Immunotherapy and breast cancer : implications for clinical practice

Prof. Anthony Gonçalves
Medical Oncology Department
Institut Paoli-Calmettes
Cancer Research Center of Marseille
Aix-Marseille University/CNRS/INSERM
Marseille, France

INSTITUT PAOLI-CALMETTES
unicancer Marseille

CRCM
Centre de Recherche en Cancérologie de Marseille

Aix*Marseille université
Initiative d'excellence

Disclosures

Research funding (for institution): Pfizer, Novartis, Lilly, MSD, Astra Zeneca

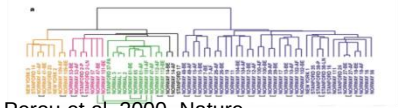
Consultant (paid to hospital) : Novartis, Pfizer, Novartis, MSD, AZ/Daiichy

No personal compensation, no stock from Pharmaceutical industry

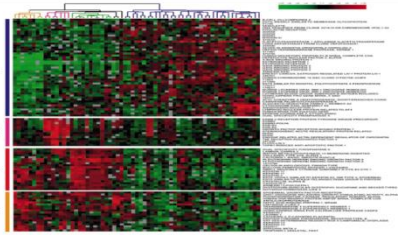
INSTITUT PAOLI-CALMETTES
unicancer Marseille
CRCM
Centre de Recherche en Cancérologie de Marseille
Aix*Marseille université
initiative d'excellence

Introduction

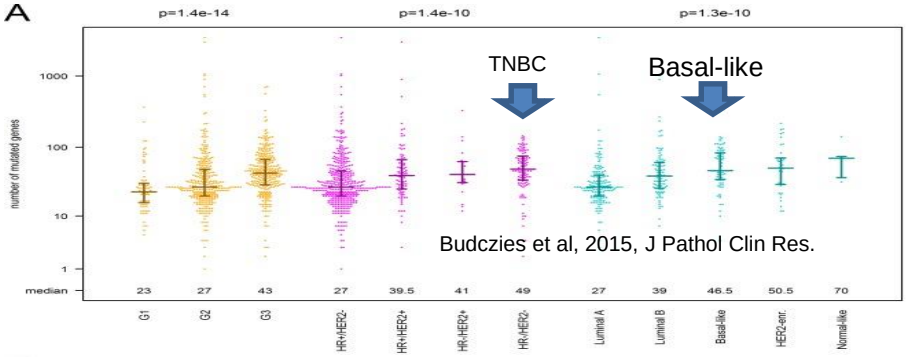
Clinical development of immunotherapy = most advanced in TNBC



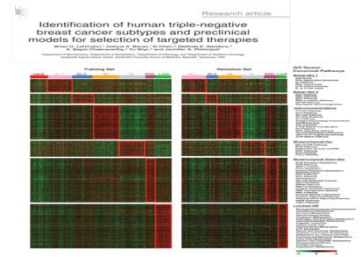
Perou et al, 2000, Nature



Genomic instability
DNA repair alterations
Higher TMB
Higher rate of neoantigens



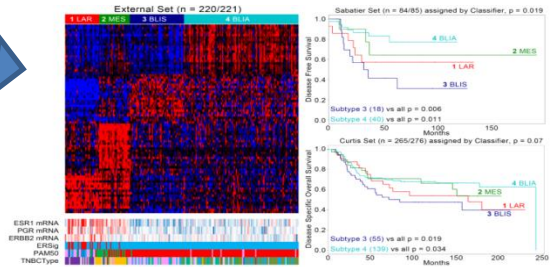
Budczies et al, 2015, J Pathol Clin Res.



Immune activated subtypes
Basal-like 1
Basal-like 2
Immuno-modulatory
Mesenchymal
Mesenchymal stem-like
Luminal androgen receptor

Lheman, 2011, J Clin Invest.

Bustein et al, 2015, Clin Cancer Res

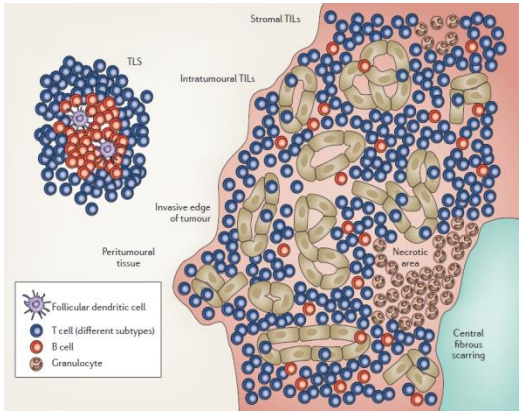


INSTITUT PAOLI-CALMETTES
unicancer Marseille
CRCM
Centre de Recherche en Cancérologie de Marseille
Aix*Marseille université
initiative d'excellence

Introduction

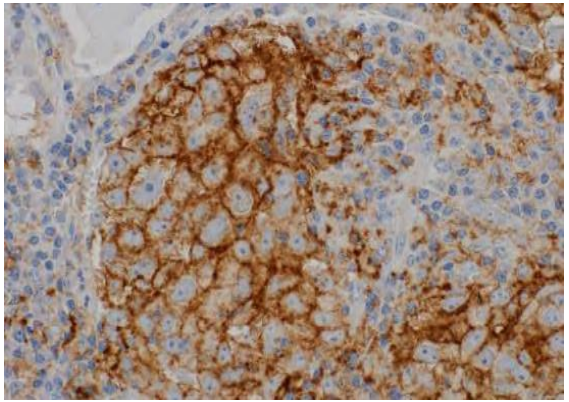
Clinical development of immunotherapy = most advanced in TNBC

Higher TILs…



Savas, 2015, Nat Rev Clin Oncol

Higher PD-L1 expression…



Mittendorf, et al, 2014, Cancer Immunol Res

Associated with
- Higher pCR
- More favorable outcome after conventional treatment

Loi et al, 2013, J Clin Oncol
Sabatier et al, 2015, Oncotarget
Denkert al, 2018, Lancet Oncol

INSTITUT PAOLI-CALMETTES
unicancer Marseille
CRCM
Centre de Recherche en Cancérologie de Marseille
Aix*Marseille université
initiative d'excellence

ADVANCED BREAST CANCER

INSTITUT PAOLI-CALMETTES
unicancer Marseille
CRCM
Centre de Recherche en Cancérologie de Marseille
Aix*Marseille université
initiative d'excellence

Immunotherapy in advanced TNBC

single-agent, non comparative studies

Anti-PD1/PDL1	RR %	% PDL1+	RR% (in PDL1+)
Pembrolizumab			
Keynote 12	18.5	100	18.5[1]
Keynote 086 A – 2d and +line	5.3	61.8	5.7[2]
Keynote 086 B – first line	21.4	100	21.4[2]
Atezolizumab			
All	10	80	12[3]
1st line	24		24
2nd and + line	6		
Avelumab			
1st and + line	5.2	18	22[4]

1- Nanda et al, 2016, J Clin Oncol
PDL1+: stroma or ≥1% tumor cells -22C3

2- Adams et al, 2019, Ann Oncol
CPS ≥1% ratio tumor, Ly, Ma/ tumor cells -22C3

3- Emens et al, 2019, JAMA Oncol
PDL1+ ≥1% IC – SP142

4- Dirix et al, 2017, Breast Cancer Res Treat
PDL1+ ≥10 IC – 73-10

- No new safety signal
- Detectable but moderate anti-tumor activity as single agent
- Higher in First-line, PD-L1 +

INSTITUT PAOLI-CALMETTES unicancer Marseille
CRCM Centre de Recherche en Cancérologie de Marseille
Aix*Marseille université initiative d'excellence

Immunotherapy in advanced TNBC

single-agent, phase III randomized study

Pembrolizumab versus investigator-choice chemotherapy for metastatic triple-negative breast cancer (KEYNOTE-119): a randomised, open-label, phase 3 trial

Eric P Winer, Oleg Lipatov, Seock-Ah Im, Anthony Goncalves, Eva Muñoz-Couselo, Keun Seok Lee, Peter Schmid, Kenji Tamura, Laura Testa, Isabell Witzel, Shoichiro Ohtani, Nicholas Turner, Stefania Zambelli, Nadia Harbeck, Fabrice Andre, Rebecca Dent, Xuan Zhou, Vassiliki Karantza, Jaime Mejia, Javier Cortes, on behalf of the KEYNOTE-119 investigators*

KEYNOTE-119 Study Design

Winer et al, 2021, Lancet Oncol

Patients
- Recurrent mTNBC
- 1 or 2 prior systemic treatments for mTNBC
- Documented disease progression on/after most recent therapy
- Previous treatment with an anthracycline and/or a taxane in the neoadjuvant/adjuvant or metastatic setting

Randomize 1:1 N = 600

- Pembrolizumab 200 mg Q3W up to 35 cycles
- Investigator choice[a] of:
  - Capecitabine
  - Eribulin
  - Gemcitabine
  - Vinorelbine

Follow-up for safety (≤90 days)
Follow-up for survival (every 3 months)

Stratification by:
- PD-L1 tumor status (CPS ≥1 vs CPS <1)
- Prior neoadjuvant/adjuvant therapy vs de novo metastatic disease at initial diagnosis

Primary
- OS in patients with PD-L1 positive tumors (CPS ≥10)
- OS in patients with PD-L1 positive tumors (CPS ≥1)
- OS in all patients

Immunotherapy in advanced TNBC

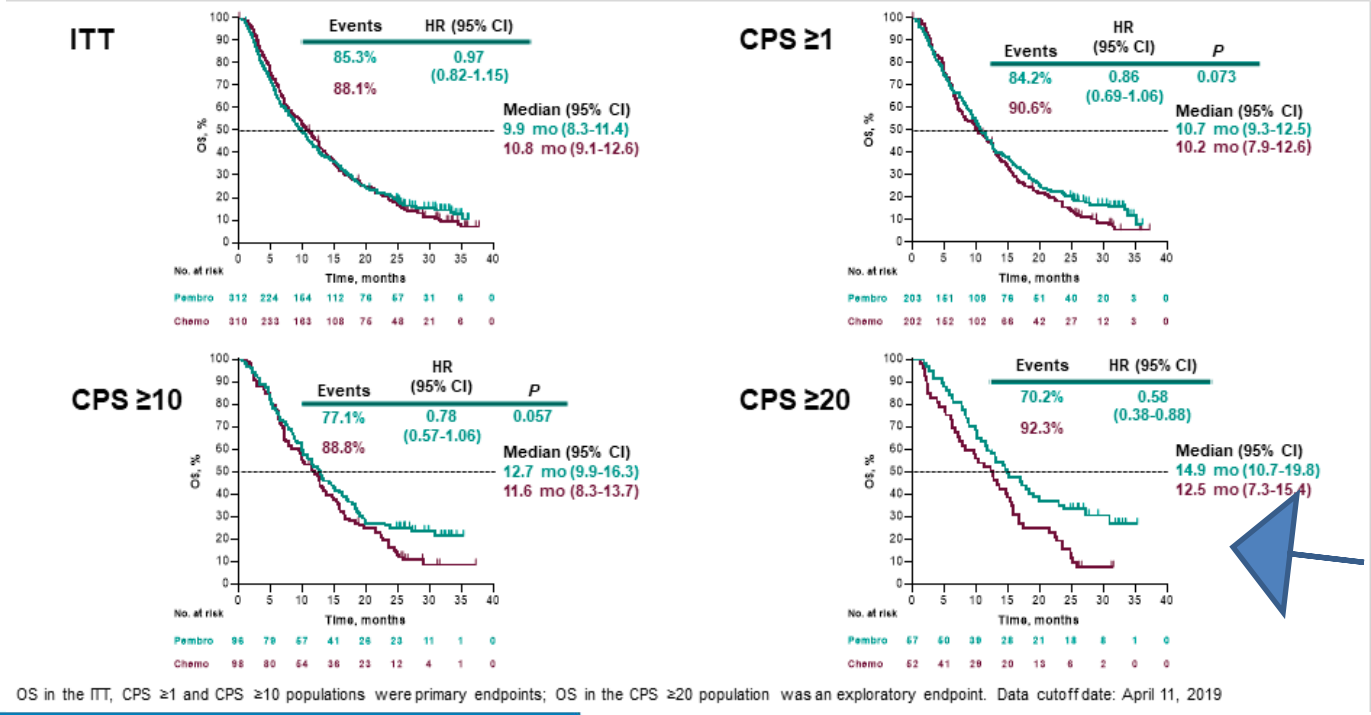
single-agent, phase III randomized study

Pembrolizumab versus investigator-choice chemotherapy for metastatic triple-negative breast cancer (KEYNOTE-119): a randomised, open-label, phase 3 trial

Eric P Winer, Oleg Lipatov, Seock-Ah Im, Anthony Goncalves, Eva Muñoz-Couselo, Keun Seok Lee, Peter Schmid, Kenji Tamura, Laura Testa, Isabell Witzel, Shoichiro Ohtani, Nicholas Turner, Stefania Zambelli, Nadia Harbeck, Fabrice Andre, Rebecca Dent, Xuan Zhou, Vassiliki Karantza, Jaime Mejia, Javier Cortes, on behalf of the KEYNOTE-119 investigators*

KEYNOTE-119 Study

Winer et al, 2021, Lancet Oncol



OS in the ITT, CPS ≥1 and CPS ≥10 populations were primary endpoints; OS in the CPS ≥20 population was an exploratory endpoint. Data cutoff date: April 11, 2019

No new safety signal

Negative study…

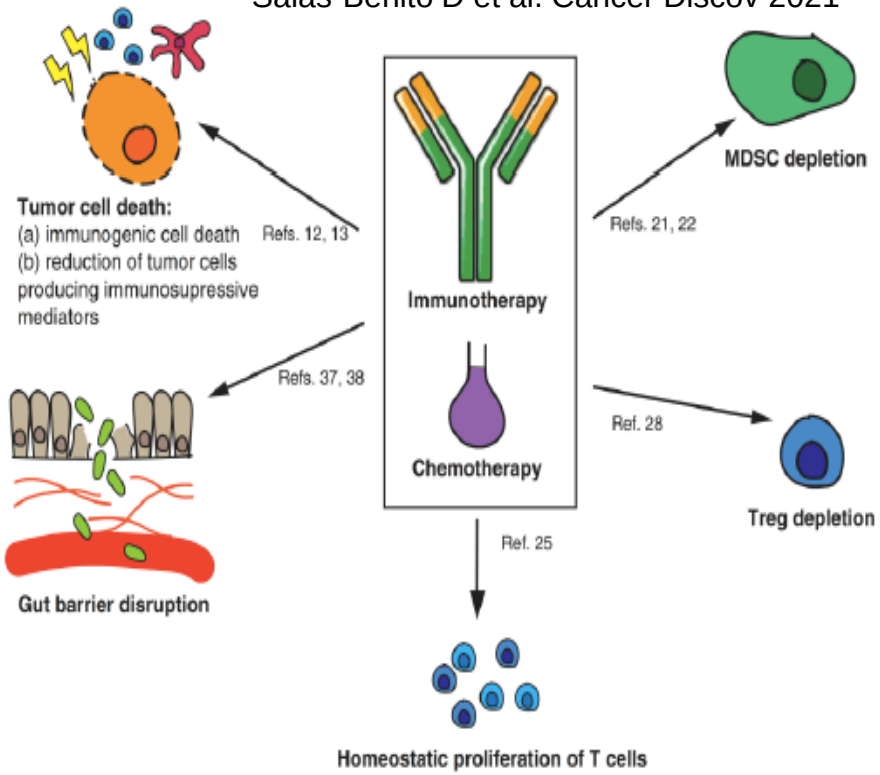
No survival gain in pre-specified subgroups…

A trend in exploratory CPS ≥ 20 subgroup?

Immunotherapy in advanced TNBC

Combination with chemo

Salas-Benito D et al. Cancer Discov 2021



Promising results in uncontrolled studies
Favorable safety profile Adams et al, 2018

Table 3. Summary of Atezolizumab Plus nab-Paclitaxel Clinical Activity

Responses	All Patients (N = 33)
Best confirmed response, No. (%)	
CR	1 (3)
PR	12 (36)
SD	13 (39)
PD	6 (18)
Missing/unevaluable	1 (3)
Confirmed ORR, No. (%) [95% CI][a]	13 (39.4) [22.9-57.9]
Duration of confirmed response, median (range), mo[b]	9.1 (2.9-20.9)[c]
Median PFS (95% CI), mo[b,d]	5.5 (5.1-7.7)
Median OS (95% CI), mo[d]	14.7 (10.1-NE)

JAMA Oncology | Original Investigation

Atezolizumab Plus nab-Paclitaxel in the Treatment of Metastatic Triple-Negative Breast Cancer With 2-Year Survival Follow-up
A Phase 1b Clinical Trial

Sylvia Adams, MD; Jennifer R. Diamond, MD; Erika Hamilton, MD; Paula R. Pohlmann, MD, PhD; Sara M. Tolaney, MD; Ching-Wei Chang, PhD; Wei Zhang, MD; Koho Iizuka, MD; Paul G. Foster, PhD; Luciana Molinero, PhD; Roel Funke, PhD; John Powderly, MD

Immunotherapy in advanced TNBC

Combination, phase III randomized studies

IMpassion 130 Study

Atezolizumab and *nab*-Paclitaxel in mTNBC

Key IMpassion130 eligibility criteria[a]:

- Metastatic or inoperable locally advanced TNBC
  - Histologically documented[b]
- No prior therapy for advanced TNBC
  - Prior chemo in the curative setting, including taxanes, allowed if TFI ≥ 12 mo
- ECOG PS 0-1

Stratification factors:

- Prior taxane use (yes vs no)
- Liver metastases (yes vs no)
- PD-L1 status on IC (positive [≥ 1%] vs negative [< 1%])[c]

R 1:1

Atezo + nab-P arm:

Atezolizumab 840 mg IV
- On days 1 and 15 of 28-day cycle

+ *Nab*-paclitaxel 100 mg/m² IV
- On days 1, 8 and 15 of 28-day cycle

Double blind; no crossover permitted

Plac + nab-P arm:

Placebo IV
- On days 1 and 15 of 28-day cycle

+ *Nab*-paclitaxel 100 mg/m² IV
- On days 1, 8 and 15 of 28-day cycle

RECIST v1.1 PD or toxicity

- Co-primary endpoints were PFS and OS in the ITT and PD-L1+ populations[d]
  - Key secondary efficacy endpoints (ORR and DOR) and safety were also evaluated

IC, tumour-infiltrating immune cell; TFI, treatment-free interval. [a] ClinicalTrials.gov: NCT02425891. [b] Locally evaluated per ASCO–College of American Pathologists (CAP) guidelines. [c] Centrally evaluated per VENTANA SP142 IHC assay (double blinded for PD-L1 status). [d] Radiological endpoints were investigator assessed (per RECIST v1.1).

Schmid P, et al. N Engl J Med. 2018 Nov 29;379(22):2108-2121

Immunotherapy in advanced TNBC

Combination, phase III randomized studies

IMpassion 130 Study

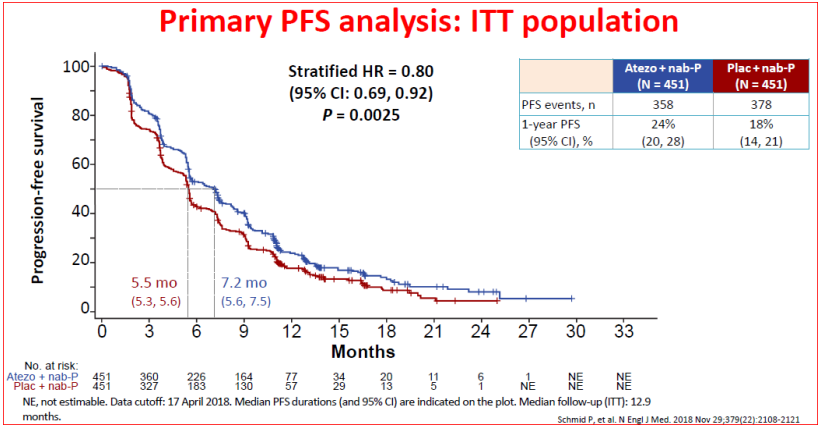
The NEW ENGLAND JOURNAL of MEDICINE

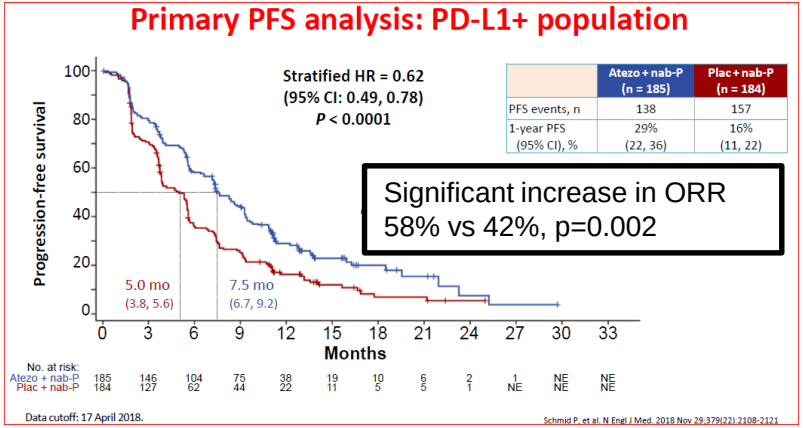
ORIGINAL ARTICLE

Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer

P. Schmid, S. Adams, H.S. Rugo, A. Schneeweiss, C.H. Barrios, H. Iwata, V. Diéras, R. Hegg, S.-A. Im, G. Shaw Wright, V. Henschel, L. Molinero, S.Y. Chui, R. Funke, A. Husain, E.P. Winer, S. Loi, and L.A. Emens, for the IMpassion130 Trial Investigators*

Schmid, 2018





A modest but significant increase in PFS, higher in PD-L1+ subgroup

No unexpected adverse events

PD-L1 IHC= SP142 Ventana

INSTITUT PAOLI-CALMETTES unicancer Marseille

CRCM Centre de Recherche en Cancérologie de Marseille

Aix*Marseille université initiative d'excellence

Immunotherapy in advanced TNBC

Combination, phase III randomized studies

IMpassion 130 Study

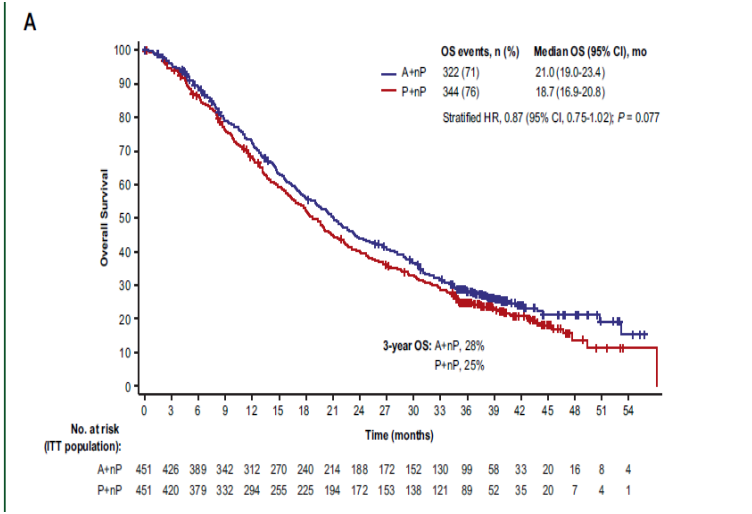
ESMO ANNALS OF ONCOLOGY

ORIGINAL ARTICLE

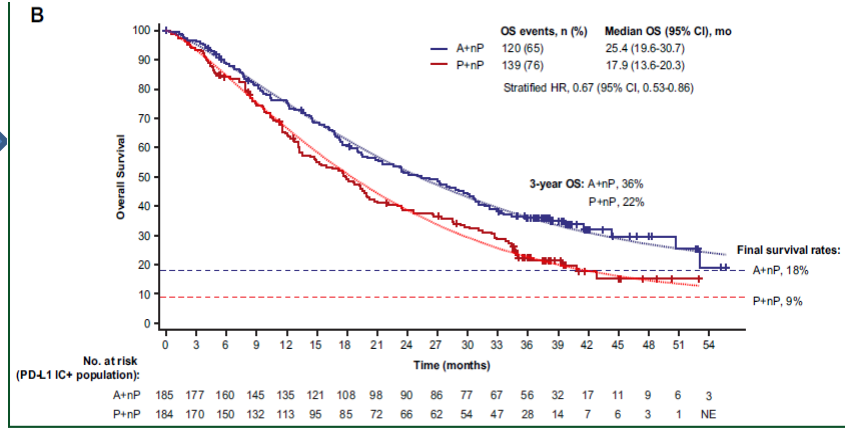
Emens, 2021

First-line atezolizumab plus nab-paclitaxel for unresectable, locally advanced, or metastatic triple-negative breast cancer: IMpassion130 final overall survival analysis

L. A. Emens[17], S. Adams[2], C. H. Barrios[3], V. Diéras[4], H. Iwata[5], S. Loi[6], H. S. Rugo[7], A. Schneeweiss[8], E. P. Winer[9], S. Patel[10], V. Henschel[11], A. Swat[12], M. Kaul[13], L. Molinero[14], S. Patel[15], S. Y. Chui[16] & P. Schmid[18]



Exploratory analysis



No significant impact on OS in ITT pop but….a clinically significant numerical advantage in PD-L1+ (+7.5 months)

INSTITUT PAOLI-CALMETTES unicancer Marseille

CRCM Centre de Recherche en Cancérologie de Marseille

Aix*Marseille université initiative d'excellence

Accelerated FDA-approval on March 2019
EMA-approved

Immunotherapy in advanced TNBC

Combination, phase III randomized studies

IMpassion 131 Study

IMpassion 131: 1st Line mTNBC Paclitaxel ± Atezolizumab

- Metastatic or unresectable locally advanced TNBC
- No prior chemotherapy or targeted therapy for advanced TNBC
- Previous eBC treatment completed ≥12 months before randomisation
- Taxane eligible
- Measurable disease
- ECOG PS 0/1

R
2:1

Atezolizumab 840 mg d1 & 15 + paclitaxel 90 mg/m² d1, 8 & 15

8–10 mg dexamethasone or equivalent for at least the first 2 infusions, cycles repeated q28d

Placebo d1 & 15 + paclitaxel 90 mg/m² d1, 8 & 15

Co-1° endpoints: PFS (investigator assessed)
Planned hierarchical look PDL1+ then ITT

Immunotherapy in advanced TNBC

Combination, phase III randomized studies

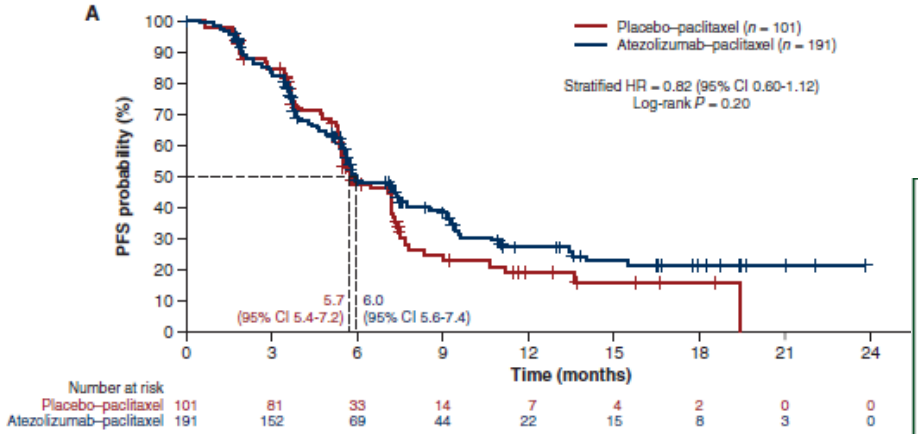
IMpassion 131 Study

ESMO Miles, 2021 ANNALS of ONCOLOGY

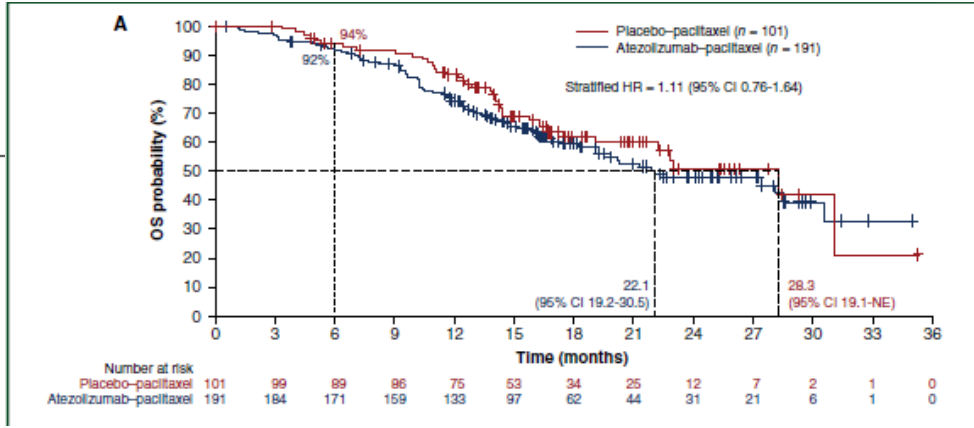
ORIGINAL ARTICLE

Primary results from IMpassion131, a double-blind, placebo-controlled, randomised phase III trial of first-line paclitaxel with or without atezolizumab for unresectable locally advanced/metastatic triple-negative breast cancer

D. Miles[17], J. Gligorov[2], F. André[3], D. Cameron[4], A. Schneeweiss[5], C. Barrios[6], B. Xu[7], A. Wardley[8,9], D. Kaen[10], L. Andrade[11], V. Semiglazov[12], M. Reinisch[13], S. Patel[14], M. Patre[15], L. Morales[15], S. L. Patel[15], M. Kaul[15], T. Barata[15] & J. O'Shaughnessy[16], on behalf of the IMpassion131 investigators[1]



No significant impact on PFS and OS in PD-L1+ patients



Genentech voluntarily withdrawal Sept. 2021

INSTITUT PAOLI-CALMETTES unicancer Marseille CRCM Centre de Recherche en Cancérologie de Marseille Aix*Marseille université initiative d'excellence

Immunotherapy in advanced TNBC

Combination, phase III randomized studies

KEYNOTE-355 Study

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

Cortes, 2020
Rugo, 2021

Key Eligibility Criteria

- Age ≥18 years
- Central determination of TNBC and PD-L1 expression
- Previously untreated locally recurrent inoperable or metastatic TNBC
- Completion of treatment with curative intent ≥6 months prior to first disease recurrence
- ECOG performance status 0 or 1
- Life expectancy ≥12 weeks from randomization
- Adequate organ function
- No systemic steroids
- No active CNS metastases
- No active autoimmune disease

PD-L1= 22C3 (CPS)

R 2:1

Pembrolizumab[a] + Chemotherapy[b]

Taxanes (nab-P, paclitaxel)
Carbo-gem

Placebo[c] + Chemotherapy[b]

Progressive disease[d]/cessation of study therapy

- Primary Endpoints
  - PFS[a] in patients with PD-L1–positive tumors[b] (CPS ≥10 and CPS ≥1) and in the ITT population
  - OS in patients with PD-L1–positive tumors[b] (CPS ≥10 and CPS ≥1) and in the ITT population

[a]Pembrolizumab 200 mg intravenous (IV) every 3 weeks (Q3W)
[b]Chemotherapy dosing regimens are as follows:
Nab-paclitaxel 100 mg/m² IV on days 1, 8, and 15 every 28 days
Paclitaxel 90 mg/m² IV on days 1, 8, and 15 every 28 days
Gemcitabine 1000 mg/m²/carboplatin AUC 2 on days 1 and 8 every 21 days

[c]Normal saline
[d]Treatment may be continued until confirmation of progressive disease
CNS=central nervous system; ECOG=Eastern Cooperative Oncology Group; PD-L1=programmed death ligand 1; R=randomized; TNBC=triple-negative breast cancer

Immunotherapy in advanced TNBC

Combination, phase III randomized studies

KEYNOTE-355 Study

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

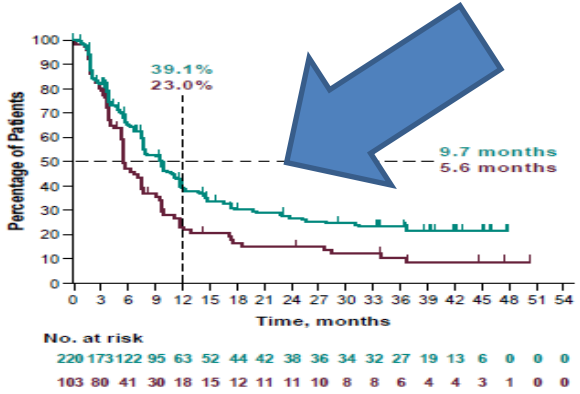
Cortes, 2020
Rugo, 2021

FDA- and EMA-approved

Progression-Free Survival

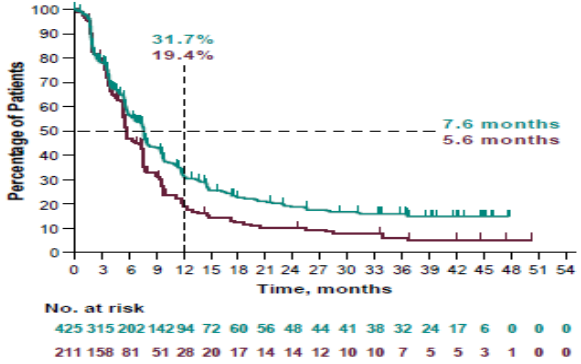
PD-L1 CPS ≥10

	n/N	Events	HR (95% CI)
Pembro + Chemo	144/220	65.5%	0.66 (0.50-0.88)
Placebo + Chemo	81/103	78.6%	



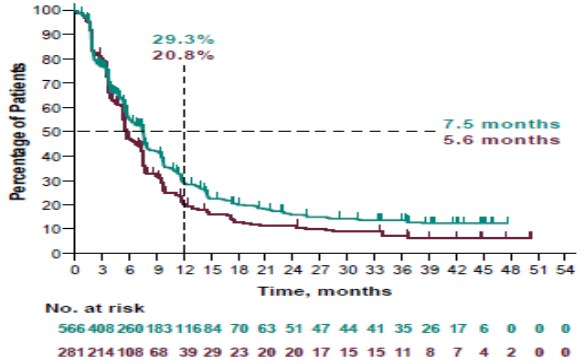
PD-L1 CPS ≥1

	n/N	Events	HR (95% CI)
Pembro + Chemo	299/425	70.4%	0.75 (0.62-0.91)
Placebo + Chemo	166/211	78.7%	



ITT

	n/N	Events	HR (95% CI)
Pembro + Chemo	406/566	71.7%	0.82 (0.70-0.98)
Placebo + Chemo	217/281	77.2%	



INSTITUT PAOLI-CALMETTES unicancer Marseille
CRCM Centre de Recherche en Cancérologie de Marseille
Aix*Marseille université Initiative d'excellence

No new safety signal

Immunotherapy in advanced TNBC

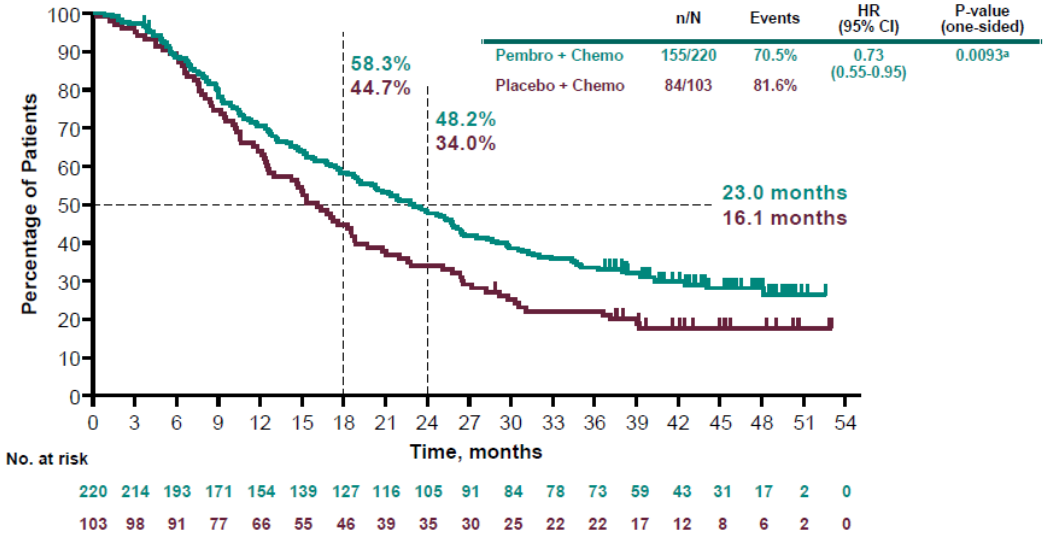
Combination, phase III randomized studies

KEYNOTE-355 Study

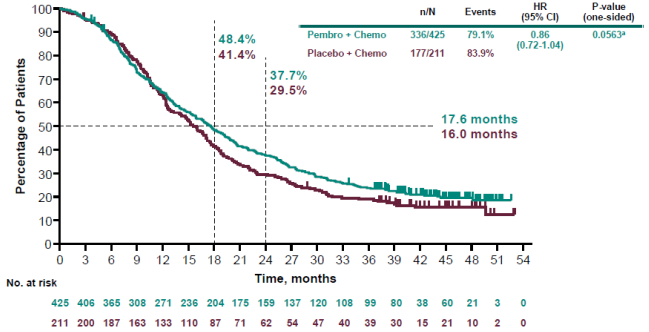
Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial

Cortes, 2020
Rugo, 2021

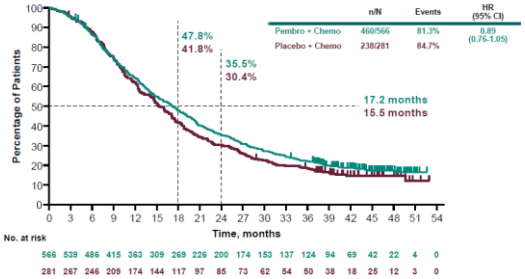
Overall Survival: PD-L1 CPS ≥10



Overall Survival: PD-L1 CPS ≥1



Overall Survival: ITT



INSTITUT PAOLI-CALMETTES unicancer Marseille
CRCM Centre de Recherche en Cancérologie de Marseille
Aix*Marseille université initiative d'excellence

Immunotherapy in advanced TNBC

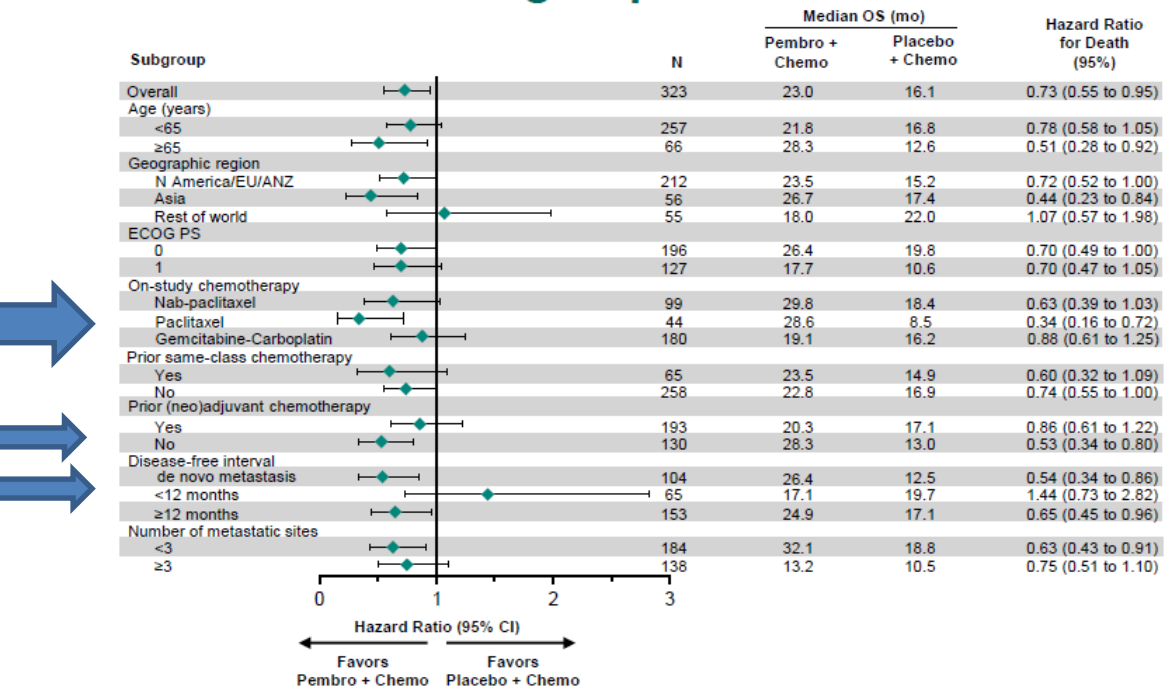
Combination, phase III randomized studies

KEYNOTE-355 Study

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

Cortes, 2020
Rugo, 2021

Overall Survival in Subgroups: CPS ≥10



Benefit higher in

- Taxanes-treated (pacli or Nab-P)
- No previous CT (adj/neoadj)
- De novo or DFI > 12 mos

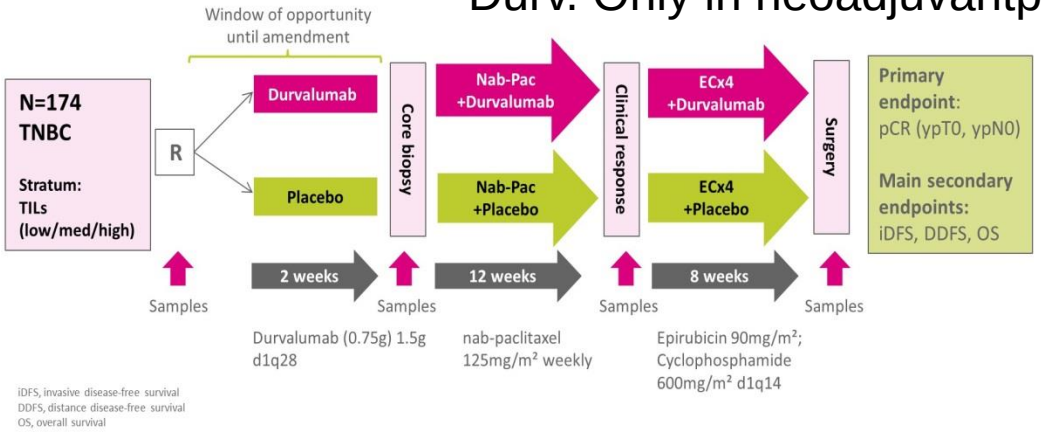
EARLY BREAST CANCER

Immunotherapy in early stage BC

Loiibl et al,
2019, 2021

GBG GERMAN BREAST GROUP **Study Design**

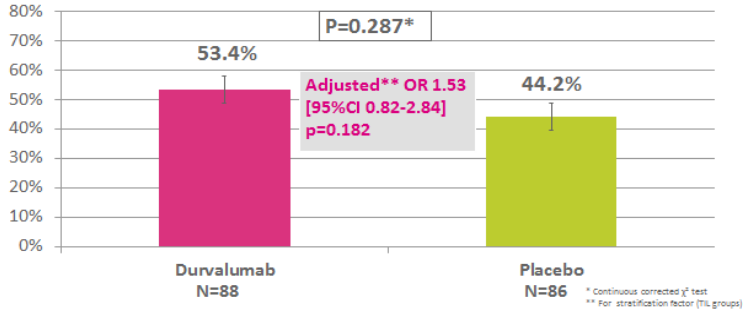
No platin
Durv. Only in neoadjuvantphase



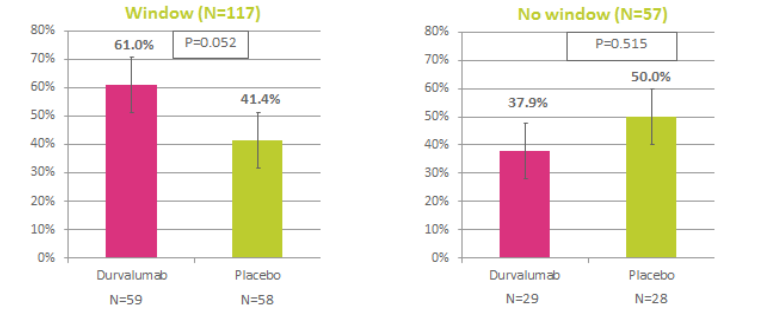
iDFS, invasive disease-free survival
DDFS, distance disease-free survival
OS, overall survival

Loibl S, et al. Ann Oncol 2019

GBG GERMAN BREAST GROUP **Primary Endpoint - pathological complete response**
pCR – ypT0, ypN0



GBG GERMAN BREAST GROUP **Subgroup Analysis of the Window Cohort**



- Non significant increase in pCR with Durv.
- Increase higher in “window” pop. ?

INSTITUT PAOLI-CALMETTES unicancer Marseille
CRCM Centre de Recherche en Cancérologie de Marseille
Aix*Marseille université initiative d'excellence

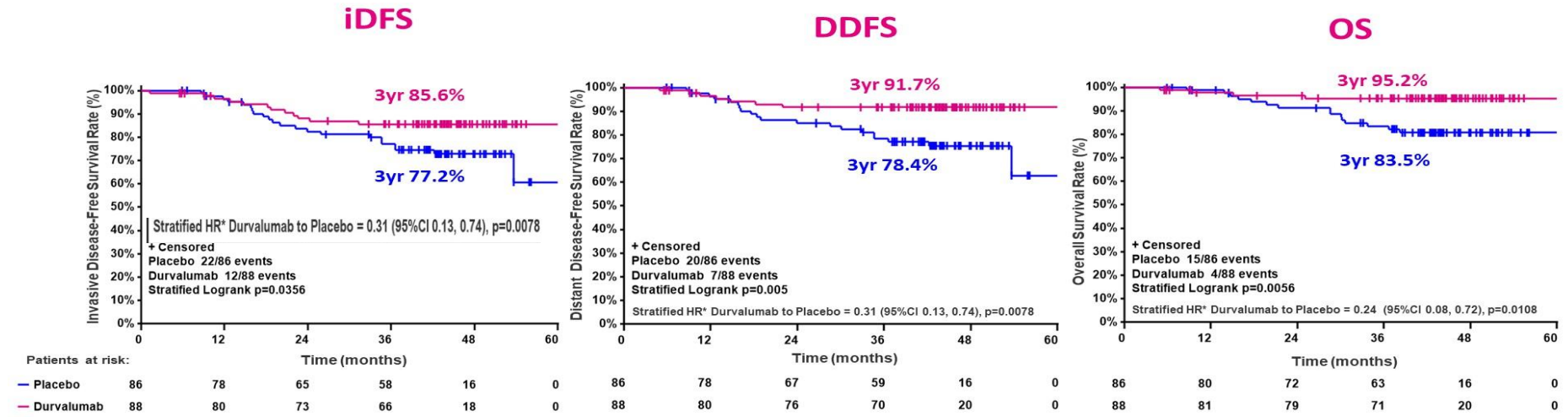
Immunotherapy in early stage BC

Loiibl et al,
2019, 2021

GBG GERMAN BREAST GROUP

iDFS, DDFS and OS Between Treatment Arms

Gepar Nuevo



Durvalumab increases survival outcome

* Stratified by sTILs

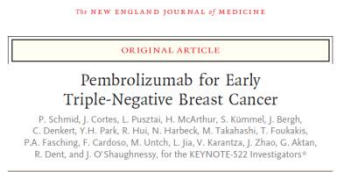
INSTITUT PAOLI-CALMETTES unicancer Marseille

CRCM Centre de Recherche en Cancérologie de Marseille

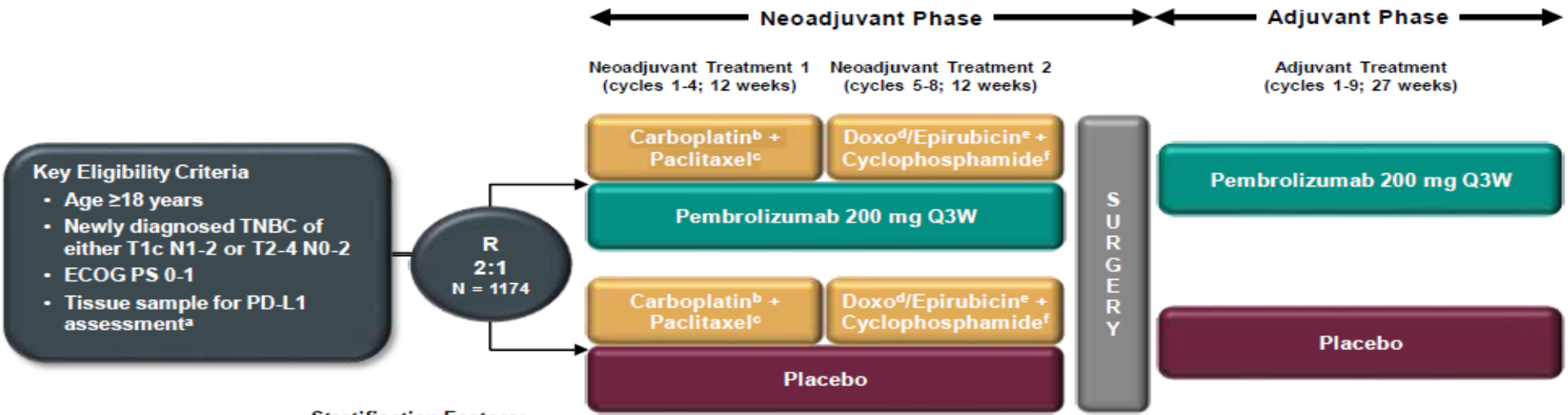
Aix*Marseille université initiative d'excellence

Immunotherapy in early stage BC

Schmid et al, 2020



KEYNOTE-522 Study Design (NCT03036488)



Stratification Factors:
- Nodal status (+ vs -)
- Tumor size (T1/T2 vs T3/T4)
- Carboplatin schedule (QW vs Q3W)

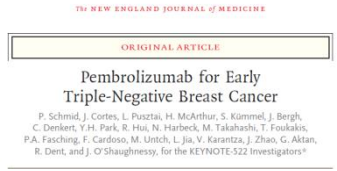
Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

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 QW.
[c]Paclitaxel dose was 80 mg/m^2 QW.
[d]Doxorubicin dose was 60 mg/m^2 Q3W.
[e]Epirubicin dose was 90 mg/m^2 Q3W.
[f]Cyclophosphamide dose was 600 mg/m^2 Q3W.

Immunotherapy in early stage BC KEYNOTE-522

Schmid et al, 2020

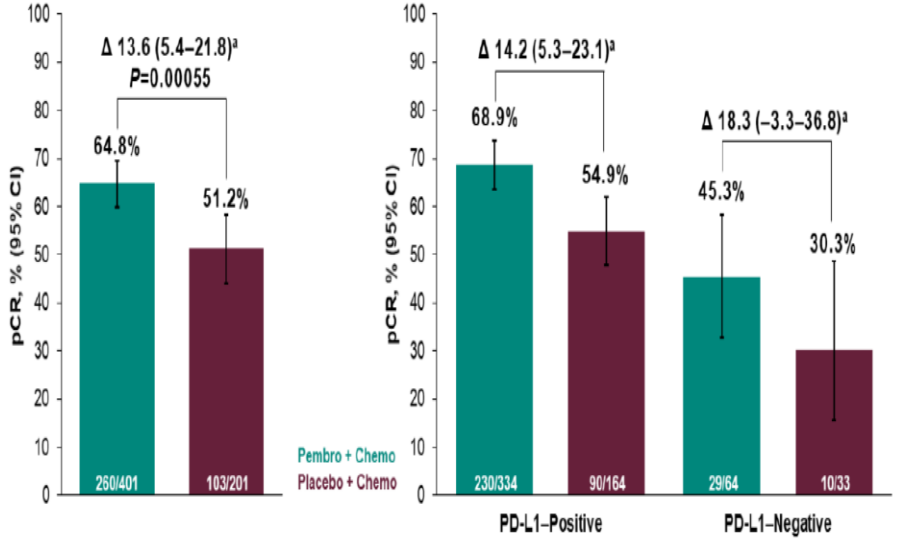

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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*

Primary Endpoint: ypT0/Tis ypN0

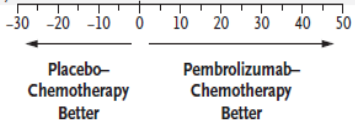


By PD-L1 Status[b]: ypT0/Tis ypN0

[a]Estimated treatment difference based on Miettinen & Nurminen method stratified by randomization stratification factors. [b]PD-L1 assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay and measured using the combined positive score (CPS; number of PD-L1–positive tumor cells, lymphocytes, and macrophages divided by total number of tumor cells x 100); PD-L1–positive = CPS ≥1. Data cutoff date: September 24, 2018.

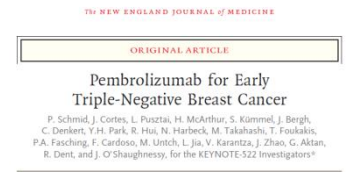
Schmid P, et al. ESMO 2019

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)

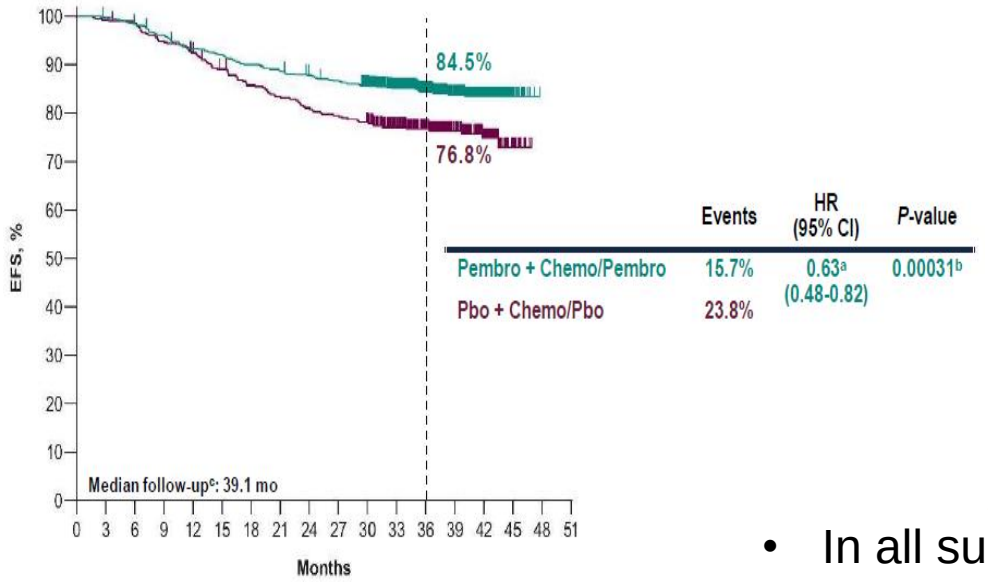


Immunotherapy in early stage BC

Schmid et al, 2020

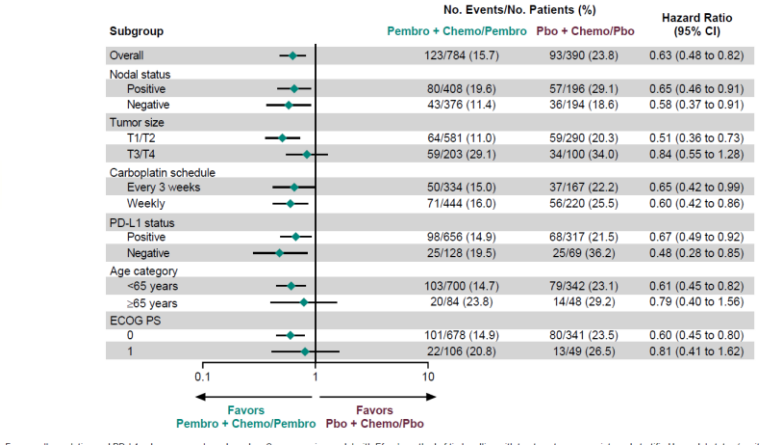


Statistically Significant and Clinically Meaningful EFS at IA4



	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	15.7%	0.63[a] (0.48-0.82)	0.00031[b]
Pbo + Chemo/Pbo	23.8%		

EFS in Patient Subgroups

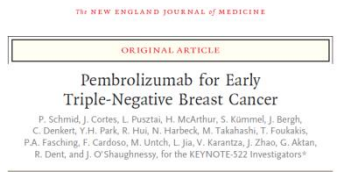


- In all subgroups…
- Distant DFS =+6,3% at 3 ys (HR=0,61)
- Trend in OS …

INSTITUT PAOLI-CALMETTES unicancer Marseille
CRCM Centre de Recherche en Cancérologie de Marseille
Aix*Marseille université initiative d'excellence

Immunotherapy in early stage BC

Schmid et al, 2020

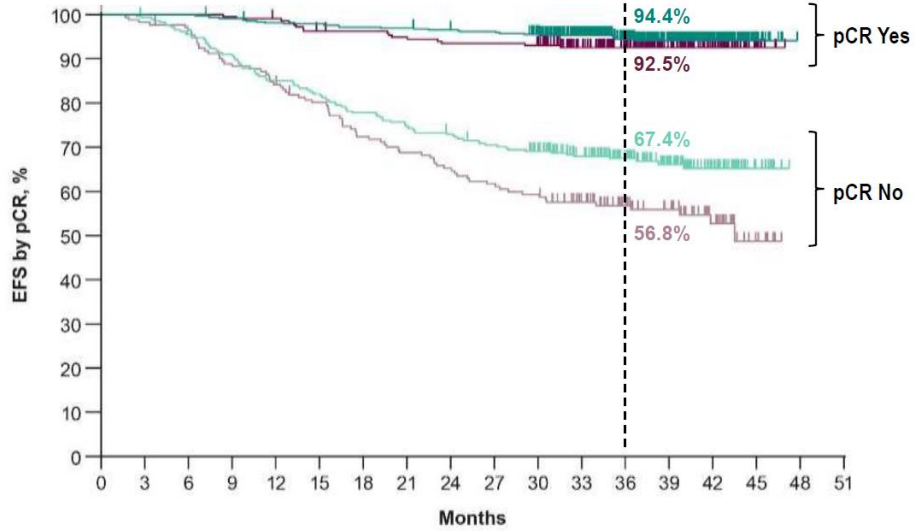

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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*

EFS by pCR (ypT0/Tis ypN0)



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

Very good outcome for pCR patients (with and withpout pembro)

Who are the pCR with chemo only ?

Role of adjuvant pembro here ?

Significant survival impact of pembro in patients with no pCR

Still a place for improvig outcome…

INSTITUT PAOLI-CALMETTES unicancer Marseille

CRCM Centre de Recherche en Cancérologie de Marseille

Aix*Marseille université initiative d'excellence

Immunotherapy in early stage BC

Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial

Elizabeth A Mittendorf, Hong Zhang, Carlos H Barrios, Shigehira Saji, Kyung Hae Jung, Roberto Hegg, Andreas Koehler, Joohyuk Sohn, Hiroji Iwata, Melinda L Telli, Cristiana Ferrario, Kevin Punie, Frédérique Penault-Llorca, Shilpen Patel, Anh Nguyen Duc, Mario Lisle-Hermoso, Vidya Maiya, Luciana Molinero, Stephen Y Chui, Nadia Harbeck

Mittendorf et al, 2020, Lancet

No platin

IMpassion031:
Phase III atezolizumab neoadjuvant study in eTNBC[1,2]

A randomised, multicentre, international, double-blind, placebo-controlled trial

N = 333
- TNBC, with primary tumour > 2 cm
- cT2-cT4, cN0-cN3, cM0
- Known PD-L1 status (IHC)
- No prior therapy for treatment or prevention of BC
- ECOG PS 0 or 1

Stratification Factors:
- Stage II vs Stage III
- PD-L1 IC < 1% vs IC ≥ 1%

R 1:1

	12 weeks	8 weeks	pCR		
Atezolizumab	840 mg IV q2w + *nab*-paclitaxel 125 mg/m² IV qw	Atezolizumab 840 mg IV q2w + Doxorubicin 60 mg/m² IV q2w Cyclophosphamide 600 mg/m² IV q2w	SURGERY	Atezolizumab 1200 mg IV q3w x 11 doses	Survival follow-up[a]
Placebo	Placebo + *nab*-paclitaxel 125 mg/m² IV qw	Placebo + Doxorubicin 60 mg/m² IV q2w Cyclophosphamide 600 mg/m² IV q2w		Survival follow-up[a]	

Co-primary endpoint: pCR (ypT0/is ypN0) in ITT and PD-L1+ (IC ≥ 1%) subpopulation

Secondary endpoints: EFS, DFS, and OS in ITT and in PD-L1+ subpopulation, safety, PROs

[a]Post-surgical management of patients was at the discretion of the treating investigator and based on local practice guidelines.
EFS, event-free survival; DFS, disease-free survival; PD-L1 IC, PD-L1–expressing tumor infiltrating immune cells as percentage of tumor area using the VENTANA SP142 assay; PRO, patient-reported outcome.

1. Mittendorf E, et al. SABCS 2017 [abstract 17-OT2-07-03]. 2. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/study/NCT03197935. Accessed 11 August 2020.

Immunotherapy in early stage BC

Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial

Mittendorf et al, 2020, Lancet

Primary = pCR

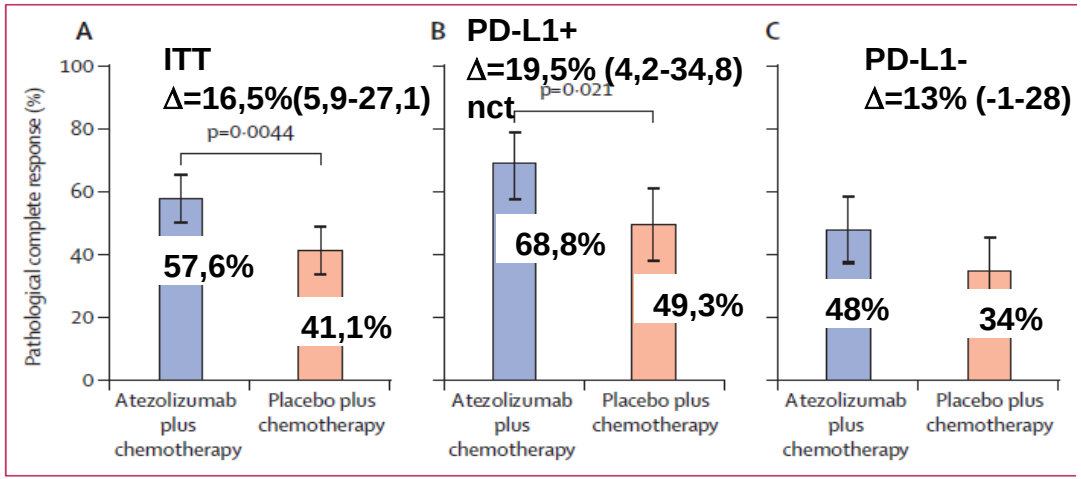


Figure 2: **Pathological complete response co-primary endpoints in the all-randomised and PD-L1-positive populations, and pathological complete response in the PD-L1-negative population**
(A) All-randomised population and PD-L1-positive populations. (B) PD-L1-positive population. (C) PD-L1-negative population (not formally tested). PD-L1=programmed cell death ligand 1.

Secondary time-to-event endpoints

		Atezolizumab-Chemo	Placebo-Chemo
EFS	Events, n/N (%)	17/165 (10.3%)	22/168 (13.1%)
	Median (95% CI)	NE (NE, NE)	NE (NE, NE)
	Stratified HR (95% CI)	**0.76** (0.40, 1.44)	
DFS	Events, n/N (%)	10/154[b] (6.5%)	13/153[b] (8.5%)
	Median (95% CI)	NE (NE, NE)	NE (NE, NE)
	Stratified HR (95% CI)	**0.74** (0.32, 1.70)	
OS	Events, n/N (%)	7/165 (4.2%)	9/168 (5.4%)
	Median (95% CI)	NE (27.40, NE)	NE (NE, NE)
	Stratified HR (95% CI)	**0.69** (0.25, 1.87)	

Harbeck N, et al. ESMO 2020

INSTITUT PAOLI-CALMETTES unicancer Marseille
CRCM Centre de Recherche en Cancérologie de Marseille
Aix*Marseille université initiative d'excellence

Immunotherapy in early stage BC

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

Design of the NeoTRIP trial

*HER-2 negative, ER and PgR negative early high-risk (T1cN1; T2N1; T3N0) or locally advanced unilateral breast cancer

No anthracyclines in CT backbone

R

Carboplatin (AUC2) + *nab*-paclitaxel (125 mg/m²) weekly for 2 wks every 3; 8 cy → S

Carboplatin (AUC2) + *nab*-paclitaxel (125 mg/m²) weekly for 2 wks every 3; 8 cy **+ Atezolizumab (1200 mg)** day 1 every 3 wks for 8 cycles → S

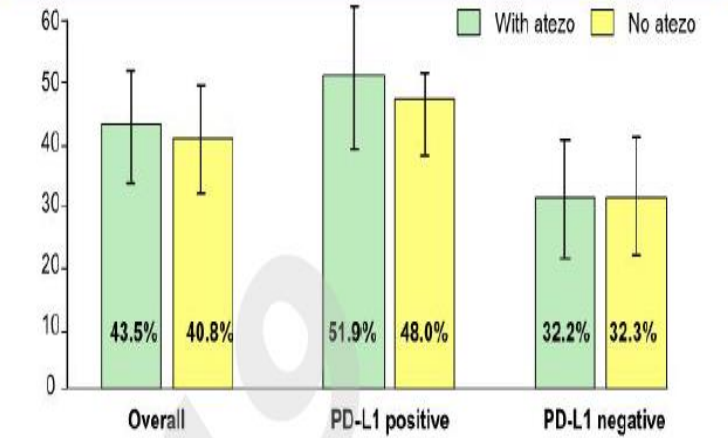
Primary = EFS

*Estrogen receptor, progesterone receptor, HER2 and PD-L1 were centrally assessed before randomization

Tumour & Blood banked for correlative studies

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

pCR rate and *PD-L1 expression*

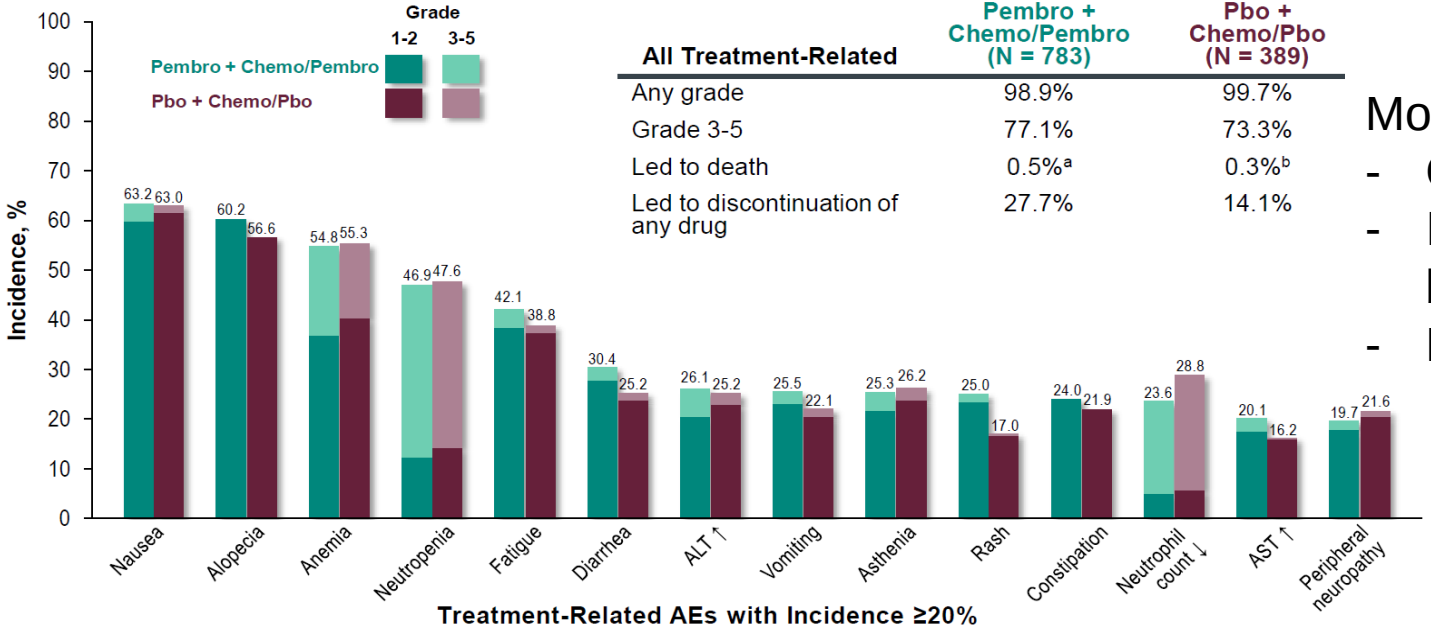


No impact on pCR (Secondary)

INSTITUT PAOLI-CALMETTES unicancer Marseille
CRCM Centre de Recherche en Cancérologie de Marseille
Aix*Marseille université initiative d'excellence

Immunotherapy in early stage BC
Toxicity

Treatment-Related AEs in Combined Phases



All Treatment-Related	Pembro + Chemo/Pembro (N = 783)	Pbo + Chemo/Pbo (N = 389)
Any grade	98.9%	99.7%
Grade 3-5	77.1%	73.3%
Led to death	0.5%[a]	0.3%[b]
Led to discontinuation of any drug	27.7%	14.1%

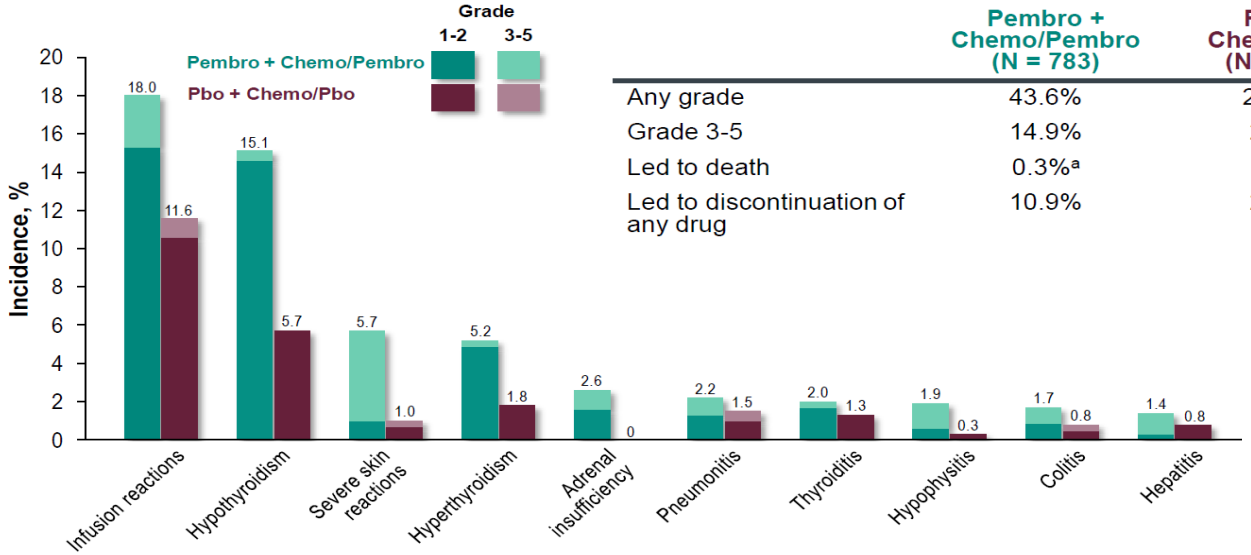
Most of toxicity
- CT-related
- Incidence comparable between arms
- During neoadj. phase

KEYNOTE-522

INSTITUT PAOLI-CALMETTES
unicancer Marseille
CRCM
Centre de Recherche en Cancérologie de Marseille
Aix*Marseille université
initiative d'excellence

Immunotherapy in early stage BC
Toxicity

Immune-Mediated AEs and Infusion Reactions in Combined Phases



	Pembro + Chemo/Pembro (N = 783)	Pbo + Chemo/Pbo (N = 389)
Any grade	43.6%	21.9%
Grade 3-5	14.9%	2.1%
Led to death	0.3%[a]	0
Led to discontinuation of any drug	10.9%	2.6%

Immune-Mediated AEs and Infusion Reactions with Incidence ≥10 Patients

Immune-related events
- As expected
- Dysthyroidisms+++
- Easily managed
  - Stop and/or
  - Hormone replacement and/or
  - Steroids
- Sometimes
  - Severe and definitive

INSTITUT PAOLI-CALMETTES unicancer Marseille
CRCM Centre de Recherche en Cancérologie de Marseille
Aix*Marseille université initiative d'excellence

KEYNOTE-522

Conclusions – perspectives
Advanced breast cancer patients(1)

- First-line, PD-L1+, TNBC
- Pembrolizumab in combination with chemotherapy (paclitaxel/nab-pac or Carbo-gem)
- Atezolizumab still registered in EU, but with nab-pac only
- Single-agent pembro in hTMB ABC from any subtype beyond 1st-line is registered in the US…

Conclusions – perspectives
Advanced Breast Cancer patients(2)

Many issues remaining….

- Adding other biomarkers than PD-L1+ ?
- Integrating novel ADCs ?
  - Sacituzumab govitecan,
  - T-DXd, Dato-Dx-D
- Investigating novel settings
  - BRCA, ER+, HER2+ ?
  - After neoadjuvant immunotherapy ?

Conclusions – perspectives
Early breast cancer patients (1)

- ***Pembro is FDA-approved but still to be approved by EMA…***
- ***Which patients ?***
  - Stage II/III TNBC
  - Fit to receive chemo without CI° to ICI
- ***Which CT backbone ?***
  - anthracyclines +++ (no benefit of atezo with anthracyclines-free CT)
  - is carboplatine needed ?
    - Benefit seen with platin-free regimen (GeparNuevo, Impassion 031) but…
    - Carboplatin improves survival in the absence of ICI (Brightness)

Conclusions – perspectives
Early breast cancer patients (2)

Adjuvant phase ?

- Is it needed if pCR attained ?
- Which adjuvant treatment if no pCR ?
  - Pembro alone ?
  - Capecitabine alone ?
  - Capecitabine pembro ?
  - What if BRCAmut = Olaparib ? Pembro ? Both ?

In lower stage ?