast cancer compared to chemotherapy alone
- Neoadjuvant chemo-immunotherapy improves pCR and event-free survival in non-small cell lung cancer compared to chemotherapy alone
- Neoadjuvant compared to adjuvant immunotherapy improves EFS in Stage III and Stage IV oligometastatic melanoma
- Pre-operative assessment by the surgeon can identify patients who may be candidates for immunotherapy
- Monitoring for immune-related adverse events should be standardized
- Early data suggests no increase in surgical complications with chemo-immunotherapy

Future Directions

- Expanding indications to other diseases/earlier stage disease
- Optimizing chemotherapy backbone
- Escalation and de-escalation trials based on response
- Predictors of response
- Novel combinations

Pre-operative evaluation after treatment with neoadjuvant immunotherapy should include which of the following studies:

A. Cardiac stress test
B. Liver function tests
C. Thyroid function tests
D. Brain MRI

Which of the following patients with triple negative breast cancer would NOT qualify to receive immunotherapy:

A. 30-year-old woman with clinical T2N0 TNBC
B. 35-year-old woman s/p lumpectomy and sentinel node biopsy with T1cN1 TNBC
C. 60-year-old woman with clinical T3N2 TNBC
D. 40-year-old woman with clinical T2N1 TNBC and lupus