Gruppo A

Coordinatori: **Catia Angiolini - Alessandra Fabi - Giovanni L. Pappagallo**

QUESITO CLINICO 1:

Nelle pazienti con carcinoma mammario triplo negativo ad alto rischio, non pretrattate, pembrolizumab in associazione a chemioterapia in fase neoadiuvante e quindi monoterapia in fase adiuvante è raccomandabile rispetto alla sola chemioterapia adiuvante?

Sintesi delle evidenze e problematiche emerse (dal lavoro di gruppo)
Laura Merlini

Quale impatto nella pratica clinica?
Alessandra Fabi

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 April 2022
EMA/257879/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Due to the design of the study, it is not possible to disentangle the benefit of neoadjuvant and adjuvant pembrolizumab, and the treatment has to be considered in its entirety.

The overall benefits of the proposed treatment shown in KEYNOTE-522 is considered to outweigh its risks.

Carcinoma mammario triplo negativo (TNBC)

KEYTRUDA, in associazione a chemioterapia come trattamento neoadiuvante e poi continuato in monoterapia come trattamento adiuvante dopo intervento chirurgico, è indicato nel trattamento di adulti con carcinoma mammario triplo negativo localmente avanzato o in fase iniziale ad alto rischio di recidiva

Pembrolizumab for Early Triple-Negative Breast Cancer

P. Schmid, J. Cortes, L. Pusztai, H. McArthur, S. Kümmel, J. Bergh, C. Denkert, Y.H. Park, R. Hui, N. Harbeck, M. Takahashi, T. Foukakis, P.A. Fasching, F. Cardoso, M. Untch, L. Jia, V. Karantza, J. Zhao, G. Aktan, R. Dent, and J. O'Shaughnessy, for the KEYNOTE-522 Investigators*

N Engl J Med 2020;382:810-21

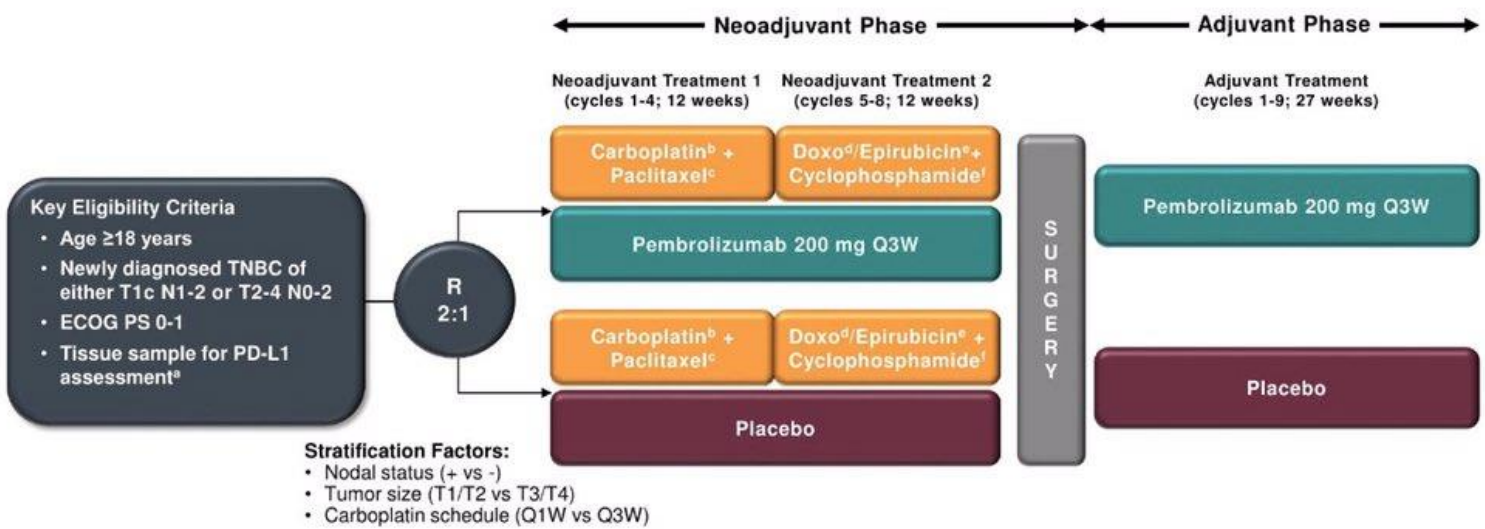
Event-free Survival with Pembrolizumab in Early Triple-Negative Breast Cancer

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

San Antonio Breast Cancer Symposium®, December 10-14, 2019

KEYNOTE-522 Study Design (NCT03036488)



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)

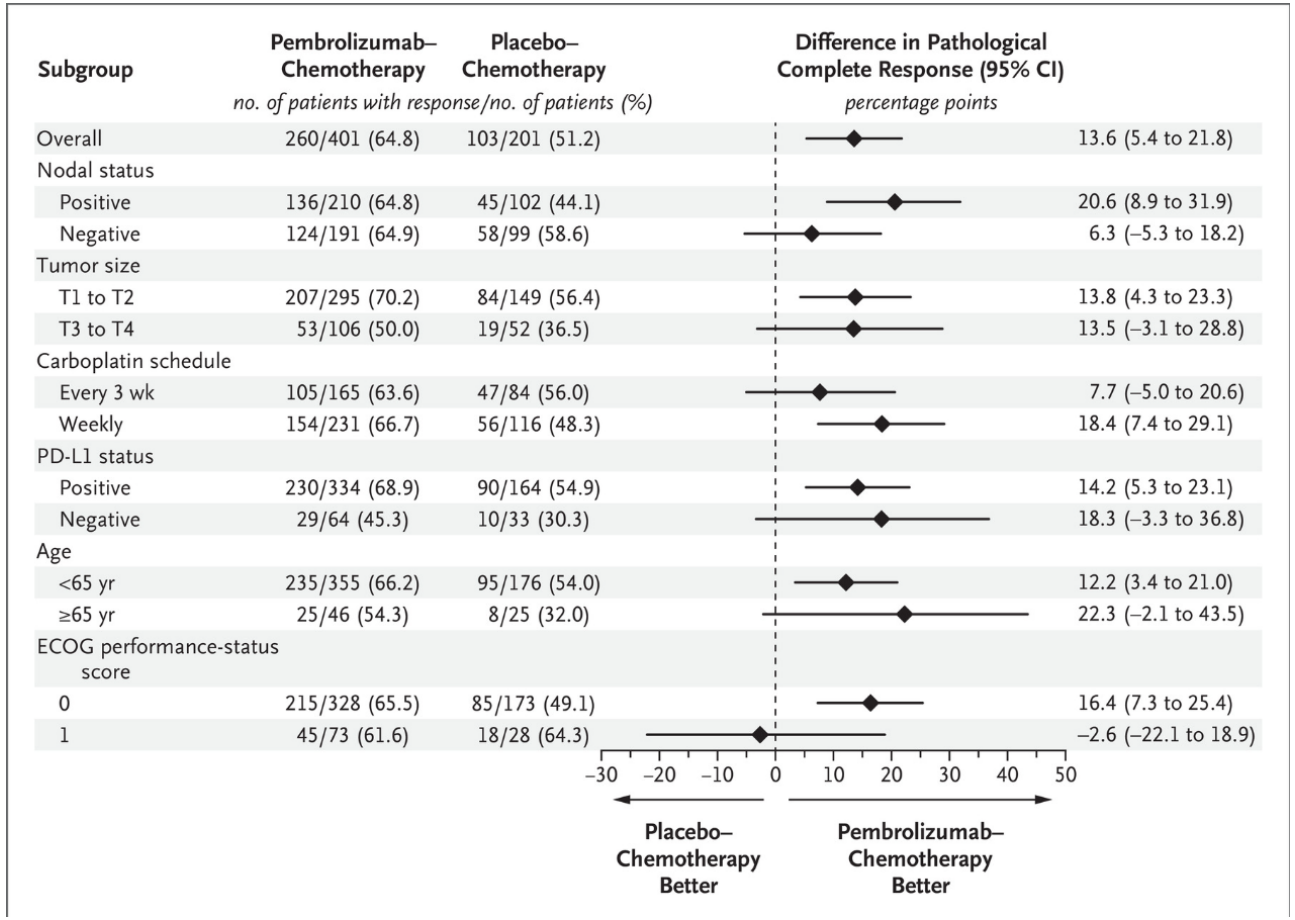
[a]Must consist of at least 2 separate tumor cores from the primary tumor.
[b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 Q1W.
[c]Paclitaxel dose was 80 mg/m² Q1W.
[d]Doxorubicin dose was 60 mg/m² Q3W.
[e]Epirubicin dose was 90 mg/m² Q3W.
[f]Cyclophosphamide dose was 600 mg/m² Q3W.

pCR according to pathological stage

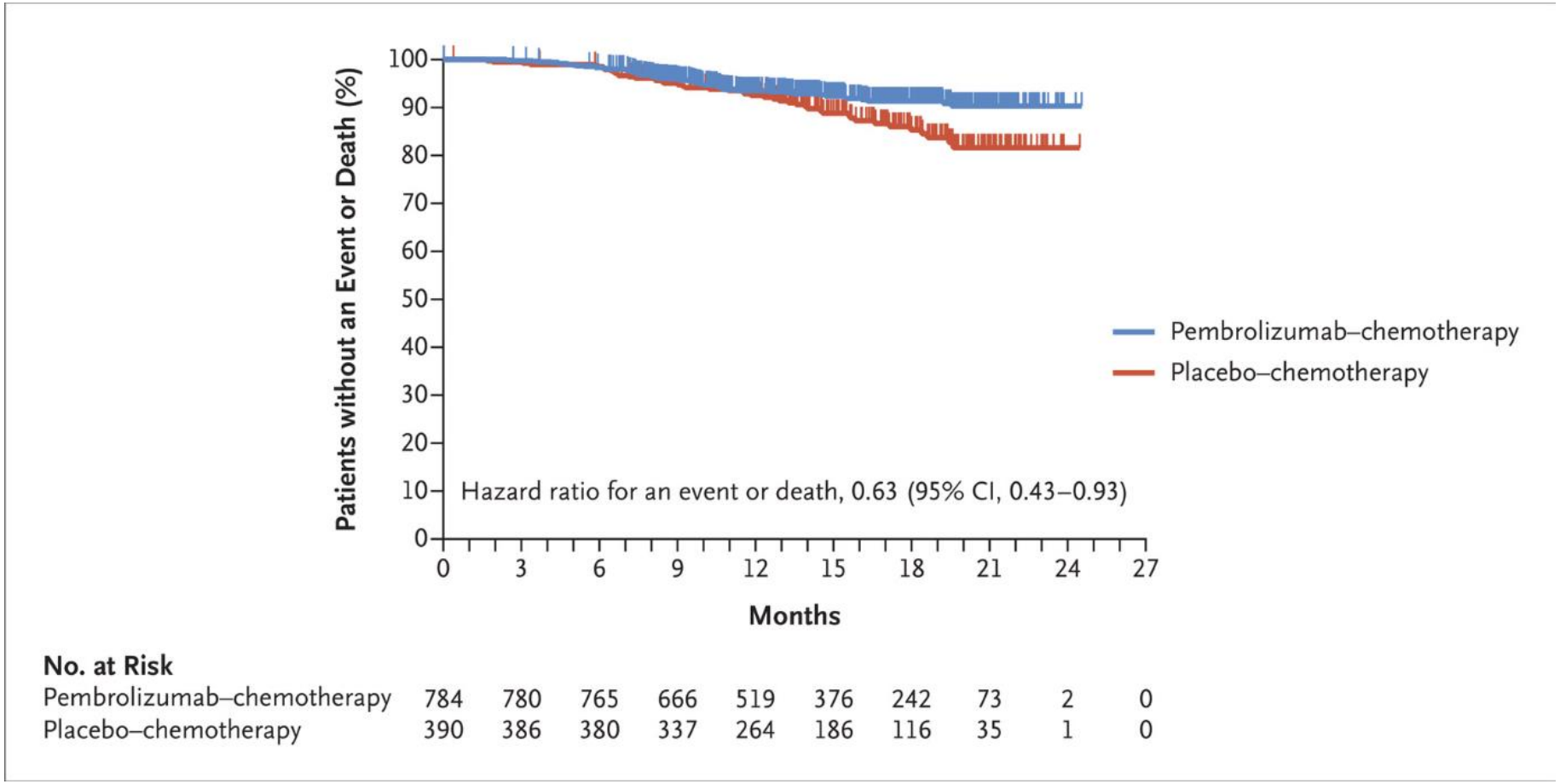
Table 2. Pathological Complete Response, According to Pathological Stage.*

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)	

pCR in key subgroups

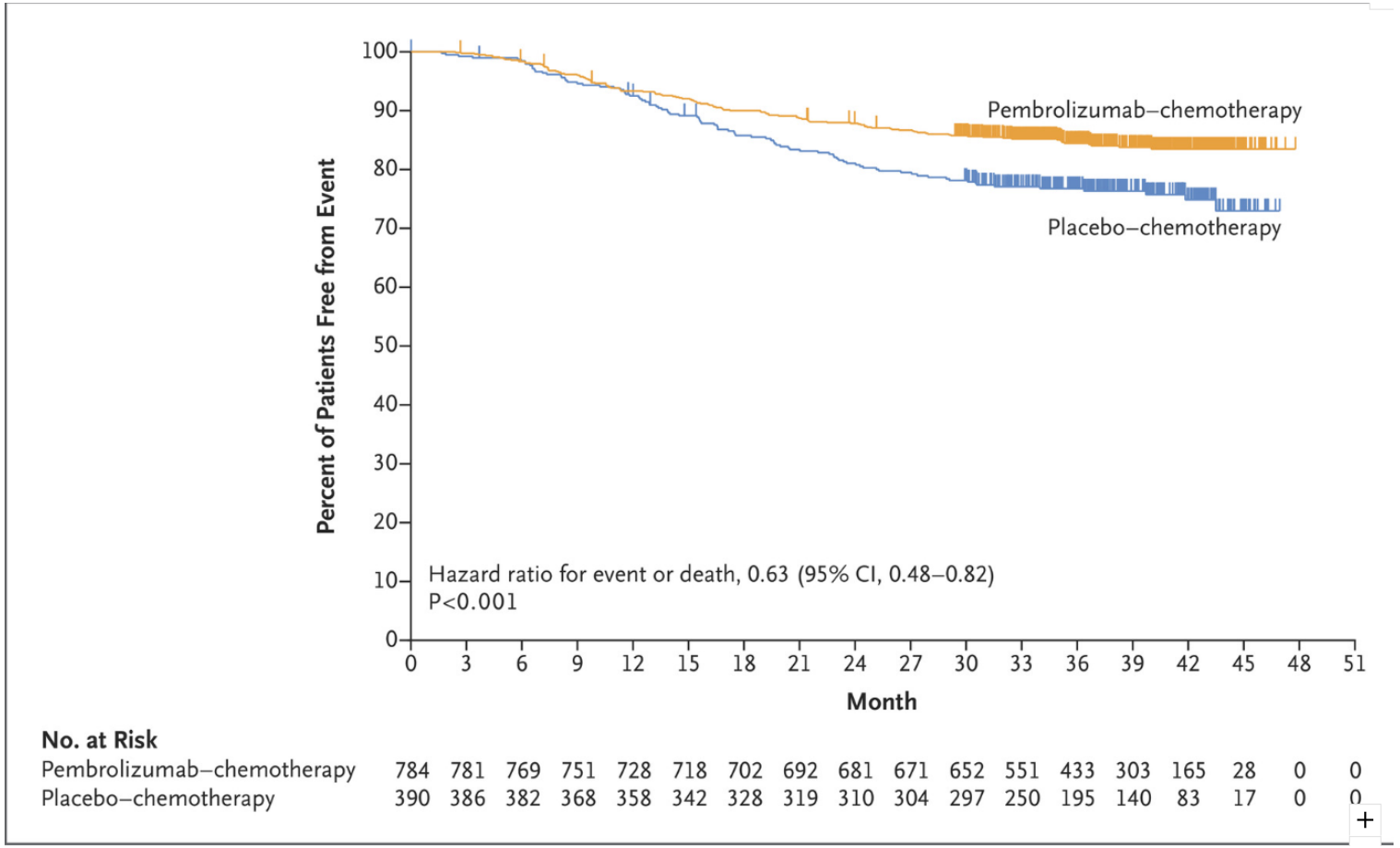


Event free survival



P.Schmid NEJM 2020

KM estimated of EFS (ITT pop)



P.Schmid NEJM 2022

The Evidence-to-Decision framework

GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction

Pablo Alonso-Coello,[1,2] Holger J Schünemann,[2,3] Jenny Moberg,[4] Romina Brignardello-Petersen,[2,5] Elie A Akl,[2,6] Marina Davoli,[7] Shaun Treweek,[8] Reem A Mustafa,[2,9] Gabriel Rada,[10,11,12] Sarah Rosenbaum,[4] Angela Morelli,[4] Gordon H Guyatt,[2,3] Andrew D Oxman[4] the GRADE Working Group

BMJ 2016;353:i2016

GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines

Pablo Alonso-Coello,[1,2] Andrew D Oxman,[3] Jenny Moberg,[3] Romina Brignardello-Petersen,[2,4] Elie A Akl,[2,5] Marina Davoli,[6] Shaun Treweek,[7] Reem A Mustafa,[2,8] Per O Vandvik,[3] Joerg Meerpohl,[9] Gordon H Guyatt,[2,10] Holger J Schünemann,[2,10] the GRADE Working Group

BMJ 2016;353:i2089

SUMMARY POINTS

- Explicit and transparent systems for decision making can help to ensure that all important criteria are considered and that decisions are informed by the best available research evidence
- The purpose of Evidence to Decision (EtD) frameworks is to help people use evidence in a structured and transparent way to inform decisions in the context of clinical recommendations, coverage decisions, and health system or public health recommendations and decisions
- EtD frameworks inform users about the judgments that were made and the evidence supporting those judgments by making the basis for decisions transparent to target audiences

Quality of Evidence	• What is the overall certainty of the evidence of effects?
Balance Benefits/Harms	• Is there important uncertainty about or variability in how much people value the main outcomes? • Do the desirable effects outweigh the undesirable effects?
Resource Use	• How large are the resource requirements? • Are the net benefits worth the incremental cost?
Feasibility	• Is the intervention feasible to implement?
Equity	• What would be the impact on health equity?
Acceptability	• Is the intervention/option acceptable to key stakeholders?

GRADEpro GDT

Should Patisiran vs. [placebo] be used in Hereditary Transthyretin Amyloidosis (mNIS+7 analysis)?

Bottom panel | Explanations

1 **Problem**
Is the problem a priority?

2 **Desirable Effects**
How substantial are the desirable anticipated effects?

3 **Undesirable Effects**
How substantial are the undesirable anticipated effects?

4 **Certainty of evidence**
What is the overall certainty of the evidence of effects?

5 **Values**
Is there important uncertainty about or variability in how much people value the main outcomes?

6 **Balance of effects**
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

7 **Resources required**
How large are the resource requirements (costs)?

8 **Certainty of evidence of required resources**
What is the certainty of the evidence of resource requirements (costs)?

Cost effectiveness

9 Does the cost-effectiveness of the intervention favor the intervention or the comparison?

10 Equity
What would be the impact on health equity?

11 Acceptability
Is the intervention acceptable to key stakeholders?

12 Feasibility
Is the intervention feasible to implement?

Time-to-event Outcomes

Outcomes	With neoadjuvant + adjuvant CT	With Neoadjuvant pembrolizumab-CT + adjuvant pembrolizumab	Difference	Relative effect (95% CI)
Pathological Complete Remission (pCR, ypT0/Tis ypN0) assessed with: cumulative incidence	56 per 100	**63 per 100** (57 to 70)	**7 more per 100** (1 more to 14 more)	**RR 1.13** (1.02 to 1.26)
Event-Free Survival assessed with: Kaplan-Meier product limit estimate follow-up: median 39.1 months	23 per 100	**15 per 100** (12 to 19)	**8 fewer per 100** (11 fewer to 4 fewer)	**HR 0.63** (0.48 to 0.82) [Event-Free Survival]
Distant Progression or Distant Recurrence-Free Survival assessed with: Kaplan-Meier product limit estimate follow-up: median 39.1 months	20 per 100	**13 per 100** (10 to 17)	**7 fewer per 100** (10 fewer to 3 fewer)	**HR 0.61** (0.46 to 0.82) [Distant Progression or Distant Recurrence-Free Survival]
Overall Survival assessed with: Kaplan-Meier product limit estimate follow-up: median 39.1 months	15 per 100	**11 per 100** (8 to 15)	**4 fewer per 100** (7 fewer to 0 fewer)	**HR 0.72** (0.51 to 1.02) [Overall Survival]

PROs (neoadjuvant phase)

Outcomes	With neoadjuvant + adjuvant CT	With Neoadjuvant pembrolizumab-CT + adjuvant pembrolizumab	Difference
Change from Neoadjuvant Baseline in EORTC QLQ-C30 Global Health Status/QoL at Neoadjuvant Week 21 assessed with: LS mean estimate	The mean change from Neoadjuvant Baseline in EORTC QLQ-C30 Global Health Status/QoL at Neoadjuvant Week 21 was **0** points	The mean change from Neoadjuvant Baseline in EORTC QLQ-C30 Global Health Status/QoL at Neoadjuvant Week 21 in the intervention group was 1,04 difference in mean points lower (3,46 lower to 1,38 higher)	difference in mean **1.04 points lower** (3.46 lower to 1.38 higher)
Change from Neoadjuvant Baseline in EORTC QLQ-BR23 Breast Symptoms at Neoadjuvant Week 21 assessed with: LS mean estimate	The mean change from Neoadjuvant Baseline in EORTC QLQ-BR23 Breast Symptoms at Neoadjuvant Week 21 was **0** points	The mean change from Neoadjuvant Baseline in EORTC QLQ-BR23 Breast Symptoms at Neoadjuvant Week 21 in the intervention group was 0,13 difference in mean points lower (1,92 lower to 1,65 higher)	difference in mean **0.13 points lower** (1.92 lower to 1.65 higher)
Analysis of Change from Neoadjuvant Baseline in EQ-5D VAS at Neoadjuvant Week 21 assessed with: LS mean estimate	The mean analysis of Change from Neoadjuvant Baseline in EQ-5D VAS at Neoadjuvant Week 21 was **0**	The mean analysis of Change from Neoadjuvant Baseline in EQ-5D VAS at Neoadjuvant Week 21 in the intervention group was 1,61 difference in mean lower (3,87 lower to 0,64 higher)	difference in mean **1.61 lower** (3.87 lower to 0.64 higher)

PROs (adjuvant phase)

Outcomes	With neoadjuvant + adjuvant CT	With Neoadjuvant pembrolizumab-CT + adjuvant pembrolizumab	Difference
Change from Adjuvant Baseline in EORTC QLQ-C30 Global Health Status/QoL at Adjuvant Week 24 assessed with: LS mean estimate	The mean change from Adjuvant Baseline in EORTC QLQ-C30 Global Health Status/QoL at Adjuvant Week 24 was **0** points	The mean change from Adjuvant Baseline in EORTC QLQ-C30 Global Health Status/QoL at Adjuvant Week 24 in the intervention group was 0,41 difference in mean points lower (2,6 lower to 1,77 higher)	difference in mean **0.41 points lower** (2.6 lower to 1.77 higher)
Analysis of Change from Adjuvant Baseline in EORTC QLQ-BR23 Breast Symptoms at Adjuvant Week 24 assessed with: LS mean estimate	The mean analysis of Change from Adjuvant Baseline in EORTC QLQ-BR23 Breast Symptoms at Adjuvant Week 24 was **0** points	The mean analysis of Change from Adjuvant Baseline in EORTC QLQ-BR23 Breast Symptoms at Adjuvant Week 24 in the intervention group was 0,29 difference in mean points higher (2,05 lower to 2,63 higher)	difference in mean **0.29 points higher** (2.05 lower to 2.63 higher)
Analysis of Change from Adjuvant Baseline in EQ-5D VAS at Adjuvant Week 24 assessed with: LS mean estimate	The mean analysis of Change from Adjuvant Baseline in EQ-5D VAS at Adjuvant Week 24 was **0**	The mean analysis of Change from Adjuvant Baseline in EQ-5D VAS at Adjuvant Week 24 in the intervention group was 0,59 difference in mean lower (2,4 lower to 1,23 higher)	difference in mean **0.59 lower** (2.4 lower to 1.23 higher)

Outcomes of Harm

Outcomes	With neoadjuvant + adjuvant CT	With Neoadjuvant pembrolizumab-CT + adjuvant pembrolizumab	Difference	Relative effect (95% CI)
Grade 3-5 Drug-related Adverse Events assessed with: cumulative incidence	73 per 100	**77 per 100** (72 to 83)	**4 more per 100** (1 fewer to 10 more)	**RR 1.05** (0.98 to 1.13)
Drug-related Adverse Events leading to Discontinuation of Any Drug assessed with: cumulative incidence	14 per 100	**28 per 100** (21 to 36)	**14 more per 100** (7 more to 22 more)	**RR 1.96** (1.50 to 2.57)
Drug-related Adverse Events leading to Death assessed with: cumulative incidence	0 per 100	**1 per 100** (0 to 5)	**0 fewer per 100** (0 fewer to 4 more)	**RR 1.99** (0.22 to 17.72)
Immune-mediated Adverse Events assessed with: cumulative incidence	22 per 100	**43 per 100** (35 to 53)	**22 more per 100** (14 more to 31 more)	**RR 1.99** (1.62 to 2.44)

CRITERIA	SUMMARY OF JUDGEMENTS						IMPORTANCE FOR DECISION
PROBLEM	No	Probably no	Probably yes	**Yes**	Varies	Don't know	**HIGH**
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large	Varies	Don't know	**HIGH**
UNDESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large	Varies	Don't know	**HIGH**
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High	No included studies		**MODERATE**
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			**LOW**
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies / Don't know	**HIGH**
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies / Don't know	**LOW**
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High	No included studies		**LOW**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies / No included studies	**LOW**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies / Don't know	**LOW**
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes	Varies / Don't know		**LOW**
FEASIBILITY	No	Probably no	**Probably yes**	Yes	Varies / Don't know		**MODERATE**