Breast Cancer Aotearoa Coalition Inc

Pembrolizumab in Early and Advanced Triple-Negative Breast Cancer

November 2022

Pembrolizumab in Early and Advanced Triple-Negative Breast Cancer (TNBC)

Background and Overall Summary

- A report by the New Zealand Breast Cancer Foundation in 2018 found that median survival after a diagnosis of metastatic/advanced breast cancer in New Zealand is 16 months, considerably worse than overseas. Survival varies greatly by subtype, from 27.3 months for Luminal A patients down to 6.6 months for triple-negative breast cancer (TNBC). Five-year survival after metastatic diagnosis is only 5% in Māori populations, compared to 15% in non-Māori populations (Breast Cancer Foundation New Zealand 2018).
- Triple-negative breast cancer is an aggressive breast cancer subtype that lacks expression of oestrogen and progesterone receptors and amplification or overexpression of human epidermal growth factor receptor 2 (HER2). The absence of these receptors renders endocrine and HER2-targeted therapies ineffective, leaving cytotoxic chemotherapy as the standard treatment option. Chemotherapy results in suboptimal antitumor response rates and short overall survival and response durations. The proportion of TNBC in the New Zealand Breast Cancer Register is 9.7%. Survival for triple-negative breast cancer at 5 years and 10 years is significantly worse than for other breast cancer subtypes: overall 10-year survival for all subtypes is 86%, but for TNBC 10-year survival is 79% (Breast Cancer Foundation New Zealand 2022). There is a pressing need for better treatment options for New Zealand women with triple-negative breast cancer (TNBC), with both early and advanced disease.
- Breast Cancer Aotearoa Coalition proposes that pembrolizumab be listed on the Pharmaceutical Schedule, consistent with both clinical evidence, MEDSAFE approval (MSD 2022), and international and New Zealand guidelines' recommendations for
    - High-risk early-stage triple-negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery.
    - In combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumours express PD-L1 CPS ≥10.
- Clinical evidence for pembrolizumab demonstrates the efficacy and safety of this agent in selected populations with TNBC.
- For patients with early TNBC, the KEYNOTE-522 Phase III clinical trial of neoadjuvant and adjuvant pembrolizumab and chemotherapy combined versus chemotherapy alone showed significant improvement in pathological complete response (64.5% versus 51.2%; treatment difference 13.6%, 95%CI 5.4-21.8, $p<0.001$) and improved event free survival (84.5% versus

76.8% at 36 months, HR 0.63, 95%CI 0.48-0.82, p<0.001) irrespective of PD-L1 status (Schmid, Cortes et al. 2020, Schmid, Cortes et al. 2022).

- For patients with advanced TNBC, the KEYNOTE-355 Phase III clinical trial showed that treatment should be targeted to those with PD-L1 CPS of 10 or more. Pembrolizumab plus chemotherapy showed significant improvement in progression free survival versus chemotherapy alone (9.7 months versus 5.6 months, HR 0.65, 95% CI 0.49-0.86, p=0.0012). Pembrolizumab plus chemotherapy showed significant improvement in overall survival in the pre-defined subgroup with PD-L1 CPS of 10 or more (23 months versus 16.1 months (HR 0.73 95%CI 0.55-0.95, p=0.0185) (Cortes, Cescon et al. 2020, Cortes, Rugo et al. 2022).
- Results from the open label multicentre KEYNOTE 119 clinical trial showed that improved overall survival was not demonstrated with pembrolizumab monotherapy versus chemotherapy in patients with advanced TNBC (OS 12.7 months for pembrolizumab versus 11.6 months for chemotherapy, (HR 0.78, 95%CI 0.57-1.06, p=0.057) in patients with PD-L1 CPS ≥10 with advanced TNBC (Winer, Lipatov et al. 2021).
- Adverse effects of treatment are increased with the addition of pembrolizumab to chemotherapy, with a higher incidence of immune-mediated adverse events. Most events were managed with treatment interruption and supportive care. This treatment has now been widely used for other indications, so the adverse event profile is well characterised.
- In summary, the evidence is supportive of the use of pembrolizumab in two settings. Firstly, for high-risk patients with early TNBC, in combination with chemotherapy,. Secondly, pembrolizumab can be used to treat patients with advanced TNBC with PD-L1 CPS score of >10.
- The availability of pembrolizumab on the Pharmaceutical Schedule will help address New Zealand's suboptimal outcomes for treatment of breast cancer. It is already recommended for use in New Zealand in the recently published Advanced Breast Cancer Treatment Guidelines, with 100% consensus from the voting panel. The voting panel was made up of New Zealand breast cancer experts including medical oncologists, radiation oncologists, breast surgeons, ABC clinical nurse specialists, GP/breast physician, patient advocates (Breast Cancer Special Interest Group (Breast SIG) New Zealand 2022). Therefore, this treatment has already received the endorsement for use in New Zealand. It is approved by MEDSAFE and available to those who can fund their own treatment directly or via private health insurance.

Summary of Published Clinical Data for pembrolizumab (KEYTRUDA®) in Early and Advanced Triple-Negative Breast Cancer (TNBC)

KEYTRUDA (pembrolizumab) is approved by MEDSAFE in New Zealand for use in two breast cancer indications:

- High-risk early-stage triple-negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery.
- In combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumours express PD-L1 (CPS ≥10).

We have undertaken searches of the literature to locate clinical trials of pembrolizumab in the approved indications. The following published clinical trials were located in that search. The Phase I and II clinical trials of pembrolizumab provide supportive evidence in TNBC but are not included in this summary. The published Phase III clinical trials in TNBC are as follows:

KEYNOTE 522

Pembrolizumab for Early Triple-Negative Breast Cancer
P. Schmid, J. Cortes, L. Pusztai, H. McArthur, S. Kümmel, J. Bergh, et al.
N Engl J Med 2020 Vol. 382 Issue 9 Pages 810-821
(First journal publication)

Event-free Survival with Pembrolizumab in Early Triple-Negative Breast Cancer
P. Schmid, J. Cortes, R. Dent, L. Pusztai, H. McArthur, S. Kümmel, et al.
N Engl J Med 2022 Vol. 386 Issue 6 Pages 556-567
(Most recent publication)

KEYNOTE 355

Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial
J. Cortes, D. W. Cescon, H. S. Rugo, Z. Nowecki, S. A. Im, M. M. Yusof, et al.
Lancet 2020 Vol. 396 Issue 10265 Pages 1817-1828
(First journal publication)

Pembrolizumab plus Chemotherapy in Advanced Triple-Negative Breast Cancer
J. Cortes, H. S. Rugo, D. W. Cescon, S. A. Im, M. M. Yusof, C. Gallardo, et al.
N Engl J Med 2022 Vol. 387 Issue 3 Pages 217-226
(Most recent publication)

KEYNOTE 119

Pembrolizumab versus investigator-choice chemotherapy for metastatic triple-negative breast cancer (KEYNOTE-119): a randomised, open-label, phase 3 trial
E. P. Winer, O. Lipatov, S. A. Im, A. Goncalves, E. Muñoz-Couselo, K. S. Lee, et al.
Lancet Oncol 2021 Vol. 22 Issue 4 Pages 499-511

KEYNOTE 522 Summary of Findings

Pembrolizumab for Early Triple-Negative Breast Cancer
P. Schmid, J. Cortes, L. Pusztai, H. McArthur, S. Kümmel, J. Bergh, et al.
N Engl J Med 2020 Vol. 382 Issue 9 Pages 810-821
(First journal publication)

Event-free Survival with Pembrolizumab in Early Triple-Negative Breast Cancer
P. Schmid, J. Cortes, R. Dent, L. Pusztai, H. McArthur, S. Kümmel, et al.
N Engl J Med 2022 Vol. 386 Issue 6 Pages 556-567
(Most recent publication)

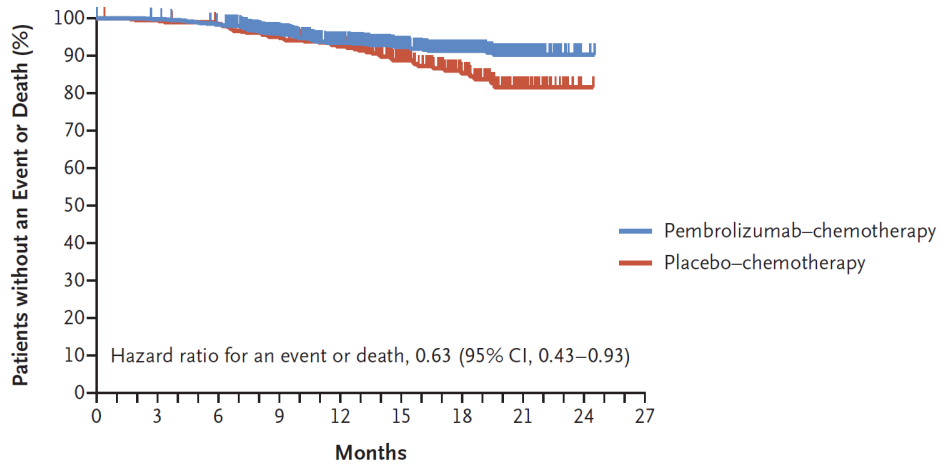
This trial investigated whether the addition of pembrolizumab to neoadjuvant chemotherapy would significantly increase the percentage of patients with early triple-negative breast cancer (TNBC) who have a pathological complete response (defined as no invasive cancer in the breast and negative nodes) at definitive surgery.

Patients with previously untreated stage II or stage III TNBC were randomly assigned (in a 2:1 ratio) to receive neoadjuvant therapy with four cycles of pembrolizumab (at a dose of 200 mg) every 3 weeks plus paclitaxel and carboplatin (784 patients; the pembrolizumab-chemotherapy group) or placebo every 3 weeks plus paclitaxel and carboplatin (390 patients; the placebo-chemotherapy group); the two groups then received an additional four cycles of pembrolizumab or placebo, and both groups received doxorubicin-cyclophosphamide or epirubicin-cyclophosphamide. After definitive surgery, the patients received adjuvant pembrolizumab or placebo every 3 weeks for up to nine cycles. The primary end points were a pathological complete response at the time of definitive surgery and event-free survival in the intention-to-treat population.

From March 2017 through September 2018, a total of 1174 patients from 181 sites (plus 2 satellite sites) in 21 countries were randomly assigned to the pembrolizumab–chemotherapy group (784 patients) or the placebo–chemotherapy group (390 patients). The baseline demographic and disease characteristics were as expected and were well balanced between the two groups.

At the first interim analysis, among the first 602 patients who underwent randomisation, the percentage of patients with a pathological complete response was 64.8% (95% CI 59.9 to 69.5) in the pembrolizumab-chemotherapy group and 51.2% (95% CI, 44.1 to 58.3) in the placebo-chemotherapy group (estimated treatment difference, 13.6 percentage points; 95% CI, 5.4 to 21.8; $p<0.001$).

At the second interim analysis with a median duration of 15.5 months [range, 2.7 to 25.0]), 1167 patients had received the first neoadjuvant treatment, 1095 patients had received the second neoadjuvant treatment, 1138 patients had undergone known definitive surgery, and 861 patients had received adjuvant treatment. The median duration of treatment exposure was 51.1 weeks (range, 0.1 to 88.4) in the pembrolizumab–chemotherapy group and 54.1 weeks (range, 0.1 to 79.3) in the placebo–chemotherapy group. At this time, 58 of 784 patients (7.4%) in the pembrolizumab-chemotherapy group and 46 of 390 patients (11.8%) in the placebo-chemotherapy group had disease progression that precluded definitive surgery, had local or distant recurrence or a second primary tumour, or died from any cause (HR 0.63; 95% CI, 0.43 to 0.93).



No. at Risk

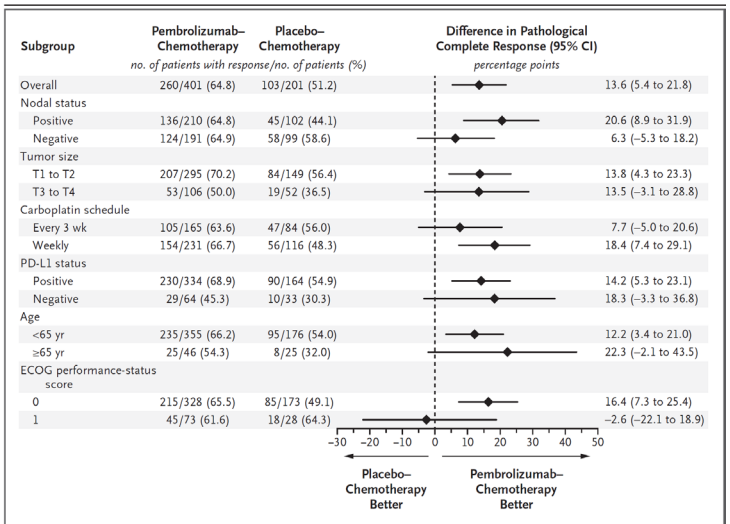
Pembrolizumab–chemotherapy	784	780	765	666	519	376	242	73	2	0
Placebo–chemotherapy	390	386	380	337	264	186	116	35	1	0

Figure 2. Kaplan–Meier Estimates of Event-free Survival, According to Trial Group in the Intention-to-Treat Population.

Tick marks indicate data censored at the last time the patient was known to be alive and without an event (disease progression that precludes definitive surgery; local or distant recurrence or a second primary tumor; or death from any cause). The hazard ratio and confidence interval were analyzed with the use of a Cox regression model with treatment as a covariate stratified according to the randomization stratification factors of nodal status (positive or negative), tumor size (T1 to T2 or T3 to T4), and frequency of carboplatin administration (once weekly or once every 3 weeks).

Source: (Schmid, Cortes et al. 2020)

The benefits of pembrolizumab–chemotherapy with respect to pathological complete response were generally consistent across subgroups, including PD-L1–expression subgroups.



Subgroup	Pembrolizumab–Chemotherapy	Placebo–Chemotherapy	Difference in Pathological Complete Response (95% CI)
	no. of patients with response/no. of patients (%)		*percentage points*
Overall	260/401 (64.8)	103/201 (51.2)	13.6 (5.4 to 21.8)
Nodal status			
Positive	136/210 (64.8)	45/102 (44.1)	20.6 (8.9 to 31.9)
Negative	124/191 (64.9)	58/99 (58.6)	6.3 (–5.3 to 18.2)
Tumor size			
T1 to T2	207/295 (70.2)	84/149 (56.4)	13.8 (4.3 to 23.3)
T3 to T4	53/106 (50.0)	19/52 (36.5)	13.5 (–3.1 to 28.8)
Carboplatin schedule			
Every 3 wk	105/165 (63.6)	47/84 (56.0)	7.7 (–5.0 to 20.6)
Weekly	154/231 (66.7)	56/116 (48.3)	18.4 (7.4 to 29.1)
PD-L1 status			
Positive	230/334 (68.9)	90/164 (54.9)	14.2 (5.3 to 23.1)
Negative	29/64 (45.3)	10/33 (30.3)	18.3 (–3.3 to 36.8)
Age			
<65 yr	235/355 (66.2)	95/176 (54.0)	12.2 (3.4 to 21.0)
≥65 yr	25/46 (54.3)	8/25 (32.0)	22.3 (–2.1 to 43.5)
ECOG performance-status score			
0	215/328 (65.5)	85/173 (49.1)	16.4 (7.3 to 25.4)
1	45/73 (61.6)	18/28 (64.3)	–2.6 (–22.1 to 18.9)

Figure 1. Subgroup Analysis of Difference in Percentages of Patients with a Pathological Complete Response (Stage ypT0/Tis ypN0).

An analysis of pathological complete response in key subgroups is shown. For the overall population and the programmed death ligand 1 (PD-L1) subgroups, the analysis is based on the Miettinen and Nurminen method stratified according to nodal status (positive or negative), tumor size (T1 [diameter >1.0 cm to 2.0 cm] to T2 [diameter >2.0 cm to 5.0 cm] or T3 [diameter >5.0 cm] to T4 [locally advanced disease]), and frequency of carboplatin administration (once weekly or once every 3 weeks). For the other subgroups, the analysis is based on the unstratified Miettinen and Nurminen method. Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.

Source: (Schmid, Cortes et al. 2020)

Across all treatment phases, the incidence of treatment-related adverse events of grade 3 or higher was 78.0% in the pembrolizumab-chemotherapy group and 73.0% in the placebo-chemotherapy group, including death in 0.4% (3 patients) and 0.3% (1 patient), respectively.

The first publication (2020) concluded that, among patients with early triple-negative breast cancer, the percentage with a pathological complete response was significantly higher among those who received pembrolizumab plus neoadjuvant chemotherapy than among those who received placebo plus neoadjuvant chemotherapy.

The subsequent publication (2022) reported primary results regarding event-free survival (a co-primary endpoint) in this trial. Event-free survival was defined as the time from randomisation 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.

The median follow-up at this fourth planned interim analysis (data cut off, March 23, 2021) was 39.1 months. The estimated event-free survival at 36 months was 84.5% (95% confidence interval [CI], 81.7 to 86.9) in the pembrolizumab-chemotherapy group, as compared with 76.8% (95% CI, 72.2 to 80.7) in the placebo-chemotherapy group (hazard ratio for event or death, 0.63; 95% CI, 0.48 to 0.82; P<0.001).

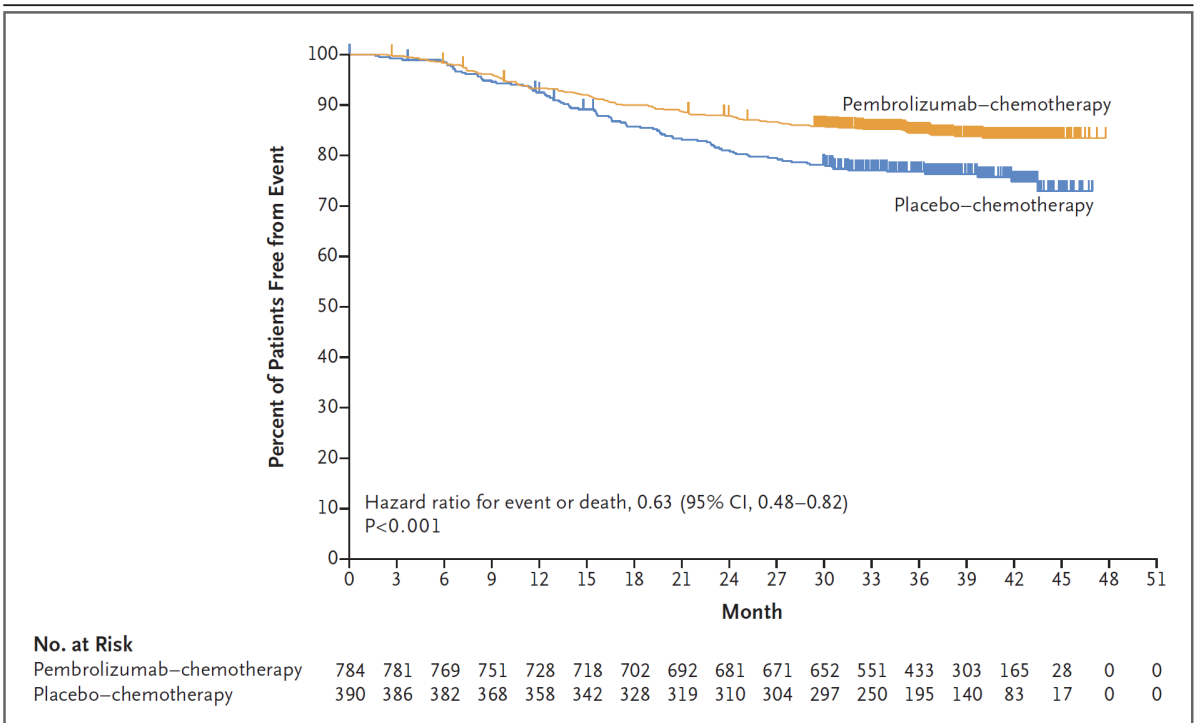


Figure 1. Kaplan–Meier Estimates of Event-free Survival According to Treatment Group (Intention-to-Treat Population).
Tick marks represent data censored at the last time that the patient was known to be alive and without an event (defined as disease progression that precluded definitive surgery, local or distant recurrence, occurrence of a second primary cancer, or death from any cause). 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 according to the randomization stratification factors of nodal status (positive or negative), tumor size (T1 [diameter, >1.0 to 2.0 cm] to T2 [diameter, >2.0 to 5.0 cm] or T3 [diameter, >5.0 cm] to T4 [locally advanced disease]), and frequency of carboplatin administration (once weekly or once every 3 weeks).

Source: (Schmid, Cortes et al. 2022)

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) (Fig. 3). 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.

Adverse events occurred predominantly during the neoadjuvant phase and were consistent with the established safety profiles of pembrolizumab and chemotherapy.

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
Anemia	429 (54.8)	141 (18.0)	215 (55.3)	58 (14.9)
Neutropenia	367 (46.9)	270 (34.5)	185 (47.6)	130 (33.4)
Fatigue	330 (42.1)	28 (3.6)	151 (38.8)	6 (1.5)
Diarrhea	238 (30.4)	20 (2.6)	98 (25.2)	5 (1.3)
Alanine aminotransferase increased	204 (26.1)	43 (5.5)	98 (25.2)	9 (2.3)
Vomiting	200 (25.5)	19 (2.4)	86 (22.1)	6 (1.5)
Asthenia	198 (25.3)	28 (3.6)	102 (26.2)	9 (2.3)
Rash	196 (25.0)	12 (1.5)	66 (17.0)	1 (0.3)
Constipation	188 (24.0)	0	85 (21.9)	0
Neutrophil count decreased	185 (23.6)	146 (18.6)	112 (28.8)	90 (23.1)
Aspartate aminotransferase increased	157 (20.1)	20 (2.6)	63 (16.2)	1 (0.3)
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

* Listed are all the adverse events that occurred during the treatment period or within 30 days after the treatment period (or, for serious adverse events, within 90 days after the treatment period). Events are listed in descending order of frequency in the pembrolizumab–chemotherapy group. The as-treated population included all the patients who had undergone randomization and received at least one trial drug or underwent surgery. The severity of adverse events was graded according to the Common Terminology Criteria for Adverse Events, version 4.0, of the National Cancer Institute.

† Treatment-related adverse events were events that were attributed to a trial treatment by the investigators. Treatment-related adverse events that occurred in at least 20% of the patients or that were considered by the investigators to be medically relevant are reported. Patients may have had more than one event. Grade 5 treatment-related adverse events were sepsis and multiple organ dysfunction syndrome (in one patient) and pneumonitis, pulmonary embolism, and autoimmune encephalitis (in one patient each) in the pembrolizumab–chemotherapy group and septic shock (in one patient) in the placebo–chemotherapy group.

‡ Immune-mediated adverse events were determined according to a list of terms specified by the sponsor, regardless of attribution to any trial treatment by the investigators. Shown are adverse events of interest that occurred in at least 15 patients in either treatment group. Grade 5 immune-mediated adverse events were pulmonary embolism and autoimmune encephalitis (in 1 patient each) in the pembrolizumab–chemotherapy group.

Source: (Schmid, Cortes et al. 2022)

It was concluded that, 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.

Outcomes in early TNBC

The use of surrogate outcomes in early breast cancer, particularly for neoadjuvant therapies has been recently discussed in the literature (Spring, Fell et al. 2020, Gion, Pérez-García et al. 2021, Gyawali, D'Andrea et al. 2021). As outlined by Gion et al. (2021) in the table below, the FDA uses pCR, EFS and DFS for accelerated and traditional approval for preoperative neoadjuvant therapy in early breast cancer. EFS and PFS are acceptable for accelerated and traditional approval. The initial justification for this approach came from the desire to expedite the approval process owing to the shorter time required for assessments based on these end points compared with OS, thus allowing patients with unmet medical needs earlier access to drugs that might be effective (Agostinetto, Gligorov et al. 2022).

Table 1. List of surrogate endpoints in adult patients with breast cancer that may be considered and discussed with FDA for individual development programs of a drug or a biological product under both accelerated and traditional approval pathways.

Patient population	Disease status	Treatment setting	Surrogate endpoint	Type of approval	Drug mechanism of action
Patients with breast cancer	Early stage	Preoperative neoadjuvant therapy	pCR	Accelerated	Agnostic[a]
Patients with breast cancer and neuroblastoma	Early stage	Preoperative neoadjuvant therapy	EFS[b]	Accelerated/ traditional[c]	Agnostic[a]
Patients receiving adjuvant therapy following complete surgical resection of colon cancer, colorectal cancer, melanoma, renal cell cancer, gastrointestinal stromal tumor, breast cancer, and adjuvant therapy for stage III non-small cell lung cancer	Early stage	Postoperative adjuvant therapy	DFS	Accelerated/ traditional[c]	Agnostic[a]
Patients with breast cancer, ovarian cancer, renal cell carcinoma, pancreatic neuroendocrine cancer, colorectal cancer, head and neck cancer, non-small cell lung cancer, melanoma, tuberous sclerosis complex-associated subependymal giant cell astrocytoma and renal angiomyolipoma, Merkel cell carcinoma, unresectable or metastatic cutaneous basal cell carcinoma, urothelial carcinoma, cervical cancer, endometrial cancer, hepatocellular carcinoma, fallopian tube cancer, microsatellite instability-high cancer, gastric cancer, thyroid cancer, astrocytoma, Kaposi's sarcoma, unresectable or metastatic cutaneous squamous cell carcinoma, *NTRK* gene fusion without a known acquired resistance mutation, prostate cancer, esophageal cancer, tumor mutational burden high solid tumors, cholangiocarcinoma, bladder cancer, and neuroblastoma	Unresectable locally advanced or metastatic stage	Therapy in metastatic setting	Durable objective ORR	Accelerated/ traditional[c]	Agnostic[a]
Patients with breast cancer; renal cell carcinoma; pancreatic neuroendocrine tumor; soft tissue sarcoma; ovarian, fallopian tube, or primary peritoneal cancer; prostate cancer; thyroid cancer; colorectal cancer; non-small cell lung cancer; head and neck cancer; tuberous sclerosis complex; Merkel cell carcinoma; basal cell carcinoma; urothelial carcinoma; cervical cancer; endometrial cancer; hepatocellular carcinoma; melanoma; astrocytoma; and gastrointestinal stromal tumors	Unresectable locally advanced or metastatic stage	Therapy for metastatic setting	PFS	Accelerated/ traditional[c]	Agnostic[a]

Recreated from the FDA's adult Surrogate Endpoint Table at https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure.
BLA, Biologic License Application; DFS, disease-free survival; EFS, event-free survival; FDA, US Food and Drug Administration; NDA, New Drug Application; NTRK, neurotrophic tyrosine receptor kinase; ORR, overall response rate; pCR, pathological complete response; PFS, progression-free survival.
[a]Since disparate mechanisms of action could be involved, mechanism agnostic refers to the absence of a causal pathway which is directly related to a surrogate endpoint.
[b]Despite not yet used to support an approved NDA or BLA, this surrogate endpoint could be appropriate for use as a primary efficacy clinical trial endpoint for a drug or biologic approval.
[c]Endpoints based on changes in tumor burden may be used for both traditional and accelerated approval depending on context of use, including factors such as disease, effect size, effect duration, residual uncertainty, and benefits of other available therapy.

A large recent analysis by Spring et al. (2020) evaluated the relationship between pCR, EFS and OS in patients who received neoadjuvant therapy (NAT). This study included patient level data from 27,905 patients who received NAT for breast cancer. Patients with a pCR after NAT had significantly better EFS (HR = 0.31; 95% PI, 0.24-0.39), particularly for triple-negative (HR = 0.18; 95% PI, 0.10-0.31) and HER2(+) (HR = 0.32; 95% PI, 0.21-0.47) disease. Similarly, pCR after NAT was also associated with improved survival (HR = 0.22; 95% PI, 0.15-0.30). The relationships for various breast cancer subtypes are shown in the graphics below.

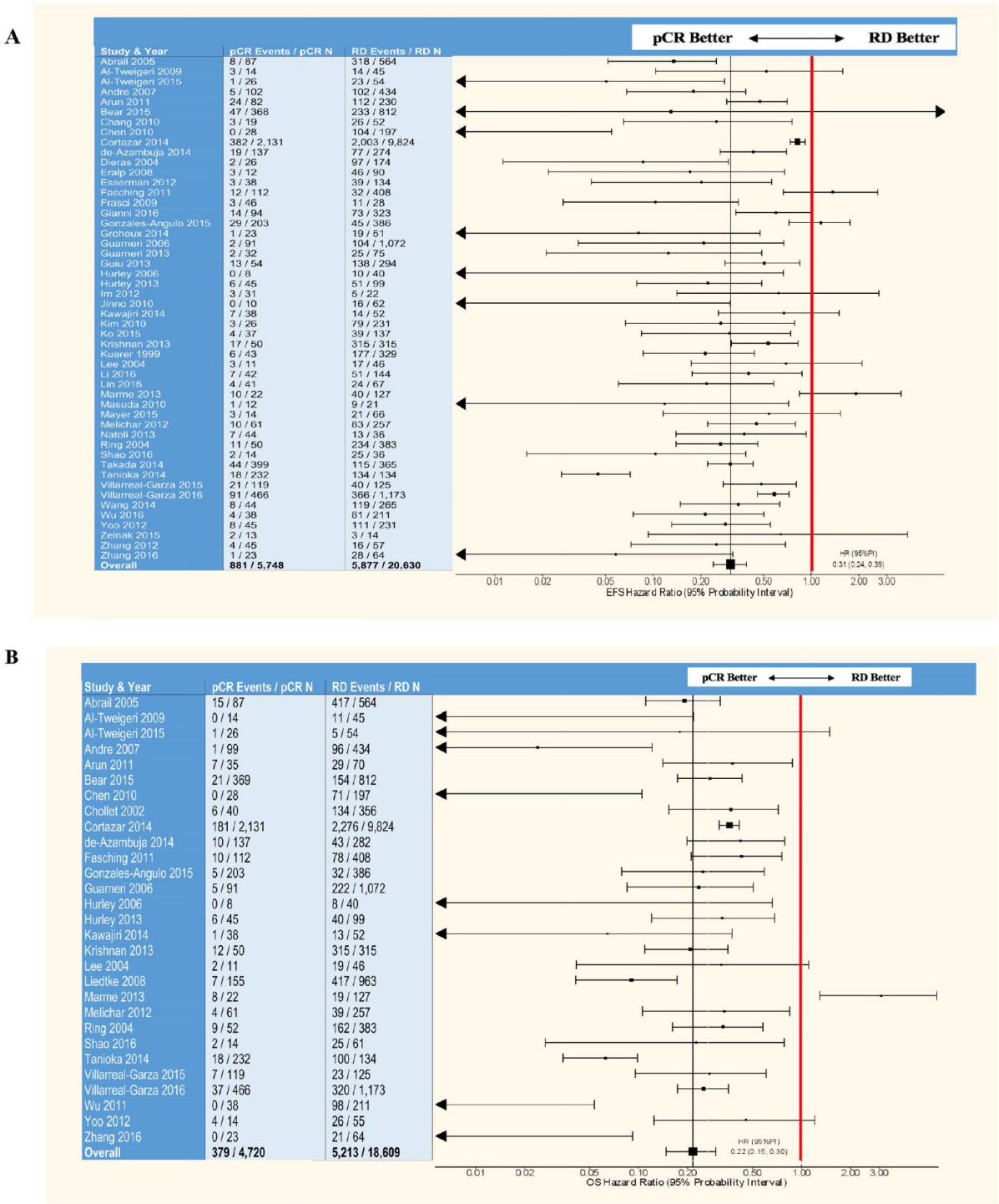


Figure 2. A-B. Association of pCR with (A) event free survival and (B) overall survival

Source:(Spring, Fell et al. 2020)

Another recent meta-analysis investigated the relationship between pCR and EFS and pCR and OS in neoadjuvant treatment of breast cancer. It included 25 publications involving 8767 patients. The EFS of patients achieved pCR after NAT improved obviously (HR = 0:27; 95% CI, 0.24-0.31), especially in triple negative (HR = 0:17; 95% CI, 0.12-0.24) and HER2 positive (HR = 0:24; 95% CI, 0.20-0.30) breast cancer patients. As such, pCR after NAT was implicated in significantly increased OS (HR = 0:32; 95% CI, 0.27–0.37). The Forest plot for the relationship between pCR and OS is shown below.

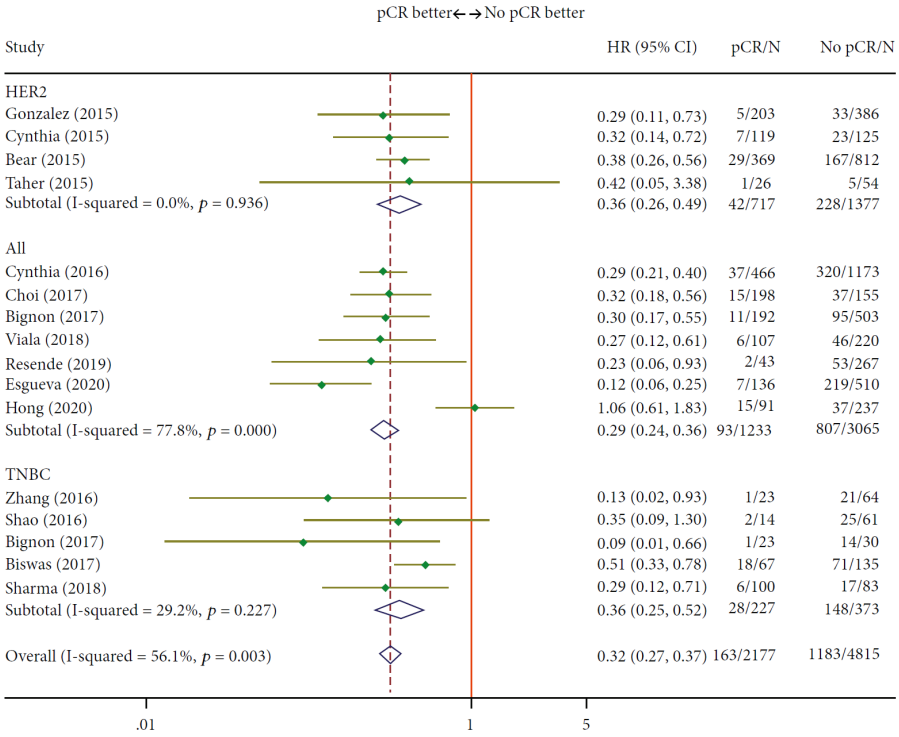


FIGURE 3: Forest plot of the summarized results regarding OS.

Source: (Liu, Lv et al. 2021)

Gyawali et al. (2021) performed a correlation analysis in which data on EFS and OS, including the hazard ratio (HR) and 95% confidence intervals (CI), were extracted from each study and the association between the trial-level EFS HR and the trial-level OS HR was estimated using a linear mixed-effects model on the log scale. Findings Of the 7 RCTs (n=2211) included in the analysis, 5 included patients with HER2 positive tumour type. The estimated linear association between log HR EFS and log HR OS indicated a positive slope ($\beta = 0.58$ [95% CI: −0.32–1.48]) and the coefficient of determination confirmed a moderate trial-level association between log HRs for OS and EFS (R^2 0.76 [95% CI 0.34–1.00], but with wide confidence intervals (Gyawali, D'Andrea et al. 2021).

An important issue is what patients with early breast cancer value in terms of outcomes, particularly in the neoadjuvant and/or adjuvant treatment setting. A German study directly addressed this issue with a quantitative survey of patients who had undergone a neoadjuvant therapy in the form of chemotherapy and, in HER2-positive cases, as a targeted antibody therapy against HER2 for the primary diagnosis of early breast cancer 12–36 months prior to the interview. With the help of analytic hierarchy process (AHP) methods, patient preferences about the treatment targets of neoadjuvant therapy were assessed quantitatively. Forty-one patients participated in the quantitative survey, of these 15 (36.6 %) had experienced HER2-positive disease. The achievement of pCR was the most important therapeutic target for the patients, even before disease-free survival, overall survival and the option for breast-preserving operation. Avoidance of side effects was considered to be the least important. In a comparison of the side effects the patients judged fatigue to be most important before nausea and loss of hair. For the patients the achievement of a pathological complete remission is considered to be an independent, relevant and highly desired target of neoadjuvant therapy (Thill, Pisa et al. 2016).

KEYNOTE 355 Summary of Findings

Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial
J. Cortes, D. W. Cescon, H. S. Rugo, Z. Nowecki, S. A. Im, M. M. Yusof, et al.
Lancet 2020 Vol. 396 Issue 10265 Pages 1817-1828
(First journal publication)

Pembrolizumab plus Chemotherapy in Advanced Triple-Negative Breast Cancer
J. Cortes, H. S. Rugo, D. W. Cescon, S. A. Im, M. M. Yusof, C. Gallardo, et al.
N Engl J Med 2022 Vol. 387 Issue 3 Pages 217-226
(Most recent publication)

This Phase III clinical trial aimed to examine whether the addition of pembrolizumab would enhance the antitumour activity of chemotherapy in patients with advanced triple-negative breast cancer. This randomised, placebo-controlled, double-blind, phase 3 trial, was conducted at 209 sites in 29 countries. Patients with untreated locally recurrent inoperable or metastatic triple-negative breast cancer were randomly assigned (2:1) using a block method (block size of 6) and an interactive voice-response system with integrated web-response to pembrolizumab (200 mg) every 3 weeks plus chemotherapy (nab-paclitaxel; paclitaxel; or gemcitabine plus carboplatin) or placebo plus chemotherapy. Randomisation was stratified by type of on-study chemotherapy (taxane or gemcitabine– carboplatin), PD-L1 expression at baseline (combined positive score [CPS] ≥1 or <1), and previous treatment with the same class of chemotherapy in the neoadjuvant or adjuvant setting (yes or no). Eligibility criteria included age at least 18 years, centrally confirmed triple-negative breast cancer; at least one measurable lesion; provision of a newly obtained tumour sample for determination of TNBC status and PD-L1 status by immunohistochemistry at a central laboratory; an ECOG performance status score 0 or 1; and adequate organ function. The sponsor, investigators, other study site staff (except for the unmasked pharmacist), and patients were masked to pembrolizumab versus saline placebo administration. In addition, the sponsor, the investigators, other study site staff, and patients were masked to patient-level tumour PD-L1 biomarker results. Dual primary efficacy endpoints were progression-free survival and overall survival assessed in the PD-L1 CPS of 10 or more, CPS of 1 or more, and intention-to-treat populations. The definitive assessment of progression-free survival was done at this interim analysis; follow-up to assess overall survival continued. For progression-free survival, a hierarchical testing strategy was used, such that testing was done first in patients with CPS of 10 or more (prespecified statistical criterion was α=0·00411 at this interim analysis), then in patients with CPS of 1 or more (α=0·00111 at this interim analysis, with partial alpha from progression-free survival in patients with CPS of 10 or more passed over), and finally in the intention-to-treat population (α=0·00111 at this interim analysis).

Between Jan 9, 2017, and June 12, 2018, of 1372 patients screened, 847 were randomly assigned to treatment, with 566 patients in the pembrolizumab–chemotherapy group and 281 patients in the placebo–chemotherapy group. At the second interim analysis, median follow-up was 25·9 months (IQR 22·8−29·9) in the pembrolizumab–chemotherapy group and 26·3 months (22·7−29·7) in the placebo–chemotherapy group.

Among patients with CPS of 10 or more, median progression-free survival was 9·7 months with pembrolizumab–chemotherapy and 5·6 months with placebo–chemotherapy (HR for progression or death, 0·65, 95% CI 0·49–0·86; one-sided p=0·0012 [primary objective met]). Median progression-free survival was 7·6 and 5·6 months (HR, 0·74, 0·61–0·90; one-sided p=0·0014 [not significant]) among

patients with CPS of 1 or more and 7·5 and 5·6 months (HR, 0·82, 0·69–0·97 [not tested]) among the intention-to-treat population. The pembrolizumab treatment effect increased with PD-L1 enrichment.

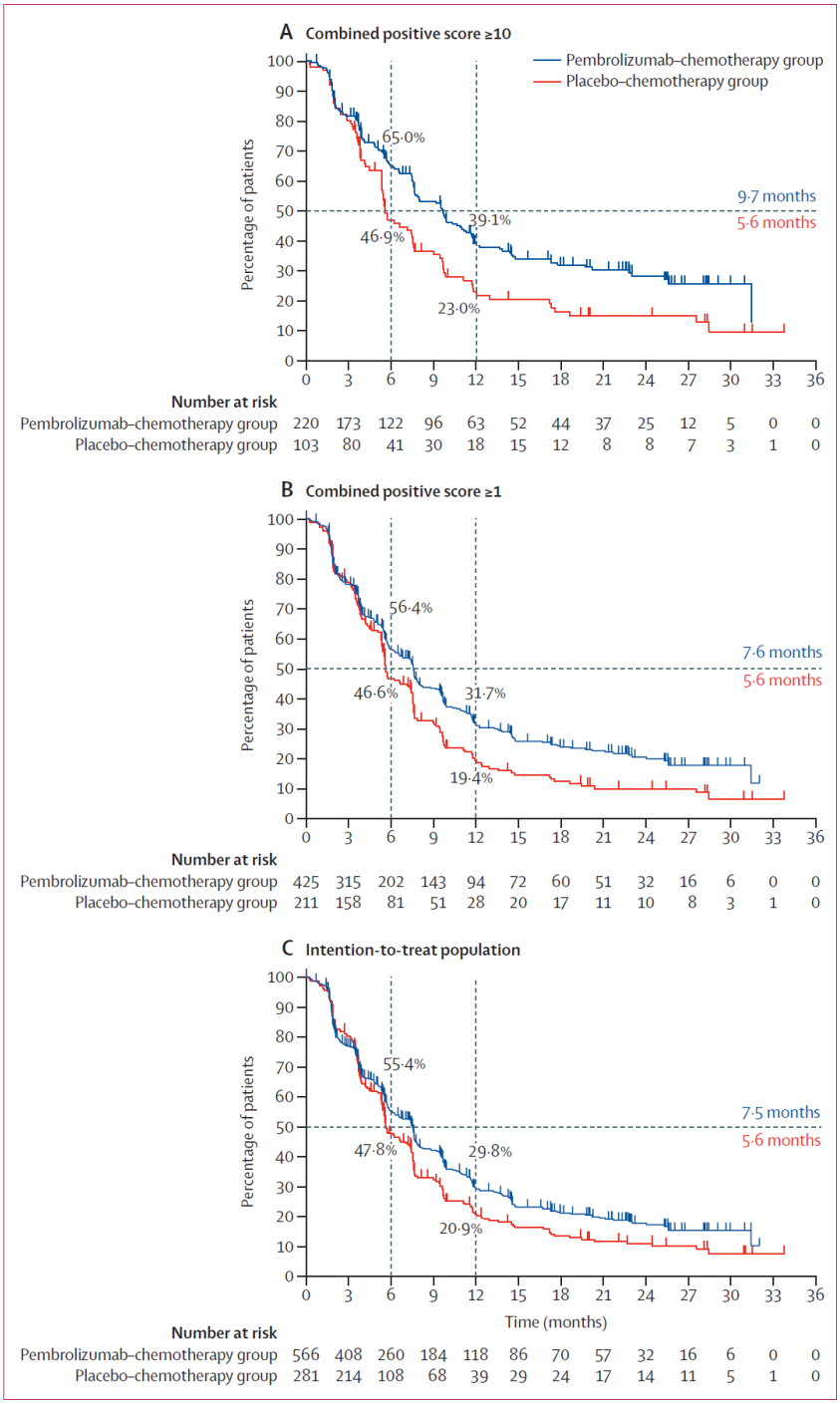


Figure 2: **Kaplan-Meier estimates of progression-free survival. (A) Patients with PD-L1-positive combined positive score ≥10 tumours. (B) Patients with PD-L1-positive CPS ≥1 tumours. (C) The intention-to-treat population**

Tick marks indicate censoring of the data at the time of the last imaging assessment.

Source: (Cortes, Cescon et al. 2020)

Grade 3–5 treatment-related adverse event rates were 68% in the pembrolizumab–chemotherapy group and 67% in the placebo–chemotherapy group, including death in <1% in the pembrolizumab–chemotherapy group and 0% in the placebo–chemotherapy group.

	Pembrolizumab–chemotherapy group (n=562)		Placebo–chemotherapy group (n=281)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any adverse event*	554 (99%)	438 (78%)	276 (98%)	207 (74%)
Treatment-related adverse event†				
Total	541 (96%)	383 (68%)	267 (95%)	188 (67%)
Anaemia	275 (49%)	92 (16%)	129 (46%)	41 (15%)
Neutropenia	231 (41%)	167 (30%)	107 (38%)	84 (30%)
Nausea	221 (39%)	9 (2%)	115 (41%)	4 (1%)
Alopecia	186 (33%)	5 (1%)	94 (33%)	3 (1%)
Fatigue	160 (28%)	16 (3%)	83 (30%)	7 (2%)
Neutrophil count decreased	125 (22%)	98 (17%)	74 (26%)	57 (20%)
Alanine aminotransferase increased	115 (20%)	33 (6%)	46 (16%)	13 (5%)
Immune-mediated adverse event‡				
Total	144 (26%)	29 (5%)	17 (6%)	0
Hypothyroidism	87 (15%)	2 (<1%)	9 (3%)	0
Hyperthyroidism	27 (5%)	1 (<1%)	3 (1%)	0
Pneumonitis	14 (2%)	6 (1%)	0	0
Colitis	10 (2%)	2 (<1%)	4 (1%)	0
Severe skin reactions	10 (2%)	10 (2%)	1 (<1%)	0

Data are n (%). *Listed are all adverse events that occurred during randomly allocated study treatment or within the 30 days thereafter (within 90 days for serious events). The as-treated population included all patients who underwent randomisation and received ≥1 dose of study treatment. Events are listed in descending order of frequency in the pembrolizumab–chemotherapy group. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. †Adverse events that were attributed to study treatment by the investigator. Treatment-related adverse events that occurred in at least 20% of patients are reported. Patients might have had more than one event. ‡Adverse events based on a list of terms specified by the sponsor and considered regardless of treatment attribution by the investigator that occurred in at least ten patients in the pembrolizumab–chemotherapy group are reported.

Table 2: **Adverse events**

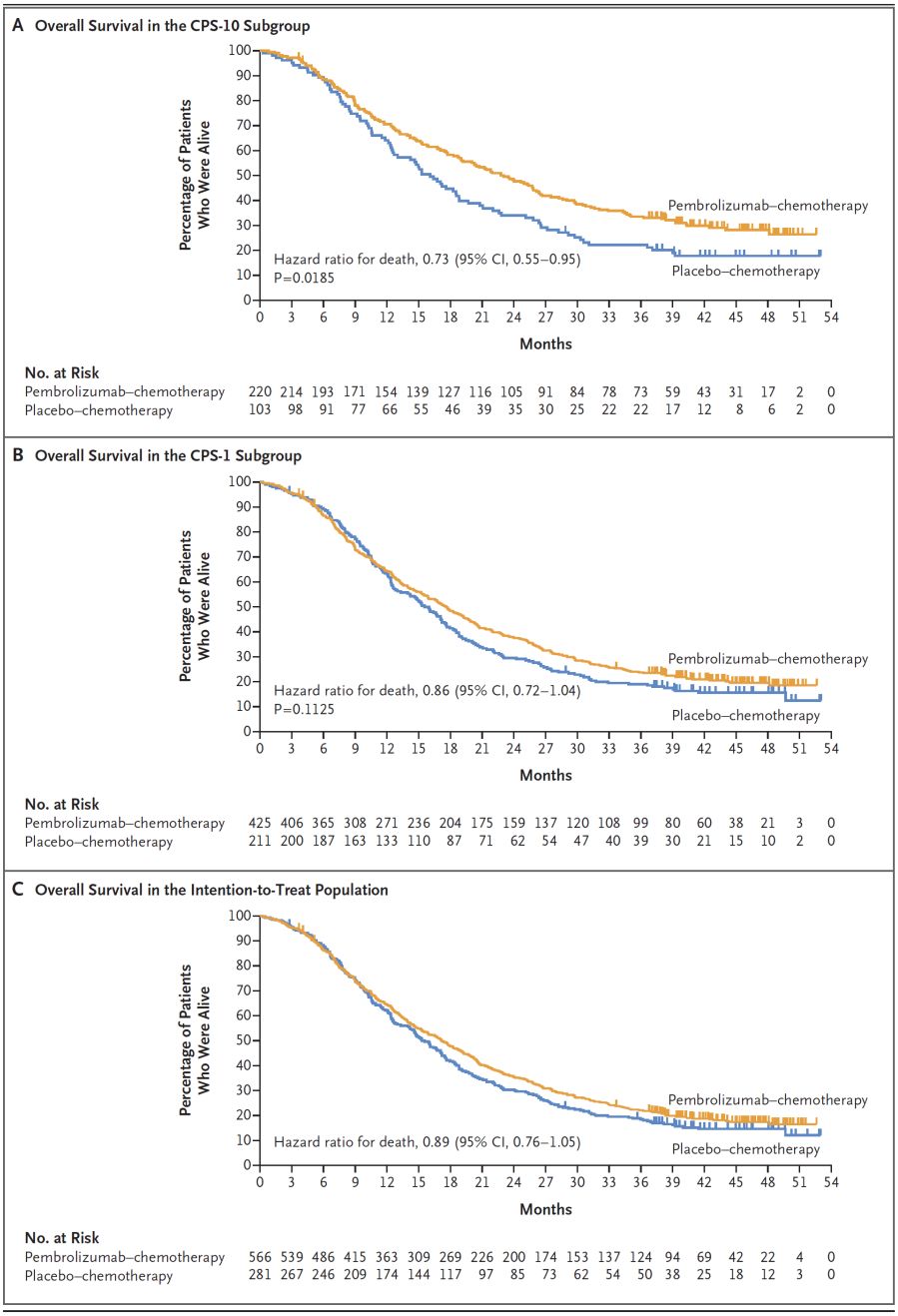
Source: (Cortes, Cescon et al. 2020)

It was concluded that pembrolizumab–chemotherapy showed a significant and clinically meaningful improvement in progression-free survival versus placebo–chemotherapy among patients with metastatic TNBC with PD-L1 CPS of 10 or more. These findings suggest a role for the addition of pembrolizumab to standard chemotherapy for the first-line treatment of metastatic TNBC (Cortes, Cescon et al. 2020).

The subsequent publication (2022) reported on overall survival among patients whose tumours expressed PD-L1 with a CPS of 10 or more (the CPS-10 subgroup), among patients whose tumours expressed PD-L1 with a CPS of 1 or more (the CPS-1 subgroup), and in the intention-to-treat population. Safety was also assessed.

The median follow-up was 44.1 months. In the CPS-10 subgroup, the median overall survival was 23.0 months in the pembrolizumab–chemotherapy group and 16.1 months in the placebo–chemotherapy

group (HR for death, 0.73; 95% confidence interval [CI], 0.55 to 0.95; two-sided p=0.0185 [criterion for significance met]); in the CPS-1 subgroup, the median overall survival was 17.6 and 16.0 months in the two groups, respectively (HR 0.86; 95% CI, 0.72 to 1.04; two-sided p=0.1125 [not significant]); and in the intention-to-treat population, the median overall survival was 17.2 and 15.5 months, respectively (HR 0.89; 95% CI, 0.76 to 1.05 [significance not tested]).



Shown are Kaplan-Meier estimates of overall survival among patients whose tumours expressed programmed death ligand 1 (PD-L1) with a combined positive score (CPS) of 10 or more (CPS-10 subgroup) (Panel A), among patients whose tumours expressed PD-L1 with a CPS of 1 or more (CPS-1 subgroup) (Panel B), and in the intention-to-treat population (Panel C). The CPS is the number of PD-L1-staining cells (tumour cells, lymphocytes, and macrophages) divided by the total number of viable tumour cells, multiplied by 100. Tick marks represent data censored at the last time the patient was known to be alive. The hazard ratios and confidence intervals were analysed on the basis of a Cox regression model with treatment group as a covariate, with stratification according to the randomization stratification factors of the type of chemotherapy received in the trial (a taxane or gemcitabine-carboplatin), tumour PD-L1 expression (CPS ≥1 or CPS <1), and previous treatment with the same class of neoadjuvant or adjuvant chemotherapy as that received in the trial (yes or

no). The prespecified statistical criteria for significance for this final analysis were an alpha level of 0.0227 for the CPS-10 subgroup and an alpha level of 0.013 (if the results for overall survival in the CPS-10 subgroup were not significant) or 0.0344 (if the results for overall survival in the CPS-10 subgroup were significant) for the CPS-1 subgroup.

Source: (Cortes, Rugo et al. 2022)

Adverse events of grade 3, 4, or 5 that were related to the trial regimen occurred in 68.1% of the patients in the pembrolizumab–chemotherapy group and in 66.9% in the placebo–chemotherapy group, including death in 0.4% of the patients in the pembrolizumab–chemotherapy group and in no patients in the placebo–chemotherapy group.

Table 1. Adverse Events.*

Event	Pembrolizumab–Chemotherapy (N = 562)		Placebo–Chemotherapy (N = 281)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
	number of patients (percent)			
Any adverse event	554 (98.6)	438 (77.9)	276 (98.2)	207 (73.7)
Adverse events that were attributed to the trial regimen†	541 (96.3)	383 (68.1)	267 (95.0)	188 (66.9)
Anemia	276 (49.1)	93 (16.5)	129 (45.9)	41 (14.6)
Neutropenia	231 (41.1)	167 (29.7)	107 (38.1)	84 (29.9)
Nausea	221 (39.3)	9 (1.6)	116 (41.3)	4 (1.4)
Alopecia	186 (33.1)	5 (0.9)	94 (33.5)	3 (1.1)
Fatigue	161 (28.6)	16 (2.8)	84 (29.9)	7 (2.5)
Neutrophil count decreased	126 (22.4)	98 (17.4)	74 (26.3)	57 (20.3)
Alanine aminotransferase increased	115 (20.5)	34 (6.0)	46 (16.4)	13 (4.6)
Immune-mediated adverse events‡	149 (26.5)	30 (5.3)	18 (6.4)	0
Hypothyroidism	89 (15.8)	2 (0.4)	9 (3.2)	0
Hyperthyroidism	24 (4.3)	1 (0.2)	3 (1.1)	0
Pneumonitis	14 (2.5)	6 (1.1)	0	0
Colitis	10 (1.8)	2 (0.4)	4 (1.4)	0
Severe skin reactions	10 (1.8)	10 (1.8)§	1 (0.4)	0

* Safety was assessed in all patients who had undergone randomization and received at least one dose of pembrolizumab, placebo, or chemotherapy. Listed are adverse events that occurred during the treatment period or within the 30 days thereafter (within 90 days for serious adverse events). Events are listed in descending order of frequency in the pembrolizumab–chemotherapy group. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Patients may have had more than one adverse event.

† Adverse events that were determined by the investigator to be related to the trial regimen and occurred in at least 20% of patients or events that were considered medically relevant are reported.

‡ Immune-mediated adverse events were those included in a list of terms specified by the sponsor and were assessed regardless of attribution to the trial regimen. Events that occurred in at least 10 patients are reported.

§ Severe skin reactions included pruritus (in 1 patient), rash (in 4 patients), and maculopapular rash (in 6 patients).

It was concluded that among patients with advanced TNBC whose tumours expressed PD-L1 with a CPS of 10 or more, the addition of pembrolizumab to chemotherapy resulted in significantly longer overall survival than chemotherapy alone (Cortes, Rugo et al. 2022).

KEYNOTE 119 Summary of findings

Pembrolizumab versus investigator-choice chemotherapy for metastatic triple-negative breast cancer (KEYNOTE-119): a randomised, open-label, phase 3 trial
E. P. Winer, O. Lipatov, S. A. Im, A. Goncalves, E. Muñoz-Couselo, K. S. Lee, et al.
Lancet Oncol 2021 Vol. 22 Issue 4 Pages 499-511

This Phase III study compared pembrolizumab with chemotherapy for second-line or third-line treatment of patients with metastatic triple-negative breast cancer. This was a randomised, open-label, phase 3 trial done at 150 medical centres (academic medical centres, community cancer centres, and community hospitals) in 31 countries. Patients aged 18 years or older, with centrally confirmed metastatic TNBC, ECOG performance status of 0 or 1, who had received one or two previous systemic treatments for metastatic disease, had progression on their most recent therapy, and had previous treatment with an anthracycline or taxane were eligible. Patients were randomly assigned (1:1) using a block method (block size of four) and an interactive voice-response system with integrated web-response to receive intravenous pembrolizumab 200 mg once every 3 weeks for 35 cycles (pembrolizumab group), or to single-drug chemotherapy per investigator's choice of capecitabine, eribulin, gemcitabine, or vinorelbine (60% enrolment cap for each; chemotherapy group). Randomisation was stratified by PD-L1 tumour status (positive [combined positive score (CPS) ≥1] vs negative [CPS <1]) and history of previous neoadjuvant or adjuvant treatment versus de-novo metastatic disease at initial diagnosis.

Primary endpoints were overall survival in participants with a PD-L1 combined positive score (CPS) of 10 or more, those with a CPS of 1 or more, and all participants; superiority of pembrolizumab versus chemotherapy was tested in all participants only if shown in those with a CPS of one or more. The primary endpoint was analysed in the intention-to-treat population; safety was analysed in the all-subjects-as-treated population.

From Nov 25, 2015, to April 11, 2017, 1098 participants were assessed for eligibility and 622 (57%) were randomly assigned to receive either pembrolizumab (312 [50%]) or chemotherapy (310 [50%]). Median study follow-up was 31·4 months (IQR 27·8–34·4) for the pembrolizumab group and 31·5 months (27·8–34·6) for the chemotherapy group. Median overall survival in patients with a PD-L1 CPS of 10 or more was 12·7 months (95% CI 9·9–16·3) for the pembrolizumab group and 11·6 months (8·3–13·7) for the chemotherapy group (hazard ratio [HR] 0·78 [95% CI 0·57–1·06]; log-rank p=0·057). In participants with a CPS of 1 or more, median overall survival was 10·7 months (9·3–12·5) for the pembrolizumab group and 10·2 months (7·9–12·6) for the chemotherapy group (HR 0·86 [95% CI 0·69–1·06]; log-rank p=0·073). In the overall population, median overall survival was 9·9 months (95% CI 8·3–11·4) for the pembrolizumab group and 10·8 months (9·1–12·6) for the chemotherapy group (HR 0·97 [95% CI 0·82–1·15]). The most common grade 3–4 treatment-related adverse events were anaemia (three [1%] patients in the pembrolizumab group vs ten [3%] in the chemotherapy group), decreased white blood cells (one [<1%] vs 14 [5%]), decreased neutrophil count (one [<1%] vs 29 [10%]), and neutropenia (0 vs 39 [13%]). 61 (20%) patients in the pembrolizumab group and 58 (20%) patients in the chemotherapy group had serious adverse events. Three (<1%) of 601 participants had treatment-related adverse events that led to death (one [<1%] in the pembrolizumab group due to circulatory collapse; two [1%] in the chemotherapy group, one [<1%] due to pancytopenia and sepsis and one [<1%] haemothorax).

Pembrolizumab did not significantly improve overall survival in patients with previously treated metastatic triple-negative breast cancer versus chemotherapy (Winer, Lipatov et al. 2021).

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