Event-free Survival with Pembrolizumab in Early Triple-Negative Breast Cancer

Journal Club
2022/07/20

報告藥師： 盧芷芸
指導藥師： 彭筠婷
Special thanks: 郭俊男 藥師

OUTLINE

01 *Introduction*

02 *Research*

Event-free Survival with Pembrolizumab in Early Triple-negative Breast Cancer

03 *Discussion*

04 *Appraisal*

Critical Appraisal Skills Programme (CASP)

01

Introduction

Triple-Negative Breast Cancer

Definition:

A type of Breast cancer which is lack expression of estrogen receptor-negative, progesterone receptor-negative, and HER2-negative.

Epidemiology:

Almost 200,000 cases each year. (Approximately 15% of breast cancers diagnosed worldwide)

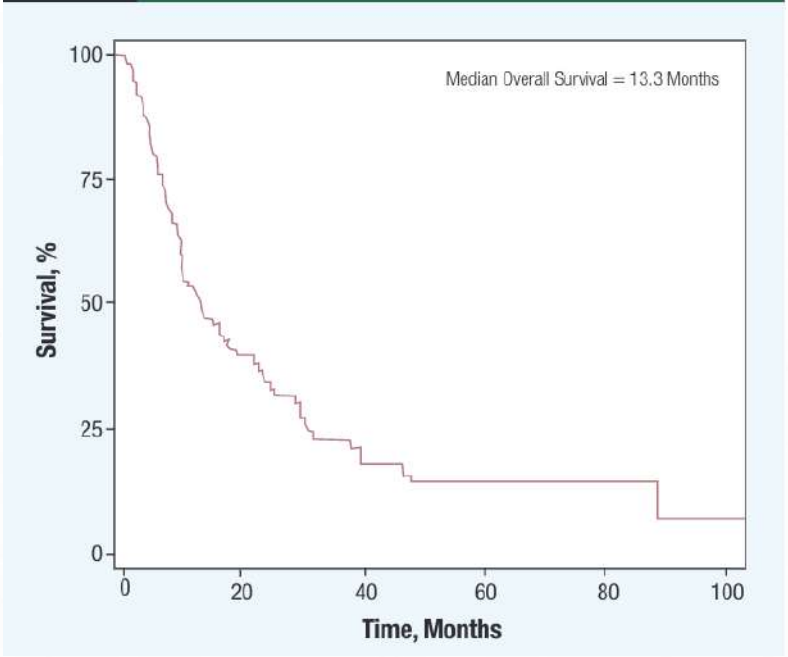
Compared with hormone receptor-positive breast cancer, TNBC is more commonly diagnosed in women younger than 40 years.

UpToDate

Triple-Negative Breast Cancer

- TNBC tends to behave more aggressively than other types of breast cancer.
- The risk of recurrence and death is high among patients with stage II or III TNBC; at 5 years, event-free survival is approximately 71% and overall survival approximately 77%.
- Poor prognosis

Figure 1 Overall Survival from Diagnosis of Distant Metastatic Disease



UpToDate, Clin Breast Cancer 2009;9:29-33

Risk Factors

- ✓ Race/ethnicity

  African American > White women.

- ✓ Premenopausal status

- ✓ Positive BRCA mutation

  Up to 20% of patients with TNBC harbor a breast cancer susceptibility gene (BRCA) mutation, particularly in BRCA1. While less than 6% of all breast cancers are associated with a BRCA mutation.

UpToDate

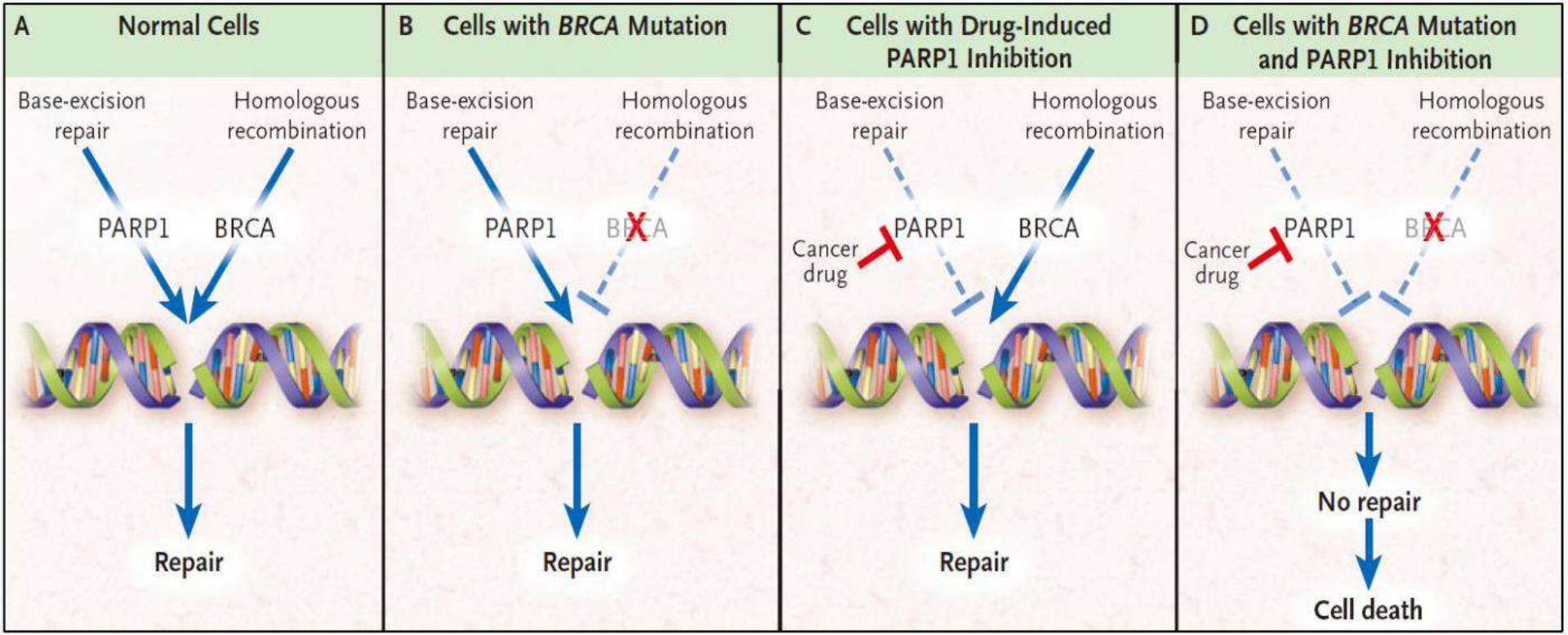
BRCA mutation & PARP (synthetic lethality)

BRCA genes are tumor-suppressor genes that are involved in DNA damage repair and mutations of BRCA genes may increase the risk of developing breast cancer due to defective DNA repair mechanisms.

PARP activity is essential for the repair of single-strand DNA breaks via the base excision repair pathway. This pathway is the default repair pathway in cells with deficient high-fidelity double-strand break homologous recombination (HR) repair, such as occurs with loss of BRCA1 or BRCA2 function.

PARP= Poly (ADP-ribose) polymerase

BRCA mutation & PARP (synthetic lethality)



N Engl J Med. 2009 Jul 9;361(2):189-91

Current Treatment

HER2-directed agents and endocrine therapy are not effective.
Surgery with adjuvant or neoadjuvant chemotherapy is recommended.

Anthracycline-based regimen such as doxorubicin and cyclophosphamide followed by a taxane (paclitaxel, docetaxel) are commonly used in current chemotherapy.

TC regimen (docetaxel and cyclophosphamide) may be a preferable option for patients with cardiac risk factors.

NCCN guideline : breast cancer

Current Treatment

For those who have BRCA1/2 mutations, PARP inhibitors such as Olaparib, Talazoparib can be considered. Since these patients might have a poor response to common TNBC chemotherapy.

High-risk (stage II-III) TNBC patients can receive preoperative pembrolizumab/carboplatin/paclitaxel, followed by preoperative pembrolizumab/cyclophosphamide/doxorubicin or epirubicin, followed by adjuvant pembrolizumab.

NCCN guideline : breast cancer

Current Treatment

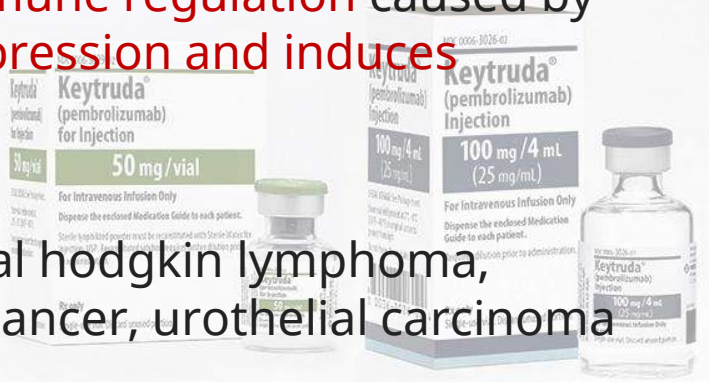
- TNBC patients with residual disease after neoadjuvant chemotherapy can receive capecitabine.
- NCCN guidelines recommend that TNBC patients who received preoperative systemic therapy could consider receiving capecitabine 6 to 8 cycles as adjuvant systemic therapy after radiation, if their pathological staging is T1-4, N0, or N≥1.
- Patients with advanced TNBC who have already tried two lines of therapy may be offered the antibody drug conjugate sacituzumab govitecan as a potential option.

NCCN guideline : breast cancer

Pembrolizumab (KEYTRUDA)

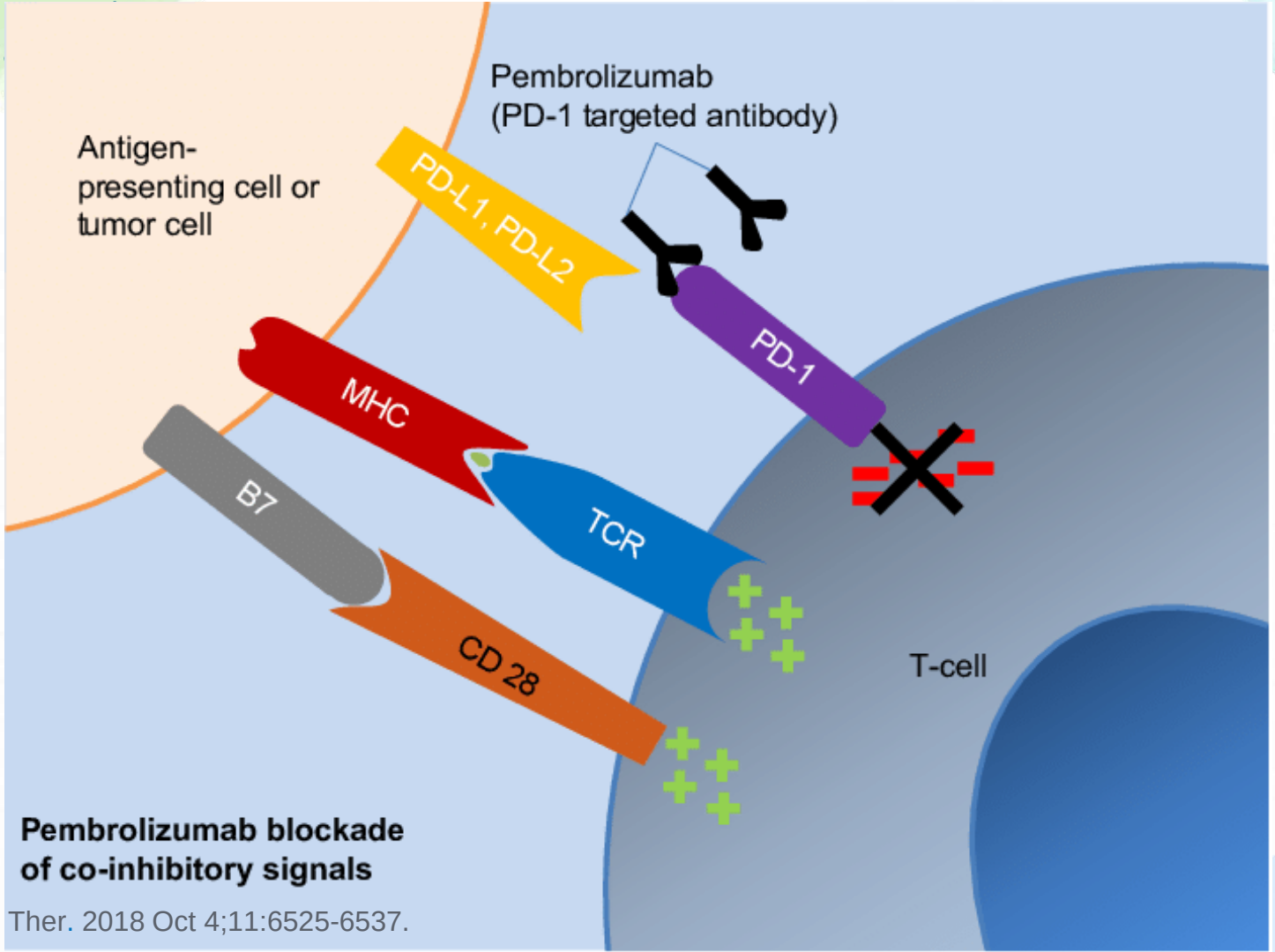
An anti–programmed death 1 (PD-1) monoclonal antibody

Mechanism:
Binding to the PD-1 receptor on T-cells to block PD-1 ligands (PD-L1 and PD-L2) from binding and inhibits the negative immune regulation caused by PD-1 receptor signaling. It reverses T-cell suppression and induces antitumor responses.



Indications:
Melanoma, non-small cell lung cancer, classical hodgkin lymphoma, squamous cell head and neck cancer, gastric cancer, urothelial carcinoma

Usual dosage:
200 mg once every 3 weeks or 400 mg once every 6 weeks.



Onco Targets Ther. 2018 Oct 4;11:6525-6537.

Pembrolizumab (KEYTRUDA)

Adverse effects:

- Endocrine toxicity (hypothyroidism, hyperthyroidism, adrenocortical insufficiency (primary and secondary), hypophysitis)
- Dermatologic toxicity (SJS, TEN, skin rash, pruritus, and vitiligo)
- GI toxicity (colitis, diarrhea, abdominal pain)
- Cardiovascular toxicity (Acute myocardial infarction, immune mediated myocarditis, pericarditis, and vasculitis)
- Hematologic toxicity (immune thrombocytopenia, utoimmune hemolytic anemia (AIHA), anemia, neutropenia)
- Hepatotoxicity (increased serum aspartate transaminase, increased serum alanine transaminase, hyperbilirubinemia)

02

Research

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Event-free Survival with Pembrolizumab in Early Triple-Negative Breast Cancer

P. Schmid, J. Cortes, R. Dent, L. Pusztai, H. McArthur, S. Kümmel, J. Bergh, C. Denkert, Y.H. Park, R. Hui, N. Harbeck, M. Takahashi, M. Untch, P.A. Fasching, F. Cardoso, J. Andersen, D. Patt, M. Danso, M. Ferreira, M.-A. Mouret-Reynier, S.-A. Im, J.-H. Ahn, M. Gion, S. Baron-Hay, J.-F. Boileau, Y. Ding, K. Tryfonidis, G. Aktan, V. Karantza, and J. O'Shaughnessy, for the KEYNOTE-522 Investigators*

N Engl J Med 2022;386:556-67.

Study design

- Based on a previous trial, Pembrolizumab for Early Triple-Negative Breast Cancer, published at 2020. [N Engl J Med 2020;382:810-21.]
- Phase 3, randomized, double-blind placebo-controlled study

P	Previously untreated stage ii or iii triple-negative breast cancer
I	Pembrolizumab 200mg every 3 weeks
C	Placebo
O	Pathological complete response, Event-free survival

Inclusion criteria

1.Above 18 years old

2.Have centrally confirmed TNBC without metastasis
-T1c, N1-N2 /T2, N0-N2 /T3, N0-N2 /T4a-d, N0-N2

3. an ECOG performance-status score21 of 0 or 1 (on a 5-point scale, with higher numbers indicating greater disability)

4. Adequate organ function.

ECOG= Eastern Cooperative Oncology Group

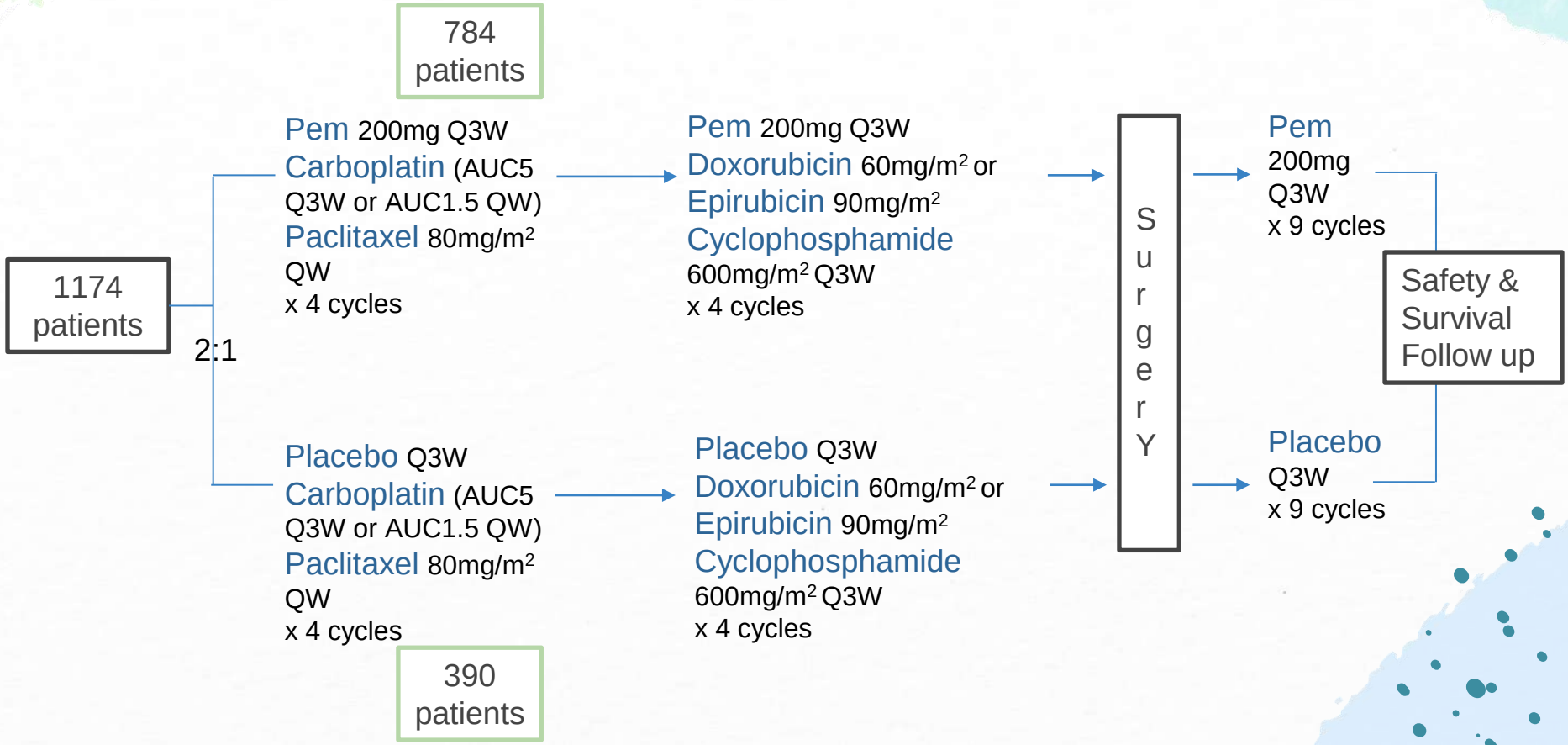
Eastern Cooperative Oncology Group (ECOG) performance status

Performance status	Definition
0	Fully active; no performance restrictions.
1	Strenuous physical activity restricted; fully ambulatory and able to carry out light work.
2	Capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair >50% of waking hours.
4	Completely disabled; cannot carry out any self-care; totally confined to bed or chair.

Exclusion criteria

1. Active autoimmune disease and received systemic treatment within the previous 2 years
2. Immunodeficiency or use of immunosuppressive therapy within the previous week
3. Noninfectious pneumonitis for which the patient had received glucocorticoids
4. Current infection (e.g. pneumonitis, active tuberculosis, active HBV, HCV),
5. Clinically significant cardiovascular disease.

Trial design



Primary Outcome

- Primary end point: Pathological complete response, Event-free survival
- Pathological complete response (pCR) : defined as pathological stage ypT0/Tis ypN0 at the time of definitive surgery
- Event-free survival : defined as the time from randomization to the date of disease progression that precluded definitive surgery, local or distant recurrence, occurrence of a second primary cancer, or death from any cause.

Secondary Outcome

- 1) Overall survival among all patients
- 2) Overall survival among patients with PD-L1(+)tumors
- 3) Event-free survival among patients with PD-L1 (+) tumors
- 4) Pathological complete response(ypT0 ypN0 and ypT0–Tis) in all patients
- 5) Pathological complete response in patients with PD-L1–(+) tumors.
- 6) Safety and tolerability

Statistical Analysis

- Efficacy analyses were performed in the intention-to-treat population
- The Kaplan–Meier method was used to estimate event-free survival and overall survival.
- The interim analyses for event-free survival are time-dependent and conducted annually after 2 years, with the final analysis being event-driven.

- We calculated that a sample of approximately 1150 patients would provide the trial with 80% power to detect a hazard ratio of 0.71 event-free survival , at a two-sided alpha level of 0.04.

- Safety was assessed in the as-treated population.

Results

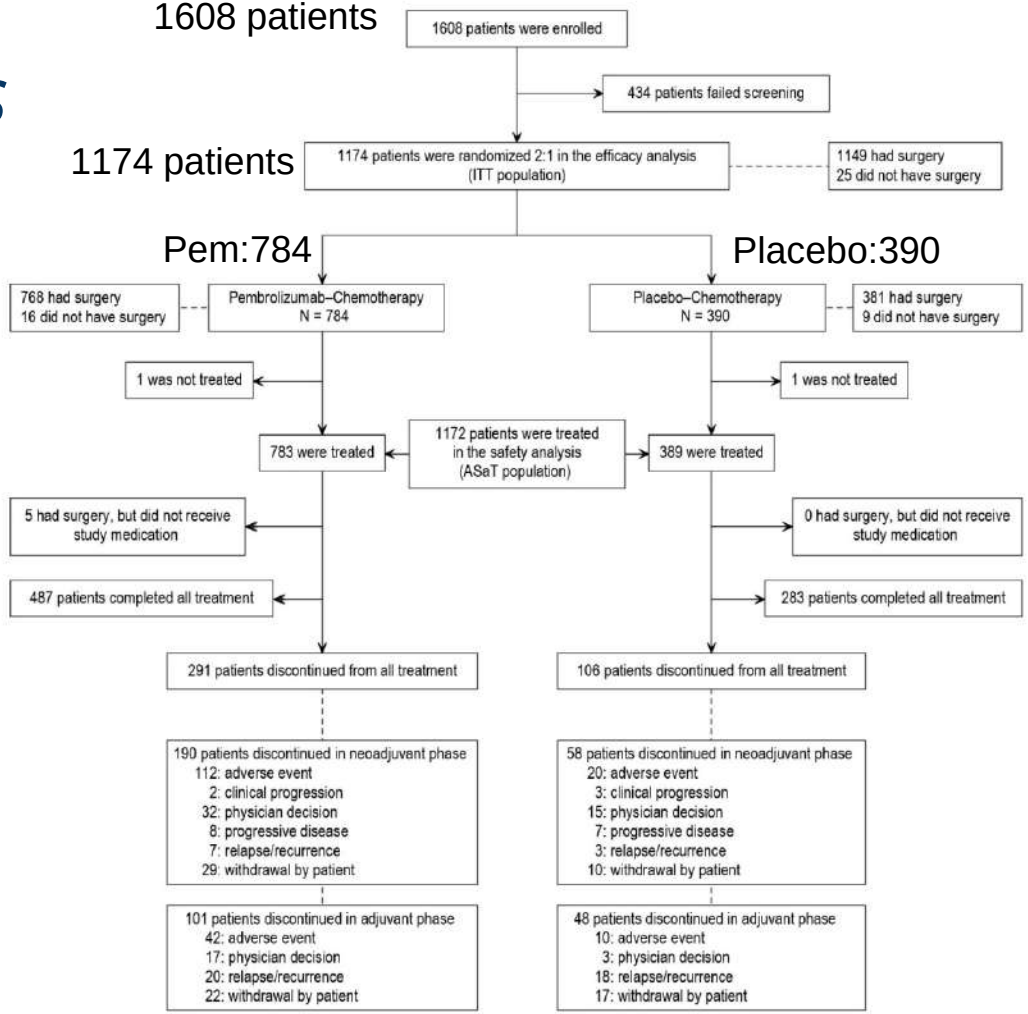
Results

1608 patients

1174 patients

Pem:784

Placebo:390



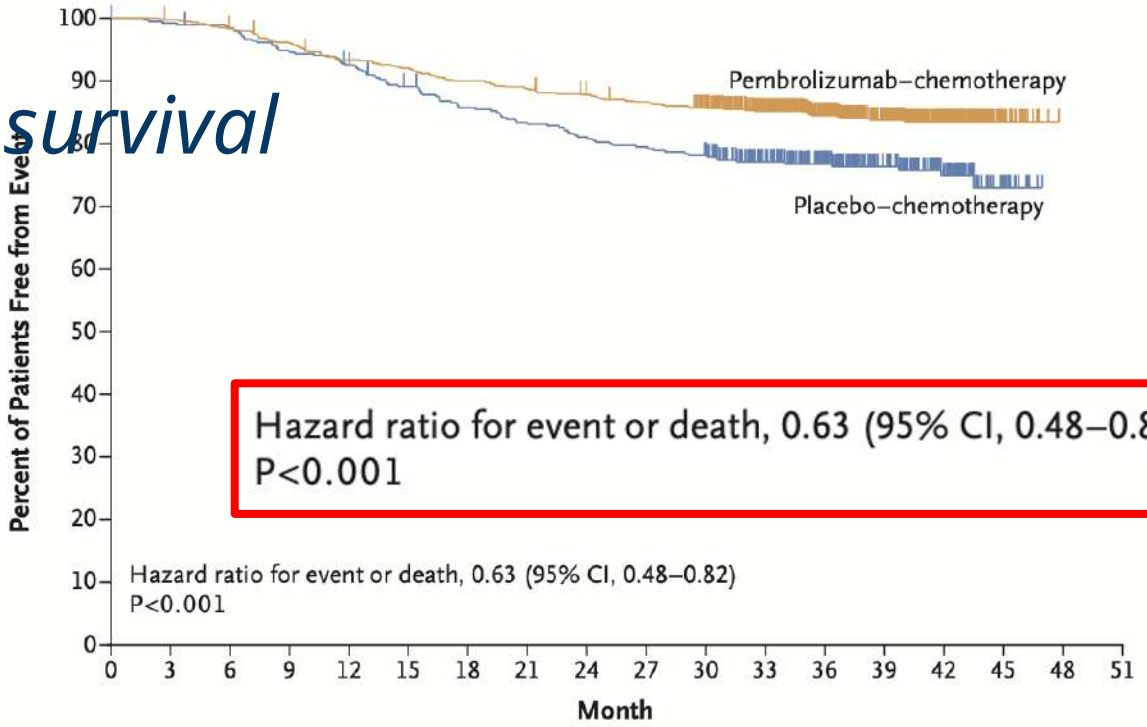
Pathological Complete Response(pCR)

Table 2. Pathological Complete Response, According to Pathological Stage.*

Variable	Pembrolizumab–Chemotherapy (N=401)	Placebo–Chemotherapy (N=201)	Estimated Treatment Difference†	P Value
			percentage points (95% CI)	
Pathological stage ypT0/Tis ypN0				
No. of patients	260	103		
Percentage of patients with response (95% CI)	64.8 (59.9–69.5)	51.2 (44.1–58.3)	13.6 (5.4–21.8)	P<0.001
Pathological stage ypT0 ypN0				
No. of patients	240	91		
Percentage of patients with response (95% CI)	59.9 (54.9–64.7)	45.3 (38.3–52.4)	14.5 (6.2–22.7)	
Pathological stage ypT0/Tis				
No. of patients	275	108		
Percentage of patients with response (95% CI)	68.6 (63.8–73.1)	53.7 (46.6–60.8)	14.8 (6.8–23.0)	

N Engl J Med 2020;382:810-21

Event-free survival



Hazard ratio for event or death, 0.63 (95% CI, 0.48–0.82)
P<0.001

No. at Risk

Pembrolizumab–chemotherapy	784	781	769	751	728	718	702	692	681	671	652	551	433	303	165	28	0	0
Placebo–chemotherapy	390	386	382	368	358	342	328	319	310	304	297	250	195	140	83	17	0	0

A total of 123 patients (15.7%) in the pembrolizumab–chemotherapy group and 93 patients (23.8%) in the placebo–chemotherapy group had an event or died (hazard ratio, 0.63; 95%CI, 0.48 to 0.82; P<0.001)

Results

According to the prespecified statistical criterion of an alpha level of 0.01034, a significant improvement in event-free survival was seen in the pembrolizumab–chemotherapy group as compared with the placebo–chemotherapy group.

The estimated event-free survival at 36 months was 84.5% (95% CI, 81.7 to 86.9) in the pembrolizumab–chemotherapy group and 76.8% (95% CI, 72.2 to 80.7) in the placebo–chemotherapy group; the median event-free survival was not reached in either group.

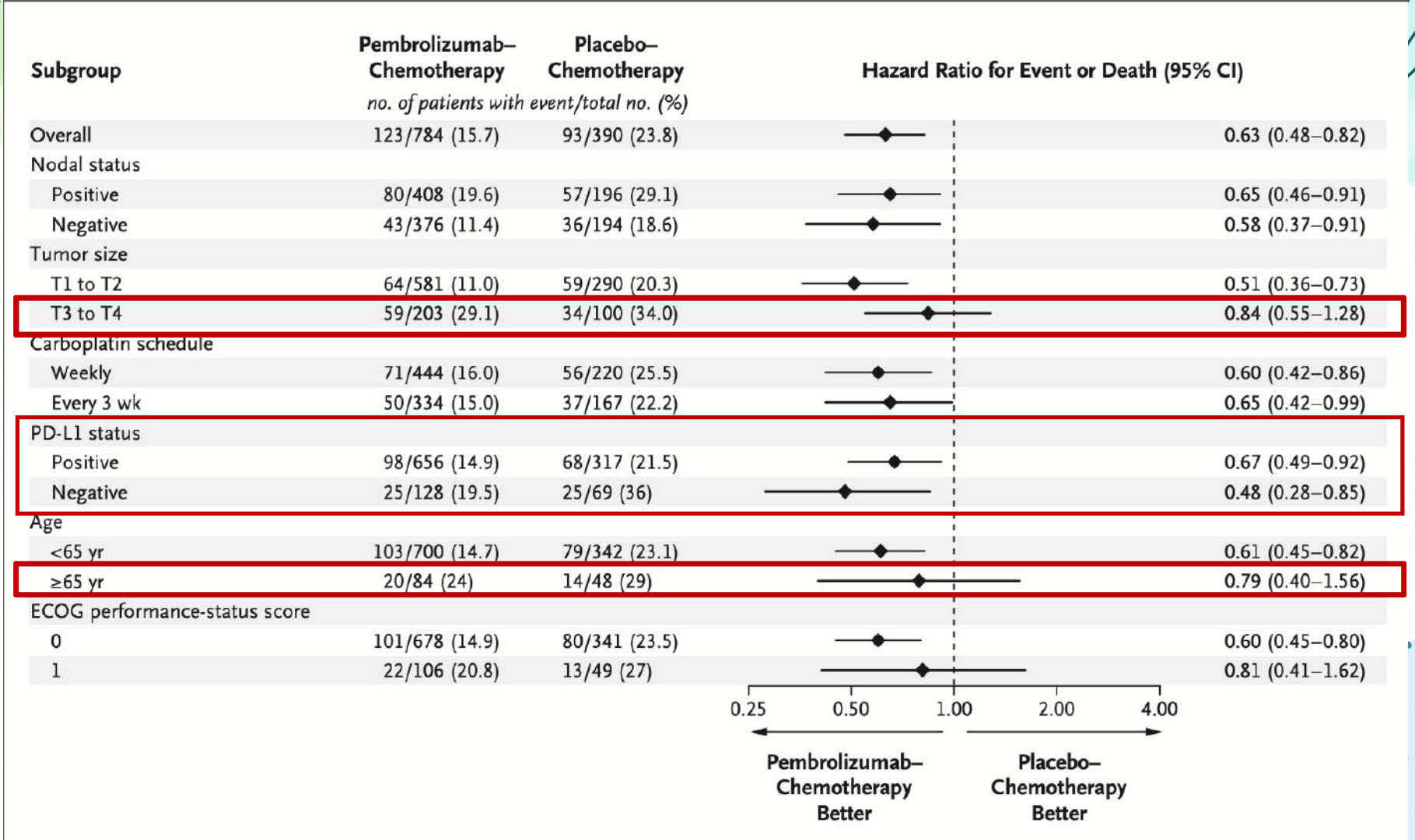
36 month: interim analysis 2

Table 1. Summary of First Events in Analysis of Event-free Survival.

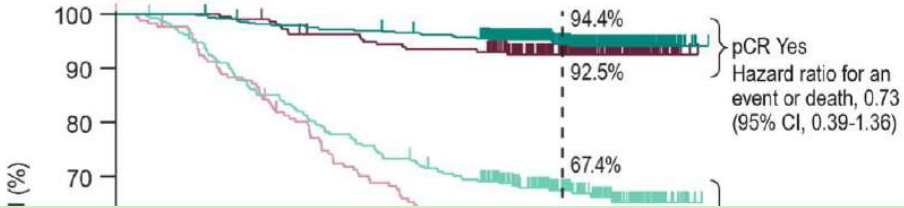
First Event	Pembrolizumab–Chemotherapy (N=784)	Placebo–Chemotherapy (N=390)
	number (percent)	
Any first event	123 (15.7)	93 (23.8)
Progression of disease that precluded definitive surgery	14 (1.8)	15 (3.8)
Local recurrence*	28 (3.6)	17 (4.4)
Distant recurrence	60 (7.7)	51 (13.1)
Second primary cancer†	6 (0.8)	4 (1.0)
Death	15 (1.9)	6 (1.5)

* A total of 13 patients in the pembrolizumab–chemotherapy group and 9 in the placebo–chemotherapy group with local recurrence had subsequent distant recurrence.

† Sites of second primary cancer included blood, bone marrow, chest wall, colon, endometrium, ovaries, stomach, and tongue.


Subgroup
Pembrolizumab–Chemotherapy
Placebo–Chemotherapy
no. of patients with event/total no. (%)
Hazard Ratio for Event or Death (95% CI)
Overall 123/784 (15.7) 93/390 (23.8) 0.63 (0.48–0.82)
Nodal status
Positive 80/408 (19.6) 57/196 (29.1) 0.65 (0.46–0.91)
Negative 43/376 (11.4) 36/194 (18.6) 0.58 (0.37–0.91)
Tumor size
T1 to T2 64/581 (11.0) 59/290 (20.3) 0.51 (0.36–0.73)
T3 to T4 59/203 (29.1) 34/100 (34.0) 0.84 (0.55–1.28)
Carboplatin schedule
Weekly 71/444 (16.0) 56/220 (25.5) 0.60 (0.42–0.86)
Every 3 wk 50/334 (15.0) 37/167 (22.2) 0.65 (0.42–0.99)
PD-L1 status
Positive 98/656 (14.9) 68/317 (21.5) 0.67 (0.49–0.92)
Negative 25/128 (19.5) 25/69 (36) 0.48 (0.28–0.85)
Age
<65 yr 103/700 (14.7) 79/342 (23.1) 0.61 (0.45–0.82)
≥65 yr 20/84 (24) 14/48 (29) 0.79 (0.40–1.56)
ECOG performance-status score
0 101/678 (14.9) 80/341 (23.5) 0.60 (0.45–0.80)
1 22/106 (20.8) 13/49 (27) 0.81 (0.41–1.62)
0.25
0.50
1.00
2.00
4.00
Pembrolizumab–Chemotherapy Better
Placebo–Chemotherapy Better

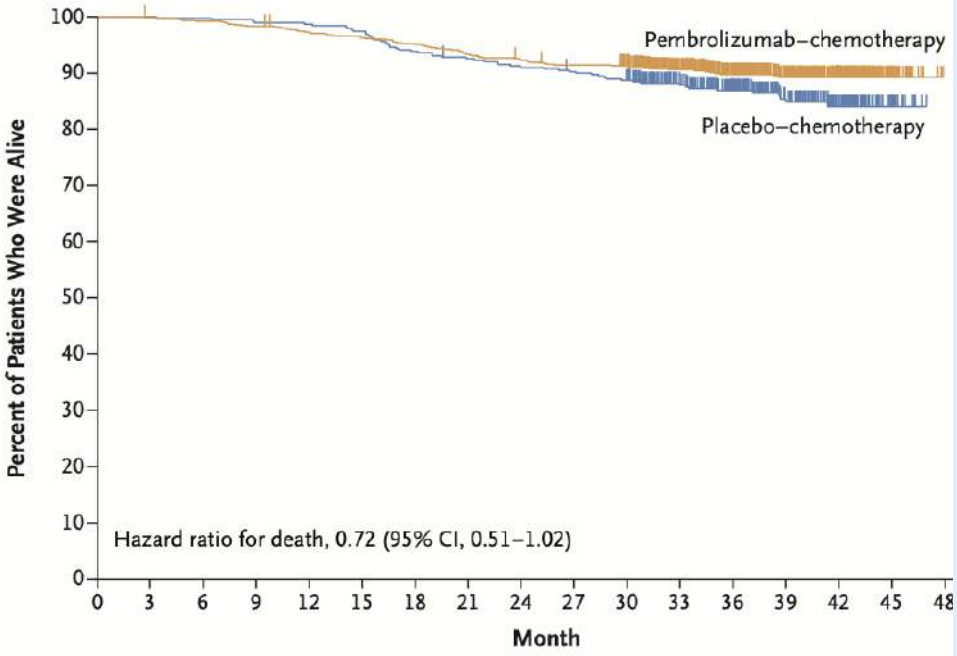
Exploratory Analysis



Among patients with a pathological complete response, 27 of 494 (5.5%) in the pembrolizumab–chemotherapy group and 16 of 217 (7.4%) in the placebo–chemotherapy group had an event or died (hazard ratio,0.73;95%CI, 0.39 to 1.36). Among patients without a pathological complete response, 96 of 290 (33.1%) in the pembrolizumab–chemotherapy group and 77 of 173 (44.5%) in the placebo–chemotherapy group had an event or died (hazard ratio, 0.70; 95% CI, 0.52 to 0.95)

No. at Risk																	
Pembrolizumab–Chemotherapy Responder	494	494	494	489	483	482	478	477	472	470	460	387	307	220	122	18	0	0
Placebo–Chemotherapy Responder	217	217	217	216	214	207	206	203	200	200	197	165	130	87	56	9	0	0
Pembrolizumab–Chemotherapy Non-Responder	290	287	275	262	245	236	224	215	209	201	192	164	126	83	43	10	0	0
Placebo–Chemotherapy Non-Responder	173	169	165	152	144	135	122	116	110	104	100	85	65	53	27	8	0	0

Overall Survival



Data on overall survival were immature at the time of this analysis. A total of 80 patients (10.2%) in the pembrolizumab–chemotherapy group and 55 patients (14.1%) in the placebo–chemotherapy group died (hazard ratio, 0.72; 95 CI, 0.51 to 1.02).The estimated overall survival at 36 months was 89.7% (95% CI, 87.3 to 91.7) in the pembrolizumab–chemotherapy group and 86.9% (95% CI, 83.0 to 89.9) in the placebo–chemotherapy group; the median overall survival was not reached in either group.

Safety

Table 2. Adverse Events in the Combined Neoadjuvant and Adjuvant Phases (As-Treated Population).*

Event	Pembrolizumab–Chemotherapy (N=783)		Placebo–Chemotherapy (N=389)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any adverse event	777 (99.2)	645 (82.4)	389 (100)	306 (78.7)
Treatment-related adverse event†	774 (98.9)	604 (77.1)	388 (99.7)	285 (73.3)
Nausea	495 (63.2)	27 (3.4)	245 (63.0)	6 (1.5)
Alopecia	471 (60.2)	0	220 (56.6)	0
Peripheral neuropathy	154 (19.7)	15 (1.9)	84 (21.6)	4 (1.0)
Immune-mediated adverse event‡	262 (33.5)	101 (12.9)	44 (11.3)	4 (1.0)
Hypothyroidism	118 (15.1)	4 (0.5)	22 (5.7)	0
Severe skin reaction	45 (5.7)	37 (4.7)	4 (1.0)	1 (0.3)
Hyperthyroidism	41 (5.2)	2 (0.3)	7 (1.8)	0
Adrenal insufficiency	20 (2.6)	8 (1.0)	0	0
Pneumonitis	17 (2.2)	7 (0.9)	6 (1.5)	2 (0.5)
Thyroiditis	16 (2.0)	2 (0.3)	5 (1.3)	0
Hypophysitis	15 (1.9)	10 (1.3)	1 (0.3)	0

Discontinuation of the trial regimen because of treatment-related adverse events occurred in 27.7% of the patients in the pembrolizumab–chemotherapy group and in 14.1% of those in the placebo–chemotherapy group.

Treatment-related adverse events led to death in 4 patients (0.5%) in the pembrolizumab–chemotherapy group and in 1 patient (0.3%) in the placebo–chemotherapy group.

Safety

Table from previous study ,Pembrolizumab for Early Triple-Negative Breast Cancer, on 2020.

The incidence of adverse events was similar among two reports.

Table 3. Adverse Events during the Neoadjuvant Phase at the Second Interim Analysis.*

Event	Pembrolizumab–Chemotherapy (N=781)		Placebo–Chemotherapy (N=389)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any adverse event	777 (99.5)	633 (81.0)	389 (100.0)	295 (75.8)
Treatment-related adverse event†	773 (99.0)	600 (76.8)	388 (99.7)	281 (72.2)
Nausea	490 (62.7)	26 (3.3)	246 (63.2)	5 (1.3)
Alopecia	471 (60.3)	14 (1.8)	220 (56.6)	8 (2.1)
Anemia	430 (55.1)	142 (18.2)	215 (55.3)	58 (14.9)
Neutropenia	365 (46.7)	270 (34.6)	183 (47.0)	129 (33.2)
Fatigue	321 (41.1)	27 (3.5)	147 (37.8)	6 (1.5)
Diarrhea	230 (29.4)	17 (2.2)	92 (23.7)	5 (1.3)
Elevated alanine aminotransferase level	199 (25.5)	41 (5.2)	96 (24.7)	9 (2.3)
Vomiting	199 (25.5)	18 (2.3)	85 (21.9)	6 (1.5)
Asthenia	191 (24.5)	25 (3.2)	99 (25.4)	9 (2.3)
Constipation	185 (23.7)	0	82 (21.1)	0
Decreased neutrophil count	185 (23.7)	146 (18.7)	112 (28.8)	90 (23.1)
Rash	170 (21.8)	7 (0.9)	59 (15.2)	1 (0.3)
Peripheral neuropathy	154 (19.7)	15 (1.9)	82 (21.1)	4 (1.0)
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)	13 (3.3)	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

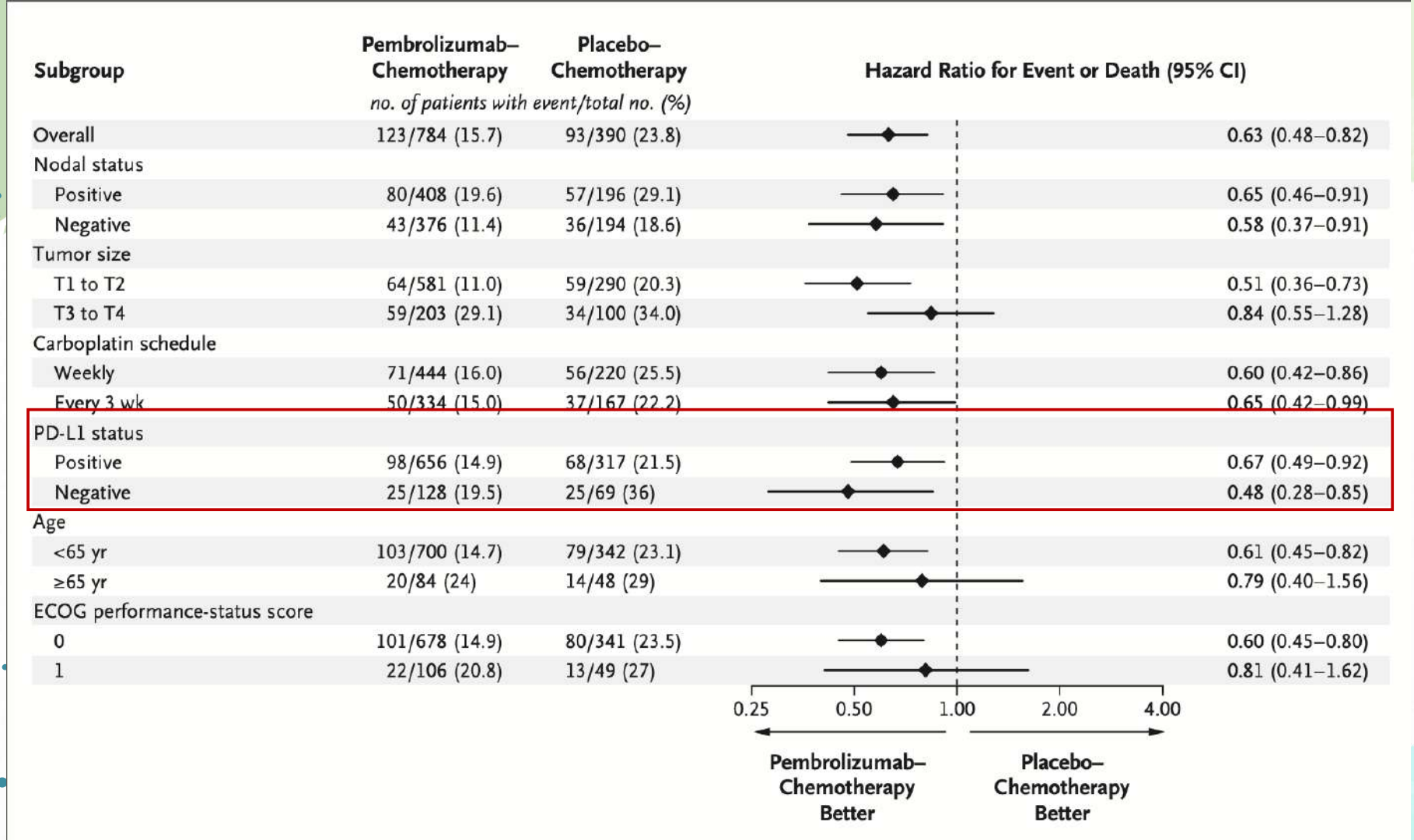
N Engl J Med 2020;382:810-21

03

Discussion

Discussion 1

Does PD-L1 status affect the result ?


Subgroup
Pembrolizumab–Chemotherapy
Placebo–Chemotherapy
no. of patients with event/total no. (%)
Hazard Ratio for Event or Death (95% CI)
Overall 123/784 (15.7) 93/390 (23.8) 0.63 (0.48–0.82)
Nodal status
Positive 80/408 (19.6) 57/196 (29.1) 0.65 (0.46–0.91)
Negative 43/376 (11.4) 36/194 (18.6) 0.58 (0.37–0.91)
Tumor size
T1 to T2 64/581 (11.0) 59/290 (20.3) 0.51 (0.36–0.73)
T3 to T4 59/203 (29.1) 34/100 (34.0) 0.84 (0.55–1.28)
Carboplatin schedule
Weekly 71/444 (16.0) 56/220 (25.5) 0.60 (0.42–0.86)
Every 3 wk 50/334 (15.0) 37/167 (22.2) 0.65 (0.42–0.99)
PD-L1 status
Positive 98/656 (14.9) 68/317 (21.5) 0.67 (0.49–0.92)
Negative 25/128 (19.5) 25/69 (36) 0.48 (0.28–0.85)
Age
<65 yr 103/700 (14.7) 79/342 (23.1) 0.61 (0.45–0.82)
≥65 yr 20/84 (24) 14/48 (29) 0.79 (0.40–1.56)
ECOG performance-status score
0 101/678 (14.9) 80/341 (23.5) 0.60 (0.45–0.80)
1 22/106 (20.8) 13/49 (27) 0.81 (0.41–1.62)
0.25
0.50
1.00
2.00
4.00
Pembrolizumab–Chemotherapy Better
Placebo–Chemotherapy Better

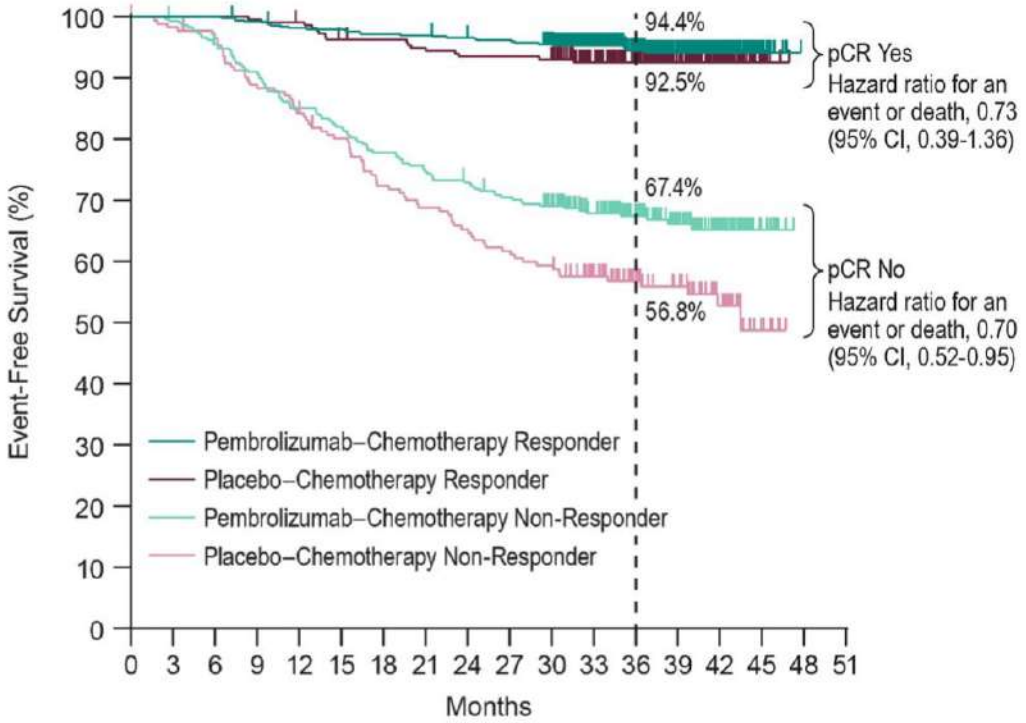
Discussion 1

The performance of pathological complete response was independent of PD-L1 expression in this trial.
By contrast, in the KEYNOTE-355 trial*, led to a significant improvement in progression-free survival, as compared with CT alone, among patients with metastatic TNBC who had a PDL1(+) expression.
Similarly, in the IMpassion031 trial, the efficacy of atezolizumab therapy^ was independent of PD-L1 expression in patients with early disease, whereas the efficacy was dependent on PD-L1 positivity in patients with metastatic disease.
Together, these findings suggest that baseline tumor PD-L1 expression plays a differential role in the efficacy of immune checkpoint inhibition in early, as compared with advanced, triple-negative breast cancer.

*: first-line treatment with pembrolizumab plus chemotherapy(taxanes and a non-taxane platinum- based regimen)
^:Neoadjuvant atezolizumab in combination with nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy

Discussion 2

Among patients with or w/o pCR, how were their EFS in both treatment groups?



No. at Risk

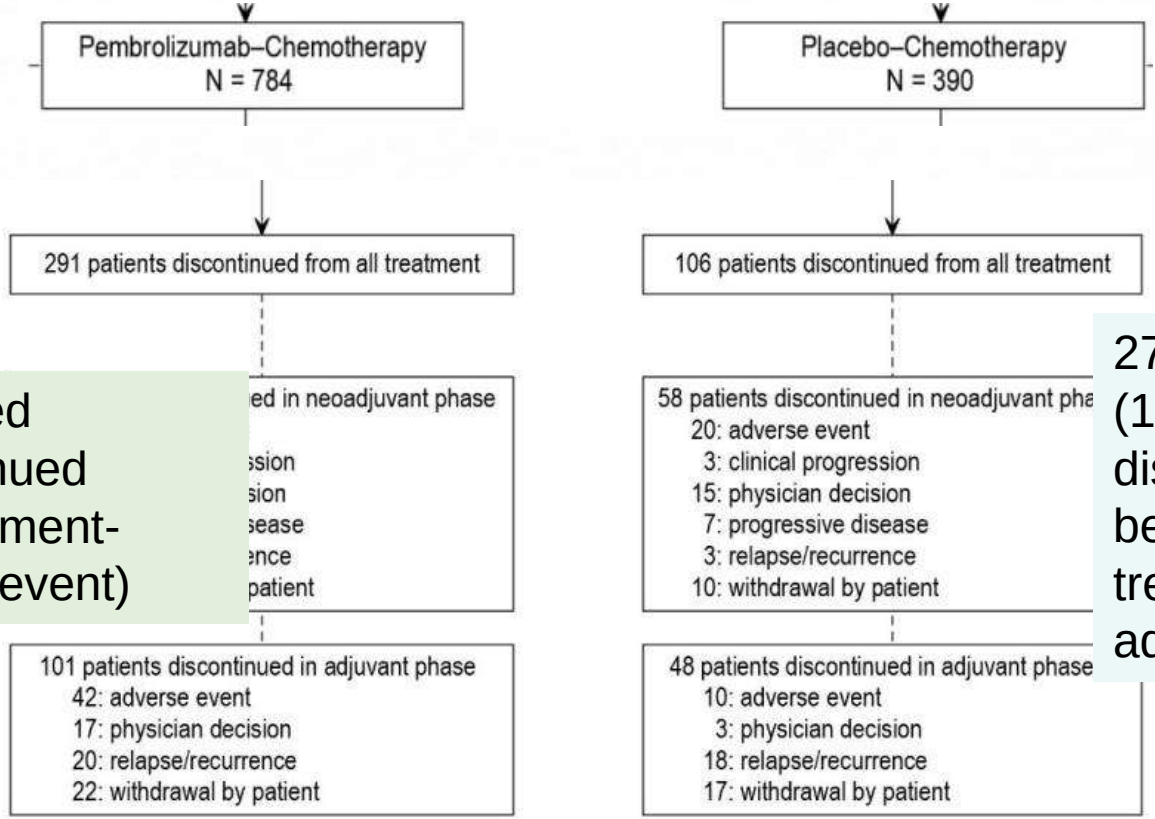
Pembrolizumab–Chemotherapy Responder	494	494	494	489	483	482	478	477	472	470	460	387	307	220	122	18	0	0
Placebo–Chemotherapy Responder	217	217	217	216	214	207	206	203	200	200	197	165	130	87	56	9	0	0
Pembrolizumab–Chemotherapy Non-Responder	290	287	275	262	245	236	224	215	209	201	192	164	126	83	43	10	0	0
Placebo–Chemotherapy Non-Responder	173	169	165	152	144	135	122	116	110	104	100	85	65	53	27	8	0	0

Discussion 2

- Pathological complete response is related to the survival.
- If the patients have pathological complete response, there are no significant difference in event-free survival between two groups.
- A relatively lower risk of events in the pembrolizumab–chemotherapy group if the patients did not acheive pathological complete response. The event-free survival was nearly 10% higher in pembrolizumab-chemotherapy group at 3 years.

Discussion 3

Safety



37% discontinued (27.7% discontinued because of treatment-related adverse event)

27% discontinued (14.1% discontinued because of treatment-related adverse event)

Table S5. Summary of Tier 2 Adverse Events during the Combined Phases.

Participants in Population	Pembrolizumab–Chemotherapy (N=783)		Placebo–Chemotherapy(N=389)		Difference in % vs. Placebo–Chemotherapy
	n	(%)	n	(%)	Estimate (95% CI)*
with one or more adverse events	777	(99.2)	389	(100.0)	-0.8 (-1.7, 0.2)
with no adverse event	6	(0.8)	0	(0.0)	0.8 (-0.2, 1.7)
with drug-related† adverse events	774	(98.9)	388	(99.7)	-0.9 (-2.0, 0.4)
with toxicity grade 3-5‡ adverse events	645	(82.4)	306	(78.7)	3.7 (-1.0, 8.7)
with toxicity grade 3-5‡ drug-related adverse events	604	(77.1)	285	(73.3)	3.9 (-1.3, 9.3)
with serious adverse events	341	(43.6)	111	(28.5)	15.0 (9.2, 20.6)
with serious drug-related adverse events	267	(34.1)	78	(20.1)	14.0 (8.7, 19.1)
with dose modification§ due to an adverse event	644	(82.2)	306	(78.7)	3.6 (-1.1, 8.6)
who died	7	(0.9)	1	(0.3)	0.6 (-0.6, 1.6)
who died due to a drug-related adverse event	4	(0.5)	1	(0.3)	0.3 (-1.0, 1.1)
discontinued drug due to an adverse event	234	(29.9)	60	(15.4)	14.5 (9.5, 19.1)
discontinued drug due to a drug-related adverse event	217	(27.7)	55	(14.1)	13.6 (8.7, 18.1)
discontinued drug due to a serious adverse event	94	(12.0)	15	(3.9)	8.1 (5.0, 11.1)
discontinued drug due to a serious drug-related adverse event	84	(10.7)	11	(2.8)	7.9 (5.0, 10.6)

CASP
Critical Appraisal
Skills Programme

04

Appraisal

Critical Appraisal Skills Programme
(CASP)

1. Did the study address a clearly focused research question?

☑ Yes ☐ No ☐ Can't tell

METHODS

We randomly assigned, in a 2:1 ratio, patients with previously untreated stage II or III triple-negative breast cancer to receive neoadjuvant therapy with four cycles of pembrolizumab (at a dose of 200 mg) or placebo every 3 weeks plus paclitaxel and carboplatin, followed by four cycles of pembrolizumab or placebo plus doxorubicin–cyclophosphamide or epirubicin–cyclophosphamide. After definitive surgery, patients received adjuvant pembrolizumab (pembrolizumab–chemotherapy group) or placebo (placebo–chemotherapy group) every 3 weeks for up to nine cycles. The primary end points were pathological complete response (the results for which have been reported previously) and event-free survival, defined as the time from randomization to the date of disease progression that precluded definitive surgery, local or distant recurrence, occurrence of a second primary cancer, or death from any cause. Safety was also assessed.

P

C

O

2. Was the assignment of participants to interventions randomized?

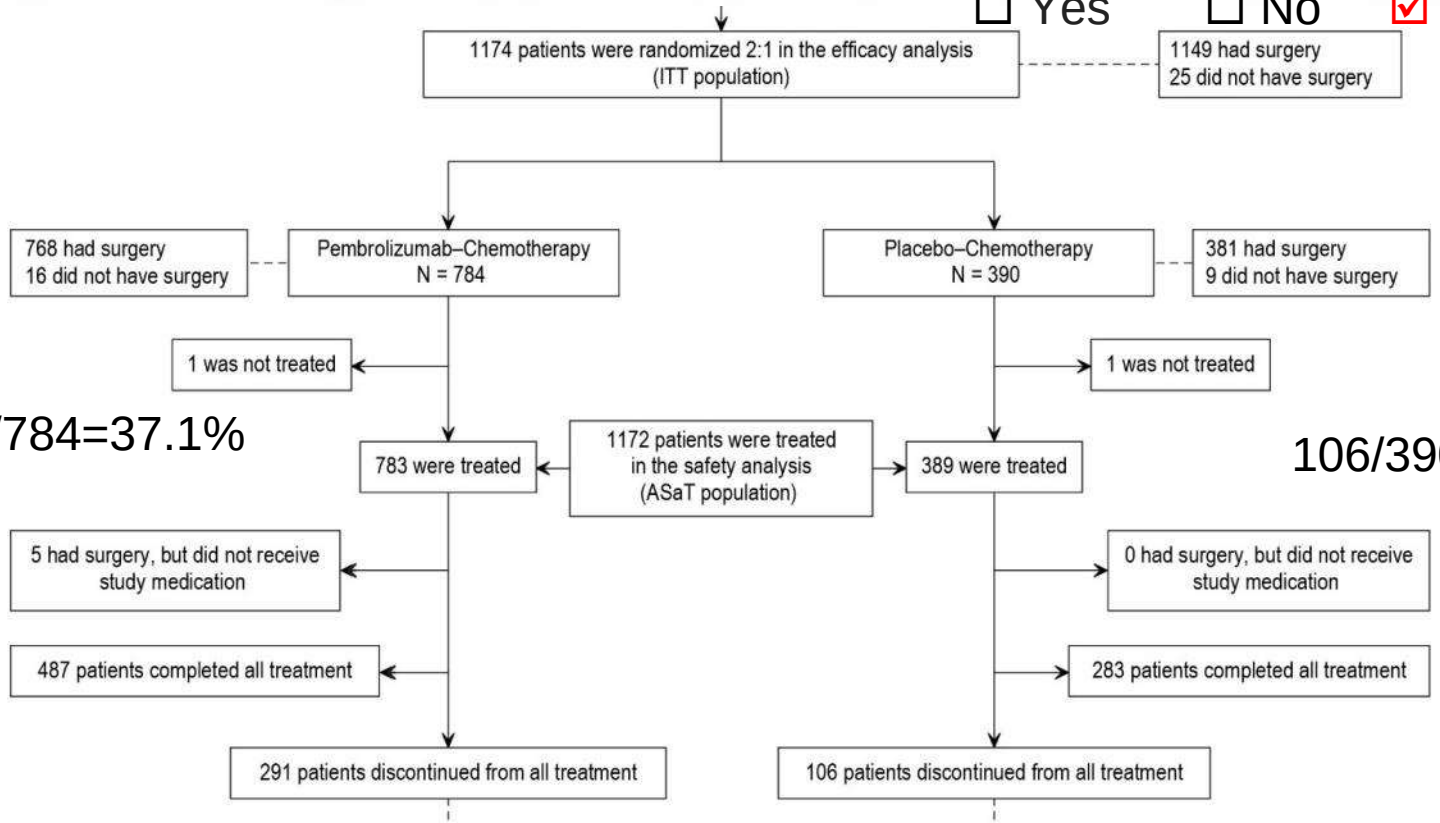
☑ Yes ☐ No ☐ Can't tell

- Randomization was performed with the use of a central interactive voice-response system with an integrated Web- response system
- The subject and the are unaware of the group assignments.
- Subjects will be assigned randomly in a 2:1 ratio to pembrolizumab and placebo
- Treatment allocation/randomization will be stratified according to the following factors:

Nodal status	Positive	Negative
Tumor size	T1/T2	T3/T4
Choice of Carboplatin	Q3W	Weekly

3. Were all participants who entered the study accounted for at its conclusion?

☐ Yes ☐ No ☑ Can't tell



291/784=37.1%

106/390=27.2%

4.Blinding

1)Were the participants 'blind' to intervention they were given?

☑ Yes ☐ No ☐ Can't tell

2)Were the investigators 'blind' to the intervention they were giving to participants?

☑ Yes ☐ No ☐ Can't tell

3)Were the people assessing/analyzing outcome/s 'blinded'?

This study will be conducted as a double-blind trial under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete. In addition, the site radiologist(s) will perform the imaging review without knowledge of treatment group assignment.

☑ Yes ☐ No ☐ Can't tell

5.Were the study groups similar at the start of the randomized controlled trial?

☑ Yes ☐ No ☐ Can't tell

Table S1. Demographic and Disease Characteristics at Baseline.*

Characteristic	Pembrolizumab–Chemotherapy (N=784)	Placebo–Chemotherapy (N=390)
Age		
Median (range) — yr	49 (22-80)	48 (24-79)
<65 yr — no. (%)	700 (89.3)	342 (87.7)
Female sex — no. (%)	783 (99.9)	390 (100.0)
Geographic region — no. (%)		
Europe	388 (49.5)	180 (46.2)
Asia	166 (21.2)	91 (23.3)
North America	166 (21.2)	78 (20.0)
Australia	23 (2.9)	16 (4.1)
Rest of world	41 (5.2)	25 (6.4)
Race		
White	504 (64.3)	242 (62.1)
Asian	149 (19.0)	89 (22.8)
Missing†	65 (8.3)	31 (7.9)
Black or African American	38 (4.8)	15 (3.8)
American Indian or Alaska Native	14 (1.8)	7 (1.8)
Multiple	13 (1.7)	6 (1.5)
Native Hawaiian or Other Pacific Islander	1 (0.1)	0
Ethnicity		
Not Hispanic or Latino	615 (78.4)	307 (78.7)
Hispanic or Latino	86 (11.0)	39 (10.0)
Not Reported	46 (5.9)	28 (7.2)
Unknown	19 (2.4)	11 (2.8)
Missing†	18 (2.3)	5 (1.3)
Menopausal status — no. (%)		
Pre-menopausal	438 (55.9)	221 (56.7)
Post-menopausal	345 (44.0)	169 (43.3)
Missing‡	1 (0.1)	0 (0.0)
PD-L1 status§ — no. (%)		
Positive	656 (83.7)	317 (81.3)
Negative	128 (16.3)	69 (17.7)
Missing	0 (0.0)	4 (1.0)
ECOG performance status		
0	678 (86.5)	341 (87.4)
1	106 (13.5)	49 (12.6)
Lactase dehydrogenase — no. (%)		
≤ULN	631 (80.5)	309 (79.2)
>ULN	149 (19.0)	80 (20.5)
Missing	4 (0.5)	1 (0.3)
Choice of carboplatin‖ — no. (%)		
Every 3 weeks	335 (42.7)	167 (42.8)
Weekly	449 (57.3)	223 (57.2)
Primary tumor classification‖— no. (%)		
T1/T2	580 (74.0)	290 (74.4)
T3/T4	204 (26.0)	100 (25.6)
Nodal involvement‖ — no. (%)		
Positive	405 (51.7)	200 (51.3)
Negative	379 (48.3)	190 (48.7)
Overall disease stage — no. (%)		
I	0 (0.0)	1 (0.3)
II	590 (75.3)	291 (74.6)
III	194 (24.7)	98 (25.1)
HER2 status — no. (%)		
0-1 by IHC	595 (75.9)	286 (73.3)
2+ by IHC¶	188 (24.0)	104 (26.7)
Missing	1 (0.1)	0 (0.0)

6.Apart from the experimental intervention, did each study group receive the same level of care (that is, were they treated equally)?

☑ Yes ☐ No ☐ Can't tell

In the neoadjuvant phase, patients received four cycles of an intravenous infusion of pembrolizumab (at a dose of 200 mg) or placebo once every 3 weeks; all patients also received paclitaxel (80 mg per square meter of body-surface area once weekly) and carboplatin (at a dose based on an area under the concentration–time curve of 5 mg per milliliter per minute, administered once every 3 weeks, or 1.5 mg per milliliter per minute, administered once weekly for the first 12 weeks) (i.e., the first neoadjuvant treatment). Patients then received four cycles of pembrolizumab or placebo; all patients also received doxorubicin (60 mg per square meter) or epirubicin (90 mg per square meter), plus cyclophosphamide (600 mg per square meter), administered once every 3 weeks for the subsequent 12 weeks (i.e., the second neoadjuvant treatment). Use of glucocorticoids was permitted in order to avoid allergic reactions before chemotherapy and for the management of immune-mediated adverse events.

7. Were the effects of intervention reported comprehensively?

☑ Yes ☐ No ☐ Can't tell

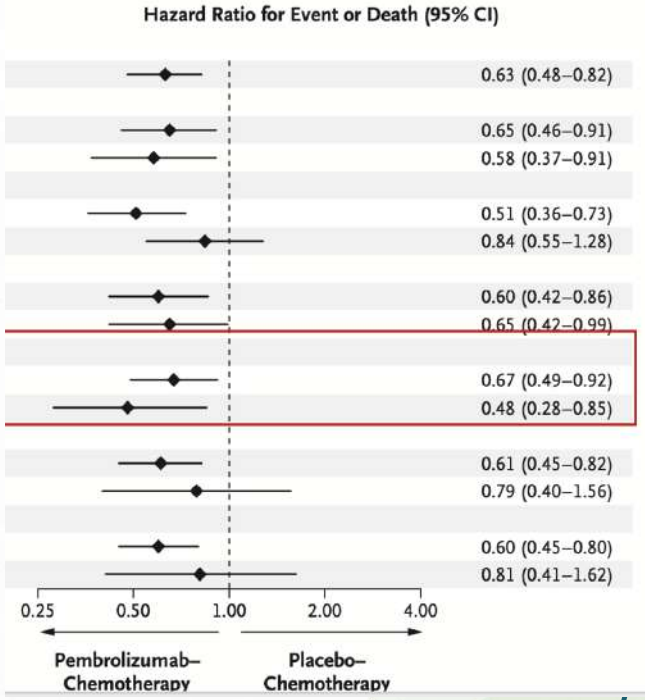
- ✓ A 80% power calculation was taken.
- ✓ P values were reported.
- ✓ Clear outcome measurement.
- ✓ Data on overall survival were immature at the time of this analysis.
- ✓ Drop-out rate is a bit higher in pembrolizumab-chemotherapy group than placebo-chemotherapy group (37% vs 27%)
- ✓ The Kaplan–Meier method was used to estimate event-free survival and overall survival.
- ✓ The hazard ratio and confidence interval were analyzed with the use of a Cox proportional-hazards model, with treatment as a covariate and with stratification.

8.Was the precision of the estimate of the intervention or treatment effect reported?

☑ Yes ☐ No ☐ Can't tell

95% confident intervals were reported.

Hazard ratio for event or death, 0.63 (95% CI, 0.48–0.82)
P<0.001



9.Do the benefits of the experimental intervention outweigh the harms and costs?

In patients with early triple-negative breast cancer, neoadjuvant pembrolizumab plus chemotherapy, followed by adjuvant pembrolizumab after surgery, resulted in significantly longer event-free survival than neoadjuvant chemotherapy alone.

The adverse events that were reported were consistent with the known safety profiles of pembrolizumab and chemotherapy. The addition of pembrolizumab did not compromise exposure to chemotherapy or increase the incidence of common chemotherapy-related toxic effects.

9.Do the benefits of the experimental intervention outweigh the harms and costs?

The higher incidence of immune-mediated adverse events in the pembrolizumab–chemotherapy group than in the placebo–chemotherapy group was driven primarily by endocrinopathies and skin reactions, which occurred mostly during the neoadjuvant phase.

These events were generally of low grade and were successfully managed with treatment interruption, glucocorticoid administration, or hormone replacement, a finding that underscores the importance of early identification and intervention to minimize risk and ensure continued treatment benefit.

9.Do the benefits of the experimental intervention outweigh the harms and costs?

☐ Yes ☐ No ☑ Can't tell

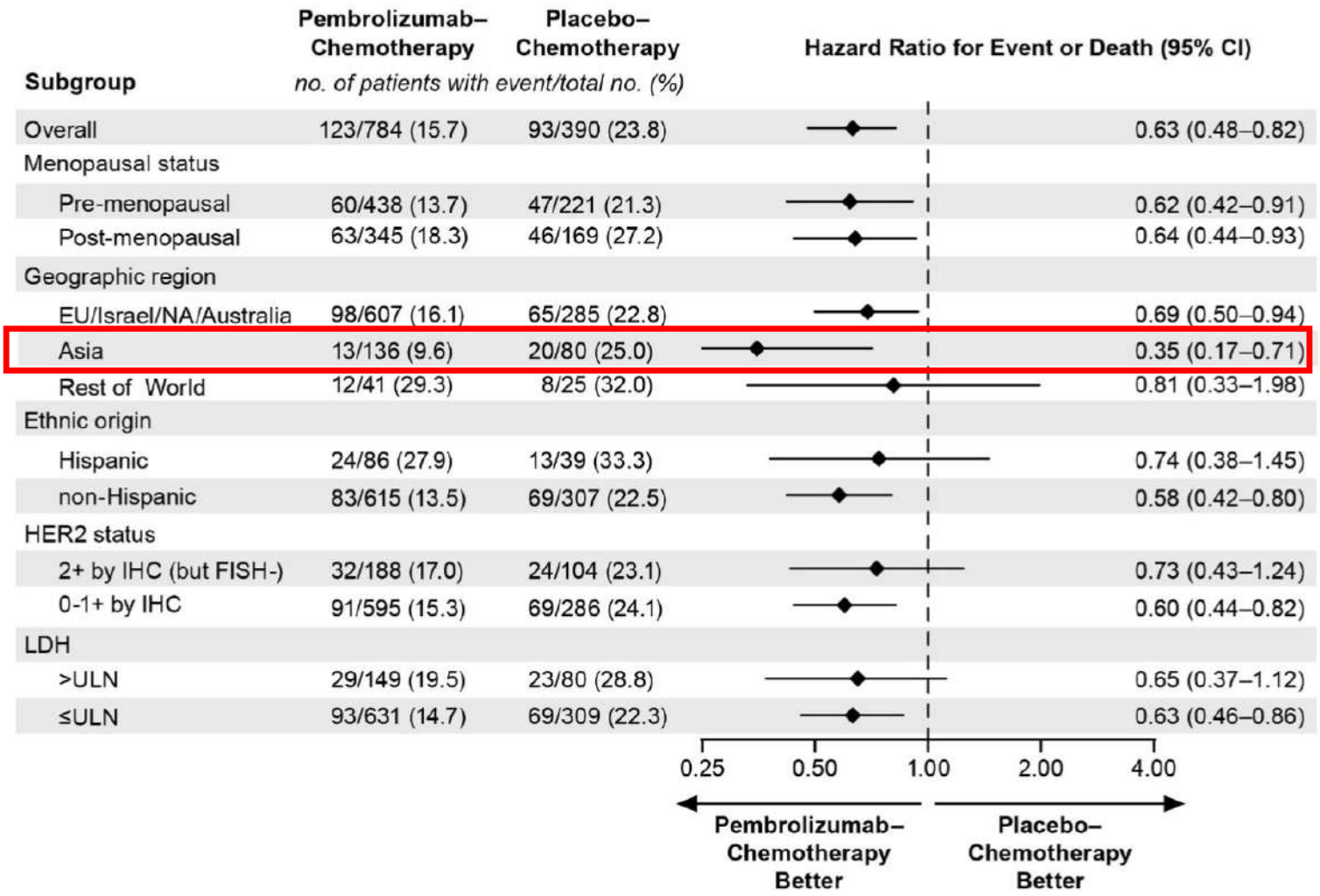
However, the cost of pembrolizumab is extremely expensive. Pembrolizumab for TNBC is not approved by Taiwan's National Healthcare insurance. Approximately NT$110000 each time. (NT$440000 for 4 cycles.)

10. Can the results be applied to your local population in your context?

Table S1. Demographic and Disease Characteristics at Baseline.*

Characteristic	Pembrolizumab–Chemotherapy (N=784)	Placebo–Chemotherapy (N=390)
Age		
Median (range) — yr	49 (22-80)	48 (24-79)
<65 yr — no. (%)	700 (89.3)	342 (87.7)
Female sex — no. (%)	783 (99.9)	390 (100.0)
Geographic region — no. (%)		
Europe	388 (49.5)	180 (46.2)
Asia	166 (21.2)	91 (23.3)
North America	166 (21.2)	78 (20.0)
Australia	23 (2.9)	16 (4.1)
Rest of world	41 (5.2)	25 (6.4)
Race		
White	504 (64.3)	242 (62.1)
Asian	149 (19.0)	89 (22.8)
Missing†	65 (8.3)	31 (7.9)
Black or African American	38 (4.8)	15 (3.8)
American Indian or Alaska Native	14 (1.8)	7 (1.8)
Multiple	13 (1.7)	6 (1.5)
Native Hawaiian or Other Pacific Islander	1 (0.1)	0
Ethnicity		
Not Hispanic or Latino	615 (78.4)	307 (78.7)
Hispanic or Latino	86 (11.0)	39 (10.0)
Not Reported	46 (5.9)	28 (7.2)
Unknown	19 (2.4)	11 (2.8)
Missing†	18 (2.3)	5 (1.3)
Menopausal status — no. (%)		

☑ Yes ☐ No ☐ Can't tell


Subgroup
Pembrolizumab–Chemotherapy
Placebo–Chemotherapy
no. of patients with event/total no. (%)
Hazard Ratio for Event or Death (95% CI)
Overall 123/784 (15.7) 93/390 (23.8) 0.63 (0.48–0.82)
Menopausal status
Pre-menopausal 60/438 (13.7) 47/221 (21.3) 0.62 (0.42–0.91)
Post-menopausal 63/345 (18.3) 46/169 (27.2) 0.64 (0.44–0.93)
Geographic region
EU/Israel/NA/Australia 98/607 (16.1) 65/285 (22.8) 0.69 (0.50–0.94)
Asia 13/136 (9.6) 20/80 (25.0) 0.35 (0.17–0.71)
Rest of World 12/41 (29.3) 8/25 (32.0) 0.81 (0.33–1.98)
Ethnic origin
Hispanic 24/86 (27.9) 13/39 (33.3) 0.74 (0.38–1.45)
non-Hispanic 83/615 (13.5) 69/307 (22.5) 0.58 (0.42–0.80)
HER2 status
2+ by IHC (but FISH-) 32/188 (17.0) 24/104 (23.1) 0.73 (0.43–1.24)
0-1+ by IHC 91/595 (15.3) 69/286 (24.1) 0.60 (0.44–0.82)
LDH
>ULN 29/149 (19.5) 23/80 (28.8) 0.65 (0.37–1.12)
≤ULN 93/631 (14.7) 69/309 (22.3) 0.63 (0.46–0.86)
0.25
0.50
1.00
2.00
4.00
Pembrolizumab–Chemotherapy Better
Placebo–Chemotherapy Better

11. Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?

☐ Yes ☐ No ☑ Can't tell

Other FDA approved new options for TNBC : PARP inhibitor, Sacituzumab govitecan-hziy
There's no head to head study to compare the efficacy of those agents.

Pembrolizumab for TNBC is not approved by Taiwan's National Healthcare insurance. Approximately 110000 NTD each time. (440000 NTD for 4 cycles.)

Summary

- Pembrolizumab could improve the event-free survival of patients with stage II-III TNBC.
- Although the rate of discontinuation due to treatment-related adverse events was higher in the pembrolizumab group, the occurrences of Grade 3 treatment-related AEs were similar between two groups.
- Immune-related adverse events are inevitable in immunotherapy, but grade 3 irAEs were less than 5%. Monitoring irAE is necessary.
- In subgroup analysis, patients with tumor size T1-T2 and age <65 showed the advantage in Pembrolizumab-chemotherapy group.
- The self-paid price is extremely high in Taiwan ($110000 each cycle).

Reference

1. Schmid P, Cortes J, Pusztai L, et al. Event-free survival with Pembrolizumab in early triple-negative breast cancer. N Engl J Med 2022;386:556-67.
2. Schmid P, Cortes J, Pusztai L, et al. Pembrolizumab for early triple-negative breast cancer. N Engl J Med 2020;382:810- 21.
3. Carey K. A., Lisa. A. C. (2022). ER/PR negative, HER2-negative (triple-negative) breast cancer. In Sadhna R V., UpToDate . (Accessed on June 23, 2022.)
4. Liu, X., Wu, K., Zheng, D., Luo, C., Fan, Y., Zhong, X., & Zheng, H. (2021). Efficacy and Safety of PARP Inhibitors in Advanced or Metastatic Triple-Negative Breast Cancer: A Systematic Review and Meta-Analysis. Frontiers in oncology, 11, 742139.
5. Aditya B.,Sara A. H., et al.(2021).Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. N Engl J Med 2021; 384:1529-1541
6. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 3.2022 – May 7, 2022. Accessed June 23, 2022. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

THANKS