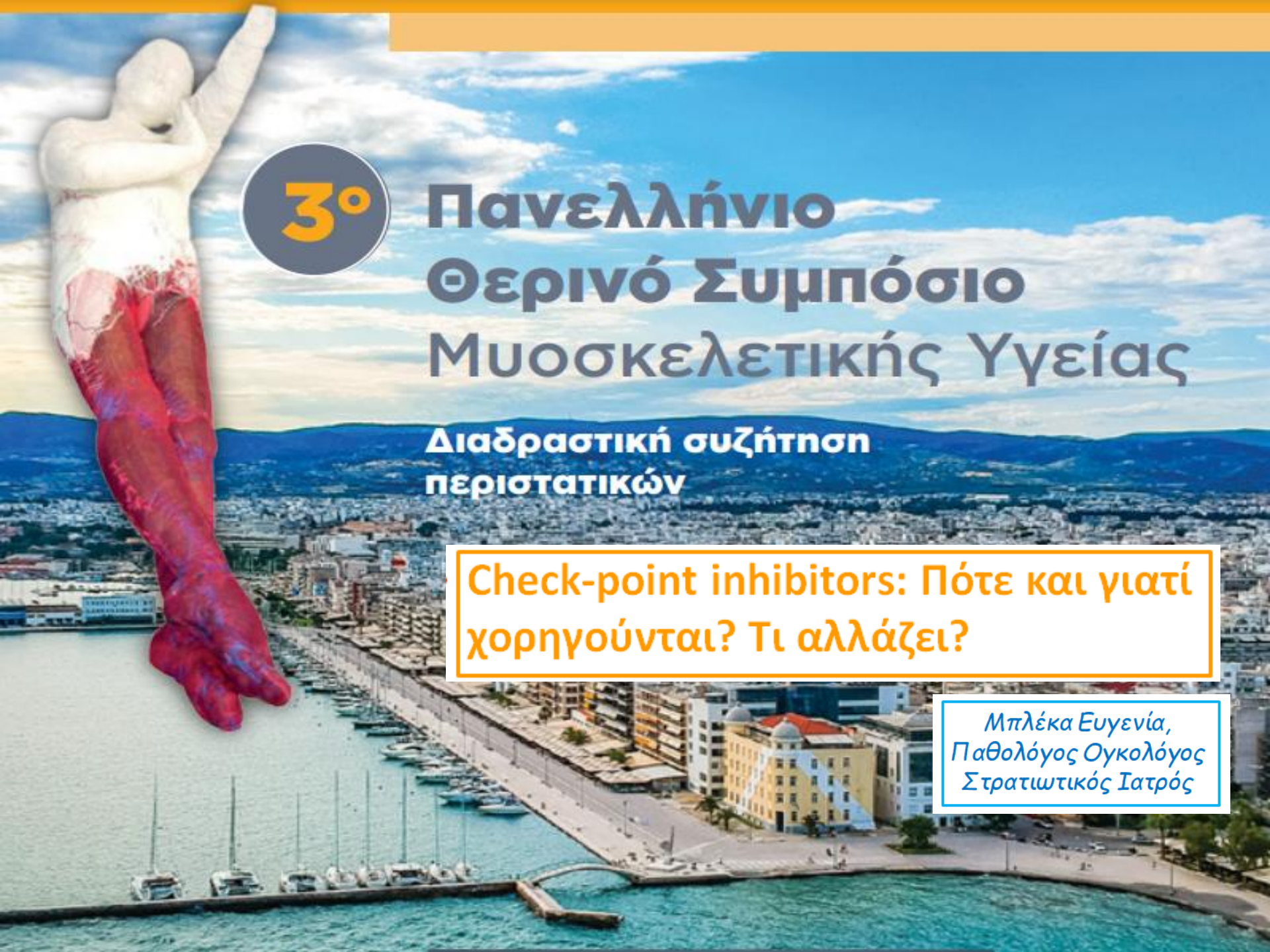
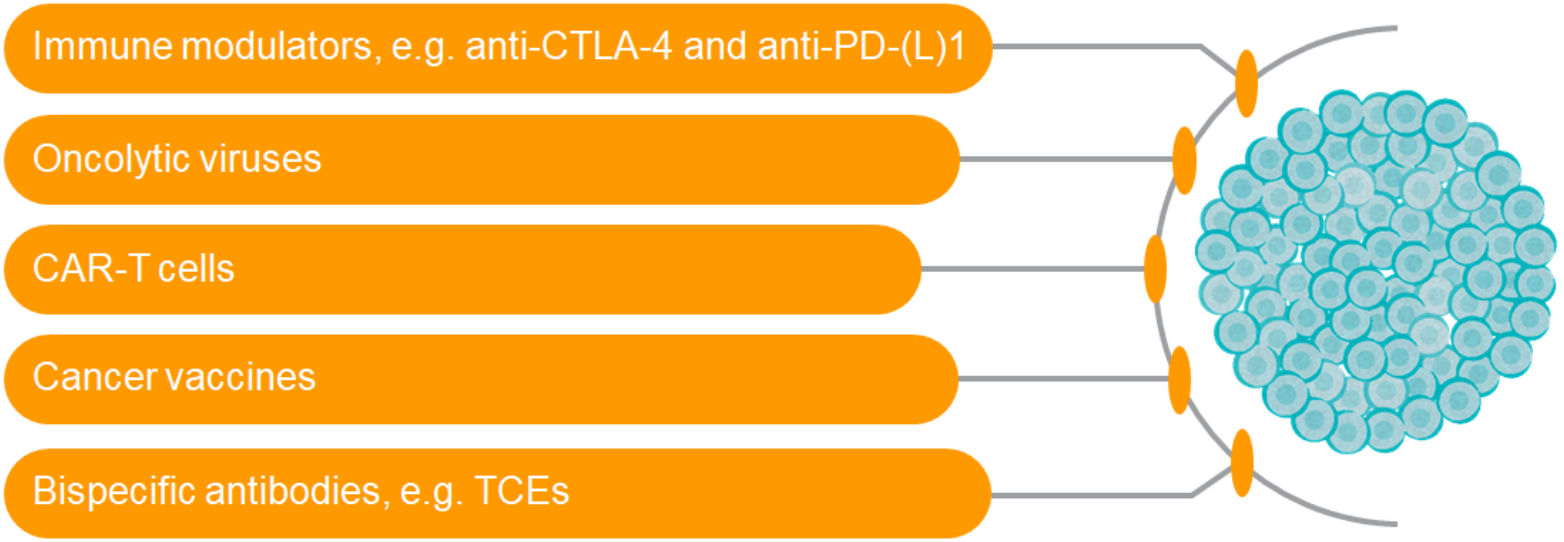

3ο
Πανελλήνιο
Θερινό Συμπόσιο
Μυοσκελετικής Υγείας
Διαδραστική συζήτηση
περιστατικών
Check-point inhibitors: Πότε και γιατί χορηγούνται? Τι αλλάζει?
Μπλέκα Ευγενία,
Παθολόγος Ογκολόγος
Στρατιωτικός Ιατρός


return
shift
Conflict of Interest
YES
NO

Immunotherapy: New options for cancer treatment

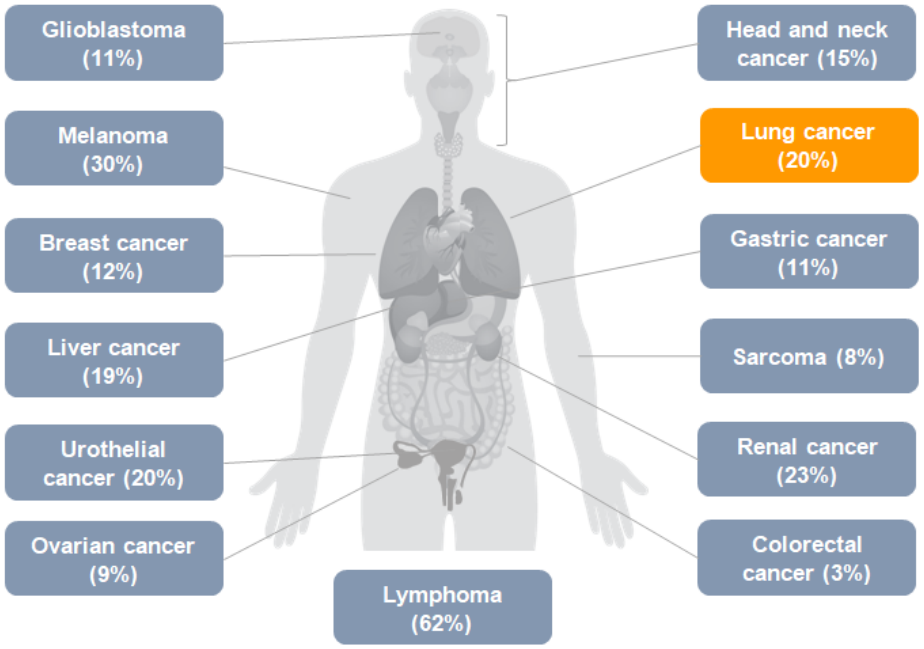
- Immuno-oncology therapies may activate the **patient's own immune system** to engage with cancer cells
- Recent advances in immunotherapeutic approaches include[2,3]:



CAR = chimeric antigen receptor; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1; TCE = T-cell engager.

1. Viardot A, et al. *Ann Hematol*. 2020;99(10):2215–2229; 2. Ellerman D. *Methods*. 2019;154:102–117; 3. Huehls AM, et al. *Immunol Cell Biol*. 2015;93(3):290–296.

Anti-PD-L1/PD-1 response rates among various tumor types[1]



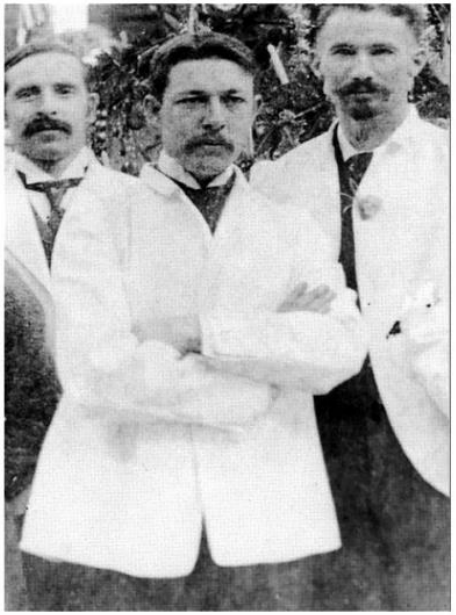
- Response rates to ICIs typically range from 10% to 30% depending on the tumor type[1-3]
  - While lymphoma typically has the highest response rate, sarcoma and ovarian cancer have the lowest

ICI = immune checkpoint inhibitor; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand 1.

1. Zhao B, et al. *Ther Adv Med Oncol*. 2020;12:1–22; 2. Sun JY, et al. *Biomark Res*. 2020;8:35; 3. Zhang T, et al. *Oncotarget*. 2016;7(45):73068–73079.

Despite broad activity of anti-PDL1/PDL1 , benefit in certain subset of patients

William Coley and the birth of cancer immunotherapy



New York Times - July 29, 1908

ERYSIPELAS GERMS AS CURE FOR CANCER

Dr. Coley's Remedy of Mixed Toxins Makes One Disease Cast Out the Other.

MANY CASES CURED HERE

Physician Has Used the Cure for 15 Years and Treated 430 Cases— Probably 150 Sure Cures.

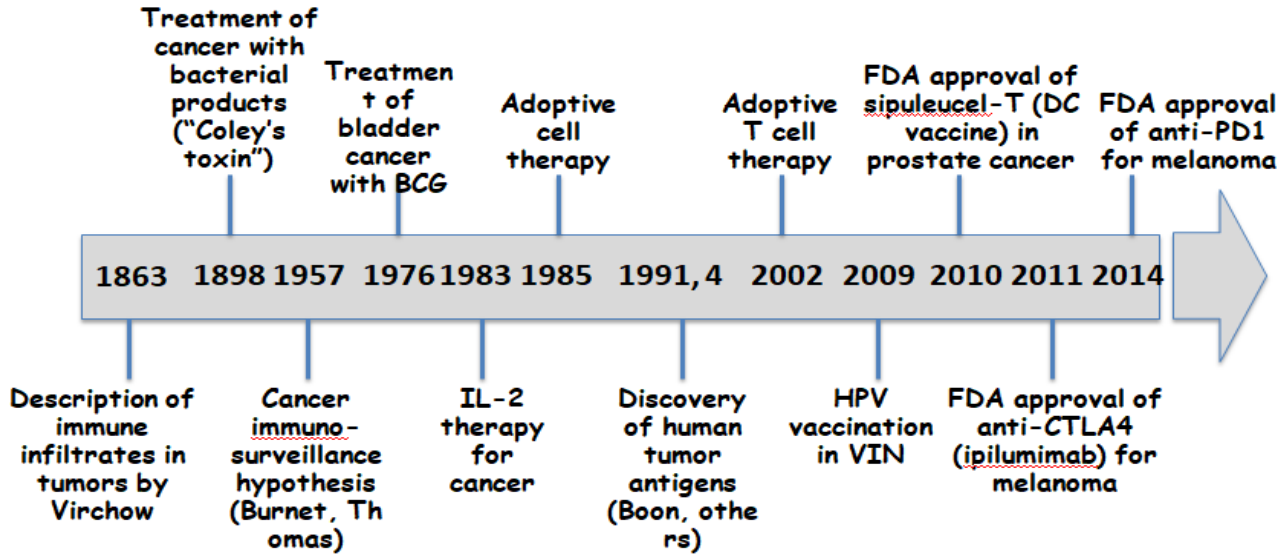
Following news from St. Louis that two men have been cured of cancer in the City Hospital there by the use of a fluid discovered by Dr. William B. Coley of New York. It came out yester-

Induce infection to recruit immune cells to kill cancer

No understanding of immune system, genes, mutations at that time

Serious AEs including death

Long road to modern immunooncology therapies



- ~120 years from Coley's Toxin (1890) to the first modern immunotherapy (Ipilimumab) 2011
- Long time to understand immune system: T-cells was discovered in 1968, different types of T-cells (CD4, CD8, CD28, etc.) distinguished later
  - Many misunderstandings about cancer and immune system eg.T-cells cannot see cancer → setbacks for immunotherapy
  - Even Ipilimumab was developed based on a misunderstanding

Immune checkpoint inhibitors

Ipilimumab, 2011

- Mistakenly thought CTLA-4 protein is an immune response gas pedal and Ipilimumab is an agonist that promotes immune response

  Actually, CTLA-4 is a brake and Ipilimumab is an CTLA-4 inhibitor. Two wrongs make one right, patent was granted
- Inhibit CTLA-4, unleash general activation of T-cell responses
  - Lots of side effects

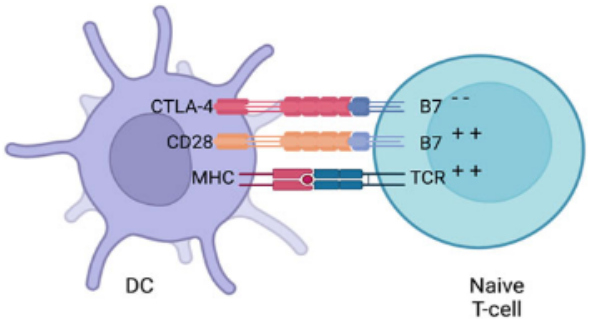


FIGURE 5. CTLA-4 suppression. Naive T-cells migrate to lymph nodes to become activated. Activationis usually provided by both MHC (loaded with an antigen) and co-stimulation from B7 (interacting with CD28) provided by a DC. After early stimulation, CTLA-4 is translocated to the surface of DCswhich then competes with B7 to bind to CD28 and downregulates T-cell activation. Whether a naiveT-cells undergoes activation or anergy is dependent on the balance of between CD28:B7 andCD28:CTLA4 signalling. Figures were created with BioRender.com.

Immune checkpoint inhibitors

- PD-1/PD-L1 Inhibitors: more specific, less side effects
  - PD-1 inhibitors:
    - **Nivolumab and Pembrolizumab, 2014**

  - PD-L1 inhibitors:
    - **Atezolizumab, 2016**

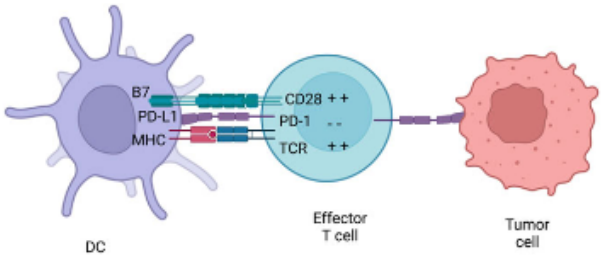


FIGURE 6. PD-1 inhibition. PD-1 is usually expressed on effector T-cells and binds to either PD-L1 or PD-L2. PD-L1 can be expressed both on immune cells and tumours. Therefore, PD-1 can inhibiteffector T-cells at different stages of an immune response. After PD-L1 is activated by the receptor,they can initiate a signalling complex able to counteract MHC and B7 signalling. Figures were created with BioRender.com.

Immune checkpoint inhibitors

- **Avelumab(Bavencio)**-anti PDL1,appr 2017→metastatic urothelial, advanced renal, Merkel cell

- **Durvalumab(Imfinzi)**-antiPDL1, appr2017 → NSCLC,SCLC,biliary tract

- **Cemiplimab (Libtayo)**-antiPD1, appr 2018→ CSCC,BCC,NSCLC

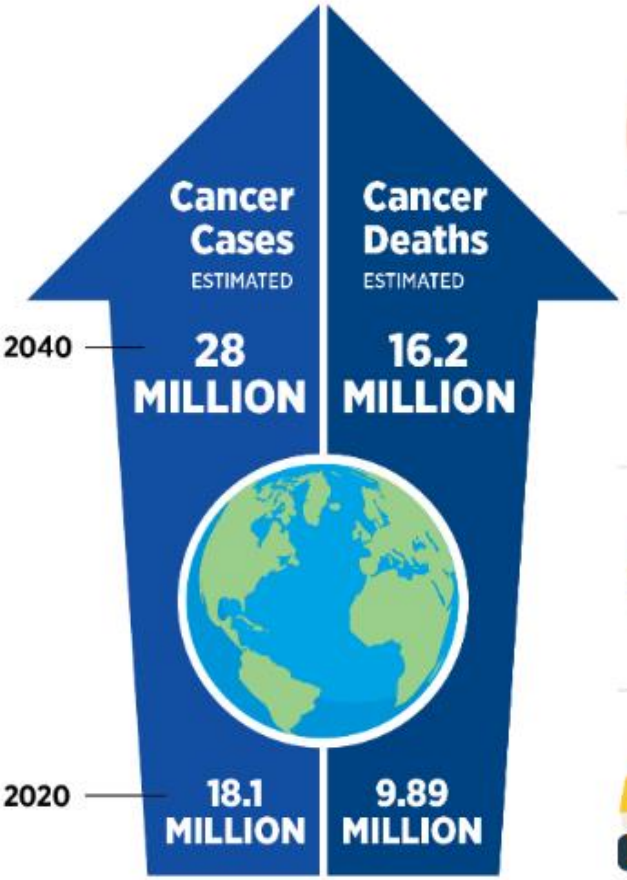
- **Dostarlimab(Jemperli)**-antiPD1, appr 2021→ recurrent endometrial, dMMR solid tumors

- **Retifanlimab(Zynyz)**-antiPD1,FDA appr 03/2023 → Merkel cell

- **Nivolumab-Relatlimab (Opdualag)**-antiPD1+antiLAG3, appr 03/2022 → 1st line unresectable/metastatic melanoma (EMA approval 09/22 only PDL1<1%)

Global Burden of Cancer

Cancer poses a major challenge to public health across the globe, as reflected by the rising number of new cancer diagnoses and cancer deaths around the world. The disparate burden of cancer based on the sociodemographic index (SDI) of a country (a composite measure of social and economic development that accounts for income per capita, average years of education, and total fertility rate for people younger than 25) highlights key barriers to achieving global health equity. The following examples offer a broad view of the global burden of cancer.



Data from https://gco.iarc.fr/.

Tracheal, bronchus, and lung cancers are the leading causes of cancer deaths worldwide. There were 2.04 million deaths from tracheal, bronchus, and lung cancers in 2019. Smoking contributed to more than 64 percent of these deaths.

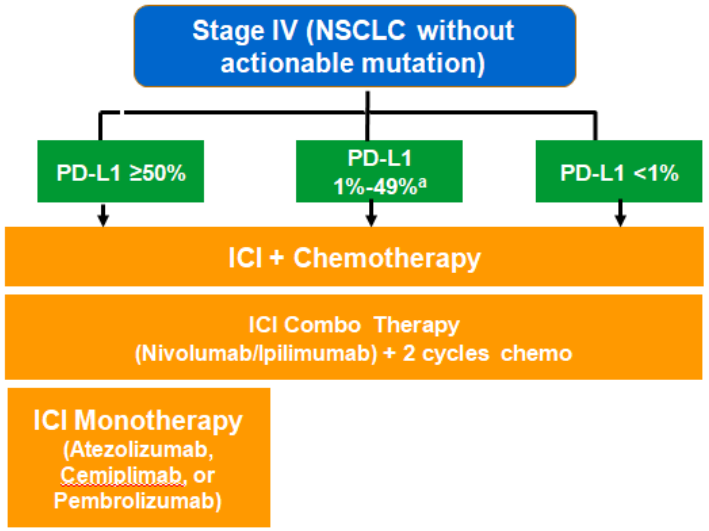
Breast cancer was the leading cause of cancer-related deaths among women in 2019 (30). There are stark disparities based on the socioeconomic status of a country, prompting researchers worldwide to provide strategies to influence global policy and improve lives of patients irrespective of where they live.

Diagnoses and deaths from colorectal cancer more than doubled over the past three decades. A substantial rise in new cases has been observed in adults younger than 50, particularly in countries with a high SDI. Poor diet, smoking, and alcohol were the main risk factors.

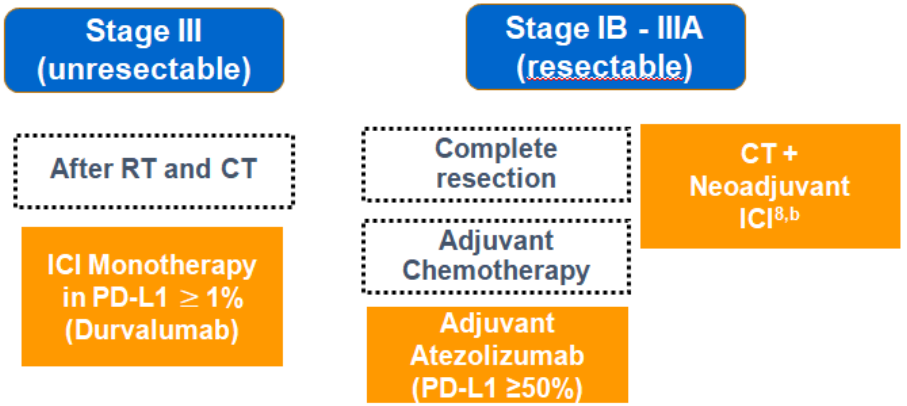
There were 1.19 million cancer cases and 396,000 cancer deaths among adolescents and young adults (people ages 15 to 39) in 2019. The highest incidence was observed in countries with higher SDI while the highest deaths occurred in countries with a lower SDI.

ICIs are rapidly expanding treatment options in NSCLC

- For first-line treatment, options include:[1-5]
  - ICI monotherapy +/- chemotherapy
  - Double ICI +/- chemotherapy
  - Double ICI + short chemotherapy (2 cycles)[6]



- Immunotherapy options are also available in other NSCLC settings:
  - In unresectable Stage III NSCLC after CT/RT
  - As adjuvant in resected NSCLC with high PD-L1 expression[7]
  - As neoadjuvant in combination with CT in resectable NSCLC[8]



Stage IV chemo+IO 5year OS 32% , double than chemo only pts

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS

Trifluridine + tipiracil ± bevacizumab[e,34,35]
Trifluridine + tipiracil 35 mg/m² up to a maximum dose of 80 mg per dose (based on the trifluridine component)
PO twice daily days 1–5 and 8–12
Bevacizumab 5 mg/kg on days 1 and 15
Repeat every 28 days

Pembrolizumab[36] (dMMR/MSI-H only)
Pembrolizumab 2 mg/kg IV every 3 weeks
or Pembrolizumab 200 mg IV every 3 weeks
or Pembrolizumab 400 mg IV every 6 weeks

Nivolumab[37] (dMMR/MSI-H only)
Nivolumab 3 mg/kg every 2 weeks
or Nivolumab 240 mg IV every 2 weeks
or Nivolumab 480 mg IV every 4 weeks

Nivolumab + ipilimumab[38] (dMMR/MSI-H only)
Nivolumab 3 mg/kg (30-minute IV infusion) and ipilimumab 1 mg/kg (30-minute IV infusion) once every 3 weeks for four doses, followed by Nivolumab 3 mg/kg IV or nivolumab 240 mg IV every 2 weeks or Nivolumab 480 mg IV every 4 weeks

Dostarlimab-gxly[39] (dMMR/MSI-H only)
Dostarlimab-gxly 500 mg IV every 3 weeks for 4 doses followed by 1000 mg IV every 6 weeks

Trastuzumab[ff] + pertuzumab[40]
(HER2-amplified and *RAS* and *BRAF* WT)
Trastuzumab 8 mg/kg IV loading dose on day 1 of cycle 1, followed by 6 mg/kg IV every 21 days
Pertuzumab 840 mg IV loading dose on day 1 of cycle 1, followed by 420 mg IV every 21 days

Trastuzumab[ff] + lapatinib[41]
(HER2-amplified and *RAS* and BRAF WT)
Trastuzumab 4 mg/kg IV loading dose on day 1 of cycle 1, followed by 2 mg/kg IV weekly
Lapatinib 1000 mg PO daily

Trastuzumab[ff] + tucatinib[42]
(HER2-amplified and *RAS* and BRAF WT),
Trastuzumab 8 mg/kg IV loading dose on day 1 of cycle 1, followed by 6 mg/kg IV every 21 days
Tucatinib 300mg PO twice daily

Fam-trastuzumab deruxtecan-nxki[43]
Fam-trastuzumab deruxtecan-nxki 6.4 mg/kg IV on day 1
Repeat every 21 days

Encorafenib + cetuximab[44-46]
(*BRAF* V600E mutation positive)
Encorafenib 300 mg PO daily
Cetuximab 400 mg/m² IV followed by 250 mg/m² IV weekly
or Cetuximab 500 mg/m² IV every 2 weeks

Encorafenib + panitumumab[44-46]
(*BRAF* V600E mutation positive)
Encorafenib 300 mg PO daily
Panitumumab 6 mg/kg IV every 14 days

Larotrectinib[47] (*NTRK* gene fusion-positive)
100 mg PO twice daily

Entrectinib[48] (*NTRK* gene fusion-positive)
600 mg PO once daily

Selpercatinib[49] (*RET* gene fusion-positive)
Patients ≥50 kg: 160 mg PO twice daily
Patients <50 kg: 120 mg PO twice daily

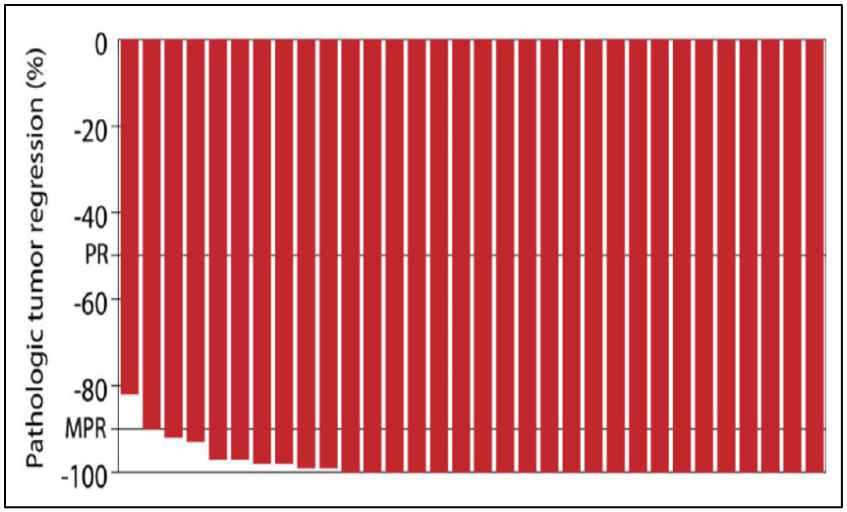

The New York Times
A Cancer Trial's Unexpected Result: Remission in Every Patient
ALJAZEERA
Tumours disappear in all participants of small cancer drug trial
ΕΘΝΟΣ
Υγεία | 11.06.2022 19:12
Νέα πειραματική θεραπεία με μονοκλωνικό αντίσωμα εξαφανίζει τον καρκίνο από ασθενείς
HEALTH
small Trial of Cancer Drug Leads to Remission for Every Patient: 'A Lot of Happy Tears'
ΤΟ ΒΗΜΑ
Science
Ανοσοθεραπεία εξαφάνισε τον καρκίνο
Πειραματική θεραπεία εξαφάνισε τον καρκίνο από όλους τους ασθενείς που συμμετείχαν στη δοκιμή
«Είναι η πρώτη φορά που συμβαίνει αυτό στην ιστορία του καρκίνου».

NICHE-1

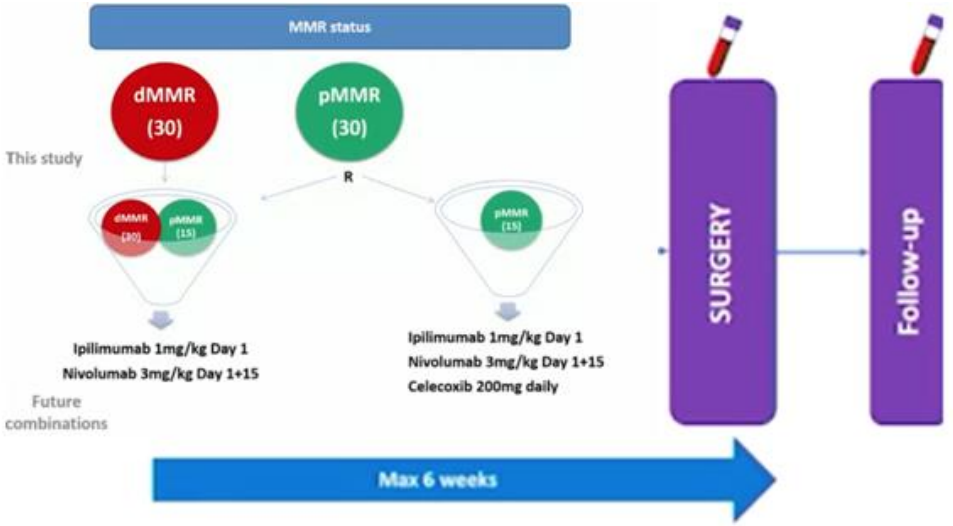
ARTICLES
https://doi.org/10.1038/s41591-020-0805-8
nature medicine

Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers

Myriam Chalabi[1,2,3], Lorenzo F. Fanchi[2,4,17], Krijn K. Dijkstra[2,4,17], José G. Van den Berg[5,17], Arend G. Aalbers[6], Karolina Sikorska[7], Marta Lopez-Yurda[7,8], Cecile Grootscholten[1], Geerard L. Beets[6,9], Petur Snaebjornsson[5], Monique Maas[10], Marjolijn Mertz[11], Vivien Veninga[2,4], Gergana Bounova[4,12], Annegien Broeks[13], Regina G. Beets-Tan[9,10], Thomas R. de Wijkerslooth[1], Anja U. van Lent[14], Hendrik A. Marsman[15], Elvira Nuijten[7], Niels F. Kok[6], Maria Kuiper[1], Wieke H. Verbeek[1], Marleen Kok[3,16], Monique E. Van Leerdam[1], Ton N. Schumacher[2,4], Emile E. Voest[1,2,4,17] and John B. Haanen[2,3,17]



- 40 patients (21 dMMR and 20 pMMR tumors)
- Treatment well tolerated, all patients underwent radical resections without delays (meeting primary endpoint)
- 20/20 dMMR tumors (100%) had pathological response - 19 MPRs (≤10% residual viable tumour) and 12 path CRs
- 4/15 pMMR tumors (27%) had path responses (3 MPRs, 1 PR, 0 CR)



2022 ESMO Congress – presented by Myriam Chalabi

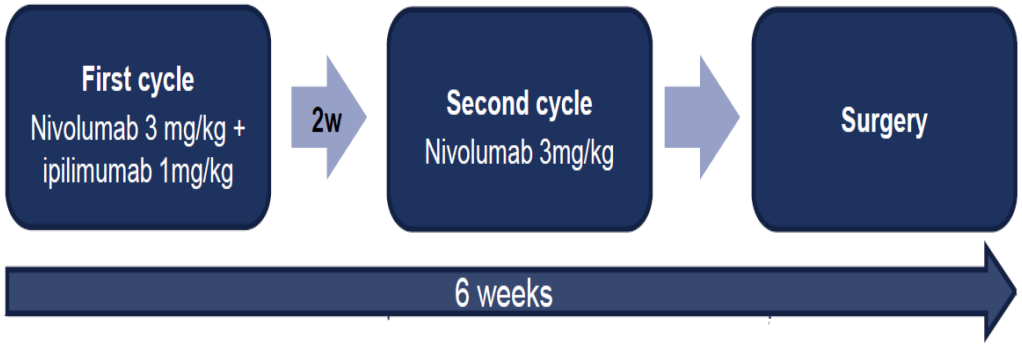
PARIS 2022 ESMO congress

NICHE-2

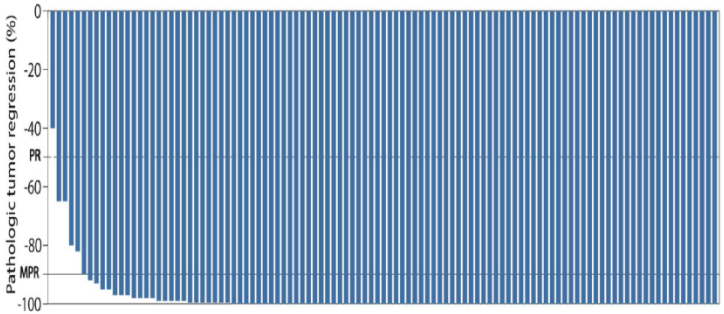
-107 pts dMMR tumors
-cT3 ή N+
(63% T4a /T4b)
-no active immune related disease

Neoadjuvant immune checkpoint inhibition in locally advanced MMR-deficient colon cancer: the NICHE-2 study

M. Chalabi[1], Y. Verschoor, J. Van den Berg, K. Sikorska, G. Beets, A. Van Lent, C. Grootscholten, A. Aalbers, N. Buller, H. Marsman, E. Hendriks, P. Burger, T. Aukema, S. Oosterling, R. Beets-Tan, T.N. Schumacher. M.E. Van Leerdam. E.E. Voest. J.B. Haanen



Major pathologic response in 95% of patients; 67% pCR



2022 ESMO Congress – presented by Myriam Chalabi

npj | breast cancer

www.nature.com/npjbcancer

REVIEW ARTICLE OPEN

Check for updates

Immunotherapy in breast cancer: an overview of current strategies and perspectives

Véronique Debien[1], Alex De Caluwé[2], Xiaoxiao Wang[3], Martine Piccart-Gebhart[4], Vincent K. Tuohy[5], Emanuela Romano[6] and Laurence Buisseret[3,7]✉

Recent progress in immunobiology has led the way to successful host immunity enhancement against breast cancer. In triple-negative breast cancer, the combination of cancer immunotherapy based on PD-1/PD-L1 immune checkpoint inhibitors with chemotherapy was effective both in advanced and early setting phase 3 clinical trials. These encouraging results lead to the first approvals of immune checkpoint inhibitors in triple-negative breast cancer and thus offer new therapeutic possibilities in aggressive tumors and hard-to-treat populations. Furthermore, several ongoing trials are investigating combining immunotherapies involving immune checkpoint inhibitors with conventional therapies and as well as with other immunotherapeutic strategies such as cancer vaccines, CAR-T cells, bispecific antibodies, and oncolytic viruses in all breast cancer subtypes. This review provides an overview of immunotherapies currently under clinical development and updated key results from clinical trials. Finally, we discuss the challenges to the successful implementation of immune treatment in managing breast cancer and their implications for the design of future clinical trials.

npj Breast Cancer (2023)9:7 ; https://doi.org/10.1038/s41523-023-00508-3

Table 1. The main results from principal phase 2 and 3 trials in metastatic and early breast cancer.

Trial	Study design	Setting	Number of subjects	Drug	Primary endpoint	Main results	Additional information	FDA approval
IMpassion130[16]	Phase 3 randomized controlled	mTNBC first line	902	**Arm A**: Nab-Paclitaxel + Atezolizumab **Arm B**: Nab-Paclitaxel + placebo	PFS and OS in ITT and PD-L1 + (hierarchical)	PFS: 7.2 vs 5.5mo HR = 0.80 (0.69-0.92) OS: 21.0 vs 18.7mo HR = 0.87 (0.725-1.02) PD-L1+: OS 25.4 vs 19.7mo HR = 0.69 (0.54-0.88) PFS: 7.5 vs 5.3 mo HR = 0.63	Testing in PD-L1+ population was not planned initially	**Withdrawn**
KEYNOTE-355[19,20]	Phase 3 randomized controlled	mTNBC first line	847	**Arm A**: Nab-Paclitaxel/Paclitaxel/Gemcitabine-Carboplatin + pembrolizumab **Arm B**: Nab-Paclitaxel/Paclitaxel/Gemcitabine-Carboplatin + placebo	PFS and OS in PD-L1 CPS score ≥10, ≥1, and ITT (hierarchical)	PFS: 7.5 vs 5.6mo HR = 0.82 (0.69-0.97) CPS ≥10: PFS: 9.7 vs 5.6mo HR = 0.66 (0.50-0.88) OS: 23 vs 16.1mo HR = 0.73 (0.55-0.95) CPS ≥1: PFS: 7.6 vs 5.6mo HR = 0.75 (0.62–0.91)	*p* value boundary for OS in CPS ≥1 not met, no ITT testing	**Yes**
IMpassion131[17]	Phase 3 randomized controlled	mTNBC first line	651	**Arm A**: Paclitaxel + Atezolizumab **Arm B**: Paclitaxel + placebo	PFS in PD-L1+ and ITT (hierarchical)	ITT: PFS: 5.7 vs 5.6mo HR = 0.86 (0.70-1.05)[a] OS: 19.2 vs 22.8 mo HR = 1.12 (0.88–1.43) PD-L1+: PFS: 6.0 vs 5.7mo HR = 0.82 (0.60–1.12) OS: 22.1 vs 28.3 mo HR = 1.11 (0.76–1.64)	[a] PFS in ITT population was not formally tested	No
SAFIR02-BREAST IMMUNO[93]	Phase 2	Metastatic HER2-negative 1st Line	199	**Arm A**: durvalumab **Arm B**: chemotherapy	PFS	mPFS: 2.7 vs 4.6mo HR = 1.4 (1.00–1.96), $p = 0.047$ mOS: 21.7 vs 17.9mo HR = 0.84 (0.54–1.29) $p = 0.423$ TNBC PD-L1+ (32) mOS = 27.3 vs 12.1mo HR = 0.37 (0.12–1.13) $p = 0.0678$	Ten patients had therapeutic break	No
KEYNOTE-119[13]	Phase 3 randomized open-label	mTNBC >1st Line	1098	**Arm A**: Pembrolizumab **Arm B**: Physician's chemotherapy choice	OS in ITT and PD-L1+	OS: 9.9 vs 10.8 mo HR = 0.97 (0.82–1.15) PFS: 2.1 vs 3.3 mo HR = 1.60 (1.33–1.92) CPS >10: OS: 12.7 vs 11.6mo HR = 0.78 (0.57–1.06) PFS: 2.1 vs 4.3 mo HR = 1.14 (0.82–1.59)		No
Topacio/ KEYNOTE-162[30]	Phase 2 open-label	mTNBC <third line	55	Niraparib + Pembrolizumab	ORR	ORR in full analysis population: 18% (90% CI 10–29) RR in *gBRCAmut*: 47% (90% CI 24–70)	DCR in full analysis 42% (90% CI 31–54)	No
PANACEA[26]	Phase 1b/2 open-label	Metastatic HER2-positive >first line	52	Trastuzumab + Pembrolizumab	OR in PD-L1+	In PD-L1+: OR: 6/40 patients (90% CI 7–29) PFS: 2.7mo (90% CI 2.6–4.0)	OS: PD-L1+: NR (13.1-NR) vs PD-L1-: 7mo (90% CI 4-9–9-8)	No
KATE2[27]	Phase 2 randomized, double-blind	Metastatic HER2-positive ≥first line	202	**Arm A**: T-DM1 + atezolizumab **Arm B**: T-DM1 + placebo	PFS in ITT	PFS: 8.2 vs 6.8 8mo HR = 0.82 (0.55–1.23) $p = 0.33$ In PD-L1 +: PFS: 8.5 vs 4.1mo HR+: HR: 1.08 (0.64–1.82) HR-: HR: 0.58 (0.31–1.10)	OS: HR = 0.74 (0.42–1.30)	No

Table 1 continued

Trial	Study design	Setting	Number of subjects	Drug	Primary endpoint	Main results	Additional information	FDA approval
ENHANCE 1[94]	Phase 2 randomized open-label	Metastatic Luminal >third line	88	**Arm A**: Eribulin + Pembrolizumab **Arm B**: Eribulin	PFS	PFS: 4.1 vs 4.2mo HR = 0.80 (0.50–1.26) $p = 0.33$	Cross-over 14 patients	No
MEDIOLA[a][29]	Phase 1b/2 open-label	Metastatic HER2-negative >first line	34	Olaparib + Durvalumab	DCR	DCR at week 12: 80% (90% CI: 64.3–90.9) DCR at week 28: 50% (90% CI 33.9–66.1)	ORR at week 12 63.3% (95% CI 48.9–80.1)	No
GELATO-trial[95]	Phase 2	Metastatic HER2-negative Lobular >third line	40	Carboplatin + Atezolizumab	PFS at 6mo	4/23 patients free of PD at week 24 ORR: 19% CBR at week 24: 39%	First analysis	
KEYNOTE-522[34]	Phase 3 randomized controlled	Neoadjuvant Adjuvant TNBC	1774	**Arm A:** Carboplatin + Paclitaxel + 4xAC + pembrolizumab -> pembrolizumab in adjuvant **Arm B:** Carboplatin + Paclitaxel + 4xAC + placebo -> placebo in adjuvant	8y-EFS	pCR: 64.8 vs 51.2% $p < 0.001$ PD-L1+: pCR 68.9 vs 54.9% Events: 15.7 vs 23.8% HR = 0.63 (0.48–0.82)	Favorable trend in OS; Long-term FU awaited	**Yes**
GeparNUEVO[36]	Phase 2 randomized controlled	Neoadjuvant TNBC	174	**Arm A:** Durvalumab + nab-paclitaxel -> EC **Arm B**: Placebo + nab-paclitaxel -> EC	pCR	pCR: 53.4 vs 44.2% OR:1.45(0.80–2.63) 3y-iDFS 84.9 vs 76.9% HR = 0.54, (0.27–1.09), stratified log-rank $p = 0.0559$ 3y-OS: 95.1 vs 83.1% HR = 0.26 (0.09–0.79) $p = 0.0076$ in PD-L1+: pCR 58 vs 50.7% $p = 0.363$	Higher pCR in high TILs and high TMB and WoO sTILs stratification for iDFS	No
NeoTRIPaPDL1[37]	Phase 3 randomized open-label	Neoadjuvant TNBC	280	**Arm A**: Carboplatin + Nab-Paclitaxel + atezolizumab -> adjuvant AC/EC **Arm B**: Carboplatin + Nab-Paclitaxel -> adjuvant AC/EC	5y-EFS	pCR: 48.6 vs 44.4% OR: 1.18 (0.74–1.89), $p = 0.48$ PD-L1+: pCR 51.9 vs 48% OR: 2.08 (1.64–2.65)	EFS data not mature TILs unbalanced	No
IMpassion031[35]	Phase 3 randomized controlled	Neoadjuvant TNBC	455	**Arm A**: Nab-paclitaxel + 4xAC+atezolizumab **Arm B**: Nab-paclitaxel + 4xAC + placebo	pCR in ITT and PD-L1+	pCR: 57.6 vs 41.1% $p = 0.0044$ PD-L1+: pCR 68.8 vs 49.3% $p = 0.021$	EFS data not mature	No
GIADA[41]	Phase 2	Neoadjuvant Luminal B	43	EC-> Nivolumab+ triptorelin + exemestane	pCR	pCR: 16.3% (7.4–34.9)	Any PD-L1	No
I-SPY 2[40]	Phase 2 randomized open-label	Neoadjuvant HER2-negative	181	**Arm A**: weekly paclitaxel followed by AC+ pembrolizumab **Arm B**: weekly paclitaxel followed by AC [other arms in I-SPY-program not mentioned here]	pCR	pCR rates: HER2-: 44 vs 17% HR+ and HER2-: 30 vs 13% TNBC: 60 vs 22%	Pembrolizumab was the first of 10 agents in the I-SPY program to graduate in the HR-positive/ERBB2-negative signature.	No

AC anthracycline-cyclophosphamide, *CBR* clinical benefit rate, *CPS* combined positive score, *DCR* disease control rate, *EC* epirubicin-cyclophosphomide, *EFS* event-free survival, *FU* follow-up, *HR* hazard ratio, *HR−* hormone-receptor negative, *HR+* hormone-receptor-positive, *ITT* intention-to-treat, *OR* overall response, *ORR* objective response rate, *OS* overall survival, *pCR* pathological complete response, *PD* progressive disease, *PD-L1* programmed death-ligand 1, *PFS* progression-free survival, *TILs* tumor-infiltrating lymphocytes, *TMB* tumor mutational burden, *TNBC* triple-negative breast cancer, *WoO* window-of-opportunity.
[a]Only breast cancer cohort.

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RESEARCH SUMMARY

Pembrolizumab plus Chemotherapy in Advanced Triple-Negative Breast Cancer

Cortes J et al. DOI: 10.1056/NEJMoa2202809

CLINICAL PROBLEM

In an interim analysis in the KEYNOTE-355 trial, pembrolizumab plus chemotherapy resulted in longer progression-free survival than chemotherapy alone among patients with advanced triple-negative breast cancer whose tumors expressed a programmed death ligand 1 (PD-L1) combined positive score (CPS; the number of PD-L1–staining tumor cells, lymphocytes, and macrophages, divided by the total number of viable tumor cells, multiplied by 100) of 10 or more. Results from the final analysis of overall survival are needed.

CLINICAL TRIAL

Design: The international phase 3, double-blind, randomized, placebo-controlled KEYNOTE-355 trial examined the efficacy and safety of pembrolizumab plus chemotherapy among patients with previously untreated, locally recurrent inoperable or metastatic triple-negative breast cancer.

Intervention: 847 patients were assigned in a 2:1 ratio to receive pembrolizumab (200 mg every 3 weeks for up to 35 infusions) plus chemotherapy or placebo plus chemotherapy. Primary end points included overall survival among patients whose tumors expressed PD-L1 with a CPS of 10 or more (CPS-10 subgroup), among those whose tumors expressed PD-L1 with a CPS of 1 or more (CPS-1 subgroup), and in the intention-to-treat population.

RESULTS

Efficacy: Overall survival was significantly longer with pembrolizumab–chemotherapy than with chemotherapy alone in the CPS-10 subgroup. In the CPS-1 subgroup, the between-group difference was not significant; significance was not assessed in the intention-to-treat population.

Safety: The incidence of any adverse event related to the trial regimen was similar in the two trial groups; anemia, neutropenia, and nausea were most common. The incidence of adverse events of grade 3, 4, or 5 was also similar in the two groups.

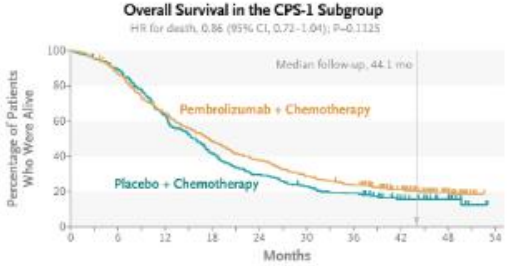
LIMITATIONS AND REMAINING QUESTIONS

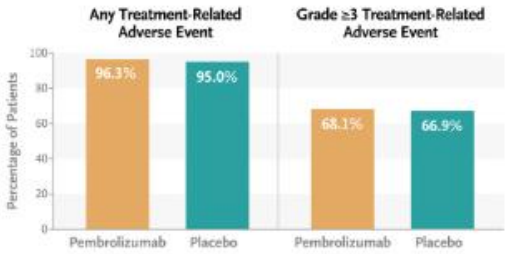
- The benefit of pembrolizumab was observed with both paclitaxel-based and nanoparticle albumin-bound paclitaxel–based chemotherapy, but the small number of patients who received paclitaxel precludes firm conclusions.

Links: Full Article | NEJM Quick Take | Editorial

Overall Survival in the CPS-10 Subgroup

Overall Survival in the CPS-1 Subgroup





CONCLUSIONS

Among patients with previously untreated advanced triple-negative breast cancer and PD-L1 expression scores of 10 or more, pembrolizumab plus chemotherapy resulted in longer overall survival than chemotherapy alone, and no new safety signals emerged.

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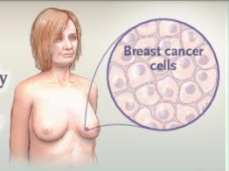
Pembrolizumab for Triple-Negative Breast Cancer

RANDOMIZED, DOUBLE-BLIND, PHASE 3 TRIAL



1174 Patients with previously untreated triple-negative breast cancer

	Neoadjuvant Pembrolizumab + chemotherapy, followed by surgery and adjuvant pembrolizumab (N=784)	Neoadjuvant Placebo + chemotherapy, followed by surgery and adjuvant placebo (N=390)
Pathological complete response at time of surgery	64.8%	51.2%
	Difference, 13.6 percentage points; 95% CI, 5.4–21.8; P<0.001	
Event-free survival	91.3% (95% CI, 88.8–93.3)	85.3% (95% CI, 80.3–89.1)
	HR for an event or death, 0.63; 95% CI, 0.43–0.93	
Grade ≥3 adverse events	76.8%	72.2%

P. Schmid et al. 10.1056/NEJMoa1910549

Immune checkpoint inhibitors- irAEs

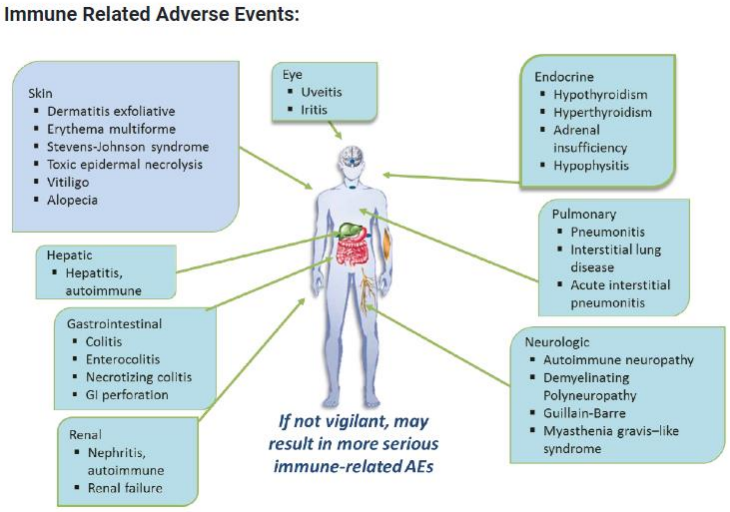
But ..toxicity matters!!

The side effects may involve any organ or system of the body but gastrointestinal, dermatological, hepatic, endocrine, and pulmonary toxicities predominate, and there should be a high level of suspicion that any changes are treatment related.

The incidence and onset of immune-related adverse effects (irAEs) varies based on the class and dose of ICPi administered, the type of cancer, and factors related to the patients.

In general, patients receiving anti-PD-1/PD-L1 antibodies have a lower incidence of any grade irAEs than those treated with anti-CTLA-4 agents, with combinations increasing the incidence, severity, and onset of irAEs.[2]

Variable onsets have been described for the different toxicities, from early occurrence within days to delayed onset up to 26 weeks, with a median onset of approximately 40 days.[2]



Immune checkpoint inhibitors in Oncology

Benefits[a]

- Improved survival
  - Long-term survival (years)
- Durable responses
- Favorable AE profile
  - Different AEs from those seen with chemotherapy or targeted therapy
  - Frequency of grade 3/4 toxicity no greater than with chemotherapy or targeted therapy

Challenges[b]

- Immune-mediated AEs
  - Can occur early or late during treatment, or after termination of therapy
  - Can present as common disease-related symptoms or non-specific symptoms
  - Can be severe or life-threatening
  - Can occur in virtually any organ in the body

a. Postow MA, et al. *J Clin Oncol.* 2015;33:1974-1982; b. Champiat S, et al. *Ann Oncol.* 2016;27:559-574.

Immune checkpoint inhibitors in Oncology

- Second revolution in checkpoint inhibition :new combinations and predictive biomarkers are being explored
- ICIs are currently tested in earlier stages of cancers as adj or neoadj therapy with impressive results in certain tumor types combined with good quality of life
- Pts should be referred to specialized centers encouraged to participate in clinical trials
- IrAEs present a unique challenge in modern oncology thus there is growing consensus regarding their pathophysiology and management in multidisciplinary teams.
- Ongoing trials aim to elucidate the relationships between irAEs and treatment outcomes, specific biomarkers that clinch an irAE diagnosis

Thank you for your attention!