FAKULTAS KEDOKTERAN
UNIVERSITAS TRISAKTI

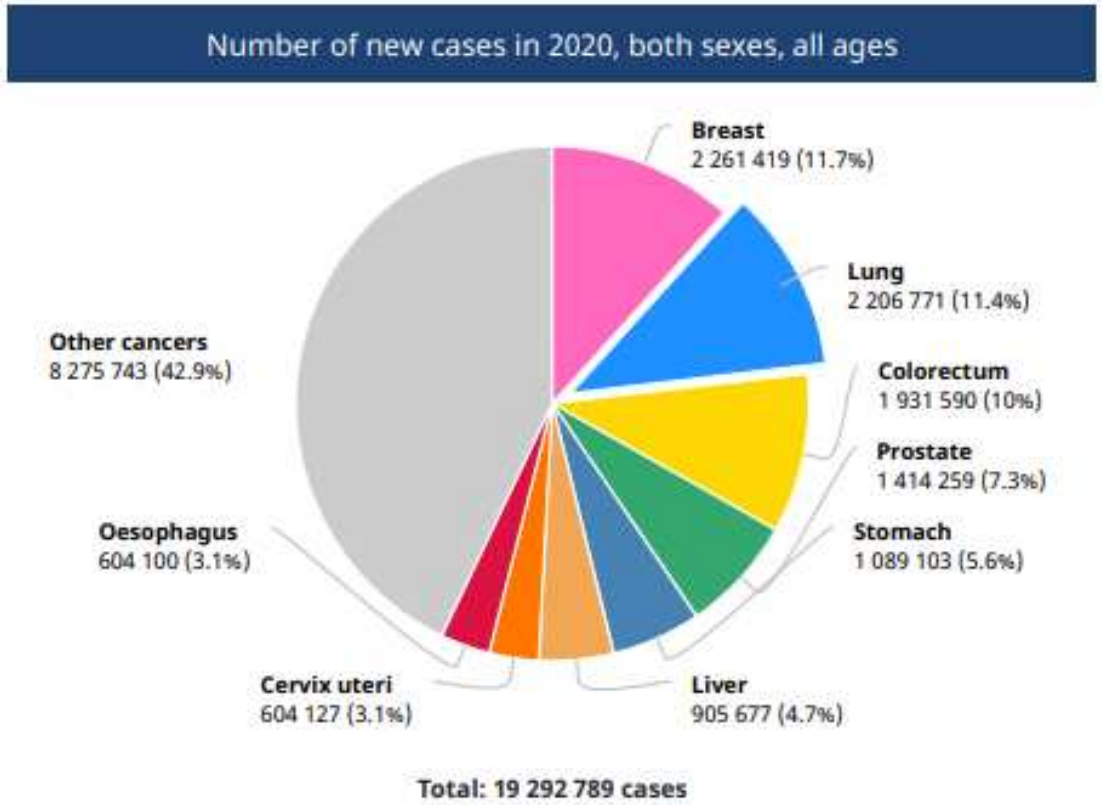
The role of Pembrolizumab for NSCLC management in Monotherapy-setting

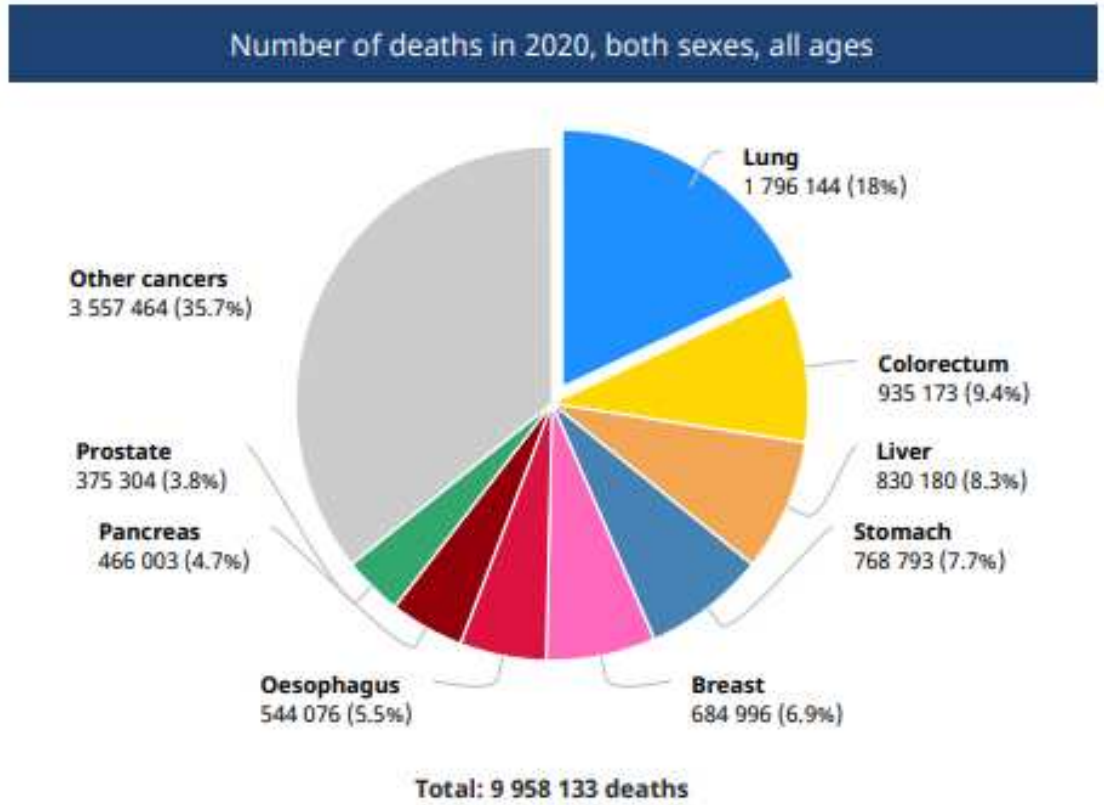
dr. Henie Widowati, Sp.P
Fakultas Kedokteran Universitas trisakti

MSD

Overview of Lung Cancer

Epidemiology: Global Incidence and Mortality for Lung Cancer

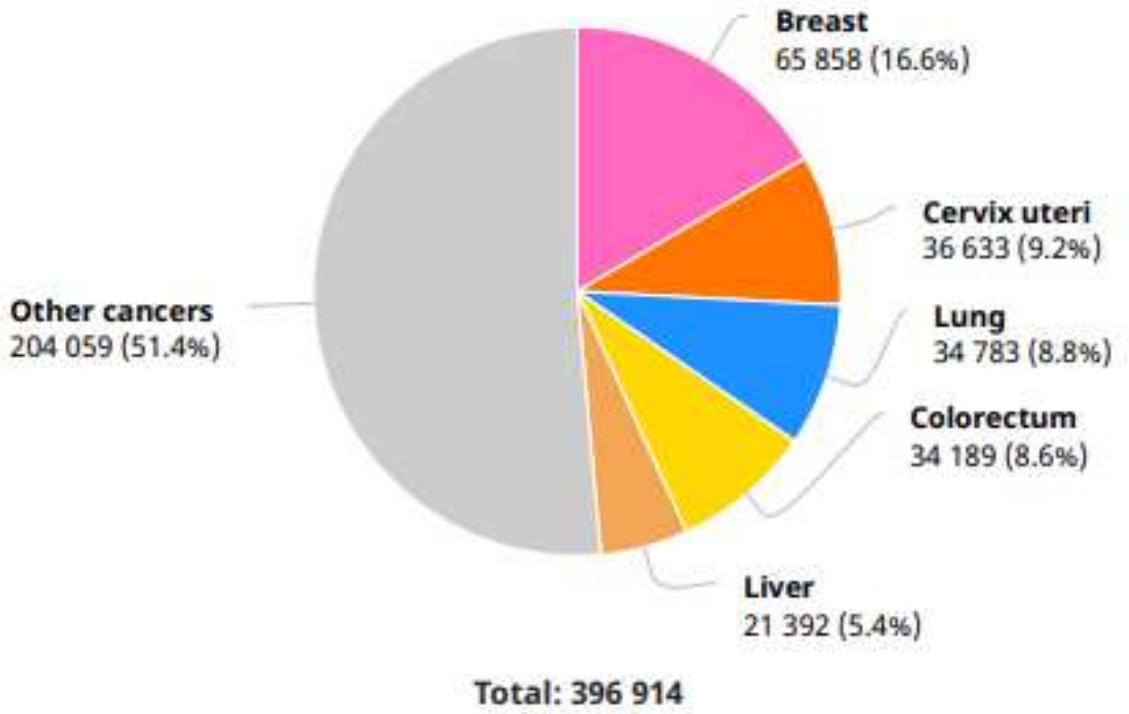




Source: Globocan 2020.

Lung cancer in Indonesia

Number of new cases in 2020, both sexes, all ages

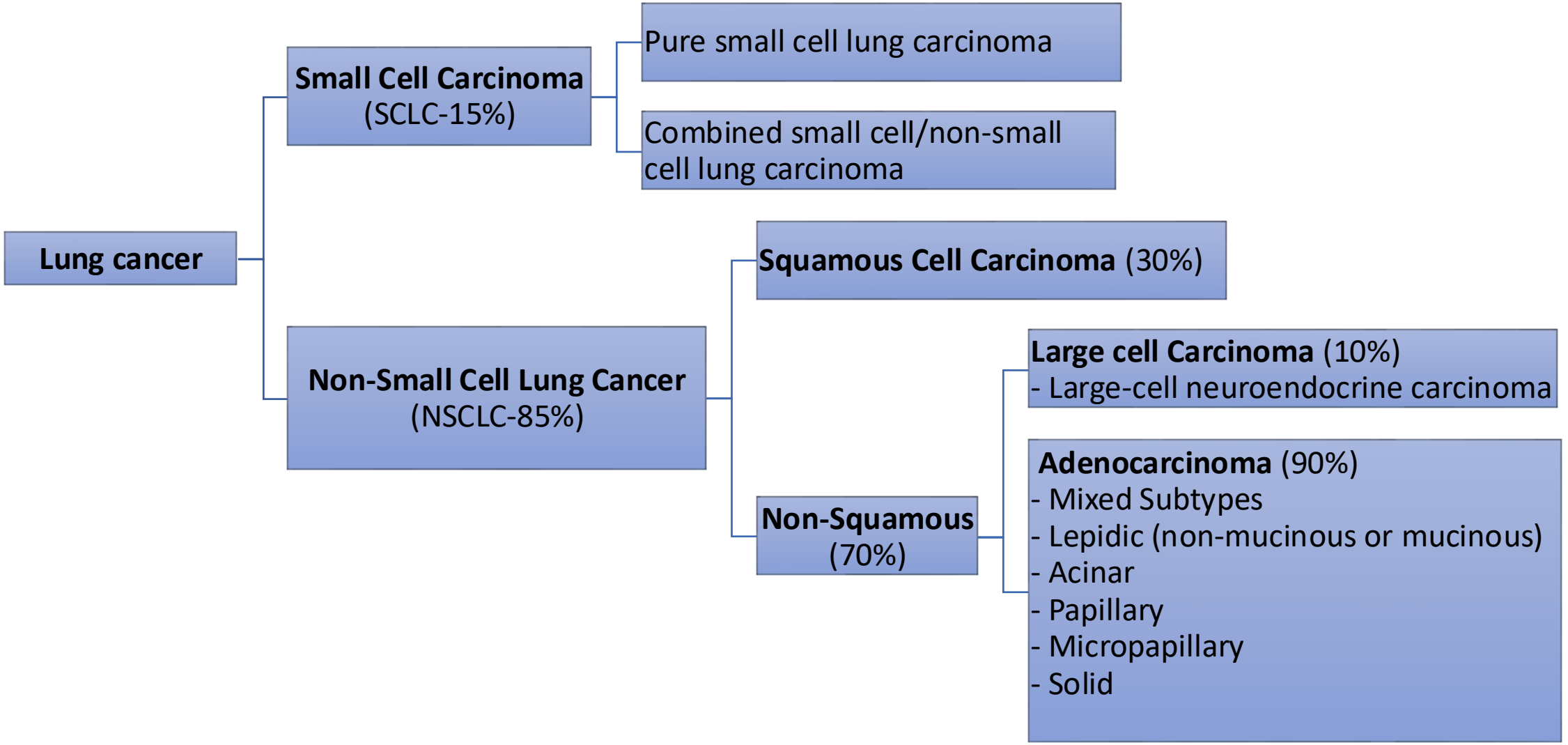


Mortality rate by cancer site

	Deaths			
Cancer	Number	Rank	(%)	Cum.risk
Breast	22 430	2	9.6	1.78
Cervix uteri	21 003	3	9.0	1.73
Lung	30 843	1	13.2	1.39
Liver	20 920	4	8.9	0.91
Nasopharynx	13 399	5	5.7	0.56
Colon	9 444	8	4.0	0.38
Non-Hodgkin lymphoma	9 024	9	3.8	0.38
Rectum	8 342	10	3.6	0.35
Leukaemia	11 530	6	4.9	0.42
Ovary	9 581	7	4.1	0.77
Prostate	4 863	13	2.1	0.38

Source: Globocan 2020.

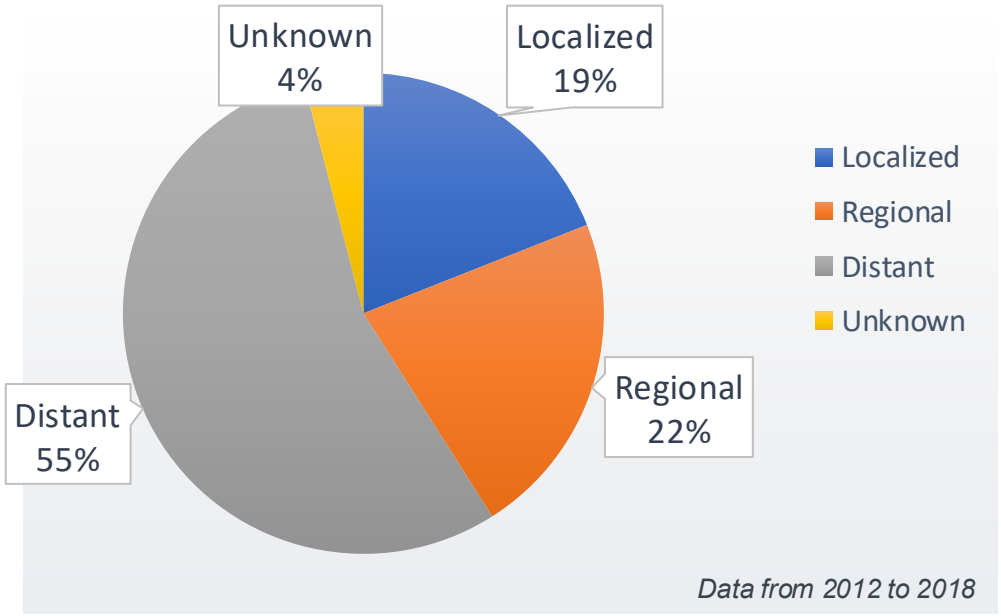
The Classification of Lung Cancer[1,2]



1. Mollberg N, et al. Adv Ther. 2011 March ; 28(3): 173–194. 2. Gridelli C, et al. Nat Rev Dis Primers. 2015 May 21;1:15009

Stage & Survival in mNSCLC

Percentage of Cases by Stage, All Races, Both Sexes [1]



Localized: Confined to Primary Site
Regional: Spread to Regional Lymph Nodes
Distant: Cancer Has Metastasized
Unknown: Unstaged

5-year relative survival rates for non-small cell lung cancer[2]

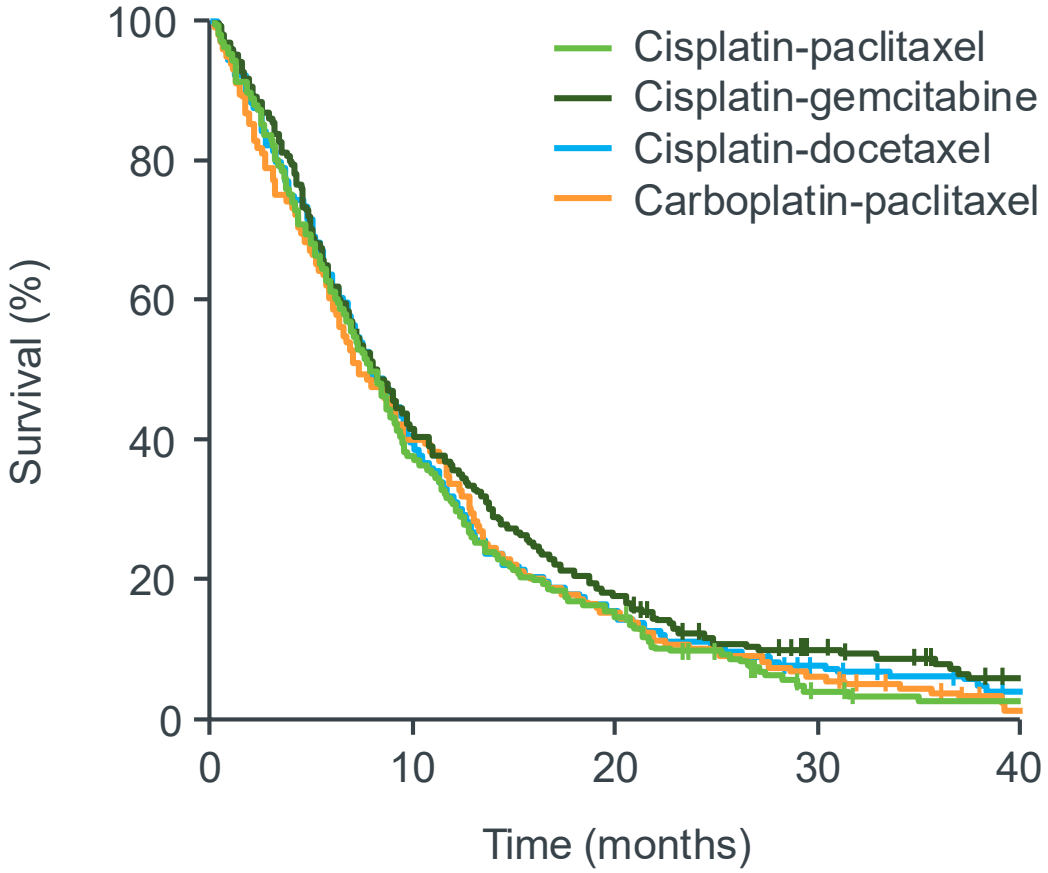
SEER stage	5-year relative survival rate
Localized	64%
Regional	37%
Distant	8%
All SEER stages combined	26%

Data from 2011 to 2017

5-year survival in population with Metastatic cancer (distant) NSCLC only 8%[2]

1. https://seer.cancer.gov/statfacts/html/lungb.html. 2. https://www.cancer.org/cancer/lung-cancer/detection-diagnosis-staging/survival-rates.html

Overall survival in NSCLC: a plateau has been reached for chemotherapy efficacy



Variable	Cisplatin + paclitaxel (N=288)	Cisplatin + gemcitabine (N=288)	Cisplatin + docetaxel (N=289)	Carboplatin + paclitaxel (N=290)
ORR – %	21	22	17	17
Median OS – mo	7.8	8.1	7.4	8.1
1 yr OS – %	31	36	31	34
Median PFS – mo	3.4	4.2†	3.7	3.1

In this pivotal trial by Schiller et al. (2002), the study design was amended to recruit only PS 0–1 patients due to high rate of SAEs seen among 66 PS 2 patients enrolled

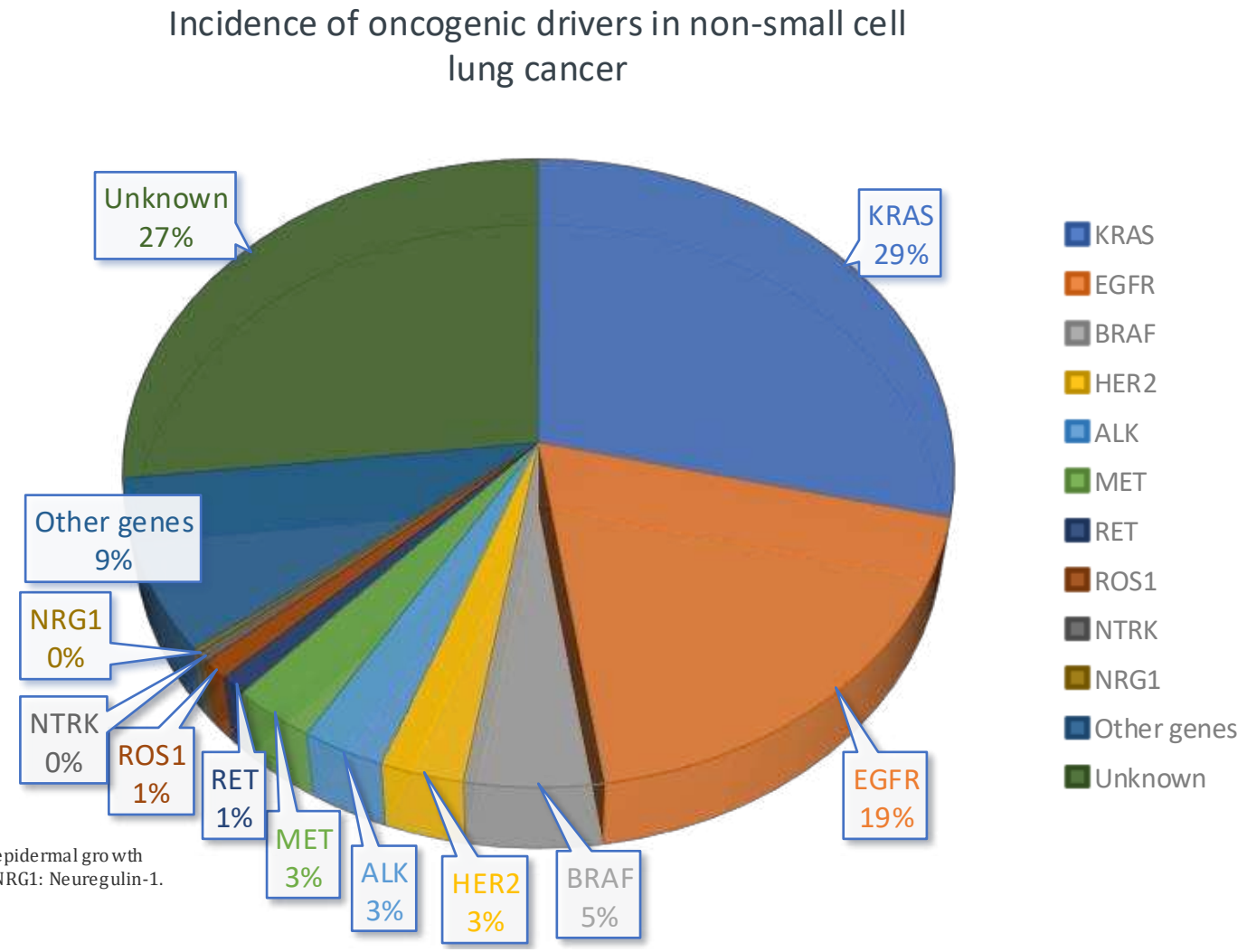
PS 2 (6% trial pop.) had a significantly lower rate of survival vs PS 0–1 patients

mo, months; PFS, progression-free survival; SAE, serious adverse event.
†p=0.001 by the log rank test for the comparison with cisplatin and paclitaxel.

Schiller JH, et al. N Engl J Med. 2002;346:92–98; Noonan KL et al. J Thorac Oncol. 2015;10:1523–1531

Oncogenic driver mutations in non-small cell lung cancer: Past, present and future

- Driver mutations have significantly altered the diagnostic work-up and reshaped the oncology treatment paradigm
- A better understanding of the biology of various subtypes of each driver mutation will help not only to match the optimal treatment to each patient, but also elucidate their respective resistance mechanisms, allowing for greater precision medicine



KRAS: Kirsten rat sarcoma; EGFR: Epidermal growth factor receptor; ALK: Anaplastic lymphoma kinase; HER2: Human epidermal growth factor 2; ROS1: c-ROS oncogene 1; NTRK: Neurotrophic receptor tyrosine kinase; RET: Rearranged during transfection; NRG1: Neuregulin-1.

Chevallier M et al. Oncogenes in NSCLC. World J Clin Oncol 2021 April 24; 12(4): 217-237

Selected oncogenic drivers and their treatments in non-small cell lung cancer

	Targeted therapy	ORR	PFS	OS
EGFR	Erlotinib	62%-83%	9.7-13.1 mo	19.3-26.3 mo
	Gefitinib	73.7%	9.5 mo	22 mo
	Afatinib	56%-67%	11.1 mo	25.8 mo
	Dacomitinib	74.9%	14.7 mo	34 mo
	Osimertinib	80%	18.9 mo	38.6 mo
ALK	Crizotinib	75.5%	11 mo	57 mo
	Ceritinib	72.5%	16.6 mo	NA
	Brigatinib0	79%	24 mo	NA
	Alectinib	82.9%	35 mo	NA
	Lorlatinib	76%	NA	NA
ROS1	Crizotinib	63-72%	15.9-19.2 mo	51 mo
	Lorlatinib	62%	19.3 mo	NA
	Entrectinib	77%	19 mo	NA
BRAF	Dabrafenib-trametinib	64%	10.9 mo	24.6 mo

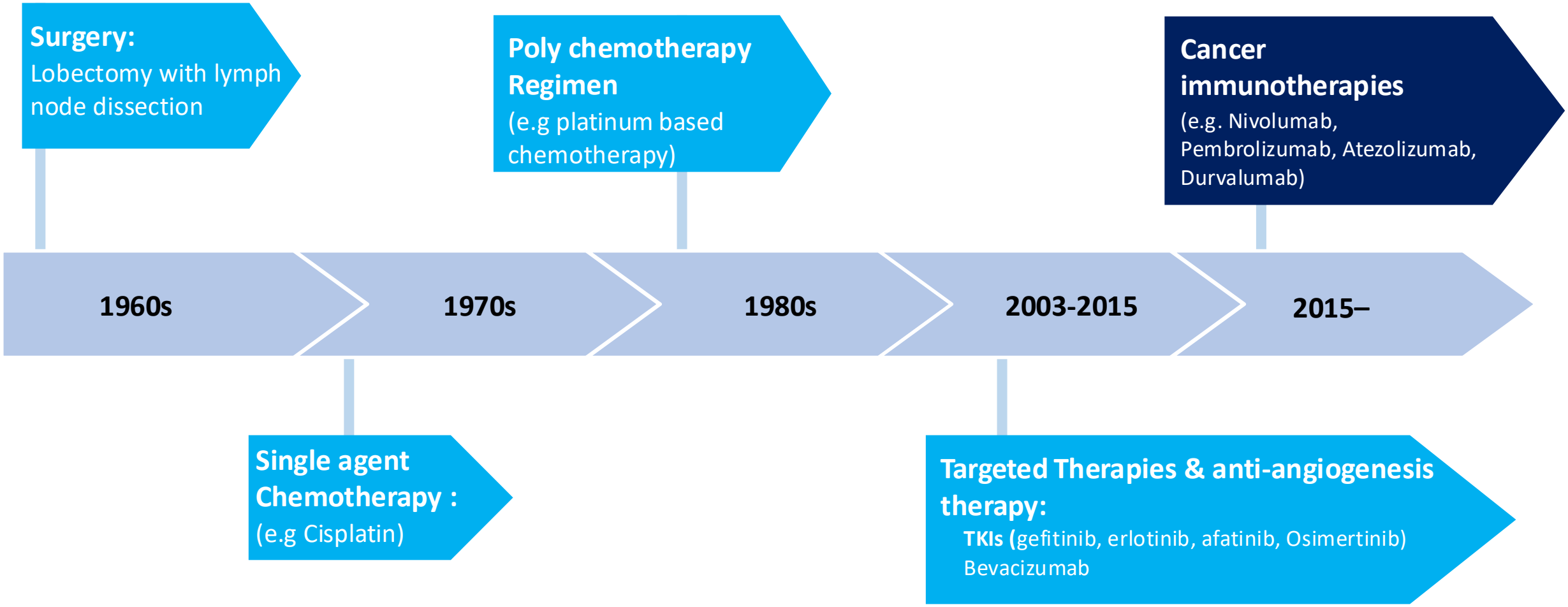
	Targeted therapy	ORR	PFS	OS
MET	Crizotinib	32%	7.3 mo	NA
	Cabozantinib	NA	NA	NA
	Capmatinib	68%	9.7 mo	NA
	Tepotinib	46%	NA	NA
NTRK	Entrectinib	70%	NA	NA
	Larotrectinib	75%	NA	NA
RET	Selpercatinib	85%	NA	NA
	Pralsetinib	70%	NA	NA
KRAS	Sotorasib	32.2%	10.2 mo	NA
	Adagrasib	45%	NA	NA
HER2	Trastuzumab-deruxtecan	62%	14 mo	NA
NRG1	Afatinib	NA	NA	NA

How about NSCLC without driver mutation…??

Chevallier M et al. Oncogenes in NSCLC. World J Clin Oncol 2021 April 24; 12(4): 217-237

Immuno-Oncology for Cancer Treatment

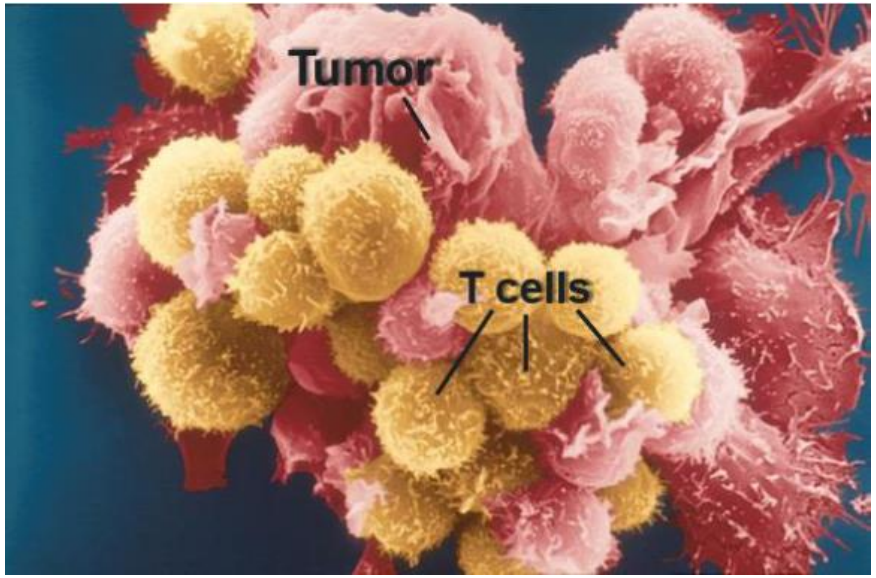
Cancer Treatment Evolution



Cheng et al. MedComm. 2021;2:692–729.

Immunotherapy shows a promising role in cancer treatment

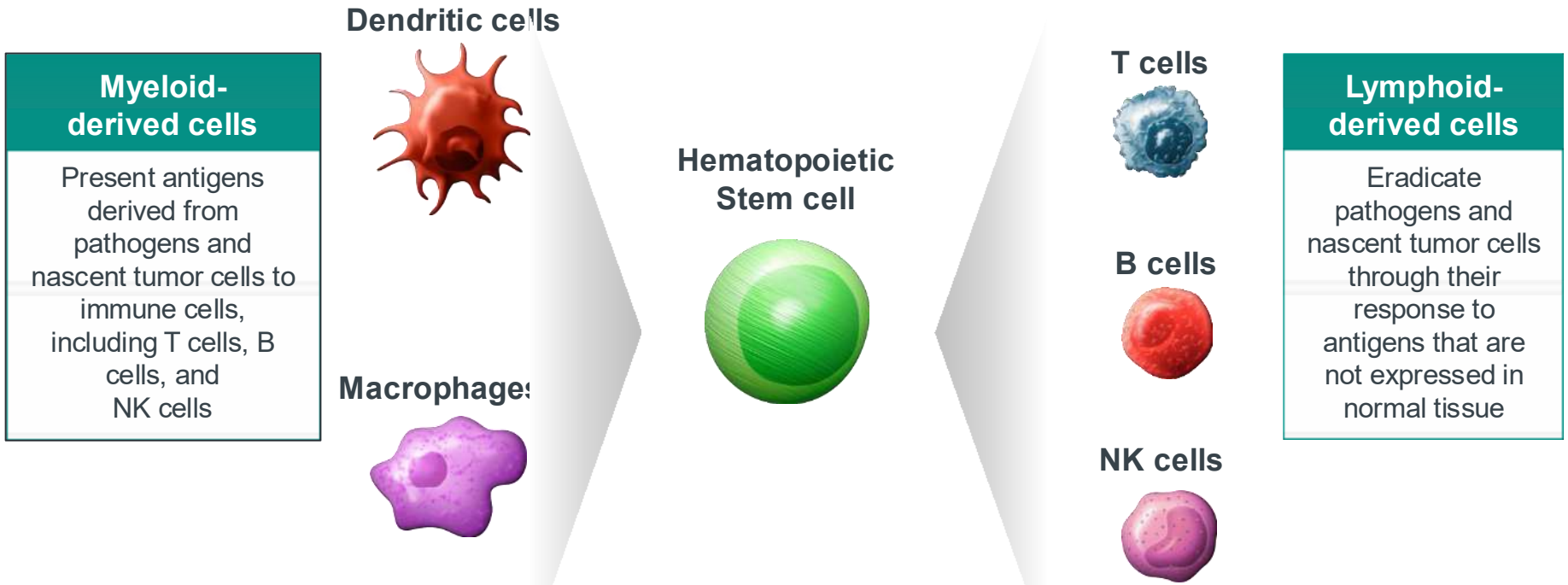
- The presence of immune cells (such as T cells) within a tumor has been correlated with better clinical outcome in some tumor types[1-3]
  - Less advanced stage
  - Absence of signs of metastasis
  - Increased survival
  - Reduced risk of relapse
- When the immune system is suppressed, the risk of developing certain cancers increases
  - HIV patients[4]
  - Transplant patients treated with immunosuppressants[5]



HIV = human immunodeficiency virus;

1. Hwang WT et al. Gynecol Oncol. 2012;124:192–198. 2. Pages F et al. N Engl J Med. 2005;353:2654–2666. 3. Loi S et al. J Clin Oncol. 2013;31:860– 867. 4. Engels EA et al. Int J Cancer. 2008;123:187–194. 5. Grulich AE et al. Lancet. 2007;370:59–67.. **6**. Drake CG *et al. Nat. Rev. Clin. Oncol*. 2014;11: 24–37.

The Immune System Can Fight Tumors Via a Variety of Functionally Specialized Cells[1]



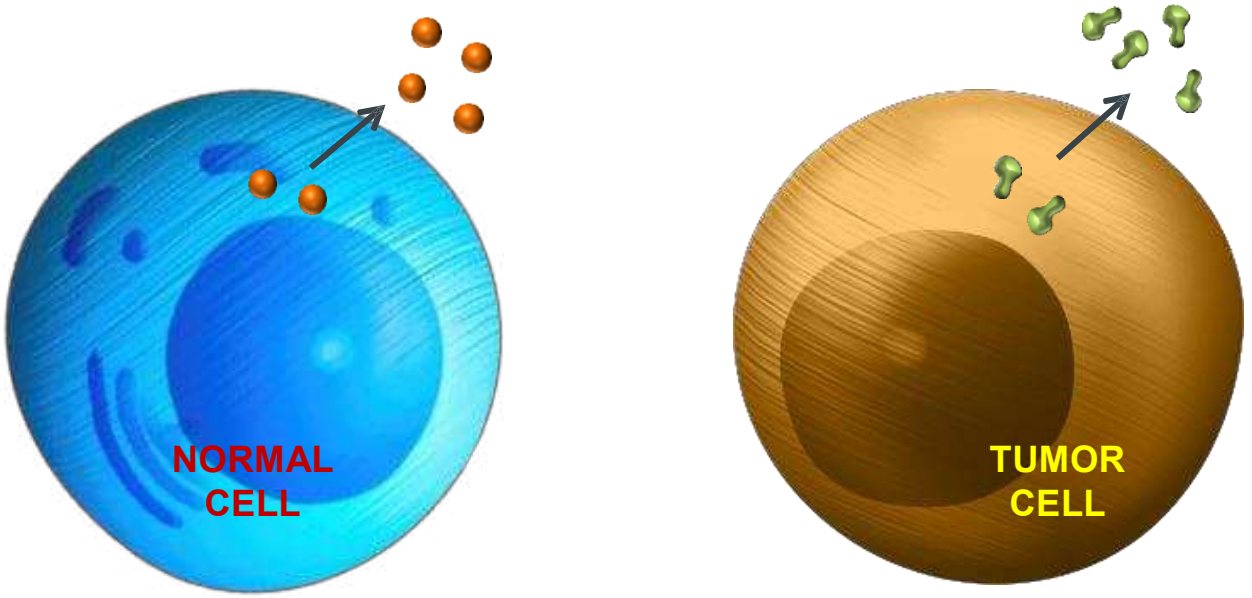
NK = natural killer.

1. Norvell A. In: Prendergast GC et al. *Cancer Immunotherapy*. 2nd ed. Elsevier; 2013:11–24.

Some Tumor Cells Express Multiple Antigens That Are Not Expressed by Normal Cells

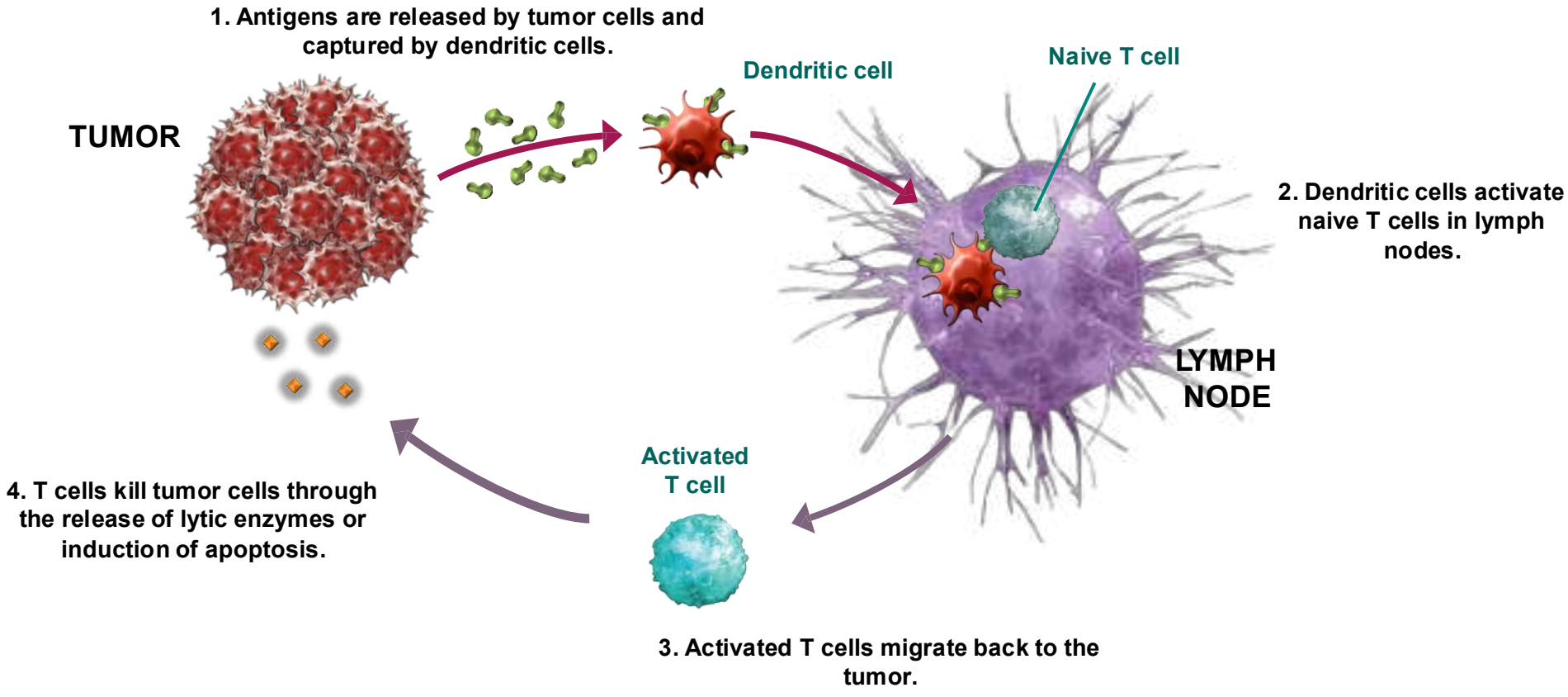
Normal cells release molecules that are captured by antigen-presenting cells, but they don't elicit an immune response.

Tumor cells release differentially expressed antigens that cause them to be recognized as foreign entities and therefore elicit an immune response.



Finn OJ. *N Engl J Med.* 2008;358:2704–2715.

T cells Are Important in the Ability of the Immune System to Detect and Destroy Tumor Cells[1]



1. May KF Jr et al. In: Prendergast GC et al. *Cancer Immunotherapy*. 2nd ed. Elsevier; 2013:101–113.

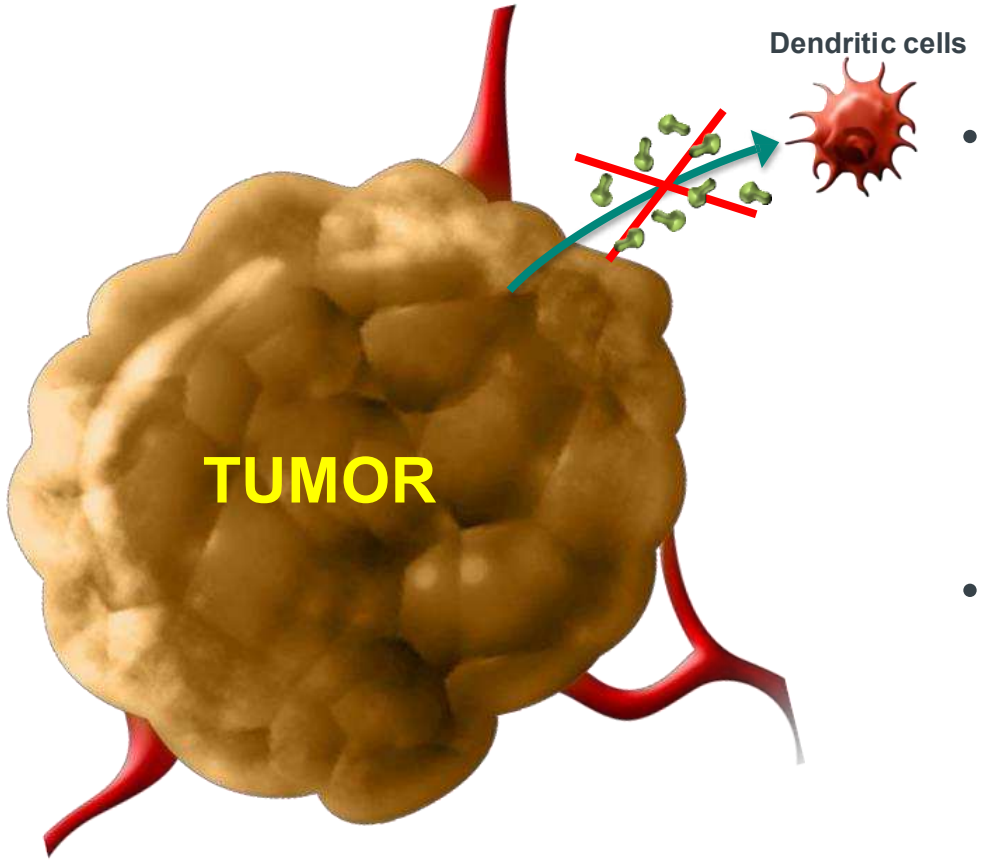
Tumor Cells Can Evade the Body's Immune Response Via Different Mechanisms

1. Loss of antigen expression[1]
2. Secreting immunosuppressive cytokines and recruiting immunosuppressive cells[2,3]
3. Exploiting immune checkpoint pathways, such as the PD-1 pathway[4]

PD-1 = programmed cell death protein 1.

1. Ahmad M et al. *Cancer Immunol Immunother.* 2004;53:844–854; **2.** Zou W. *Nat Rev Immunol*. 2006;6:295–307; **3.** Finn OJ. *N Engl J Med*. 2008;358:2704–2715; **4.** Pardoll DM. *Nat Rev Cancer*. 2012;12:252–264.

1. Loss of Antigen Expression

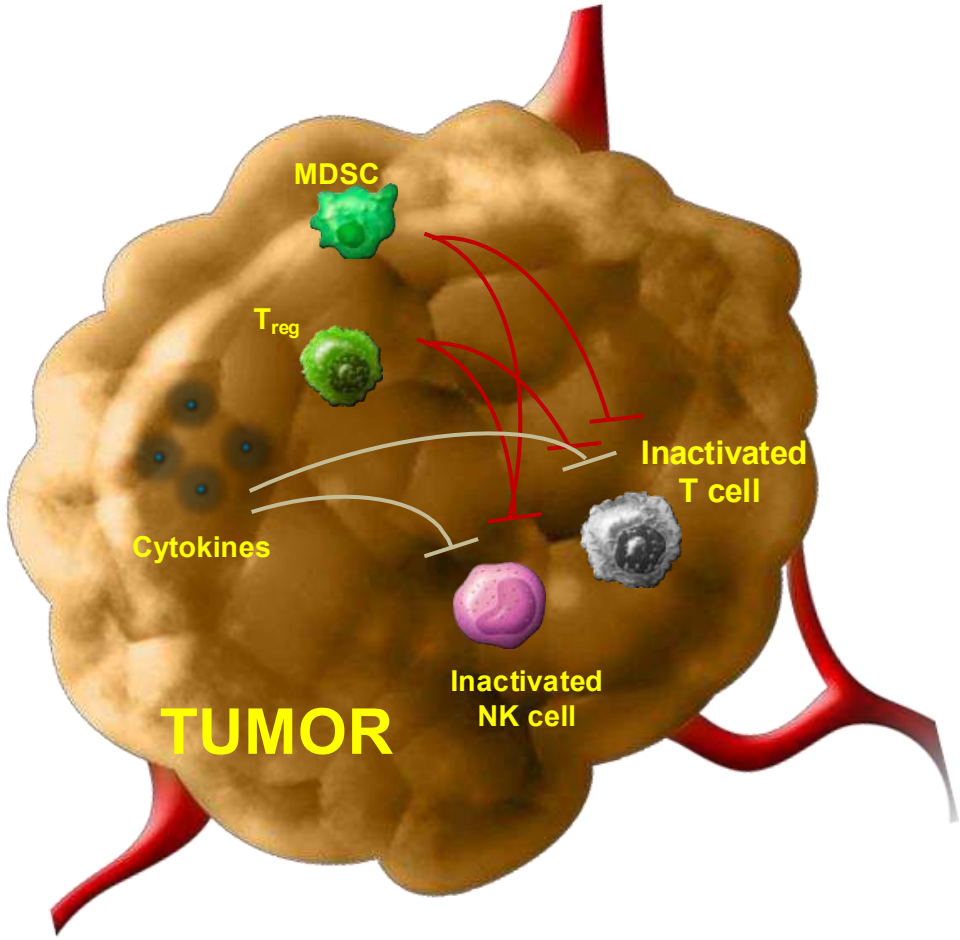


- In the adaptive immune response, the first step of tumor cell detection is antigen capture and presentation by dendritic cells[1]
- Tumors can escape detection by decreasing or completely shutting down antigen expression[2]

1. Pinzon-Charry A et al. *Immunol Cell Biol*. 2005;83:451–461.
2. Ahmad M et al. *Cancer Immunol Immunother.* 2004;53:844–854.

2. Secreting Immunosuppressive Cytokines and Recruiting Immunosuppressive Cells

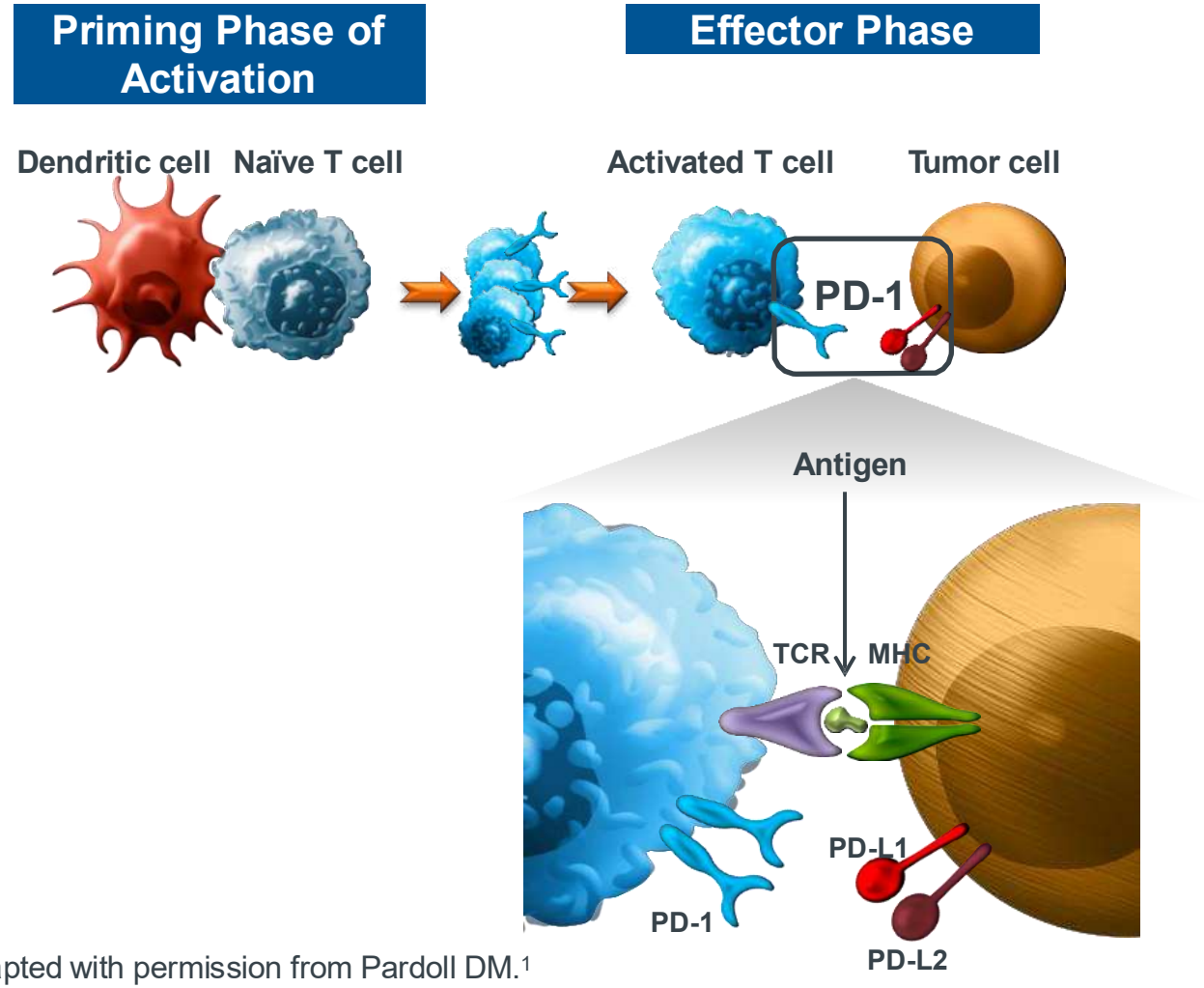
- Tumor cells can secrete cytokines (TGF-β, IL-10, VEGF) that have an inhibitory effect on T and NK cell function[1]
- Tumor cells can be infiltrated by immunosuppressive cells that can inhibit T cell function[2]:
  - T_{reg} cells
  - MDSCs



TGF-β = transforming growth factor β; IL-10 = interleukin10; VEGF = vascular endothelial growth factor; NK = natural killer; T_{reg} = T regulatory; MDSCs = myeloid-derived suppressor cells.

1. Zou W. *Nat Rev Immunol*. 2006;6:295–307; **2.** Finn OJ. *N Engl J Med*. 2008;358:2704–2715.

3. Exploiting the PD-1 Immune Checkpoint Pathway



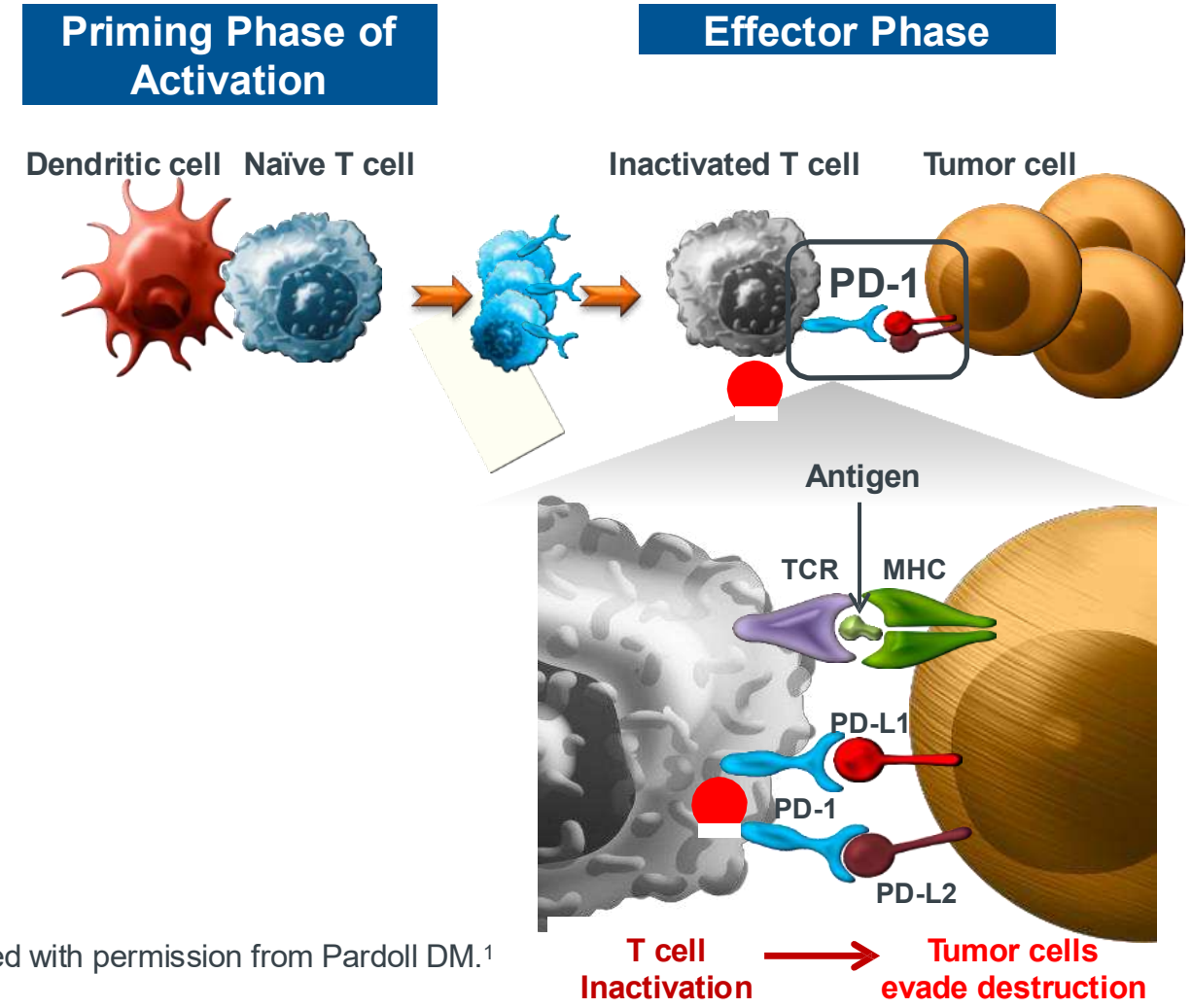
Adapted with permission from Pardoll DM.[1]

- Emerging research has identified PD-1 as an immune checkpoint pathway that tumor cells may exploit to evade immune surveillance
- Tumor cells may block immune responses via the PD-1 immune checkpoint pathway by expressing the dual PD-1 ligands, PD-L1 and PD-L2

PD-1 = programmed cell death protein 1; TCR = T-cell receptor; MHC = major histocompatibility complex; PD-L1 = programmed cell death ligand 1; PD-L2 = programmed cell death ligand 2.

1. Pardoll DM. *Nat Rev Cancer*. 2012;12:252–64.

3. Exploiting the PD-1 Immune Checkpoint Pathway



Adapted with permission from Pardoll DM.[1]

- PD-1 is upregulated on activated T cells during the effector phase of the immune response
- PD-L1 and PD-L2 engage the PD-1 receptor on T cells to downregulate T-cell activity in the effector phase

PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand 1; PD-L2 = programmed cell death ligand 2.

1. Pardoll DM. *Nat Rev Cancer*. 2012;12:252–264.

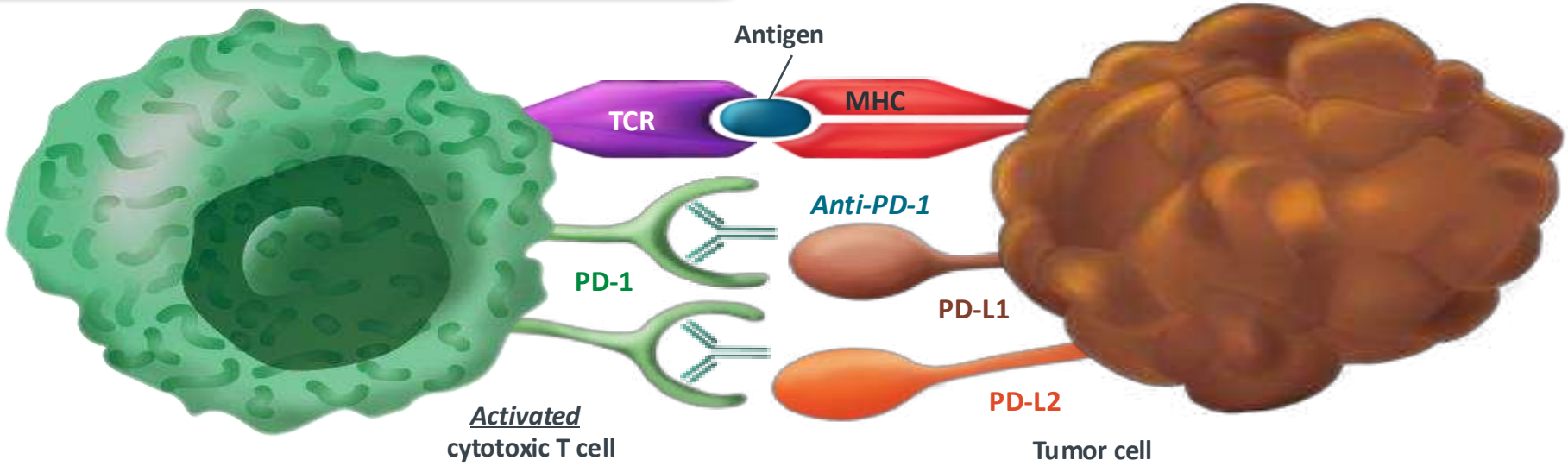
PD-1 Receptor Inhibition May Provide More Complete Pathway Blockade Than Targeting a Single Ligand

PD-1 Receptor Inhibition

- PD-1 is a receptor located on T cells
- Antibodies directed against the PD-1 receptor on T cells block the binding of both PD-L1 and PD-L2
- Signaling activities of both PD-L1 and PD-L2 are inhibited
- PD-L2 is expressed in bladder cancer and may be an essential part of its immuno-biology

PD-L1 Ligand Inhibition

- PD-L1 and PD-L2 are ligands located on tumor cells
- Antibodies targeting the PD-L1 ligand on tumor cells only block the binding of PD-L1 to the PD-1 receptor
- Signaling activities of PD-L2 are not inhibited



PD-1 = programmed death receptor-1; PD-L1 = programmed death ligand 1; PD-L2 = programmed death ligand 2.

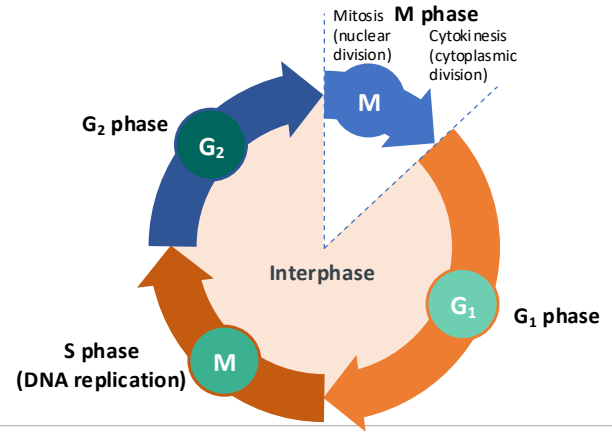
1. McDermott DF, Atkins MB. *Cancer Med.* 2013;2(5):662–673. Figure: Pardoll DM. *Nat Rev Cancer.* 2012;12:252–264.

IO therapy differs from conventional anticancer treatments

Immuno-oncology (IO) therapy, or cancer immunotherapy, differs from chemotherapy and targeted therapy:[1,2,3]

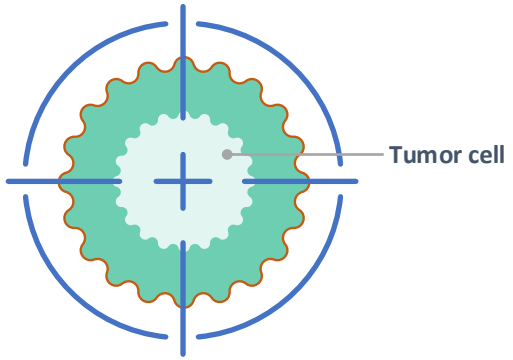
- Ideally, by modulating the immune system, it can be effective in a broad range of tumors, independent of tumor histology or driver mutations
- However, these therapies can also effect normal, healthy cells

Cytotoxic Chemotherapy



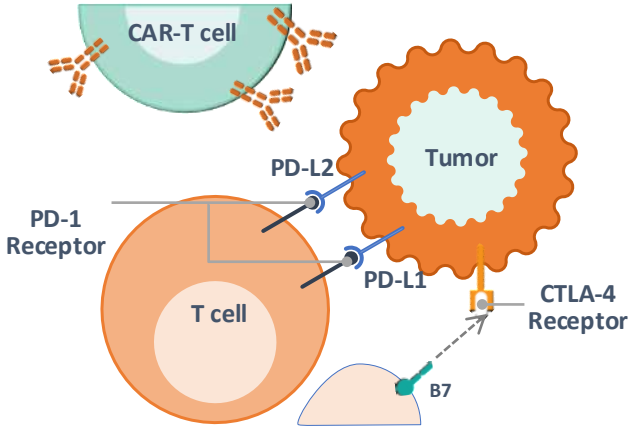
- Acts on all rapidly dividing cells, including tumor cells and some normal cells[2,3]
- Prevents cell growth and division[2,3]

Targeted Therapy



- Targets changes in cancer cells that promote growth, division, and spread (often as a result of mutation)[4,5]

IO Therapy

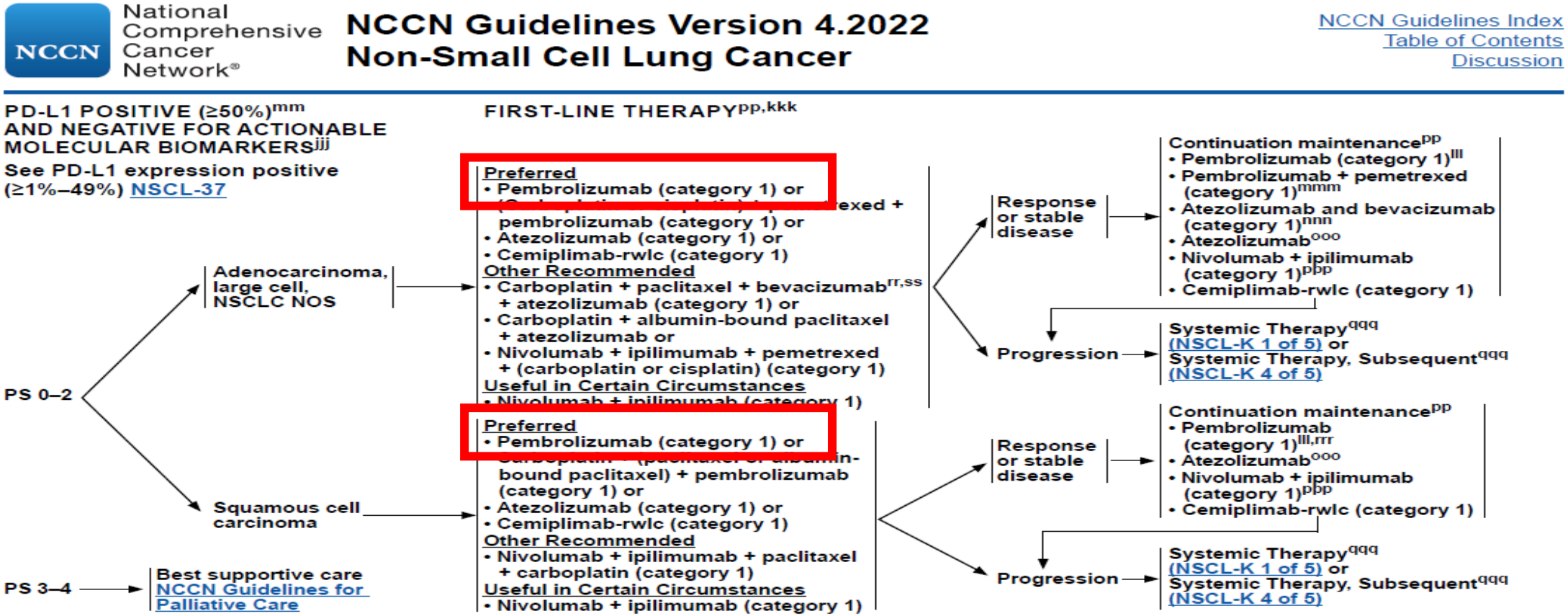


- Acts on the body's own immune system to fight cancer[5]
- Modulates immune inhibitory mechanisms to reactivate antitumor immunity[6,7]

1. Emens LA et al. *Eur J Cancer*. 2017;81:116–129. 2. *Molecular Biology of the Cell*, sixth edition by Bruce Alberts et al. Copyright © 2015 by Bruce Alberts, Alexander Johnson, Julian Lewis, David Morgan, Martin Raff, Keith Roberts, and Peter Walter. Used by permission of W. W. Norton & Company, Inc. 3. National Cancer Institute. Chemotherapy to treat cancer. https://www.cancer.gov/about-cancer/treatment/types/chemotherapy. Accessed on: 14 August 2020. 4. National Cancer Institute. Targeted therapy to treat cancer. https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies. Accessed on: 14 August 2020. 5. Boolell V et al. *Cancers (Basel).* 2015;7(3):1815–1846. 6. Pardoll DM. *Nat Rev Cancer*. 2012;12(4):252–264. 7. Garon EB. *Semin Oncol.* 2015;42(suppl 2):S11–S18.

Immunotherapy in Monotherapy-setting

First Line Setting management (PD-L1 ≥ 50%): NCCN Guideline



[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).
[pp] Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease (NSCL-J).
[rr] Criteria for treatment with bevacizumab: non-squamous NSCLC, and no recent history of hemoptysis.
[ss] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[jjj] Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents or presence of an oncogene, which would predict lack of benefit. If there are contraindications, refer to NSCL-K 1 of 5 (adenocarcinoma) or NSCL-K 2 of 5 (squamous cell carcinoma).
[kkk] For patients who require an urgent start to therapy but molecular testing is pending, consider holding immunotherapy for one cycle, unless confirmed that no driver mutations are present.
[lll] If pembrolizumab monotherapy given.
[mmm] If pembrolizumab/carboplatin/pemetrexed or pembrolizumab/cisplatin/pemetrexed given.
[nnn] If atezolizumab/carboplatin/paclitaxel/bevacizumab given.
[ooo] If atezolizumab/carboplatin/albumin-bound paclitaxel or atezolizumab given (category 1 following atezolizumab alone).
[ppp] If nivolumab + ipilimumab ± chemotherapy given.
[qqq] If patient has not received platinum-doublet chemotherapy, refer to "systemic therapy." If patient received platinum chemotherapy and anti-PD-1/PD-L1, refer to "subsequent therapy."
[rrr] If pembrolizumab/carboplatin/(paclitaxel or albumin-bound paclitaxel) given.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

KEYNOTE-024: Pembrolizumab vs platinum-doublet chemotherapy as first line mNSCLC treatment

(5 Years Follow-up)

Reck M, et al. J Clin Oncol. 2021 Jul 20; 39(21):2339-2349

KEYNOTE-024: Pembrolizumab vs platinum-doublet chemotherapy as first line mNSCLC treatment

Patients (N=305):

Key Eligibility Criteria

- Untreated Stage IV NSCLC
- PD-L1 TPS ≥50%
- ECOG PS 0 – 1
- No EGFR mutation or ALK translocation
- No untreated brain metastases
- No Active autoimmune disease requiring systemic therapy

R 1:1

Pembrolizumab 200 mg + *(Q3W, 2 years)*

Second-Course Pembrolizumab[c]

Pembrolizumab 200 mg *(Q3W, up to17 cycles)*

Treatment continued until PD, TRAEs of unacceptable severity, withdrawal of consent, or investigator decision to withdraw the patient

Platinum-doublet Chemotherapy [a] *(Q3W, 4-6 cycles)*

PD[d]

Crossover Pembrolizumab

Pembrolizumab 200 mg *(Q3W, up to 35 cycles)*

Primary End Points:

PFS (RECIST v1.1 per BICR)

Secondary End Points:

OS, Safety, ORR

Exploratory: DOR

Chemotherapy treatment:

- Pemetrexed + carboplatin/cisplatin[b]
- Paclitaxel + carboplatin
- Gemcitabin + carboplatin/cisplatin

[a]Optional pemetrexed maintenance therapy for nonsquamous disease. [b]Permitted for nonsquamous disease only. [c]Patients randomized to pembrolizumab who completed 2 years of therapy or who stop pembrolizumab after achieving CR and then had PD were eligible for a second course of pembrolizumab monotherapy [d]Prior to the DMC recommendation and amendment 6, which permitted those in the chemotherapy arm to be offered pembrolizumab (based on interim analysis 2 data), patients were eligible for crossover when PD was confirmed by blinded, independent central radiology review.

Brahmer JR, et al. KEYNOTE-024 5 years OS update: First-line Pembrolizumab vs platinum-based chemotherapy in patients with mNSCLC and PD-L1 TPS≥50%. Presented virtually at the 2020 European Society for Medical Oncology (ESMO) Sep 19-21, 2020

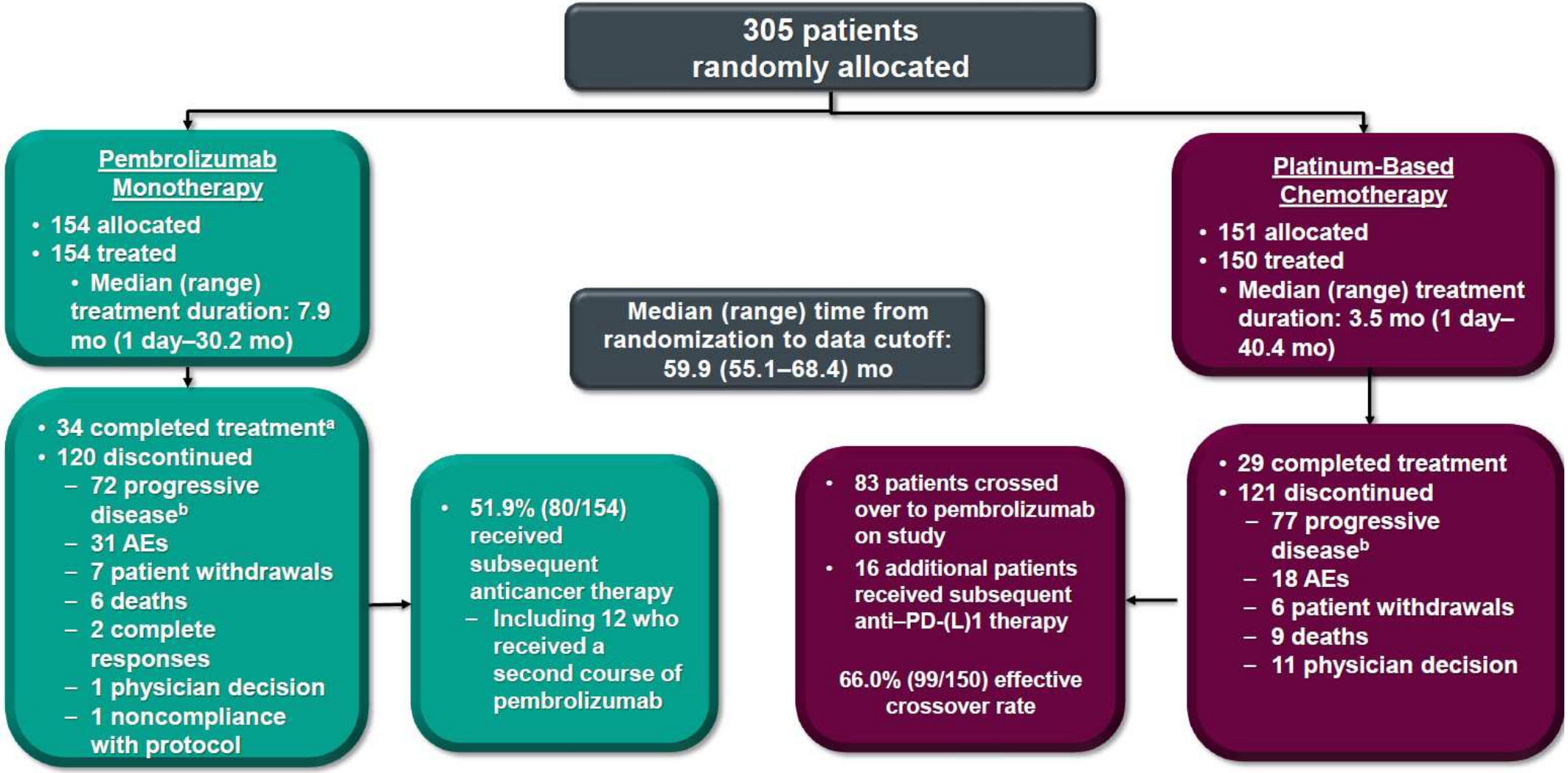
KEYNOTE-024: Baseline Characteristics

	Pembrolizumab n=154	Chemotherapy n=151	2 years (35 cycles) of pembrolizumab n=39[a]	Second Course of Pembrolizumab N=12[b]
Median age, years (range)	64.5 (33–90)	66.0 (38–85)	61.0 (43–80)	60.0 (43-77)
Men, n (%)	92 (59.7)	95 (62.9)	25 (64.1)	8 (66.7)
ECOG PS 1, n (%)	99 (64.3)	98 (64.9)	23 (59.0)	9 (75.0)
East Asian enrollment site, n (%)	21 (13.6)	19 (12.6)	8 (20.5)	3 (25.0)
Squamous histology, n (%)	29 (18.8)	27 (17.9)[c]	2 (5.1)	1 (8.3)
Current/former smoker, n (%)	149 (96.8)	132 (87.4)	37 (94.9)	12 (100)
Treated Brain metastases, n (%)	18 (11.7)	10 (6.6)	9 (23.1)	1 (8.3)
Prior neoadjuvant therapy, n (%)	3 (1.9)	1 (0.7)	0	0
Prior adjuvant therapy, n (%)	6 (3.9)	3 (2.0)	0	0

NOTE. Values are presented as No. (%) unless noted otherwise.
Abbreviation: ECOG, Eastern Cooperative Oncology Group.
[a]Includes only those patients initially allocated to pembrolizumab who received 35 cycles of pembrolizumab according to actual exposure assessment.
[b]Includes only those patients initially allocated to pembrolizumab who received a second course of pembrolizumab therapy according to actual exposure assessment.
[c]Includes patients with squamous cell carcinoma and poorly differentiated squamous cell carcinoma.

Reck M, et al. J Clin Oncol. 2021 Jul 20; 39(21):2339-2349

Disposition of Study Treatment

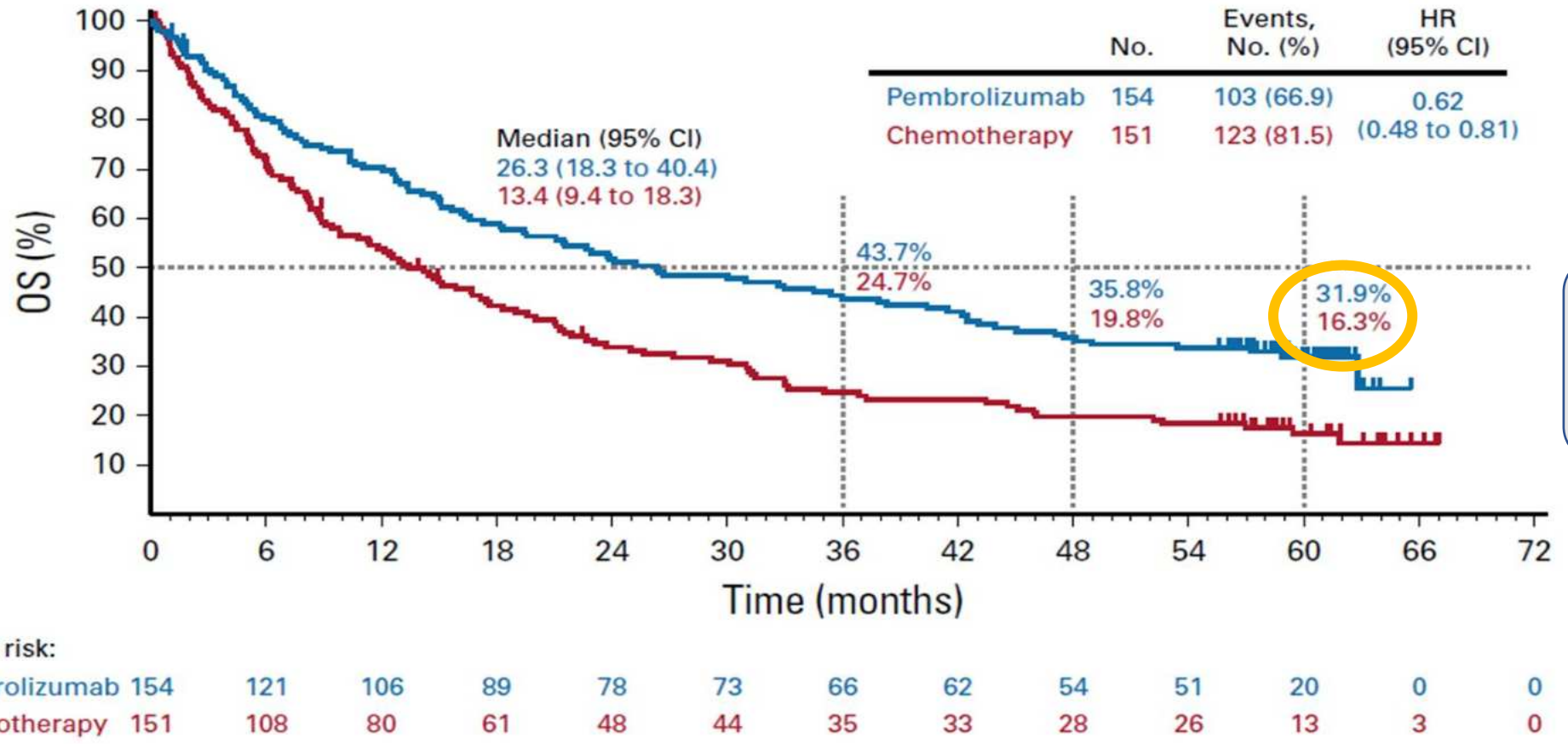


[a]Number of patients who completed treatment, as reported by investigator. [b]Includes patients with clinical progression or progressive disease. Data cutoff: June 1, 2020.

Reck M, et al. J Clin Oncol. 2021 Jul 20; 39(21):2339-2349

Kaplan-Meier estimates of Overall Survival

3 OUT OF 10 still alive after 5 years with KEYTRUDA for first-line mNSCLC



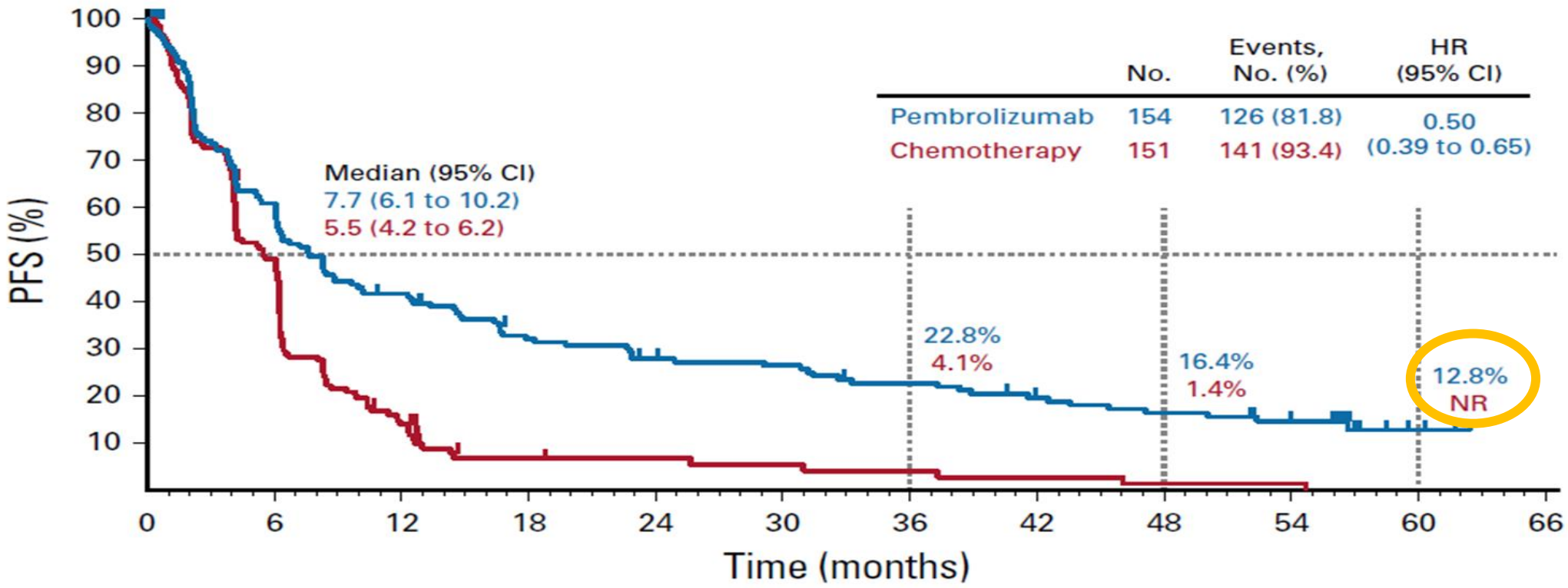
66% patients crossover from chemotherapy to anti PD-(L)1

Reck M, et al. J Clin Oncol. 2021 Jul 20; 39(21):2339-2349

Data cutoff: June 1, 2020

Kaplan-Meier estimates of Progression Free Survival

13% of patients who received Pembrolizumab have ***not progressed or died after 5 years***



	No.	Events, No. (%)	HR (95% CI)
Pembrolizumab	154	126 (81.8)	0.50 (0.39 to 0.65)
Chemotherapy	151	141 (93.4)	

50% Risk Reduction

No. at risk:

Pembrolizumab	154	92	62	46	38	36	30	24	20	15	3	0
Chemotherapy	151	73	20	6	5	4	3	2	1	1	0	0

HR, hazard ratio; NR, not reached

Reck M, et al. J Clin Oncol. 2021 Jul 20; 39(21):2339-2349

Data cutoff: June 1, 2020

ORR & DOR (Per RECIST v1.1 by investigator review)

Roughly half of the patients who received Pembrolizumab demonstrated response to treatment, with almost ***5 times in Median DOR*** Vs. Chemotherapy

	Pembrolizumab N = 154	Chemotherapy N = 151
Objective response, n (%)	71 (46.1)	47 (31.1)
Best objective response, n (%)		
Complete response	7 (4.5)	0
Partial response	64 (41.6)	47 (31.1)
Stable disease	37 (24.0)	60 (39.7)
Progressive disease	35 (22.7)	25 (16.6)
Not evaluable	0	1 (0.7)
No assessment	11 (7.1)	18 (11.9)
Time to response, median (range), mo	2.1 (1.4–14.6)	2.1 (1.1–12.2)
DOR, median (range), mo	29.1 (2.2–60.8+)	6.3 (3.1–52.4)

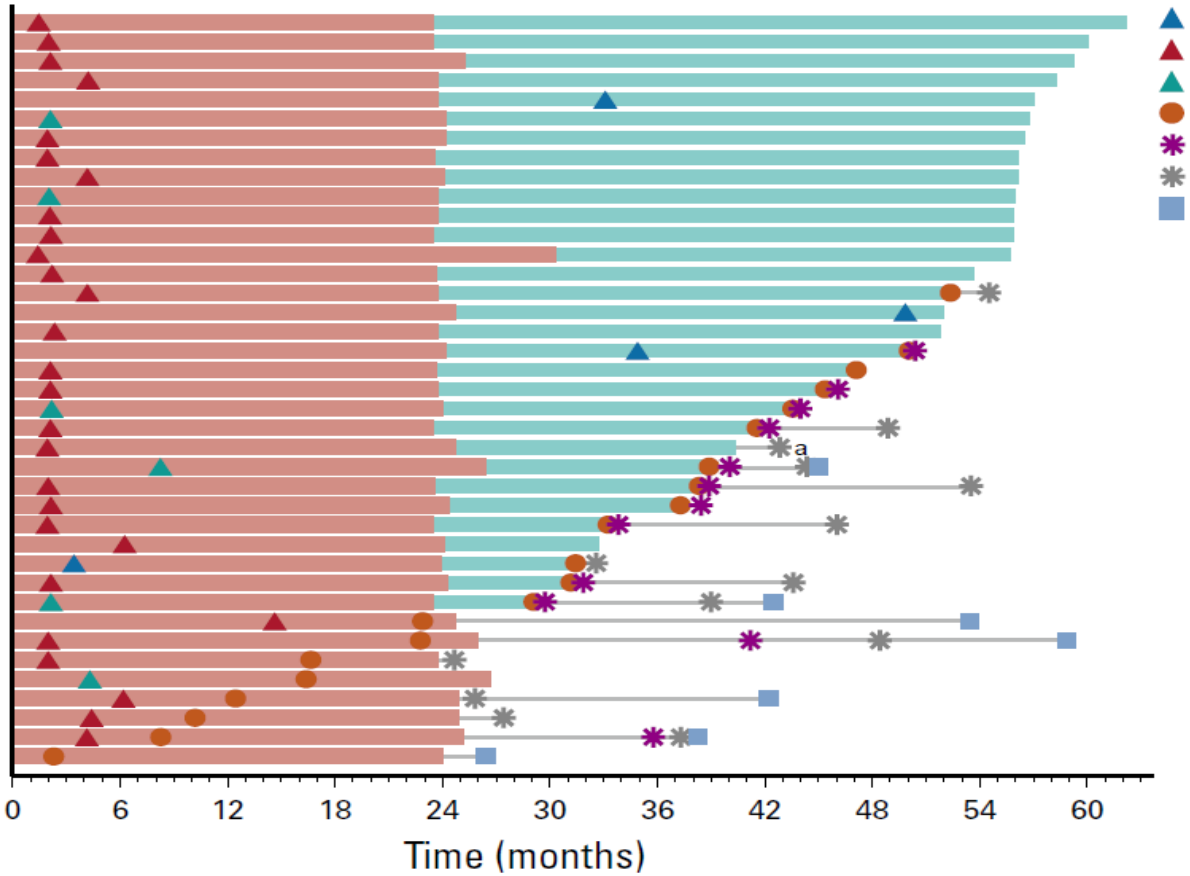
CR, complete response; DOR, duration of response; PD, progressive disease; PR, partial response; SD, stable disease.

Reck M, et al. J Clin Oncol. 2021 Jul 20; 39(21):2339-2349

Data cutoff: June 1, 2020

Patients who received pembrolizumab (35 cycles)

81.4% of patients were still alive after 5 years and ***46.2% patients*** were alive without PD or subsequent therapy for NSCLC



	N = 39[b]
3-year OS rate from completion of pembrolizumab, %	81
Objective response, n (%)	32 (82)
Best objective response, n (%)	
Complete response	4 (10)
Partial response	28 (72)
Stable disease	6 (15)
Progressive disease	1 (3)

Data cutoff: June 1, 2020

Light red bars indicate the first course of pembrolizumab treatment duration. Light teal bars indicate the first course follow-up duration. Follow-up was defined as the time to progression or last nonprogression assessment by investigator

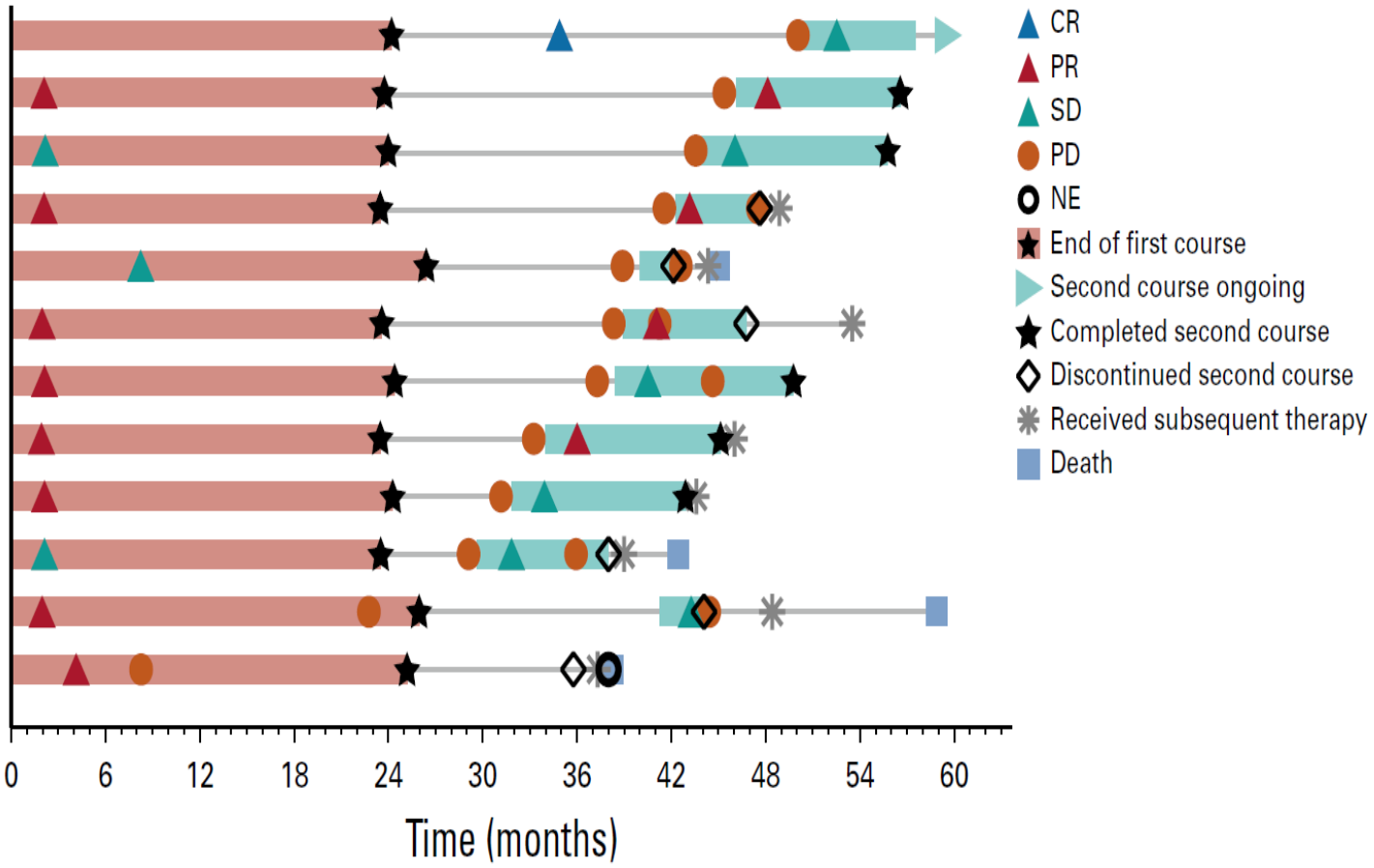
[a]Patient developed a secondary malignancy. [b]7 patients died, all due to PD; 2 did not receive any additional treatment

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Reck M, et al. J Clin Oncol. 2021 Jul 20; 39(21):2339-2349

Patients Who Received a Second Course of Pembrolizumab

At data cutoff, ***5/12 patients (42%)*** were alive without PD per investigator assessment



	N = 12[c]
Alive at data cutoff, n (%)	8 (67)
Objective response during second course, n (%)	4 (33)
Best objective response, n (%)	
Complete response	0
Partial response	4 (33)
Stable disease	6 (50)
Progressive disease	1 (8)

CR, complete response; NE, nonevaluable; PD, progressive disease; PR, partial response; SD, stable disease.

Light red bars indicate the first course of pembrolizumab treatment duration. Light teal bars indicate the second course of treatment duration.
Follow-up was defined as the time to progression or last nonprogression assessment by investigator
The maximum treatment duration for the second course was 17 cycles. C5 patients (42%) experienced treatment related AEs during second-course treatment, all grade 1-2; 1 was an immune-mediated AE (grade 1 hypothyroidism)

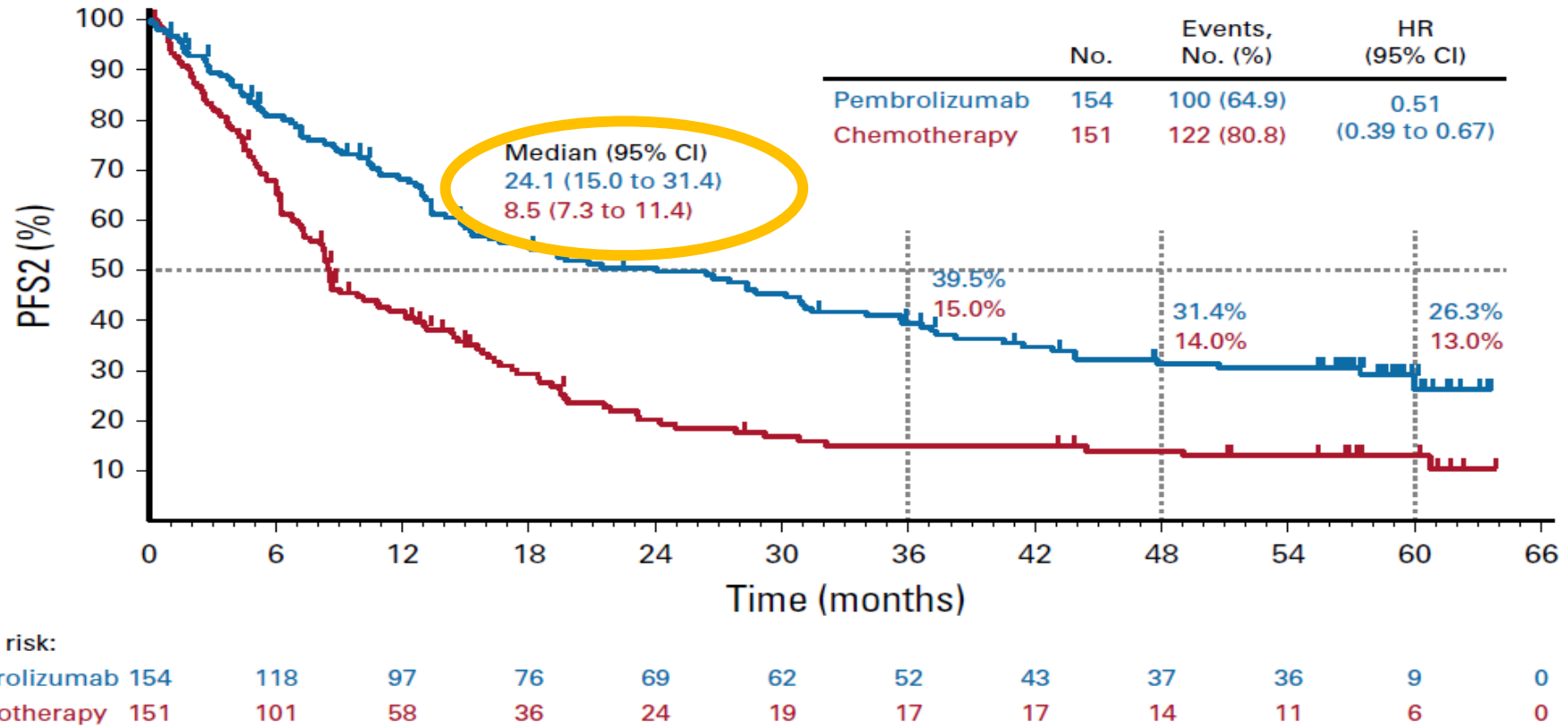
Data cutoff: June 1, 2020

Reck M, et al. J Clin Oncol. 2021 Jul 20; 39(21):2339-2349

Kaplan-Meier estimates of PFS2

PFS 2: time from randomization to subsequent disease progression after initiation of new anticancer therapy or death from any cause

With a ***doubling of the median OS and the improvement in PFS2*** among patients who received pembrolizumab, these data continue ***to support a first-line immunotherapy approach***, which permits early inhibition of PD-1 signaling, in this patient population.



Reck M, et al. J Clin Oncol. 2021 Jul 20; 39(21):2339-2349

Data cutoff: June 1, 2020

Safety Profile

Grade 3 – 5 Treatment-related Adverse Events ***are 22% lower*** with Pembrolizumab vs Chemotherapy

	Pembrolizumab[a] N = 154	Chemotherapy[a] N = 150	35 Cycles (2 Years) of Pembrolizumab[a] N = 39
Treatment-related AEs, n (%)	118 (76.6)	135 (90.0)	34 (87.2)
Grade 3–5[b]	48 (31.2)	80 (53.3)	6 (15.4)
Serious	35 (22.7)	31 (20.7)	4 (10.3)
Led to discontinuation	21 (13.6)	16 (10.7)	0
Led to death	2 (1.3)	3 (2.0)	0
Immune-mediated AEs and infusion reactions, n (%)[c]	53 (34.4)	8 (5.3)	12 (30.8)
Grade 3–5	21 (13.6)	1 (0.7)	3 (7.7)
Led to death	1 (0.6)	0	0

Exposure-adjusted AE rates in the ITT population decreased over time in both treatment groups

[a]During treatment with the initially assigned therapy. [b]7 additional patients in the pembrolizumab arm and no additional patients in the chemotherapy arm had treatment-related grade 3–5 AEs since the initial publication of KEYNOTE-024 (Reck M, et al. *N Engl J Med*. 2016;375:1823-1833). There was no change since the updated analysis at 25.2 months median follow-up (Reck M, et al. *J Clin Oncol*. 2019;37:537-546). [c]Irrespective of attribution to treatment by the investigator.
Data cutoff: June 1, 2020.

Brahmer JR et al. Presented at ESMO 2020

Conclusions

- With 5 years of follow-up, pembrolizumab continues to show meaningful improvements in OS and durable responses versus chemotherapy in KEYNOTE-024
  - Despite the 66% effective crossover rate, the 5-year OS rate was approximately doubled in the pembrolizumab group (31.9% vs 16.3%) with a median DOR of 29.1 months in the pembrolizumab group
- Patients who completed 35 cycles (2 years) of pembrolizumab experienced long-term OS
  - Second-course pembrolizumab at the time of disease progression was feasible and associated with antitumor activity
- Incidence of any-grade and grade 3–5 treatment-related AEs was lower with pembrolizumab versus chemotherapy
  - Long term treatment with pembrolizumab did not identify new safety signals
- KEYNOTE-024 is the first phase 3 study to demonstrate 5-year efficacy for first-line immunotherapy and demonstrates that pembrolizumab monotherapy is an effective first-line treatment regimen in patients with metastatic NSCLC and PD-L1 TPS ≥50%
  - These data confirm 5-year OS outcomes among previously untreated patients in the single-arm KEYNOTE-001 study[1]

1. Garon EB, et al.J Cin Oncol. 2019; 37: 2518-2527. 2.Brahmer JR et al. Presented at ESMO 2020

Second Line Setting management: NCCN Guideline
Progress after received platinum chemotherapy

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2022
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE – SUBSEQUENT

ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 0–2)

Preferred (no previous IO):
Systemic immune checkpoint inhibitors[e]
- Nivolumab (category 1)
- Pembrolizumab (category 1)[q]
- Atezolizumab (category 1)

Other Recommended (no previous IO or previous IO):[r]
- Docetaxel
- Pemetrexed
- Gemcitabine
- Ramucirumab/docetaxel
- Albumin-bound paclitaxel

SQUAMOUS CELL CARCINOMA (PS 0–2)

Preferred (no previous IO):
Systemic immune checkpoint inhibitors[e]
- Nivolumab (category 1)
- Pembrolizumab (category 1)[q]
- Atezolizumab (category 1)

Other Recommended (no previous IO or previous IO):[r]
- Docetaxel
- Gemcitabine
- Ramucirumab/docetaxel
- Albumin-bound paclitaxel

ADENOCARCINOMA, LARGE CELL, NSCLC NOS, SQUAMOUS CELL CARCINOMA (PS 3–4)

Best supportive care See NCCN Guidelines for Palliative Care

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE – PROGRESSION

ADENOCARCINOMA, LARGE CELL, NSCLC NOS[e,r]
- PS 0–2: nivolumab, pembrolizumab, or atezolizumab, docetaxel (category 2B), pemetrexed (category 2B), gemcitabine (category 2B), ramucirumab/docetaxel (category 2B), or albumin-bound paclitaxel (category 2B)
- PS 3–4: Best supportive care
- Options for further progression are best supportive care or clinical trial.

SQUAMOUS CELL CARCINOMA[e,r]
- PS 0–2: nivolumab, pembrolizumab, or atezolizumab, docetaxel (category 2B), gemcitabine (category 2B), ramucirumab/docetaxel (category 2B), or albumin-bound paclitaxel (category 2B)
- PS 3–4: Best supportive care
- Options for further progression are best supportive care or clinical trial.

References

[e] If progression on PD-1/PD-L1 inhibitor, using a PD-1/PD-L1 inhibitor is not recommended.
[q] Pembrolizumab is approved for patients with NSCLC tumors with PD-L1 expression levels ≥1%, as determined by an FDA-approved test.
[r] If not previously given.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

KEYNOTE-010:
Pembrolizumab Versus Docetaxel for Previously Treated, Programmed Death-Ligand 1–Positive Advanced NSCLC (TPS ≥1%)

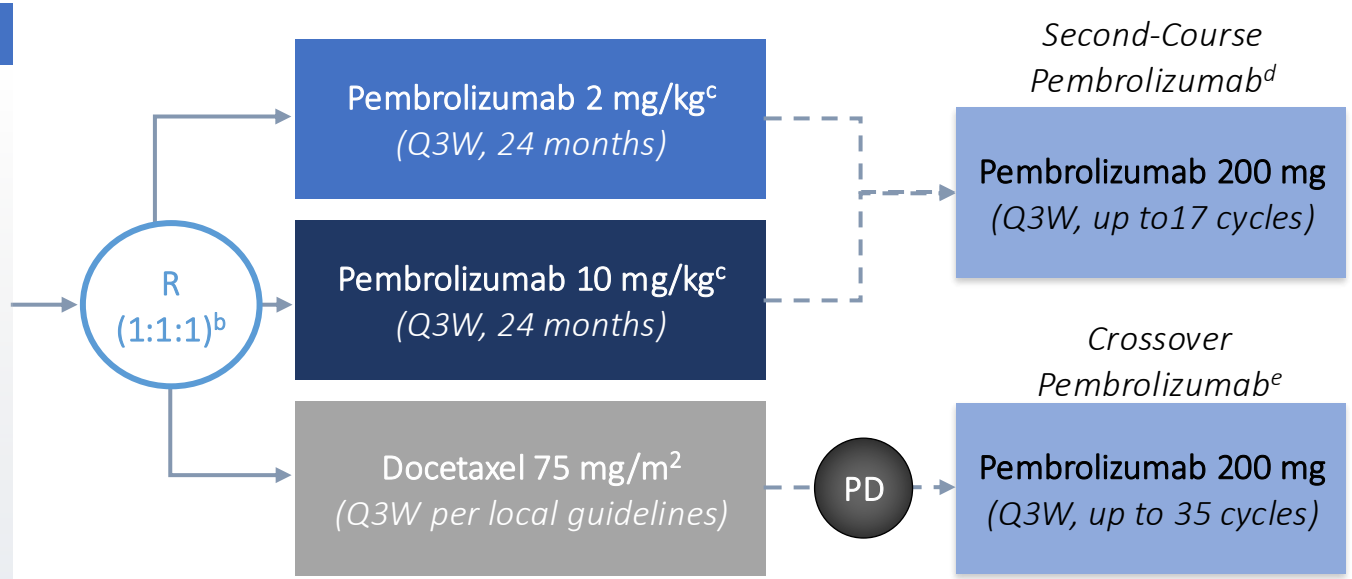
(5 Years Follow Up)

KEYNOTE-010: Phase 2/3 Study of Pembrolizumab vs Docetaxel in Previously Treated Patients With Advanced NSCLC, PD-L1 positive (TPS ≥1%)

Patients (N=1,034):

Key Eligibility Criteria

- Advanced NSCLC
- Confirmed PD after ≥1 line of chemotherapy[a]
- No active brain metastases
- PD-L1 TPS ≥1%
- ECOG PS 0–1
- No ILD or pneumonitis requiring systemic steroids
- No active/history of autoimmune disease requiring systemic therapy



Stratification Factors Considered:

- ECOG PS (0 vs 1)
- Region (eastern Asia vs noneastern Asia)
- PD-L1 status[b] (TPS ≥50% vs 1%–49%)

Primary End Points:

OS, PFS(RECIST version 1.1, independent central review)

Secondary End Points:

ORR, DOR, safety

ILD; interstitial lung disease; R, randomization

[a]included ≥2 cycles of platinum-doublet chemotherapy. An appropriate tyrosine kinase inhibitor was required for patients with EGFR/ALK alterations. [b]Randomization was stratified by ECOG PS (0 vs 10, region (East Asia vs non-East Asia), and PD-L1 status (TPS ≥50% vs 1%-49%). [c]Because no differences in OS were observed between 2mg/kg and 10mg/kg pembrolizumab dose groups in the primary analysis[1], pembrolizumab doses were pooled for this analysis. [d]Patients randomized to pembrolizumab who completed 35 cycles (~2 years) of pembrolizumab or who stop pembrolizumab after achieving CR and receiving ≥6 months of treatment, but then had PD were eligible for a second-course pembrolizumab if they had received no other anticancer therapy since the last dose of pembrolizumab. [e]After the primary analysis, crossover from docetaxel to pembrolizumab was allowed for patients with PD

1. Herbst RS et al. Lancet. 2016;387:1540-1550. 2. Herbst RS et al. 5 year survival update from KEYNOTE-010: Pembrolizumab Versus Docetaxel in Previously Treated, PD-L1–Positive Advanced NSCLC . Presented virtually at the 2020 World Conference on Lung Cancer(WCLC) Jan 28-31, 2021

KEYNOTE-010: Baseline Characteristics

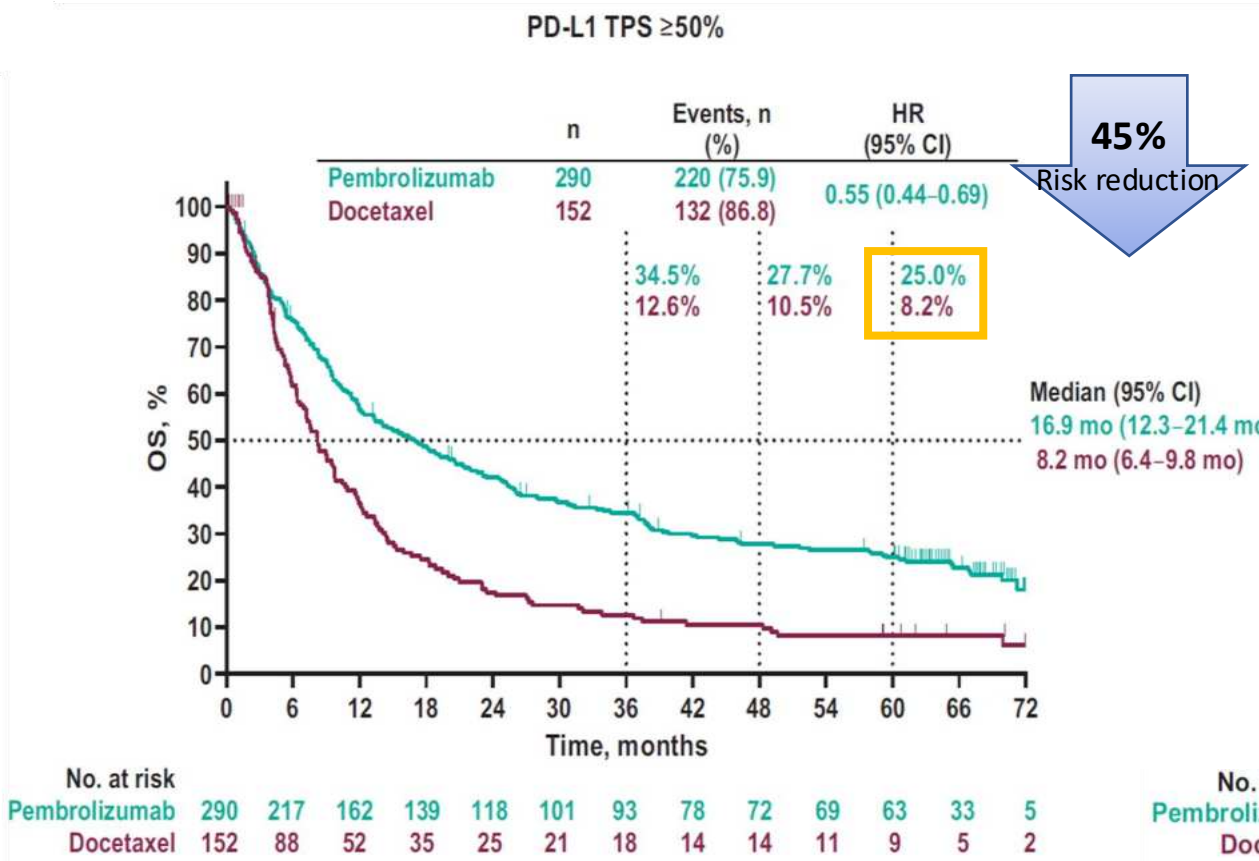
Characteristic, n (%)	Pembrolizumab[a] N = 690	Chemotherapy N = 343	35 Cycles (2 Years) of Pembrolizumab N = 79	Second-Course Pembrolizumab N = 21
Age, ≥65 y	295 (42.8)	134 (39.1)	24 (30.4)	6 (28.6)
Male	425 (61.6)	209 (60.9)	53 (67.1)	16 (76.2)
ECOG PS 1	455 (65.9)	224 (65.3)	54 (68.4)	16 (76.2)
East Asian enrollment site	128 (18.6)	62 (18.1)	17 (21.5)	6 (28.6)
Squamous histology	156 (22.6)	66 (19.2)	21 (26.6)	6 (28.6)
Current/former smoker	565 (81.9)	269 (78.4)	72 (91.1)	16 (76.2)
PD-L1 TPS				
≥50%	290 (42.0)	152 (44.3)	58 (73.4)	12 (57.1)
1%–49%	400 (58.0)	191 (55.7)	21 (26.6)	9 (42.9)
Prior lines of systemic therapy				
1	477 (69.1)	236 (68.8)	63 (79.7)	18 (85.7)
≥2	198 (28.7)	104 (30.3)	15 (19.0)	3 (14.3)

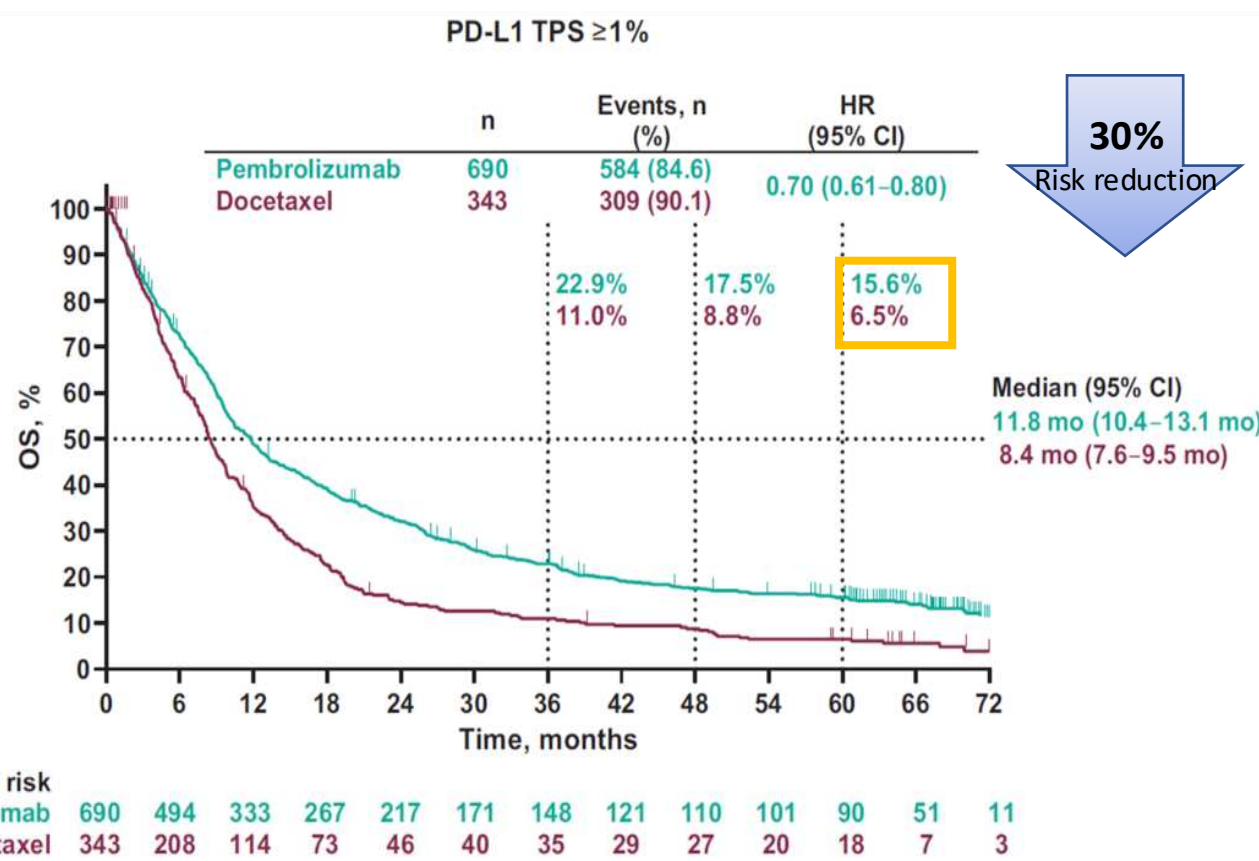
[a]Because no differences in OS were observed between the 2 mg/kg and 10 mg/kg pembrolizumab dose groups in the primary analysis, pembrolizumab doses were pooled for this analysis.
Data cutoff: April 8, 2020.

1. Herbst RS et al. Lancet. 2016;387:1540-1550. 2. Herbst RS et al. 5 year survival update from KEYNOTE-010: Pembrolizumab Versus Docetaxel in Previously Treated, PD-L1–Positive Advanced NSCLC . Presented virtually at the 2020 World Conference on Lung Cancer(WCLC) Jan 28-31, 2021

Kaplan-Meier estimates of Overall Survival

1 OUT OF 4 Patients still alive after 5 years with KEYTRUDA as Second-line or later treatment in NSCLC PD-L1 TPS ≥ 50%





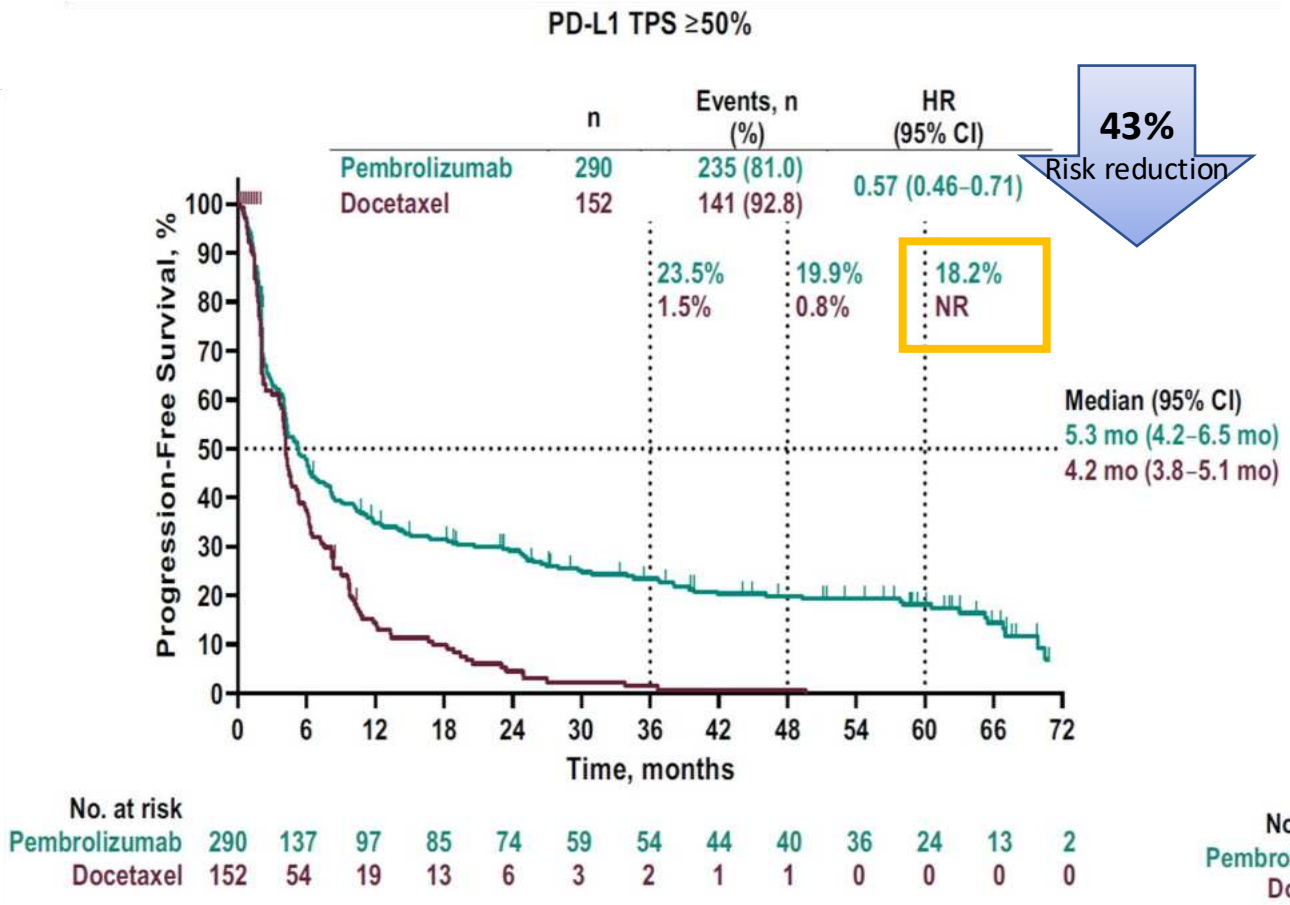
Data cutoff: 8 April 2020

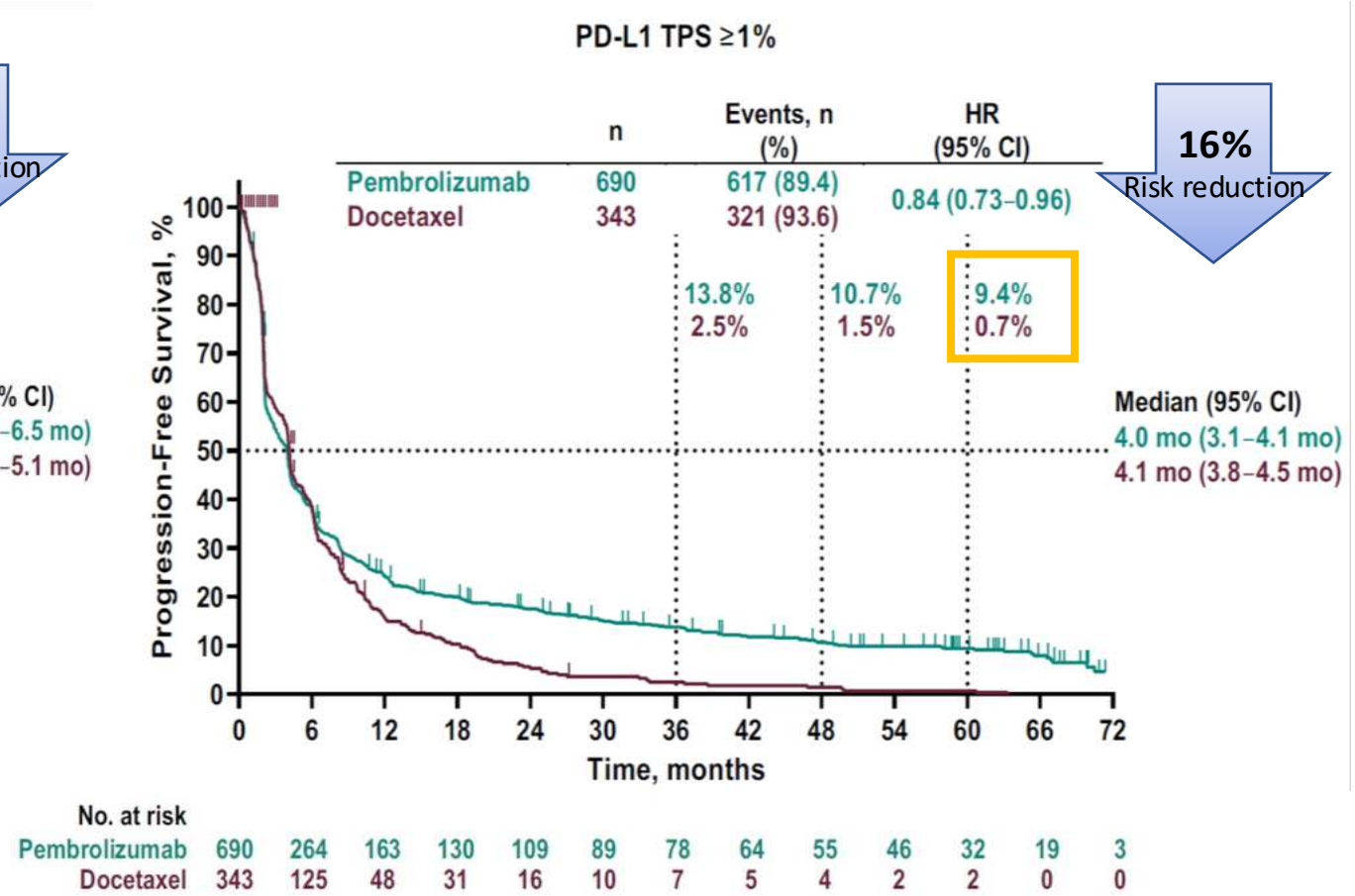
CI, confidence interval; HR, hazard ratio; OS, Overall survival; PD-L1,programmed death ligand 1; TPS, tumor proportion score

1. Herbst RS et al. Lancet. 2016;387:1540-1550. 2. Herbst RS et al. 5 year survival update from KEYNOTE-010: Pembrolizumab Versus Docetaxel in Previously Treated, PD-L1–Positive Advanced NSCLC . Presented virtually at the 2020 World Conference on Lung Cancer(WCLC) Jan 28-31, 2021

Kaplan-Meier estimates of Progression Free Survival[a]

KEYTRUDA as Second-line shown ***18% of patients*** still not progress or Died after 5 years





Data cutoff: 8 April 2020

[a]Per RECIST v1.1 by independent central review

CI, confidence interval; HR, hazard ratio; NR, not reached; PD-L1,programmed death ligand 1; TPS, tumor proportion score; RECIST, Response Evaluation Criteria in Solid Tumors

1. Herbst RS et al. Lancet. 2016;387:1540-1550. 2. Herbst RS et al. 5 year survival update from KEYNOTE-010: Pembrolizumab Versus Docetaxel in Previously Treated, PD-L1–Positive Advanced NSCLC . Presented virtually at the 2020 World Conference on Lung Cancer(WCLC) Jan 28-31, 2021

ORR and DOR[a]

Double ORR vs docetaxel and Median DOR up to ***68 months (8x vs docetaxel)***
With KEYTRUDA as Second-line in Advanced NSCLC, PD-L1 positive (TPS ≥1%)

	PD-L1 TPS ≥50%		PD-L1 TPS ≥1%	
	Pembrolizumab N = 290	Docetaxel N = 152	Pembrolizumab N = 690	Docetaxel N = 343
Objective response rate, % (95% CI)	33.1 (27.7–38.8)	9.2 (5.1–15.0)	21.2 (18.2–24.4)	9.6 (6.7–13.2)
Time to response, median (range), mo	2.2 (1.9–16.4)	2.1 (1.2–51.8)	2.1 (1.1–51.8)	2.1 (1.3–18.9)
DOR, median (range), mo[b]	68.4 (2.0+ to 71.7+)	8.5 (2.6 to 16.8)	68.4 (2.0+ to 71.7+)	7.5 (1.4+ to 16.8)
Patients with ongoing response, n (%)[c]	41 (43.0)	0	51 (35)	0

[a]Per RECIST v1.1. by independent central review
[b]"+" symbol indicates there is no progressive disease by the time of last disease assessment
[c]Includes all patients with a response who are alive, progression free, have not initiated new anticancer therapy, and have not been lost to follow-up
Data cutoff: April 8, 2020

1. Herbst RS et al. Lancet. 2016;387:1540-1550. 2. Herbst RS et al. 5 year survival update from KEYNOTE-010: Pembrolizumab Versus Docetaxel in Previously Treated, PD-L1–Positive Advanced NSCLC . Presented virtually at the 2020 World Conference on Lung Cancer(WCLC) Jan 28-31, 2021

ORR[a] and OS (Patients who received pembrolizumab 35 cycles/2 years)

83 % of patients were still alive after 5 years and ***77.2% patients*** were alive without PD

	N = 79
Objective response, n (%)	78 (98.7)
Best overall response, n (%)	
Complete response	15 (19.0)
Partial response	63 (79.7)
Stable disease	1 (1.3)

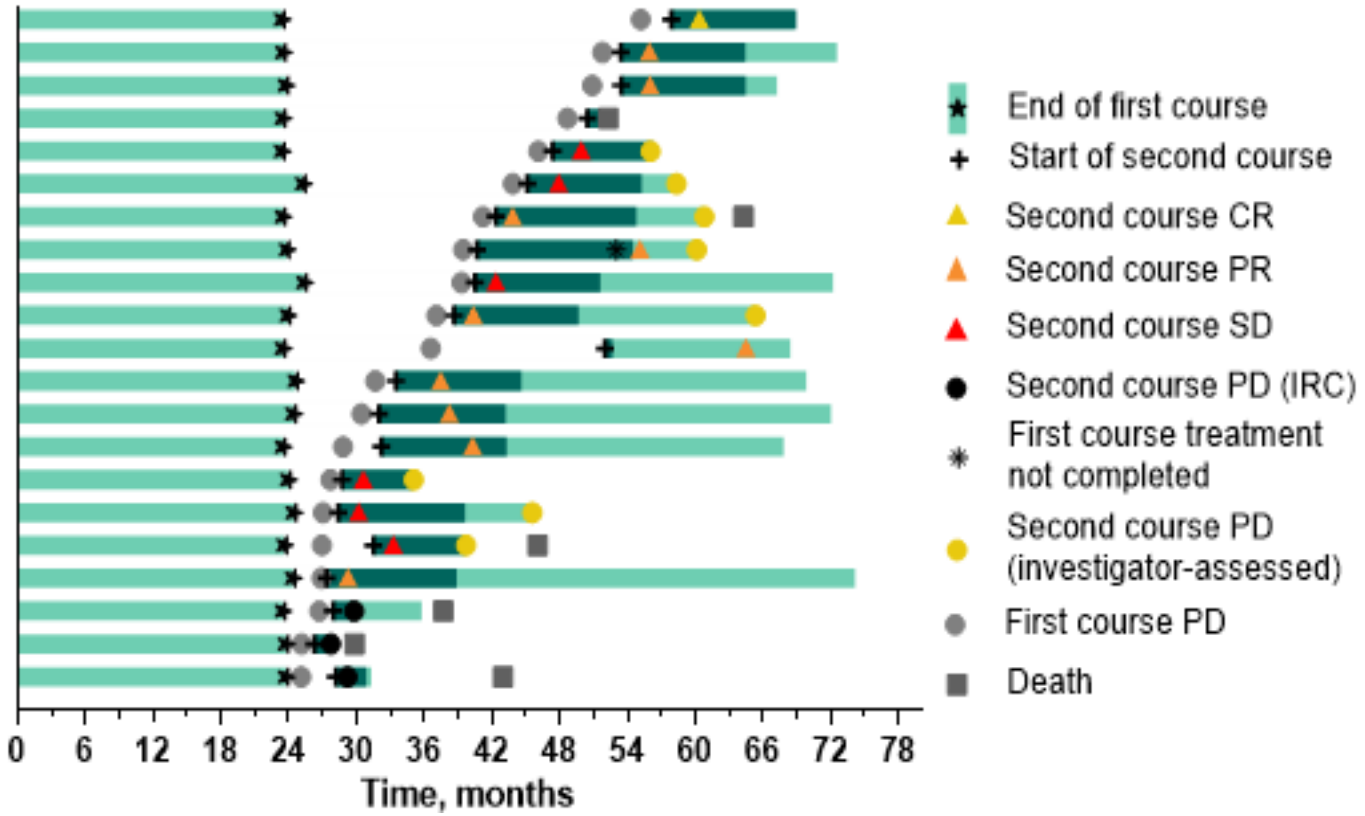
- 3-year OS rate from completion of 35 cycles/2 years pembrolizumab (ie, ~5 years from randomization) was 83.0%
- At data cutoff, 61/79 patients (77.2%) were alive, 38 of whom were alive without PD

[a]Per RECIST v1.1. by independent central review
Data cutoff: April 8, 2020

1. Herbst RS et al. Lancet. 2016;387:1540-1550. 2. Herbst RS et al. 5 year survival update from KEYNOTE-010: Pembrolizumab Versus Docetaxel in Previously Treated, PD-L1–Positive Advanced NSCLC . Presented virtually at the 2020 World Conference on Lung Cancer(WCLC) Jan 28-31, 2021

Patients Who Received a Second Course of Pembrolizumab[a]

At data cutoff, ***15/21 patients (71.4%)*** were alive



Second-Course Response	N = 21
Objective response[b], n (%)	11 (52.4)
Best objective response[b], n (%)	
Complete response	1 (4.8)
Partial response	10 (47.6)
Stable disease	6 (28.6)
Progressive disease[c]	3 (14.3)
No assessment	1 (4.8)

At data cutoff, 15/21 patients (71.4%) were alive

Bar lengths indicate duration of second-course treatment (dark green) and months of second-course follow-up (light green bar following dark green bar). Follow-up was defined as the last known nonprogression scan or date of last investigator assessment the patient was alive. [a]One patient received a second course of pembrolizumab but did not meet eligibility criteria for having completed 35 cycles or 2 years of first-course pembrolizumab. [b]Response was assessed during second-course treatment by RECIST v1.1 by independent central review, PD is per immune-related response criteria (irRC) by investigator review. [c]Eight patients with PR/SD after starting second-course subsequently had PD per immune-related response criteria (irRC) by investigator review. Data cutoff: April 8, 2020

1. Herbst RS et al. Lancet. 2016;387:1540-1550. 2. Herbst RS et al. 5 year survival update from KEYNOTE-010: Pembrolizumab Versus Docetaxel in Previously Treated, PD-L1–Positive Advanced NSCLC . Presented virtually at the 2020 World Conference on Lung Cancer(WCLC) Jan 28-31, 2021

Treatment Exposure and Adverse Events

Grade 3 – 5 Treatment-related Adverse Events ***are 20% lower*** with Pembrolizumab vs Docetaxel

	Pembrolizumab[a] N = 682	Docetaxel[a] N = 309	35 Cycles/2 Years of Pembrolizumab N = 79
Median (range) treatment duration, mo	3.5 (1 day to 31.7)	2.0 (1 day to 26.4)	24.0 (23.4 to 31.7)
Treatment-related AEs, n (%)	462 (67.7)	255 (82.5)	66 (83.5)
Grade 3–5	110 (16.1)	113 (36.6)	14 (17.7)
Led to discontinuation	40 (5.9)	37 (12.0)	1 (1.3)
Led to death	5 (0.7)	5 (1.6)	0
Immune-mediated AEs and infusion reactions, n (%)	157 (23.0)	31 (10.0)	31 (39.2)
Grade 3–5	43 (6.3)	5 (1.6)	5 (6.3)
Led to death	3 (0.4)	1 (0.3)	0

[a]During treatment with the initially assigned therapy
Data cutoff: April 8, 2020

1. Herbst RS et al. Lancet. 2016;387:1540-1550. 2. Herbst RS et al. 5 year survival update from KEYNOTE-010: Pembrolizumab Versus Docetaxel in Previously Treated, PD-L1–Positive Advanced NSCLC . Presented virtually at the 2020 World Conference on Lung Cancer(WCLC) Jan 28-31, 2021

Conclusions

- With ~5 years of median follow-up, pembrolizumab monotherapy continued to provide clinically meaningful improvements in OS and PFS vs docetaxel as second-line or later treatment in patients with advanced NSCLC with PD-L1 TPS ≥1%
  - 5-year OS rates were more than doubled in pembrolizumab-treated patients compared with those receiving docetaxel
  - 15.6% of patients with PD-L1 TPS ≥1% in the pembrolizumab group were alive at 5 years
- Patients who completed 35 cycles or 2 years of pembrolizumab experienced durable responses
- Second-course pembrolizumab provided meaningful disease control
- Incidence of any grade and grade 3–5 treatment-related AEs was lower with pembrolizumab versus docetaxel
  - Long-term treatment with pembrolizumab did not identify new safety signals
- Pembrolizumab monotherapy is a standard-of-care treatment for patients with immunotherapy-naïve, previously treated, PD-L1–positive advanced NSCLC

1. Herbst RS et al. Lancet. 2016;387:1540-1550. 2. Herbst RS et al. 5 year survival update from KEYNOTE-010: Pembrolizumab Versus Docetaxel in Previously Treated, PD-L1–Positive Advanced NSCLC . Presented virtually at the 2020 World Conference on Lung Cancer(WCLC) Jan 28-31, 2021

Elderly Patients:

Safety and efficacy of pembrolizumab monotherapy in elderly patients with PD-L1–positive advanced non–small-cell lung cancer: Pooled analysis from the KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042* studies

*Pembrolizumab monotherapy is not approved in Indonesia for PD-L1 TPS 1-49% population

Background

Objective: Most lung cancer diagnoses occur in elderly patients, who are underrepresented in clinical trials. We present a pooled analysis of safety and efficacy in elderly patients (≥75 years) who received pembrolizumab (a programmed death 1 inhibitor) for advanced non–small-cell lung cancer (NSCLC) with programmed death ligand 1 (PD-L1)–positive tumors.[1]

Clinical study	Trial design
KEYNOTE-010[2] Phase 2/3	▪ Pembrolizumab 2mg/kg Q3W vs Pembrolizumab 10mg/kg Q3W vs Docetaxel ▪ 1:1:1 randomization ratio ▪ Previously Treated Patients With Advanced NSCLC, PD-L1 positive (TPS ≥1%)
KEYNOTE-024[3] phase 3	▪ Pembrolizumab 200 mg Q3W vs Platinum-doublet Chemotherapy ▪ 1:1 randomization ratio ▪ Previously untreated stage IV NSCLC; no *EGFR/ALK* alteration, PD-L1 TPS ≥50%
KEYNOTE-42*[4] phase 3	▪ Pembrolizumab 200 mg Q3W vs Platinum-doublet Chemotherapy ▪ 1:1 randomization ratio ▪ Previously untreated stage IV NSCLC; no *EGFR/ALK* alteration, PD-L1 positive (TPS ≥1%)

- Pembrolizumab has shown efficacy as monotherapy in both patients with previously treated and treatment-naive advanced NSCLC
- Pooled analysis was conducted To evaluate the efficacy and safety of pembrolizumab monotherapy in elderly patients (≥75 years)

*Pembrolizumab monotherapy is not approved in Indonesia for PD-L1 TPS 1-49% population

1. Nosaki K et al. Lung Cancer. 2019 Sep;135:188-195.. 2. Herbst RS et al. Lancet. 2016;387:1540-1550. 3. Reck M, et al. J Clin Oncol. 2021 Jul 20; 39(21):2339-2349. 4. Mok TSK, et al. Lancet. 2019;393:1819-1830.

Baseline Characteristics patients ≥75 years of age

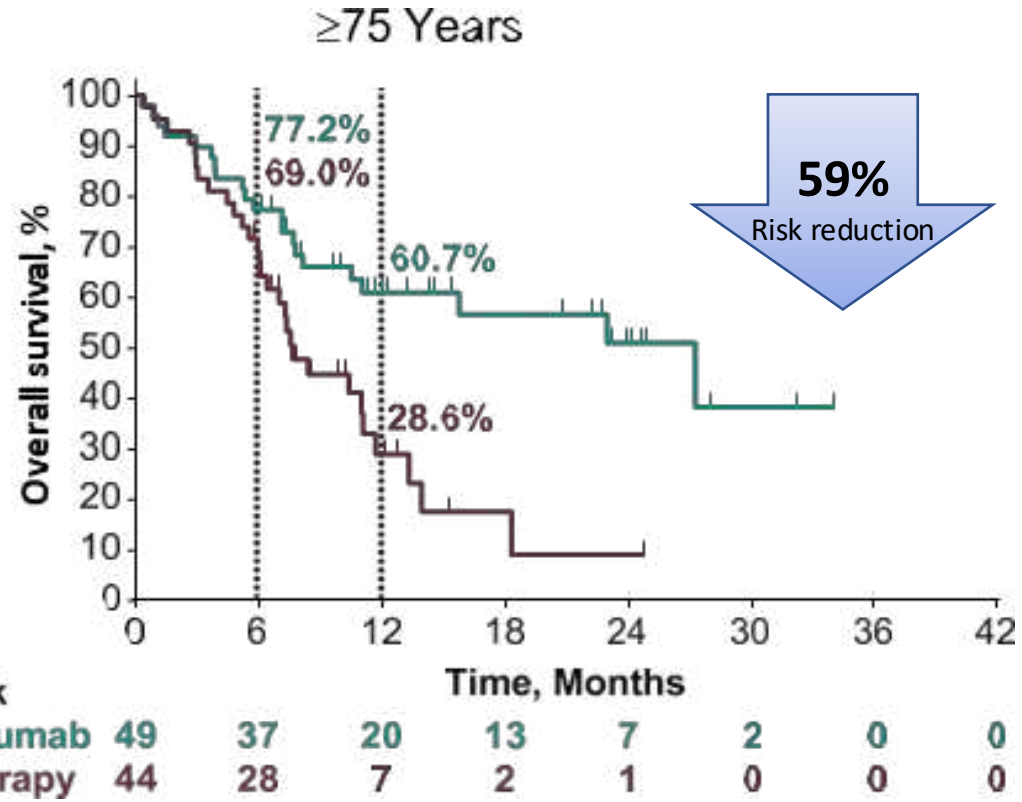
	All (n=264)	Pembrolizumab (n=149)	Chemotherapy (n=115)
Male	173 (65.5)	100 (67.1)	73 (63.5)
PD-L1 TPS ≥1% ≥50%	 264 (100.0) 132 (50.0)	 149 (100.0) 77 (51.7)	 115 (100.0) 55 (47.8)
ECOG 1	195 (73.9)	110 (73.8)	85 (73.9)
Squamous Histology	83 (31.4)	55 (36.9)	28 (24.3)
Current or former smoker	90 (34.1)	59 (39.6)	31 (27.0)
Brain metastasis at baseline	15 (5.7)	8 (5.4)	7 (6.1)
Previously untreated for advanced disease	173 (65.5)	87 (58.4)	86 (74.8)
Prior adjuvant therapy	7 (2.7)	6 (4.0)	1 (0.9)
Prior neoadjuvant therapy	3 (1.1)	3 (2.0)	0
Prior radiotherapy	45 (17.0)	36 (24.2)	9 (7.8)

Values are n (%) unless otherwise noted.
ECOG, Eastern Cooperative Oncology Group; TPS, tumor proportion score.

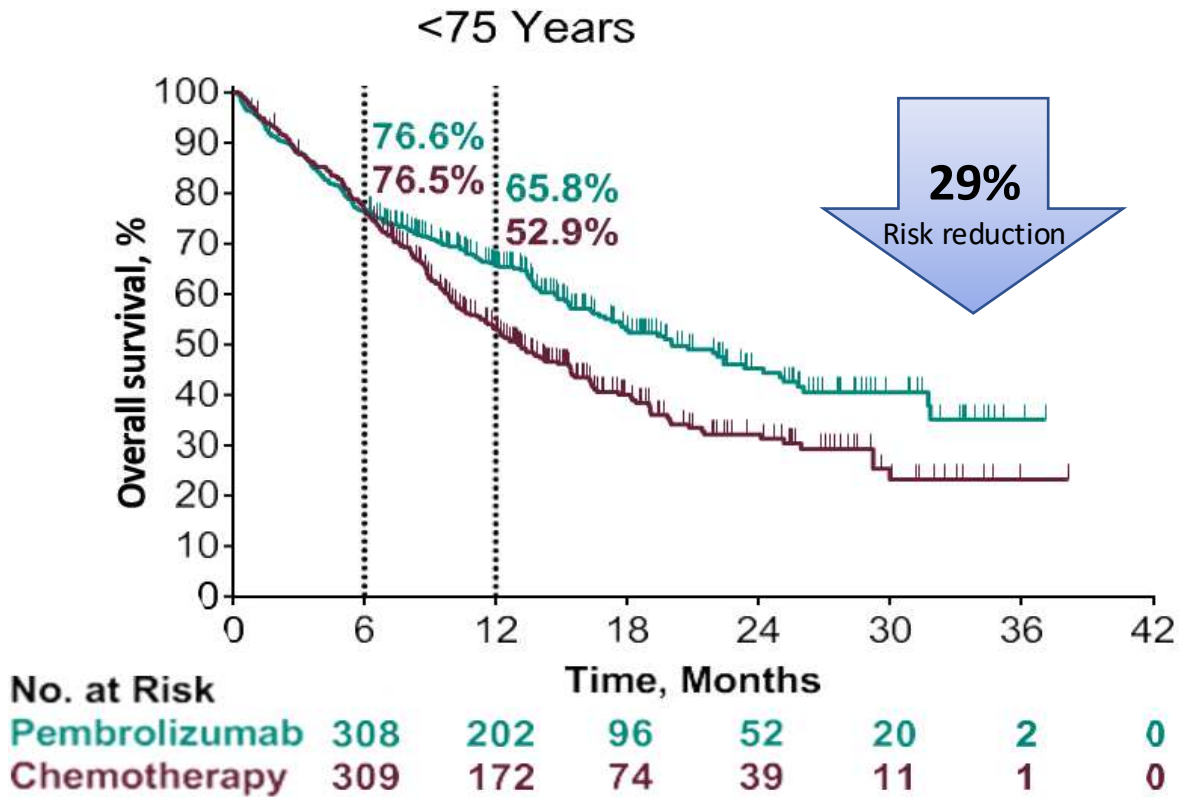
Nosaki K et al. Lung Cancer. 2019 Sep;135:188-195..

Overall Survival in first-line setting (PD-L1 TPS ≥ 50%) in pooled analysis from KEYNOTE-024 and KEYNOTE-042* studies

Triple median OS Vs. Chemotherapy in elderly patients with mNSCLC, PD-L1 TPS ≥ 50%



	mOS, months (95% CI)	HR (95% CI)
Pembrolizumab	**27.4 [10.6–not reached]**	0.41 [0.23–0.73]
Chemotherapy	**7.7 [6.1–11.1]**	



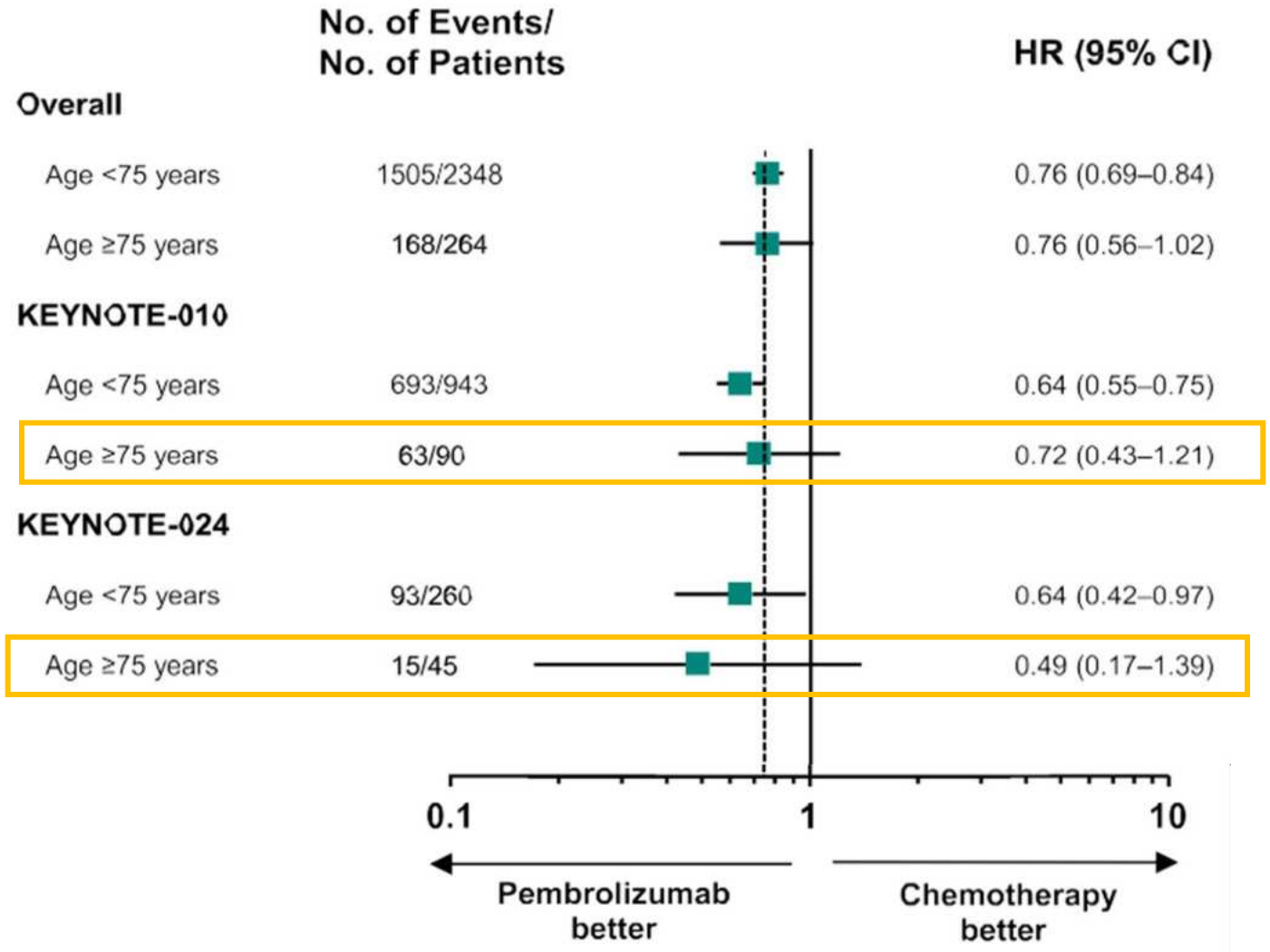
	mOS, months (95% CI)	HR (95% CI)
Pembrolizumab	**20.0 [16.7–25.1]**	0.71, [0.59–0.87]
Chemotherapy	**13.0 [11.3–15.4]**	

HR, hazard ratio; ITT, intent-to-treat; PD-L1, programmed death ligand 1; TPS, tumor proportion score. Data cutoff dates: KN 024, May 9 2016; KN 042*, Feb 26, 2018

*Pembrolizumab monotherapy is not approved in Indonesia for PD-L1 TPS 1-49% population

Nosaki K et al. Lung Cancer. 2019 Sep;135:188-195..

Overall Survival pooled population in panel



Pembrolizumab monotherapy ***improved OS*** compared with chemotherapy in ***patients of ≥75 years of age as first-line & Second-line therapy***

HR, hazard ratio; ITT, intent-to-treat; PD-L1, programmed death ligand 1; TPS, tumor proportion score.
Data cutoff dates: KN 024, May 9 2016; KN 010, Mar 24, 2017

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Summary of AEs in a Pooled Analysis of Patients With PD-L1 TPS ≥ 1%

Double in Grade 3 – 5 Treatment-related Adverse Events with chemotherapy Vs. Pembrolizumab

Patients With ≥1 Event, n (%)[a]	Pembrolizumab		Chemotherapy	
	Age ≥75 Years, n = 149	Age < 75 Years, n = 1323	Age ≥75 Years, n = 105	Age < 75 Years, n = 969
Treatment-related AEs	102 (68.5)	862 (65.2)	99 (94.3)	840 (86.7)
Grade 3-5	36 (24.2)	224 (16.9)	64 (61.0)	379 (39.1)
Led to death[b]	2 (1.3)	17 (1.3)	2 (1.9)	20 (2.1)
Led to discontinuation	16 (10.7)	90 (6.8)	16 (15.2)	93 (9.6)
Immune-mediated Aes and infusion reactions, n(%)	37 (24.8)	331 (25.0)	7 (6.7)	57 (5.9)
Grade 3-5	14 (9.4)	94 (7.1)	0	13 (1.3)

AE, adverse event; PD-L1, programmed death ligand 1; TPS, tumor proportion score; WBC, white blood cell.

[a] All patients as treated (those who received ≥1 dose of study drug).

[b] The treatment-related AEs leading to death among elderly patients were sepsis in 1 patient, and 1 death had an unspecified cause in the pembrolizumab group; and infection and pulmonary sepsis in 1 patient each in the chemotherapy group. Among younger patients, treatment-related AEs leading to death in the pem- brolizumab group were pneumonitis in 4 patients, acute cardiac failure, myocardial infarction, ileus, Klebsiella infection, Pneumocystis jirovecii pneumonia, malignant neoplasm progression, encephalopathy, hemoptysis, pulmonary embolism, respiratory failure, and hypovolemic shock in 1 patient each; 2 of the deaths in this group had an unspecified cause. Treatment-related AEs leading to death in younger patients in the chemotherapy group were pneumonia in 4 patients, febrile neutropenia, pancytopenia, cardiac failure, acute cardiac failure, neutropenic sepsis, pulmonary sepsis, respiratory tract infection, septic shock, dehydration, ketoacidosis, dys- pnea, interstitial lung disease, pulmonary alveolar hemorrhage, pulmonary embolism, and respiratory distress in 1 patient each; 1 death in this group had an unspecified cause.

Nosaki K et al. Lung Cancer. 2019 Sep;135:188-195..

Brain Metastases:

Outcomes With Pembrolizumab Monotherapy in Patients With Programmed Death-Ligand 1–Positive NSCLC With Brain Metastases: Pooled Analysis of KEYNOTE-001, 010, 024, and 042*

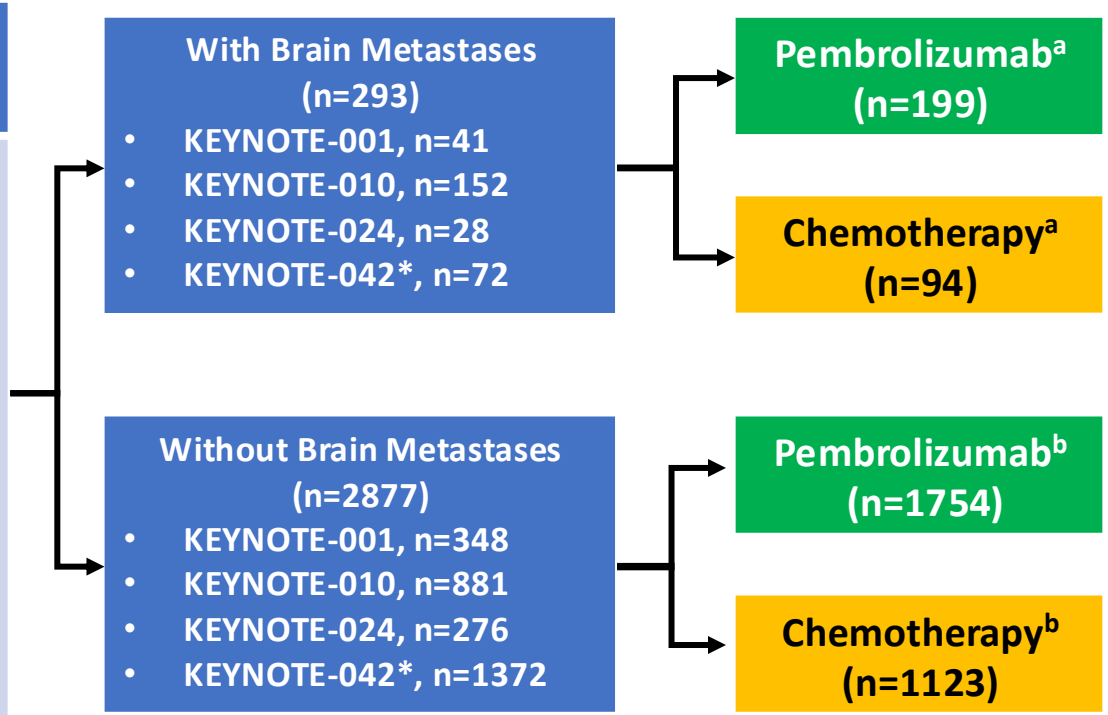
*Pembrolizumab monotherapy is not approved in Indonesia for PD-L1 TPS 1-49% population

Background & Pooled Analysis Study Design

Objective: evaluated outcomes in patients with programmed death-ligand 1 (PD-L1)–positive NSCLC to determine whether baseline (i.e., at study enrollment) brain metastases were associated with the efficacy of pembrolizumab versus chemotherapy.

Pooled Studies (n=3170)

- **KEYNOTE-001:** Pembrolizumab 2 or 10 mg/kg Q3W or 10 mg/kg Q2W in locally advanced or metastatic NSCLC
- **KEYNOTE-010:** Pembrolizumab 2 or 10 mg/kg Q3W (up to 35 cycles) vs docetaxel 75 mg/m² Q3W (per local guidelines) in previously treated advanced NSCLC with PD-L1 TPS ≥1%
- **KEYNOTE-024:** Pembrolizumab 200 mg Q3W (up to 35 cycles) vs platinum chemotherapy (4-6 cycles) in previously untreated advanced NSCLC with PD-L1 TPS ≥50% and no EGFR or ALK genomic tumor aberrations
- **KEYNOTE-042*:** Pembrolizumab 200 mg Q3W (up to 35 cycles) vs platinum chemotherapy (≤6 cycles maximum) in previously untreated advanced NSCLC with PD-L1 TPS ≥1% and no EGFR or ALK genomic tumor aberrations



ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; N = number; NSCLC = non-small cell lung cancer; PD-L1 = programmed death-ligand 1; Q2W = every 2 weeks; Q3W = every 3 weeks; TPS = tumor proportion score. [a]Three patients allocated to pembrolizumab and four to chemotherapy did not receive study treatment. [b]A total of 11 patients allocated to pembrolizumab and 57 to chemotherapy did not receive study treatment.

*Pembrolizumab monotherapy is not approved in Indonesia for PD-L1 TPS 1-49% population

Mansfield AS, et al. JTO Clin Res Rep. 2021 Jul 1;2(8):100205

Baseline Characteristics in Patients With and Without Brain Metastases (Pooled Intent-to-Treat Population)

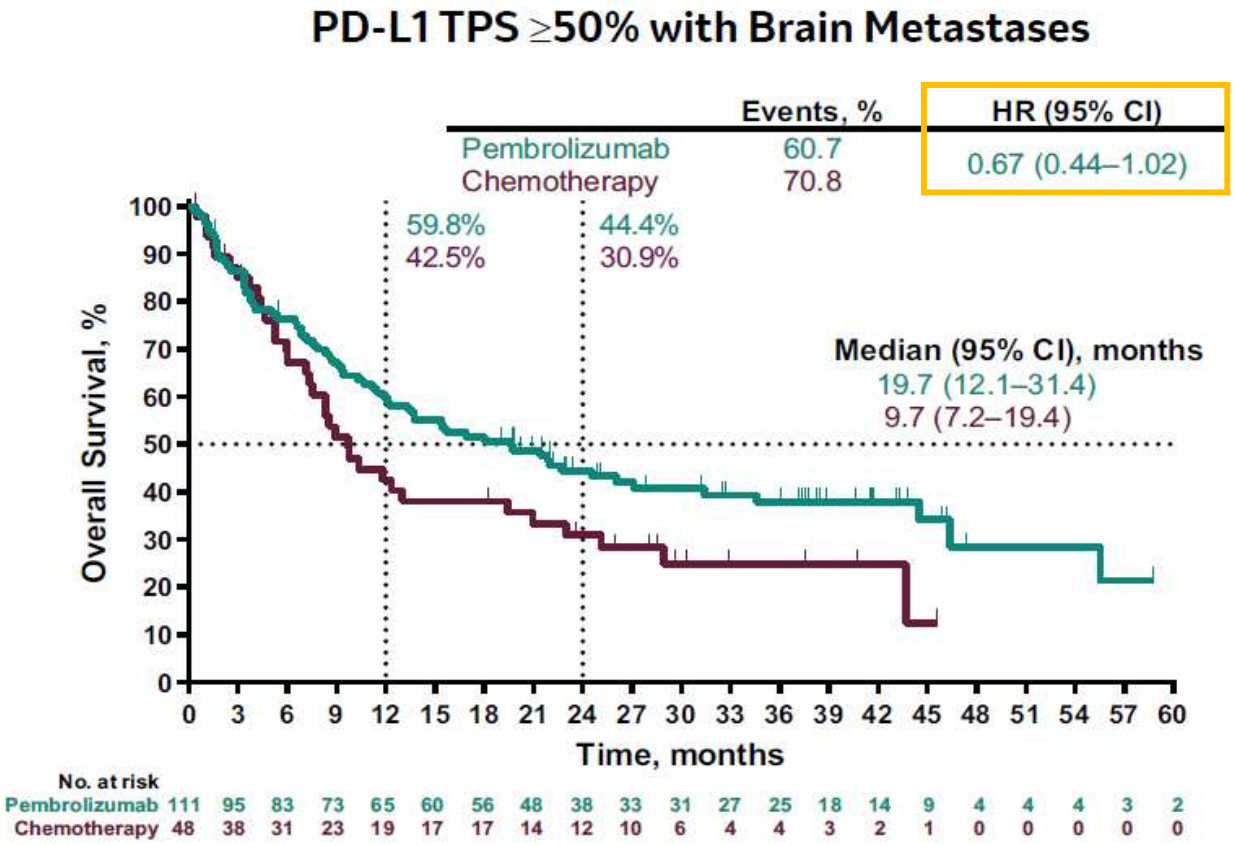
Characteristics	With Brain Metastases		Without Brain Metastases	
	Pembrolizumab (n=199)	Chemotherapy (n=94)	Pembrolizumab (n=1754)	Chemotherapy (n=1123)
Male	99 (49.7)	53 (56.4)	1146 (65.3)	778 (69.3)
Age, median (range), y	59.0 (31–88)	60.0 (31–81)	64.0 (20–93)	64.0 (32–90)
ECOG ≤ 1	198 (99.4)	94 (100)	1747 (99.6)	1120 (99.7)
Current or former smoker	159 (79.9)	77 (81.9)	1407 (80.2)	888 (79.1)
Squamous	21 (10.6)	8 (8.5)	523 (29.8)	523 (29.8)
EGFR mutation[a]	27 (13.6)	6 (6.4)	82 (4.7)	21 (1.9)
ALK translocation[a]	2 (1.0)	0	13 (0.7)	2 (0.2)
Previous systemic therapies[b] ≤ 1	116 (58.4)	75 (79.8)	1395 (79.5)	1037 (92.3)
PD-L1 TPS ≥50%	112 (56.3)	48 (51.1)	842 (48.0)	598 (53.3)

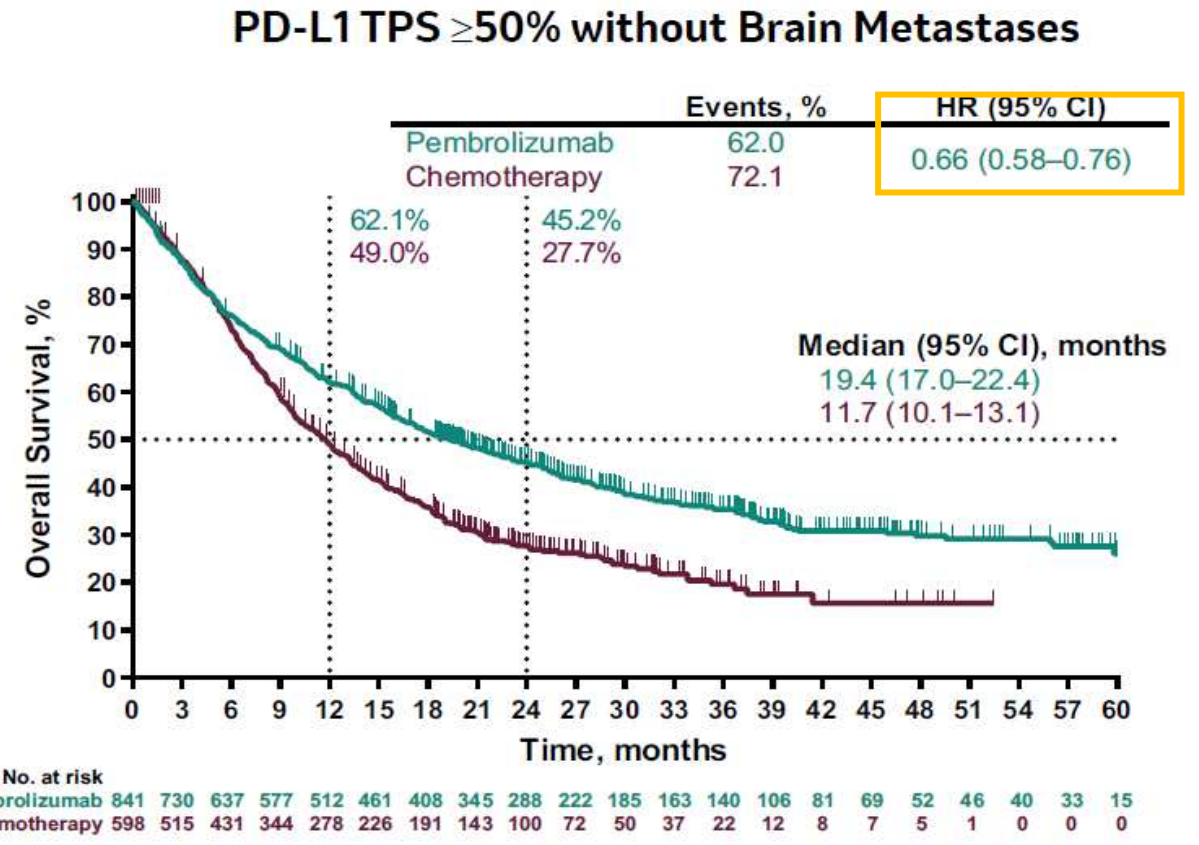
Note: Values are n (%) of patients unless indicated otherwise.. [a]Patients with EGFR or ALK genomic tumor aberrations were not excluded from enrollment in KEYNOTE-001 or KEYNOTE-010. [b]Includes adjuvant and neoadjuvant therapies.ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand-1; TPS, tumor proportion score.

Mansfield AS, et al. JTO Clin Res Rep. 2021 Jul 1;2(8):100205.

Overall Survival in first-line setting (PD-L1 TPS ≥ 50%)

Pembrolizumab ***improved OS*** versus chemotherapy in patients with PD-L1 TPS ≥50% and ***baseline brain metastases***, as well as in patients without baseline brain metastases.





CI, confidence interval; HR, hazard ratio; PD-L1, programmed death-ligand 1; TPS, tumor proportion score. The response was assessed per Response Evaluation Criteria in Solid Tumors version 1.1 by blinded, independent central review. Four patients in the pooled intent-to-treat population had missing progression-free survival data.
Data cutoff dates: November 5, 2018 (KEYNOTE-001), March 16, 2018 (KEYNOTE-010), July 10, 2017 (KEYNOTE-024), September 4, 2018 (KEYNOTE-042)*.

*Pembrolizumab monotherapy is not approved in Indonesia for PD-L1 TPS 1-49% population

Mansfield AS, et al. JTO Clin Res Rep. 2021 Jul 1;2(8):100205.

ORR in Patients With and Without Brain Metastases by PD-L1 TPS (Pooled ITT Population)

Double median OS, Double 12-month PFS & Double ORR Vs. Chemotherapy in NSCLC with Brain metastases, PD-L1 TPS ≥ 50%

	With Brain Metastases		Without Brain Metastases	
Outcome	**Pembrolizumab**	**Chemotherapy**	**Pembrolizumab**	**Chemotherapy**
PD-L1 TPS ≥50%	(n=112)	(n=48)	(n=842)	(n=598)
OS, median (95% CI), months	19.7 (12.1-31.4)	9.7 (7.2-19.4)	19.4 (17.0-22.4)	11.7 (10.1-13.1)
HR (95% CI)	0.67 (0.44-1.02)		0.66 (0.58-0.76)	
12-month, %	59.8	42.5	62.1	49.0
PFS, median (95% CI), months	4.1 (2.3-10.6)	4.6 (3.5-8.4)	6.5 (6.1-8.1)	6.1 (5.8-6.2)
HR (95% CI)	0.70 (0.47-1.03)		0.69 (0.62-0.78)	
12-month, %	38.9	13.5	38.0	23.5
ORR, n (%)	38 (33.9)	7 (14.6)	321 (38.1)	156 (26.1)
Response, n (%)				
Complete response	3 (2.7)	0	22 (2.6)	2 (0.3)
Partial response	35 (31.3)	7 (14.6)	299 (35.5)	154 (25.8)
Stable disease	24 (21.4)	19 (39.6)	233 (27.7)	246 (41.1)
Progressive disease	36 (32.1)	11 (22.9)	190 (22.6)	97 (16.2)
Not evaluable	3 (2.7)	2 (4.2)	18 (2.1)	11 (1.8)
No assessment	9 (8.0)	9 (18.8)	75 (8.9)	88 (14.7)
Response duration, median (range), months	NR (4.0+ to 41.7+)	7.6 (2.9+ to 28.6+)	33.9 (1.4+ to 49.3+)	8.2 (1.6+ to 30.4+)

Note: Responses were based on blinded, independent central review assessment per RECIST version 1.1.CI, confidence interval; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PD-L1, programmed death ligand-1; RECIST, Response Evaluation Criteria in Solid Tumors; TPS, tumor proportion score.
Data cutoff dates: November 5, 2018 (KEYNOTE-001), March 16, 2018 (KEYNOTE-010), July 10, 2017 (KEYNOTE-024), September 4, 2018 (KEYNOTE-042)*.

*Pembrolizumab monotherapy is not approved in Indonesia for PD-L1 TPS 1-49% population

Mansfield AS, et al. JTO Clin Res Rep. 2021 Jul 1;2(8):100205.

Safety profile in Patients With and Without Brain Metastases (Pooled Safety Population)

30% lower in Treatment-related Aes Grade 3 – 5 with Pembrolizumab Vs. chemotherapy in NSCLC with Brain metastases

	With Brain Metastases		Without Brain Metastases	
Treatment-Related AEs	**Pembrolizumab (n=196)**	**Chemotherapy (n=90)**	**Pembrolizumab (n=1743)**	**Chemotherapy (n=1066)**
Any	130 (66.3)	76 (84.4)	1172 (67.2)	941 (88.3)
Grade 3-5	29 (14.8)	41 (45.6)	311 (17.8)	460 (43.2)
Leading to discontinuation of study treatment	12 (6.1)	9 (10.0)	144 (8.3)	117 (11.0)
Leading to death	3 (1.5)	3 (3.3)	22 (1.3)	21 (2.0)
Affecting CNS	19 (9.7)	24 (26.7)	122 (7.0)	283 (26.5)
Most common (≥2% in any group)				
Peripheral neuropathy	1 (0.5)	7 (7.8)	9 (0.5)	83 (7.8)
Dysgeusia	3 (1.5)	8 (8.9)	23 (1.3)	45 (4.2)
Peripheral sensory neuropathy	1 (0.5)	3 (3.3)	12 (0.7)	58 (5.4)
Paresthesia	1 (0.5)	5 (5.6)	12 (0.7)	34 (3.2)
Headache	7 (3.6)	3 (3.3)	24 (1.4)	11 (1.0)
Hypesthesia	0	1 (1.1)	3 (0.2)	25 (2.3)
Immune-mediated AEs and infusion reactions[a], %	41 (20.9)	8 (8.9)	440 (25.2)	80 (7.5)
Grade 3-5	10 (5.1)	1 (1.1)	129 (7.4)	17 (1.6)

Note: AE graded on the basis of National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Values are n (%) of patients. [a]Immune-mediated AEs were classified on the basis of a list of preferred terms identified by the sponsor as potentially being caused by the immune system. All immune-mediated AEs and infusion reactions are included, regardless of relationship to study drug.AE, adverse event.Data cutoff dates: November 5, 2018 (KEYNOTE-001), March 16, 2018 (KEYNOTE-010), July 10, 2017 (KEYNOTE-024), September 4, 2018 (KEYNOTE-042)*.

*Pembrolizumab monotherapy is not approved in Indonesia for PD-L1 TPS 1-49% population

Nosaki K et al. Lung Cancer. 2019 Sep;135:188-195..

Minimum Product Information

INDIKASI: • KEYTRUDA, dikombinasikan dengan pemetrexed dan kemoterapi platinum, diindikasikan sebagai pengobatan lini pertama pada pasien dengan kanker paru karsinoma bukan sel kecil (NSCLC) metastatik non skuamosa, tanpa kelainan genomik EGFR atau ALK pada tumor. • KEYTRUDA, dikombinasikan dengan karboplatin dan antara paclitaxel atau nab-paclitaxel, diindikasikan sebagai pengobatan lini pertama untuk pasien dengan NSCLC skuamosa yang telah metastasis. • KEYTRUDA sebagai monoterapi diindikasikan sebagai pengobatan pada pasien dengan NSCLC stadium lanjut dimana tumor mengekspresikan PD-L1 sebagaimana telah ditentukan oleh tes yang tervalidasi, dan telah mendapatkan kemoterapi mengandung platinum sebelumnya. Pasien dengan kelainan genomik EGFR atau ALK harus sudah pernah mendapatkan terapi untuk kelainan tersebut sebelum mendapatkan KEYTRUDA. • KEYTRUDA sebagai monoterapi diindikasikan sebagai pengobatan pada pasien dengan NSCLC stadium lanjut lokal atau metastasis dimana tumor mengekspresikan PD-L1 dengan tumor proportion score (TPS) ≥50% sebagaimana telah ditentukan oleh tes yang tervalidasi, tanpa kelainan genomik EGFR atau ALK pada tumor, dan belum mendapatkan kemoterapi sistemik untuk NSCLC metastasis sebelumnya. • KEYTRUDA, dikombinasikan dengan paclitaxel, diindikasikan sebagai pengobatan pada pasien dengan triple-negative breast cancer (TNBC) yang telah metastasis, tidak dapat di reseksi, atau mengalami kekambuhan lokal dimana tumor mengekspresikan PD-L1 (CPS ≥10) sebagaimana telah ditentukan oleh tes yang tervalidasi. • KEYTRUDA, dikombinasikan dengan axitinib, diindikasikan sebagai pengobatan lini pertama pada pasien dengan *renal cell carcinoma* (RCC) stadium lanjut dengan resiko menengah atau buruk. • KEYTRUDA monoterapi diindikasikan sebagai pengobatan pasien dengan karsinoma urothelial metastasis atau stadium lanjut lokal yang telah mendapatkan kemoterapi mengandung platinum. • KEYTRUDA diindikasikan sebagai pengobatan pada pasien dengan kanker kolorektal (CRC) metastasis dengan status microsatellite instability-high (MSI-H) atau mismatch repair deficient (dMMR). • KEYTRUDA sebagai monoterapi diindikasikan sebagai pengobatan pada pasien dengan kanker kepala dan leher sel skuamosa (HNSCC) non nasofaring metastasis atau yang tidak dapat di reseksi dan kambuh kembali, dimana tumor mengekspresikan PD-L1 [Combined Positive Score (CPS) ≥1]. • KEYTRUDA, dikombinasikan dengan kemoterapi platinum dan 5-fluorouracil (5-FU), diindikasikan sebagai pengobatan pada pasien dengan kanker kepala dan leher sel skuamosa (HNSCC) non nasofaring metastasis atau yang tidak dapat di reseksi dan kambuh kembali, dimana tumor mengekspresikan PD-L1 [Combined Positive Score (CPS) ≥1]. • KEYTRUDA diindikasikan sebagai pengobatan pasien dengan melanoma metastasis atau yang tidak dapat di reseksi. • KEYTRUDA diindikasikan sebagai pengobatan adjuvan pada pasien dengan melanoma yang telah menyebar ke kelenjar getah bening, dan telah melakukan reseksi menyeluruh (complete resection). • KEYTRUDA diindikasikan sebagai pengobatan pasien dewasa dan anak dengan classical Hodgkin Lymphoma (cHL) yang telah kambuh kembali (relapsed atau refractory) dan telah kambuh setelah pengobatan dua atau lebih lini terapi. • KEYTRUDA diindikasikan sebagai pengobatan pasien dengan kanker esofagus metastasis atau stadium lanjut lokal yang kambuh kembali, dimana tumor mengekspresikan PD-L1 [Combined Positive Score (CPS) ≥10] sebagaimana telah ditentukan oleh tes yang tervalidasi, dan telah mendapatkan satu lini terapi sistemik sebelumnya. • KEYTRUDA dengan kemoterapi platinum dan fluoropyrimidine, diindikasikan sebagai pengobatan lini pertama pada pasien dengan kanker esofagus stadium lanjut lokal, yang tidak dapat direseksi, atau metastasis, atau adenokarsinoma GEJ dengan HER-2 negatif yang memiliki ekspresi PD-L1 CPS ≥10. • KEYTRUDA diindikasikan sebagai pengobatan pada pasien dengan TNBC (triple negative breast cancer) stadium awal dengan resiko tinggi, dimana KEYTRUDA dikombinasikan dengan kemoterapi sebagai pengobatan neoadjuvan, lalu dilanjutkan sebagai monoterapi pada pengobatan adjuvan setelah pembedahan. • KEYTRUDA, dalam kombinasi dengan kemoterapi, dan dengan atau tanpa bevacizumab, diindikasikan sebagai pengobatan kanker serviks yang persisten telah mengalami kekambuhan atau metastasis, dimana tumor mengekspresikan PD-L1 [*Combined Positive Score* (CPS) ≥1] sebagaimana telah ditentukan oleh tes yang tervalidasi. • KEYTRUDA, sebagai monoterapi, diindikasikan sebagai terapi adjuvan untuk pasien dengan *renal cell carcinoma* (RCC) dengan resiko kekambuhan menengah-tinggi atau tinggi setelah nefroktomi, atau setelah nefroktomi dan reseksi dari lesi metastasis. • KEYTRUDA diindikasikan sebagai pengobatan pada pasien dengan karsinoma hepatoseluler (HCC) yang telah mendapatkan terapi sorafenib sebelumnya.

DOSIS: Rekomendasi dosis KEYTRUDA pada triple negative breast cancer (TNBC), sebagai monoterapi pada kanker esofagus yang telah diobati sebelumnya dan sebagai terapi kombinasi pada kanker esofagus di lini pertama, terapi kombinasi atau monoterapi pada NSCLC yang belum diobati sebelumnya, terapi adjuvan pada melanoma, HNSCC yang belum diobati sebelumnya, terapi kombinasi pada RCC, terapi adjuvant RCC, karsinoma urothelial, cHL, kanker kolorektal, kanker serviks atau karsinoma hepatoseluler adalah 200 mg. Rekomendasi dosis KEYTRUDA pada melanoma metastasis atau yang tidak dapat di reseksi, atau NSCLC yang telah diobati sebelumnya adalah 2 mg/kg sebagai monoterapi.

KONTRAINDIKASI: KEYTRUDA dikontraindikasikan pada pasien dengan hipersensitivitas terhadap pembrolizumab atau bahan tambahan lain dari obat tersebut.

PERINGATAN: Efek samping terkait sistem imun, termasuk kasus-kasus berat dan fatal, telah terjadi pada pasien yang mendapatkan KEYTRUDA. Efek samping terkait sistem imun yang mempengaruhi lebih dari satu sistem tubuh dapat terjadi bersamaan. Efek samping terkait sistem imun yang dilaporkan pada pasien yang mendapatkan KEYTRUDA meliputi pneumonitis, kolitis, hepatitis, nefritis, endokrinopati, reaksi kulit yang berat, uveitis, myositis, sindrom Guillain-Barre, pankreatitis, ensefalitis, sarkoidosis, sindrom myastenik/myasthenia gravis (termasuk eksaserbasi), myelitis, vasculitis, hipoparatiroidisme, efek samping terkait transplantasi, dan efek samping terkait infusi.

EFEK SAMPING UMUM: Untuk monoterapi, efek samping yang terjadi pada pasien dengan HNSCC, kanker esofagus, karsinoma urothelial, cHL, CRC, terapi adjuvant RCC, atau HCC umumnya serupa dengan yang terjadi pada pasien melanoma atau NSCLC. Untuk terapi kombinasi, pasien dengan HNSCC yang mendapatkan KEYTRUDA plus kemoterapi (platinum dan 5-FU), efek samping yang terjadi pada tingkat (grade) yang lebih tinggi (Grade 3-4) dan insiden lebih tinggi (perbedaan ≥2%) dibandingkan dengan cetuximab plus kemoterapi (platinum dan 5-FU) adalah: kelelahan (7% vs. 4.9%), inflamasi mukosa (10% vs. 5%), dan stomatitis (8% vs. 3.5%). Efek samping paling umum yang terjadi pada minimal 20% dari pasien RCC yang belum diobati sebelumnya lalu mendapatkan KEYTRUDA dan axitinib pada KEYNOTE-426 adalah diare, hipertensi, kelelahan, hipotiroidisme, penurunan nafsu makan, sindrom palmar plantar erythrodysaesthesia, mual, peningkatan ALT, peningkatan AST, dysphonia, batuk dan konstipasi. Pada pasien dengan TNBC yang mendapatkan KEYTRUDA plus kemoterapi (paclitaxel, nab-paclitaxel, atau gemcitabine dan carboplatin), efek samping yang terjadi pada minimal 20% dari pasien dan pada insiden lebih tinggi (perbedaan ≥5%) dibandingkan dengan pasien TNBC yang mendapatkan placebo plus kemoterapi (paclitaxel, nab-paclitaxel, atau gemcitabine dan carboplatin) adalah diare (28% vs. 23%), berkurangnya nafsu makan (21% vs. 14%), dan ruam (20% vs. 12%). Pada pasien dengan TNBC stadium awal dengan risiko tinggi yang mendapatkan KEYTRUDA plus kemoterapi (karboplatin dan paclitaxel dilanjutkan dengan doxorubicin atau epirubicin dan siklofosfamid), diberikan sebagai pengobatan neoadjuvan lalu dilanjutkan sebagai monoterapi pada pengobatan adjuvan, efek samping yang terjadi pada miniimal 20% dari pasien dan pada insiden lebih tinggi (perbedaan ≥5%) dibandingkan dengan pasien TNBC yang mendapatkan placebo plus kemoterapi adalah diare (41% vs. 34%), ruam (30% vs. 24%), pyrexia (28% vs. 19%), dan penurunan nafsu makan (23% vs. 17%). Pada pasien kanker serviks yang mendapatkan KEYTRUDA plus chemotherapy (paclitaxel dan cisplatin atau paclitaxel dan carboplatin) dengan atau tanpa bevacizumab, efek samping yang terjadi pada insiden yang lebih tinggi (≥2%) dan tingkat keparahan 3-5 untuk KEYTRUDA plus kemoterapi dengan atau bevacizumab dibandingkan dengan placebo plus kemoterapi dengan atau tanpa bevacizumab adalah anemia (30% vs. 27%), neutropenia (12% vs. 10%), trombositopenia (8% vs. 5%), asthenia (3.6% vs. 1.6%).

Thank You