IMMUNOTHERAPY IN LUNG CANCER

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IMMUNOTHERAPY IN LUNG CANCER

- Introduction, challenges, epidemiology, evolution, personalized medicine
- Era of immunotherapy
- Early approvals
- When to use
- Indications in metastatic, adjuvant, and neoadjuvant setting
- Biomarkers
- Immuno-toxicities
- Future prospects

CHALLENGES IN TREATING CANCER

- EVERY TUMOR IS DIFFERENT
- EVERY PATIENT IS DIFFERENT
- PERSONALISED DIAGNOSIS
- PERSONALISED THERAPY

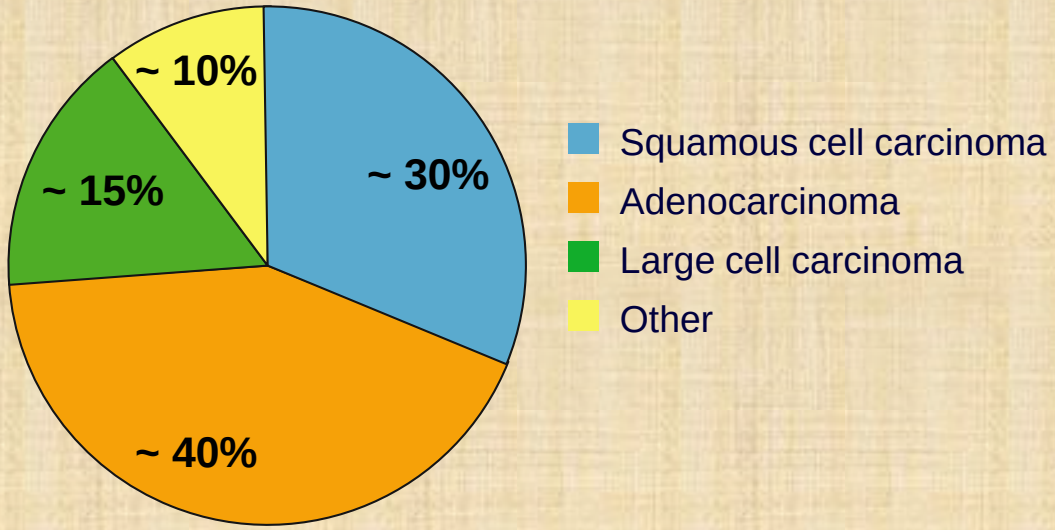
ONE SIZE DOESN'T FIT ALL

EPIDEMIOLOGY OF NSCLC

- NSCLC divided into squamous (~ 30%) and nonsquamous (~ 70%)
- Nonsquamous includes
  - Adenocarcinoma: most common form; originates from mucus-secreting cells
  - Large cell carcinoma: heterogeneous group of undifferentiated epithelial neoplasms

- More than one half of patients diagnosed with lung cancer succumb to their disease within 1 year of diagnosis

Prevalence of NSCLC Subtypes



. American Cancer Society. Cancer A-Z: NSCLC. 2017. 2. Zappa C, et al. Transl Lung Cancer Res. 2016;5:288-300. 3. Howlander N, et al. SEER Cancer Statistics Review, 1975-2014.

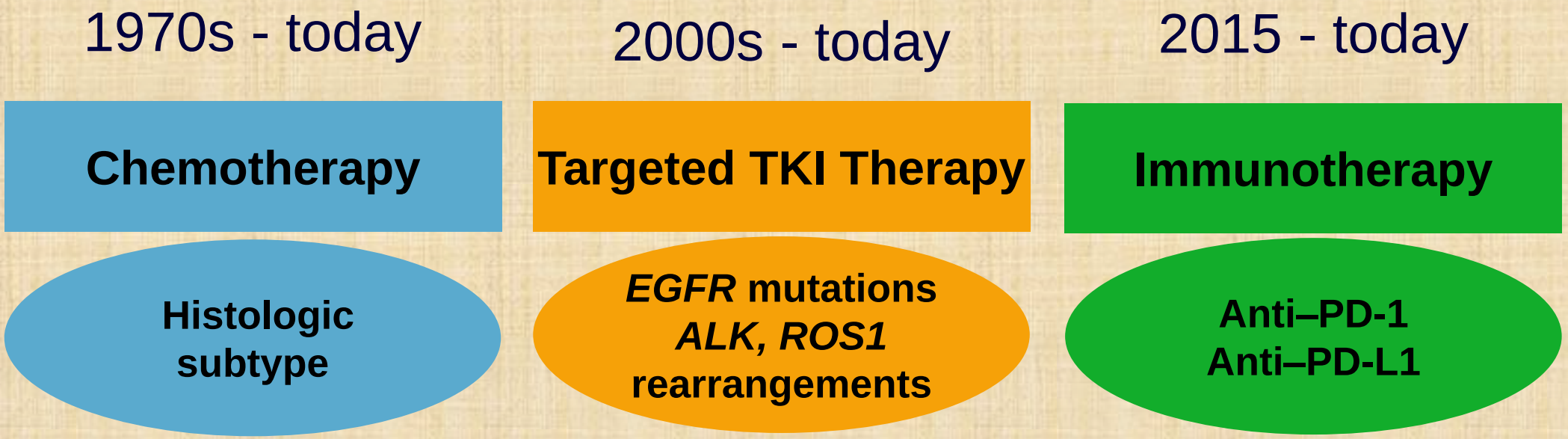
EPIDEMIOLOGY OF NSCLC

- **AMONGST TOP 5 CANCER KILLERS**
- **5 YEAR SURVIVAL RATES**

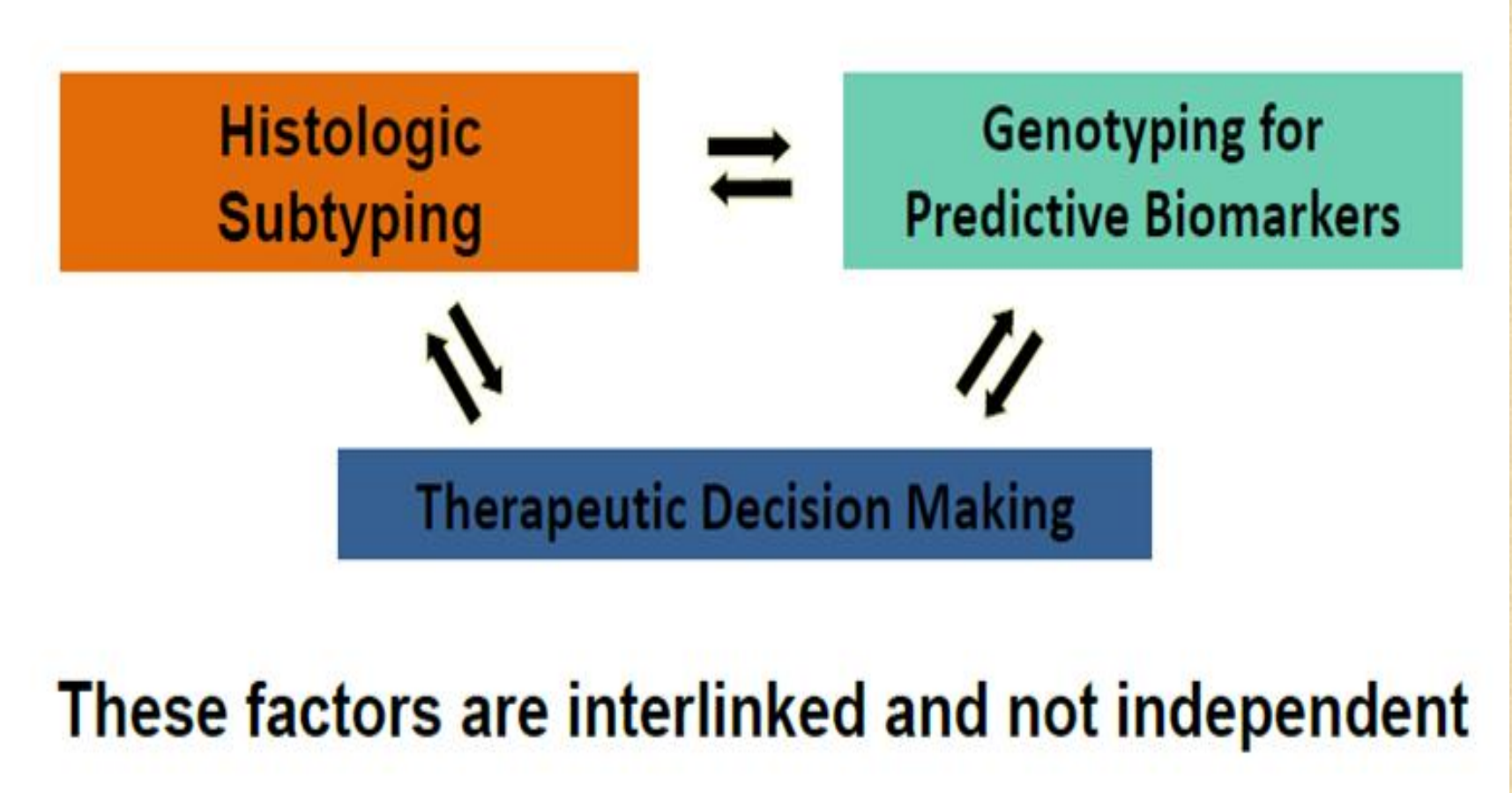
  OVERALL : 18- 20 %

  METASTATIC :< 5%

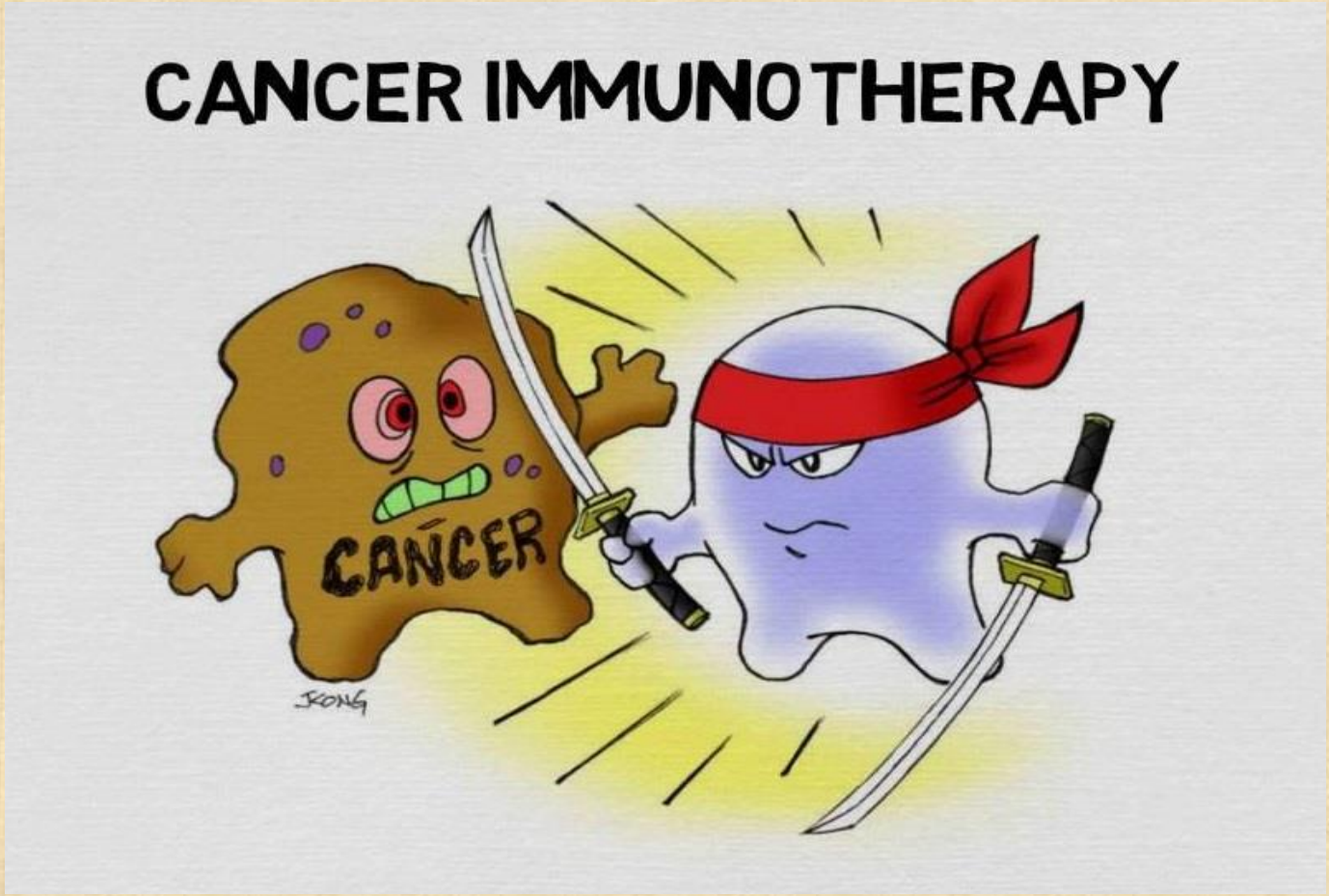
PERSONALIZED THERAPY EVOLUTION



DECISION MAKING IN LUNG CANCER: INTERLINKS



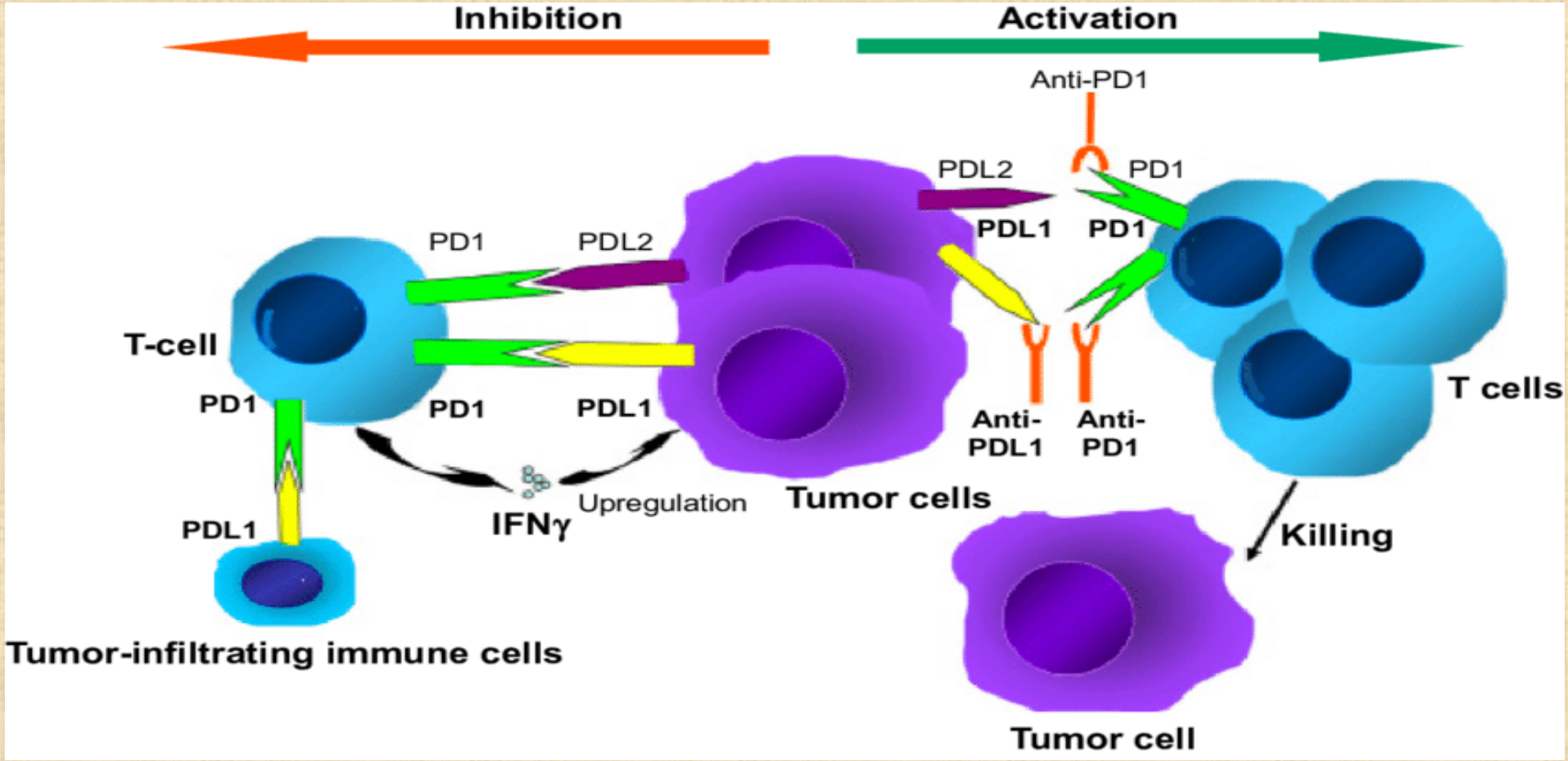
IMMUNOTHERAPY: FIFTH PILLAR OF ONCOLOGY



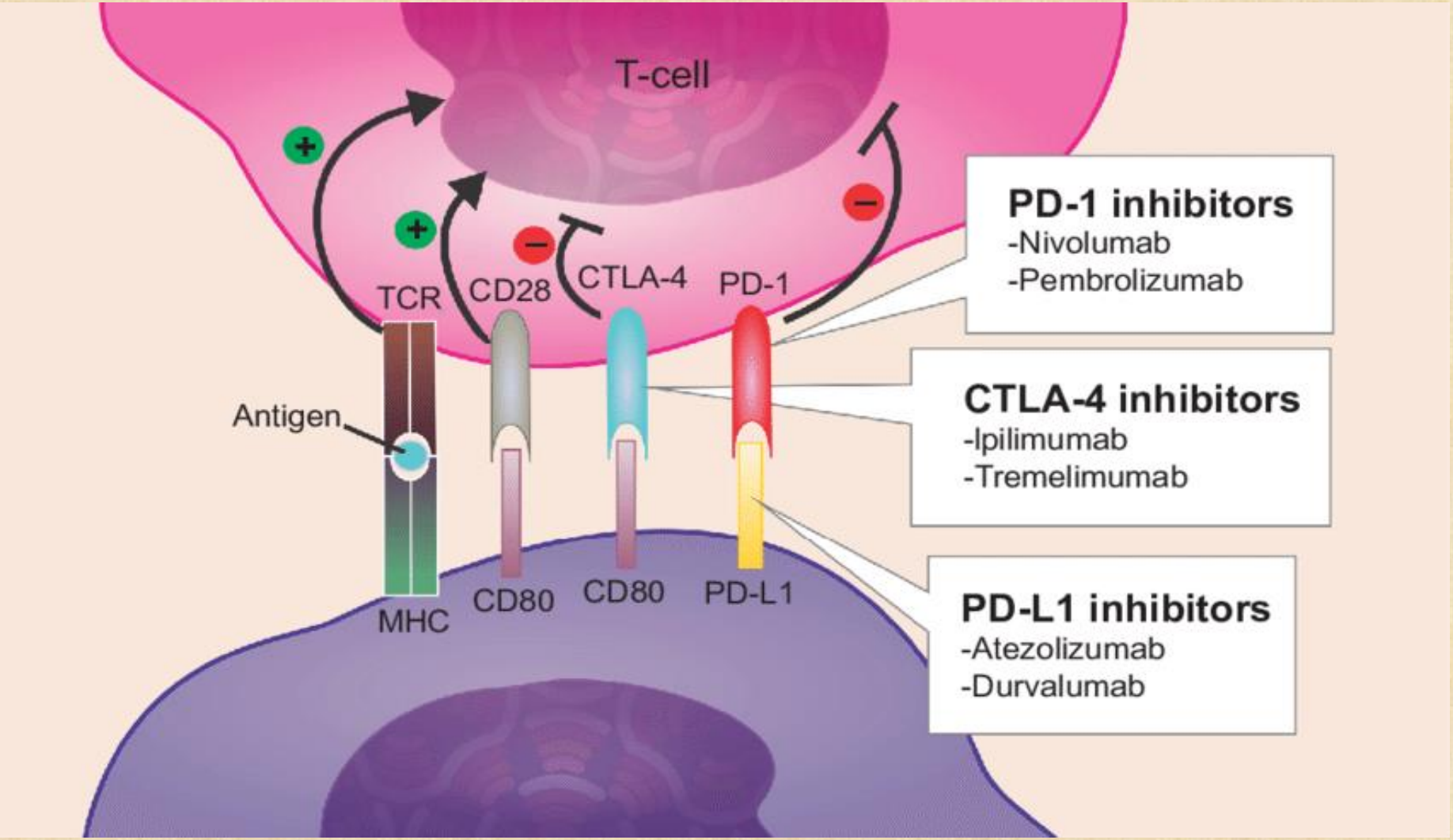
IMMUNOTHERAPY

THE IMMUNOLOGICAL BASIS OF IMMUNE THERAPEUTIC AGENTS

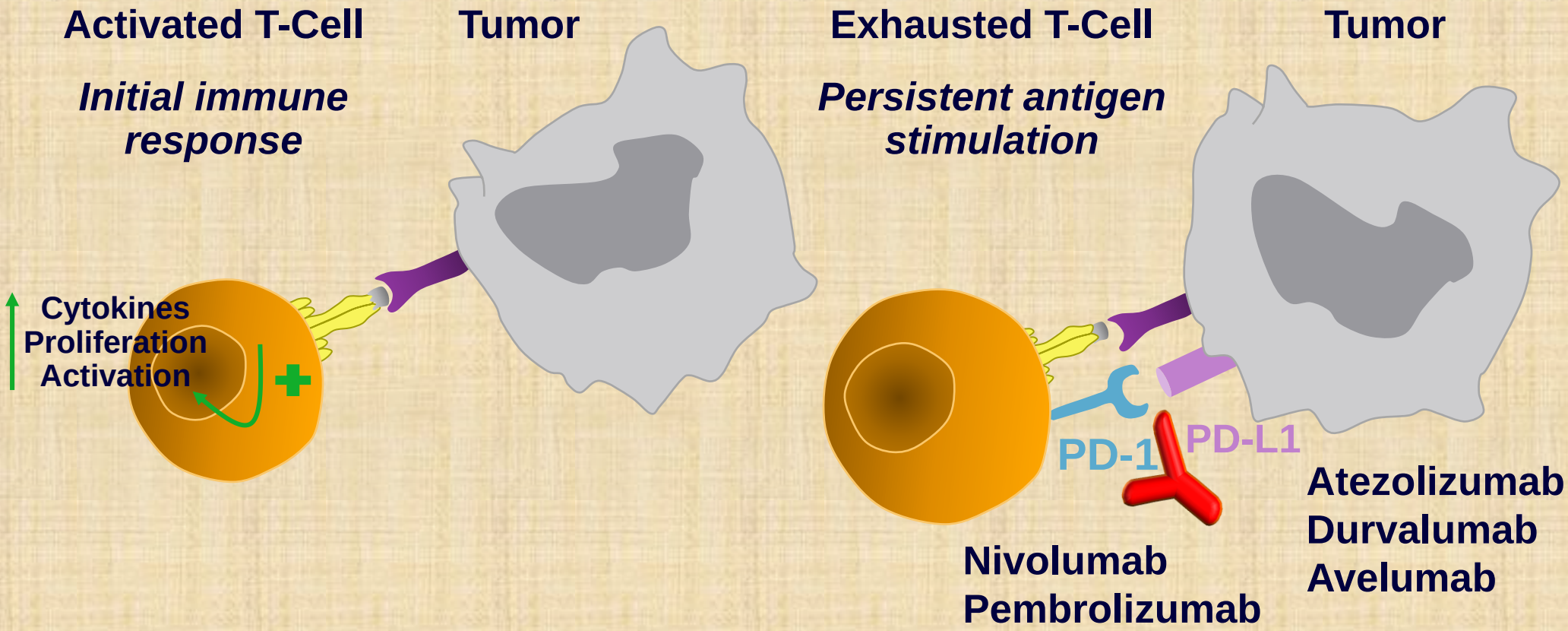
PD-1 & PDL-1


Inhibition
Activation
Anti-PD1
PDL2
PD1
PDL1
PD1
PD1
PDL2
T-cell
PD1
PD1
PDL1
Anti-
PDL1
Anti-
PD1
T cells
IFNγ
Upregulation
Tumor cells
PDL1
Killing
Tumor-infiltrating immune cells
Tumor cell

IMMUNOTHERAPY : MECHANISM OF ACTION



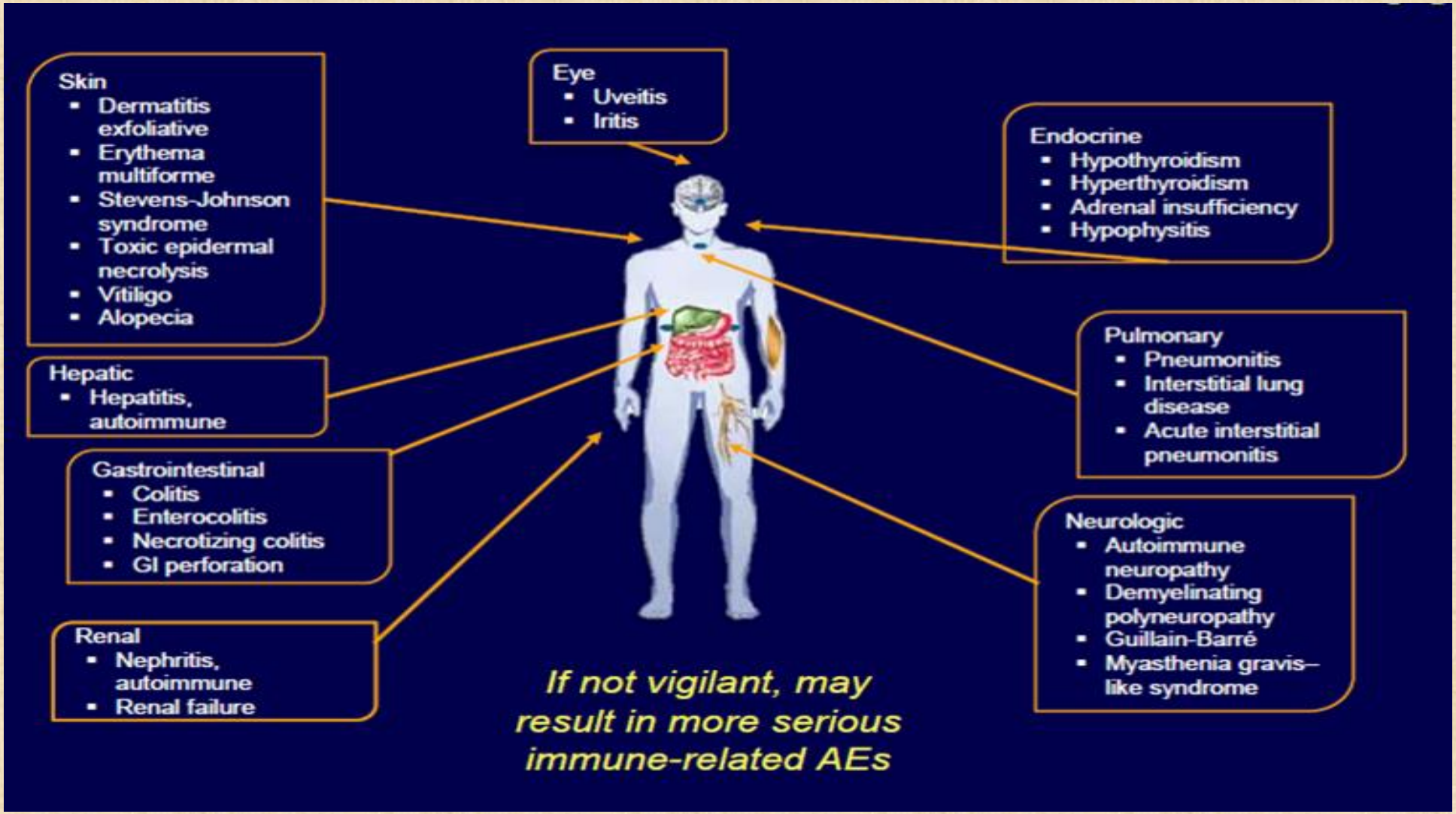
PD-1/PD-L1 AS A TARGET IN CANCER THERAPY



IMMUNOTHERAPY

- Immune checkpoint inhibition removes tumor repression of the immune system and activates potency of immune cells against tumor cells
- In stage IV NSCLC, immune checkpoint inhibition achieved durable and prolonged responses in some patients
  - Median OS ranges from 15 to 27 mos

IMMUNOTHERAPY RELATED ADVERSE EVENTS



NOBEL PRIZE(MEDICINE) 2018

JAMES ALLISON

TASUKO HONJO

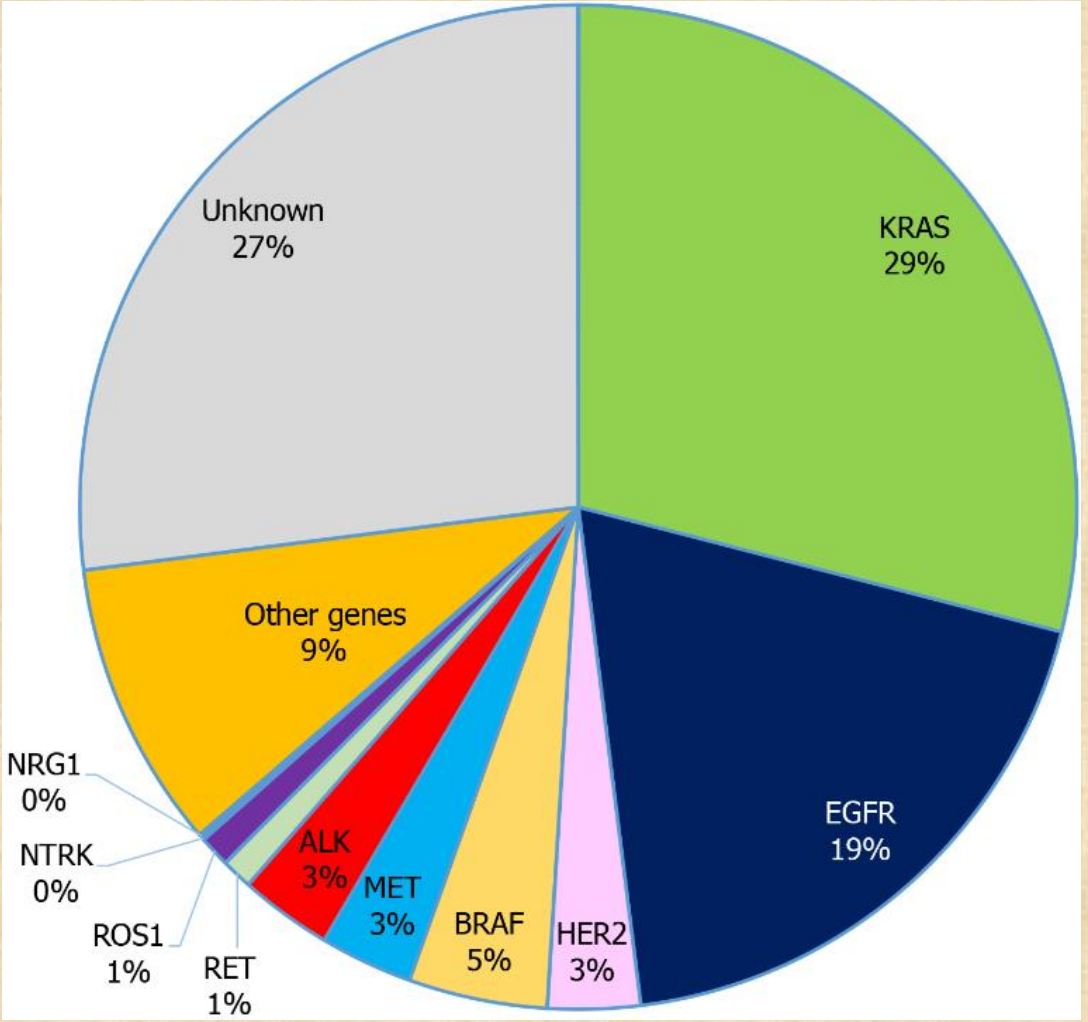
WHEN TO USE

- NOT RECOMMENDED
- 1. C/I – ACTIVE OR PREVIOUSLY DOCUMENTED AUTO-IMMUNE DISORDER
- CURRENT USE OF IMMUNOSUPPRESSIVE DRUGS
- PRESENCE OF A TARGET THAT PRECLUDE LACK OF BENEFIT (BASED ON DATA FROM EARLIEST STUDY OF io IN PATIENTS WITH A TARGETABLE MUTATION)- EXCESS TOXICITIES WITHOUT ANY CLINUICAL BENEFIT
- FINANCIAL TOXICITIES

RESPONSE RATE

	EGFR	ALK	ROS1	BRAF	HER2	MET	RET
TARGETED THERAPY	80%	83%	77%	64%	55%	71%	68%
IO	11%	4%	14%	24%	15%	23%	11%
IO + TARGETED	75%	81% (increased toxicities)					
CHEMO+IO	81%						

- Testing for driver mutations(NGS/individually)
- Testing for PDL1



IMMUNOTHERAPY (METASTATIC SETTING)

SECOND LINE

- CHECKMATE 017 TRIAL
- Phase III, randomized, open-label study (n=272), nivolumab vs. docetaxel; metastatic squamous NSCLC, disease progression during or after one prior platinum doublet based chemotherapy
    - Median Overall Survival (OS) = 9.2 months on nivolumab (n=132) vs. 6.0 months on docetaxel (n=137)

CHECKMATE 057 TRIAL

Phase III randomized, metastatic non-squamous NSCLC nivolumab vs docetaxel in second or later lines of therapy

- Median Overall Survival (OS) = 12.2 months on nivolumab vs. 9.5 months on docetaxel
- Response rates around 20% for nivolumab vs 9-12% for docetaxel in both the trials

- SECOND LINE
- KEYNOTE010
- RANDOMIZED 1:1:1 PEMBROLIZUMAB 2MG/KG VS 10 MG/KG VS DOCETAXEL, IN SECOND OR LATER LINES FOR SQ/NON SQ HISTOLOGY
- OS 10.4 VS 12.7 VS 8.5 MONTHS, SHOWING GREATEST BENEFIT FOR TUMORS PDL-1>50%

- SECOND LINE
- OAK TRIAL: PHASE 3 TRIAL ATEZOLIZUMAB VS DOCETAXEL IN SECOND OR LATER LINES IN SQ/NONSQ.
- OS 13.8 VS 9.6 MONTHS IRRESPECTIVE OF PDL1 EXPRESSION

Study name	Phase	Histology, PD-L1	Line of treatment	Study design	Control arm outcome	Experimental arm outcome	Hazard ratio (95% Confidence Interval, p value)
Later-line ICI							
CheckMate017	III	Squamous	Second or later	Nivolumab vs. docetaxel	mOS 6.0 months	mOS 9.2 months	0.62 (0.47–0.80)
CheckMate057	III	Nonsquamous	Second or later	Nivolumab vs. docetaxel	mOS 12.2 months	mOS 9.5 months	0.75 (0.63–0.91)
KEYNOTE-010	II/III	NSCLC, PD-L1 TPS≥1%	Second or later	Pembrolizumab 2 mg/kg or 10 mg/kg vs. docetaxel	mOS 8.5 months	2 mg/kg: mOS 10.4 months	2 mg/kg: 0.71, p=0.0008
						10 mg/kg: mOS 12.7 months	10 mg/kg: 0.61, p<0.0001
OAK	III	NSCLC	Second or later	Atezolizumab vs. docetaxel	mOS 9.6 months	mOS 13.8 months	0.73 (0.62–0.87), p=0.0003

IMMUNOTHERAPY(2ND AND SUBSEQUENT LINE)

- - CONSISTENT IMPROVEMENT IN OS, ORR WITH IMMUNOTHERAPY
- LESSER TOXICITY AS COMPARED TO CHEMOTHERAPY
- CUT-OFFS FOR PDL1 NOT DEFINED
- DIAGNOSTIC METHODS FRO PDL1 TESTING NOT DEFINED
- UNCLEAR WHETHER PDL1 TESTING SHOULD BE DONE FOR SECOND LINE THERAPY OR NOT

IMMUNOTHERAPY IN UNTREATED NSCLC(METASTATIC)

- Keynote 024; PHASEIII, nsclc(sq/nonsq) qwith PDL-1 50% OR MORE(tps) PEMBROLIZUMAB WITH STANDARD [PLATINUM DOUBLET. PFS 10.3 VS 6.0 MONTHS

- KEYNOTE 042: SIMILAR TRIAL BUT PDL-1 >1% WERE ELIGIBLE. OS BENEFIT WAS GREATEST IN TPS >50% AND NOT PRESENT IN LOWER SCORE

IMMUNOTHERAPY IN UNTREATED NSCLC(METASTATIC)

- CHECKMATE 026 PHASE III , NIVOLUMAB VS PLATINUM DOUBLET IN NSCLC, PDL-1 TPS ≥ 1%.
- NO BENEFIT IN PFS OR OS, SUBGROUP ANALYSIS ALSO FUTILE.
- HOWEVER, A TMB ANALYIS REVEALED AN INCREASED RR(47 VS 28%) AND PFS(9.7 MONTHS VS 5.8), BUT NO DIFFERENCE IN OS.

IMMUNOTHERAPY IN UNTREATED NSCLC(METASTATIC)

- MYSTIC TRIAL. DURVALUMAB VS DURVA + TREMELIMUMAB VS PLATINUM DOUBLET.
- DID NOT MEET ENDPOINT (pfs)

- IMPOWER 110: PHAE III ATEZOLIZUMAB VS PLATINUM DOUBLET IN NSCLC
- OS 20.2 MONTHS VS 11.0 MONTHS

IMMUNOTHERAPY IN UNTREATED NSCLC(METASTATIC)

Study name	Phase	Histology, PD-L1	Line of treatment	Study design	Control arm outcome	Experimental arm outcome	Hazard ratio (95% Confidence Interval, p value)
First-line ICI only							
KEYNOTE-024	III	NSCLC, PD-L1 TPS≥50%	Treatment-naïve	Pembrolizumab vs. chemotherapy	mOS 14.2 months	mOS 30.0 months	0.63 (0.47–0.86), p=0.002
KEYNOTE-042	III	NSCLC, PD-L1 TPS≥1%	Treatment-naïve	Pembrolizumab vs. chemotherapy	mOS 12.1 months	mOS 16.7 months	0.85 (0.71–0.93), p=0.0018
CheckMate026	III	NSCLC, PD-L1 TPS≥1%	Treatment-naïve	Nivolumab vs. chemotherapy	mOS 13.2 months	mOS 14.4 months	1.02 (0.80–1.30), p=NS
MYSTIC	III	NSCLC	Treatment-naïve	D vs. D+Tr vs. chemotherapy	mOS 12.9 months	mOS 16.3 months (D) mOS 11.9 months (D+Tr)	D vs. Chemotherapy: 0.76 (0.56–1.02). p=NS D+Tr vs. Chemotherapy: 0.85 (0.61–1.17), p=NS

IMMUNOTHERAPY IN UNTREATED NSCLC(METASTATIC)

- CONCLUSION
- PDL1 OR TMB ARE NOT A CONSISTENT BIOMARKER TO PREDICT EFFICACY ACROSS VARIOUS ICI.
- PEMBROLIZUMAB, ATEZOLIZUMAB, CEMIPLIMAB-rwlc REMIANS THE ONLY APROVED ICI IN FIRST LINE SETTING IN ADVANCED NSCLC PATIENTS (tps >50%).

IMMUNOTHERAPY IN COMBINATION WITH CHEMOTHERAPY NSCLC(METASTATIC)

- NEED?
- patients with a tumor proportion score of 50% or greater represent a minority of those with NSCLC
- less than one half of patients ever receive second-line therapy.

- HYPOTHESIS
- Modulation of the immune response through PD-1 inhibition may be enhanced by the potential immunogenic effects of cytotoxic chemotherapy

IMMUNOTHERAPY IN COMBINATION WITH CHEMOTHERAPY NSCLC(METASTATIC)

- KEYNOTE-189 PHASE III , FIRSTLINE SETTING , NONSQ NSCLC , PEM + PLATINUM + PEMBRO VS PEM + PLATINUM

- ORR 47.6% VS 18.9%
- 3 YEAR OS 31.3% VS 17.4% (SEEN IRRESPECTIVE OF PDL-1 STATUS)

IMMUNOTHERAPY IN COMBINATION WITH CHEMOTHERAPY NSCLC(METASTATIC)

- Impower 150/Impower 132: PHASE III ATEZOLIZUMAB +CHEMOTHERAPY, in nonsquamous nsclc, favourable rrsult irrespective of pdl-1 expression

- Keynote-407 impower 131 phase III TRIAL OF PEMBROLIZUMAB AND ATEZOLIZUMAB RESPECTIVELY, IN CONBINATION WITH CHEMOTHERAPY IN ADVANCED SQUAMOUS NSCLC, WITH FAVOURABLE RESULTS.

First-line ICI+Chemotherapy combination							
KEYNOTE-189	III	Nonsquamous	Treatment-naïve	Pem/C±pembrolizumab vs. placebo	12-month OS 49.4%	12-month OS 69.2%	0.49 (0.38–0.64), p<0.001
IMpower150	III	Nonsquamous, including EGFR/ALK+	Treatment-naïve	B/Pac/C±atezolizumab	mOS 14.7 months	mOS 19.2 months	0.78 (0.64–0.96), p=0.02
IMpower132	III	Nonsquamous	Treatment-naïve	Pem/P±atezolizumab	mPFS 5.2 months	mPFS 7.6 months	0.60 (0.49–0.73), p<0.0001
KEYNOTE-407	III	Squamous	Treatment-naïve	T/C±pembrolizumab	mOS 11.3 months	mOS 15.9 months	0.64 (0.49–0.85), p<0.001
IMpower131	III	Squamous	Treatment-naïve	Nab/C±atezolizumab	mPFS 5.6 months	mPFS 6.3 months	0.715 (0.603–0.848), p=0.0001

Combination immunotherapy in first line setting

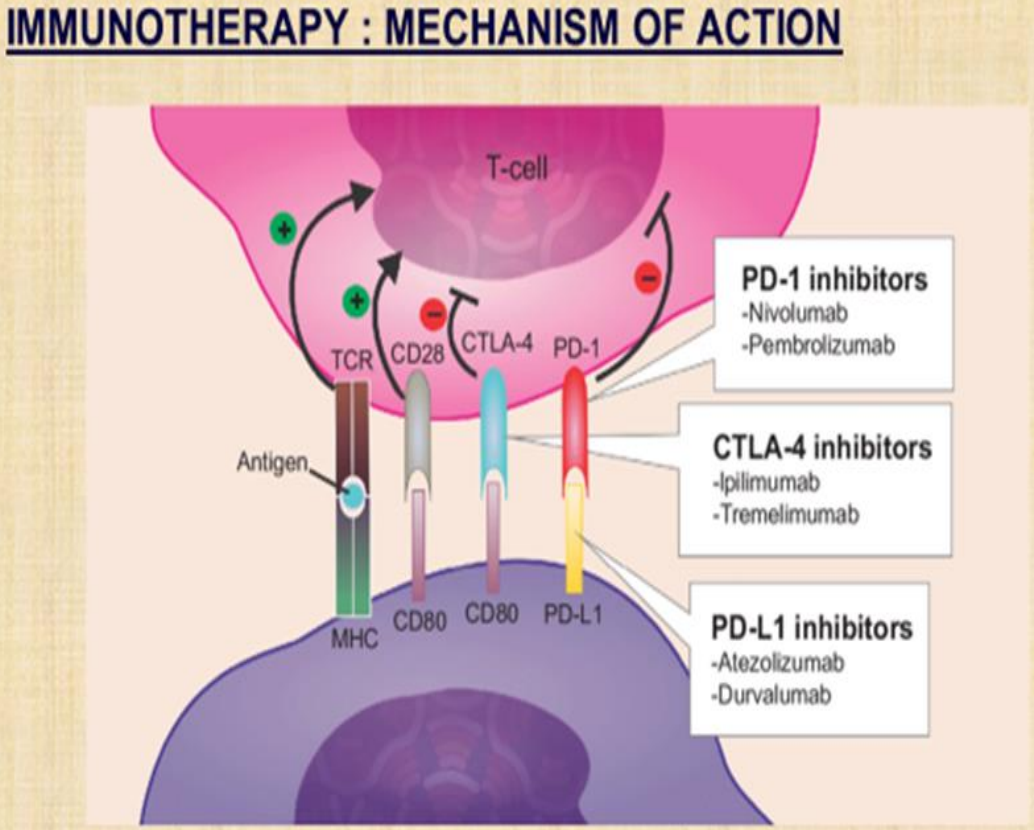
- Nivolumab + ipilimumab (irrespective of pdl1 status)

IMMUNOTHERAPY IN ADJUVANT SETTING

IMMUNE-BIOMARKERS

- NIVO/PEMBRO/CEMIP-rwlc
- PD-1

- ATEZO/DURVA PDL-1



PDL-1 : NOT AN OPTIMAL BIOMARKER?

- Expression is dynamic/variable/temporal : difficult to define a cut off
- Each drug trial used different antibody clones/assays (Dako 28-8, Dako 22C3, Ventana SP142, Ventana SP263 for nivolumab,
- pembrolizumab, atezolizumab and durvalumab, respectively)
- Cross compatibility of various platforms have failed to provide a uniform result
- Moreover, even PD-L1 negative patients may respond to anti-PD-1/PD-L1 inhibitor
- while some PD-L1 highly positive patients do not show response

PDL-1 : NOT AN OPTIMAL BIOMARKER?

- Multiple studies have shown an absence of association between PD-L1 expression and OS in ICI therapy

TMB

- GOLDIE-COLDMAN HYPOTHESIS

  As tumor grows, genetic alterations/mutations accumulate

- The number of genetic alterations within a tumor genome is considered correlative with mutant protein burden
- HIgher the mutaations.alterations , more the mutant protein and hence immunogenicity- more likelihood of response to IO

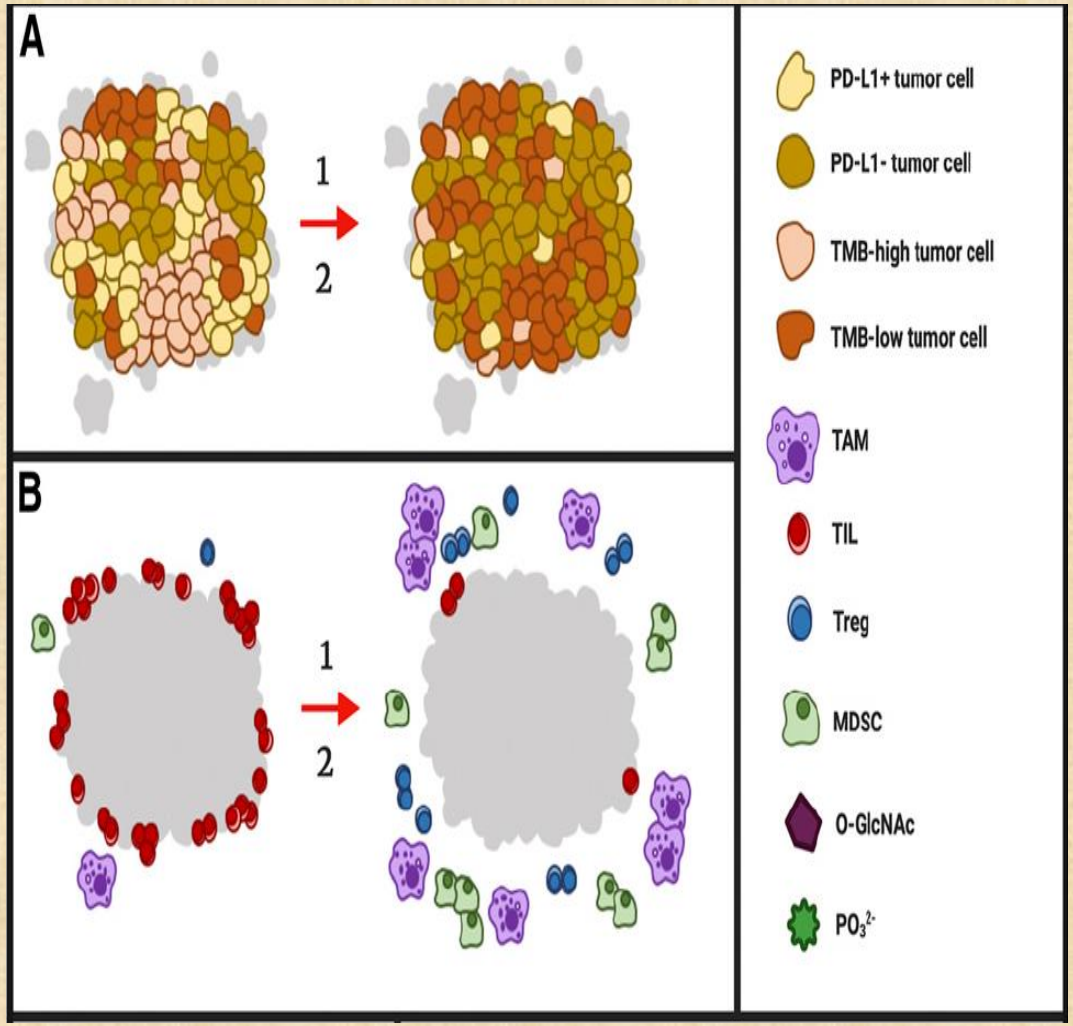
- However, the relationship between TMB and response to immune checkpoint inhibitors is imperfect across and within tumor types
- Imperfect correlation between OS, RR and TMB across various studies with IO
- TMB doesnot identify patients who will respond to immun-chemotherapy
- determination of TMB and the TMB thresholds predicting response to immune checkpoint blockade have been developed independently in each tumor type, they are likely to differ across tumor types,

- and also across testing platforms (eg, blood versus tumor tissue
- So, a lack of agreement on a cut-off value
- Lack of standardization of TMB across labs
- Time consuming
- In 2020 NCCN panel removed TMB as an emerging biomarker for patients with NSCLC and donot recommend TMB measurement before deciding for IO

OTHER BIOMARKERS

- MMR/MSI
- TUMOR INFILTRATING LYMPGOCYTES
- GENE EXPRESSION PROFILE
- Treg

- None approved as companion diagnostic for the use of IO in lung cancer



- A. (A) Intratumoral (and intrapersonal) cellular heterogeneity Further dynamic alterations in clonal composition under the pressure of time (1) and therapy (2) prohibit pretreatment biomarker accuracy.

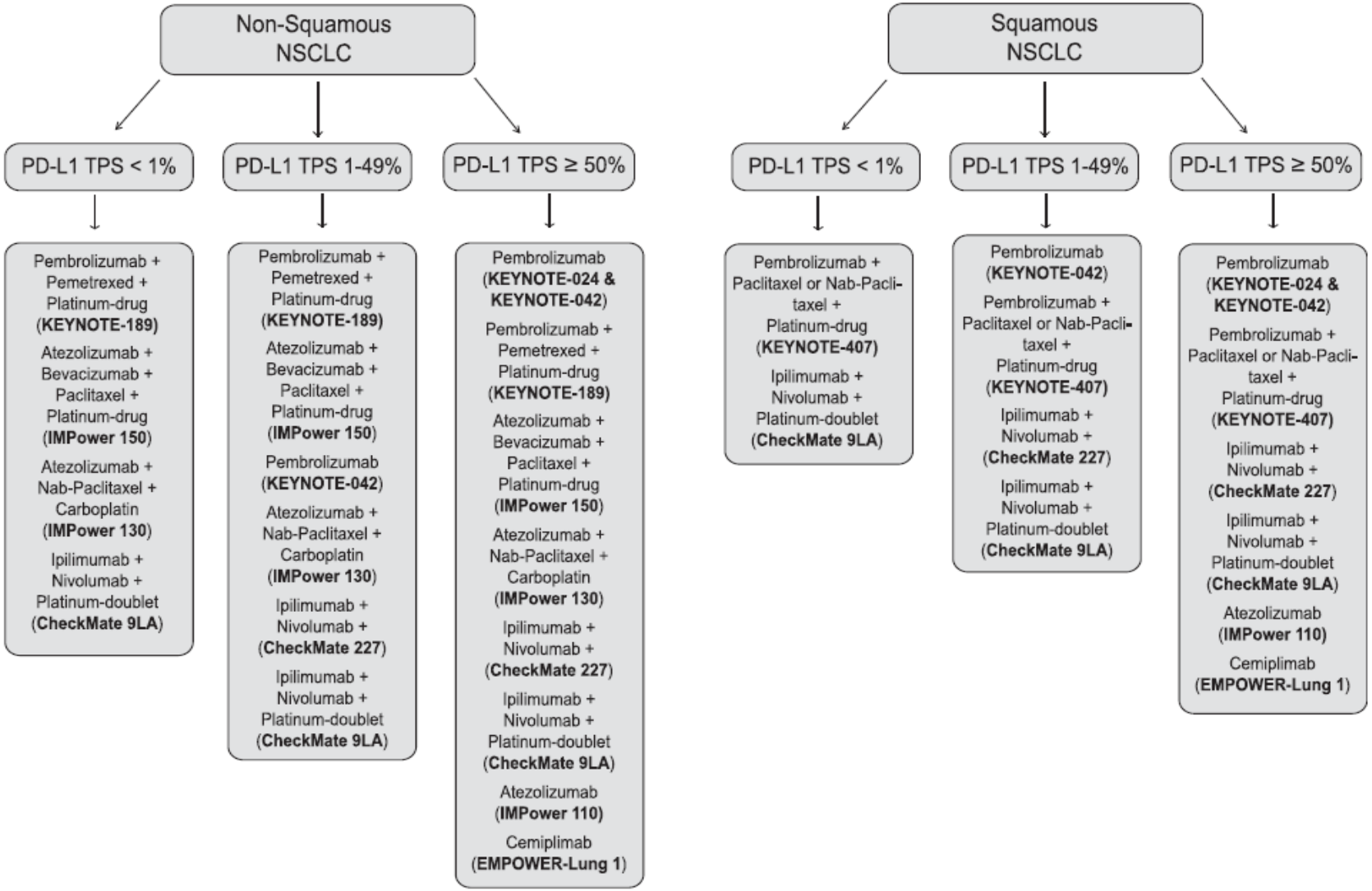
- B. Patient host immunity & tumor microenvironment remain highly individualized and responsive to progressive cytokine (1) and/or treatment (2) exposure

- retrospective analysis of clinical trials (2011–2019) prompting FDA approval of checkpoint inhibitor regimens identified PD-L1 as a predictive biomarker in only 28.9% of cases.

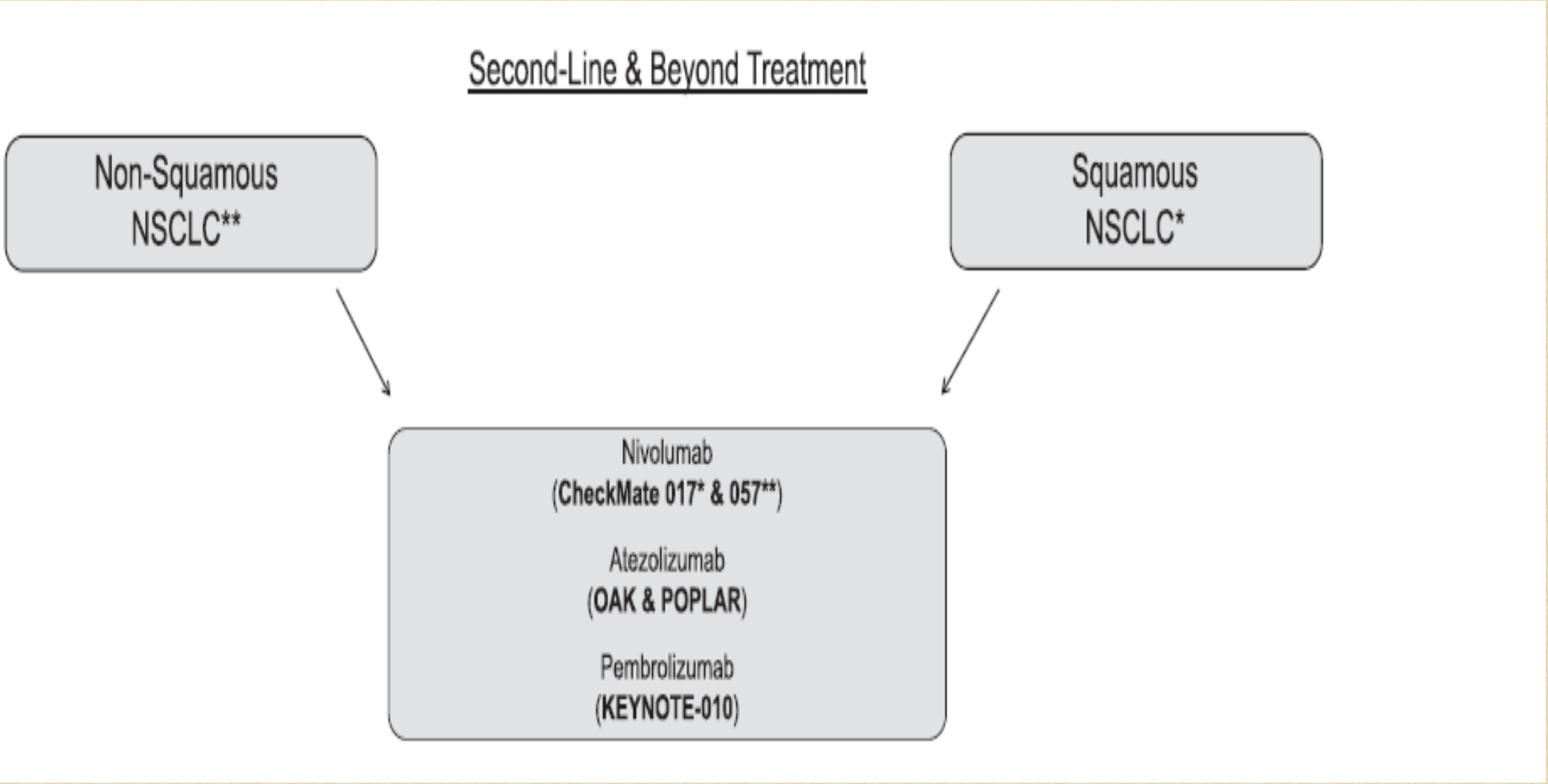
- Davis AA, Patel VG. The role of PD-L1 expression as a predictive biomarker: an analysis of all US Food and Drug Administration (FDA) approvals of immune checkpoint inhibitors. J Immunother Cancer. 2019;7:278

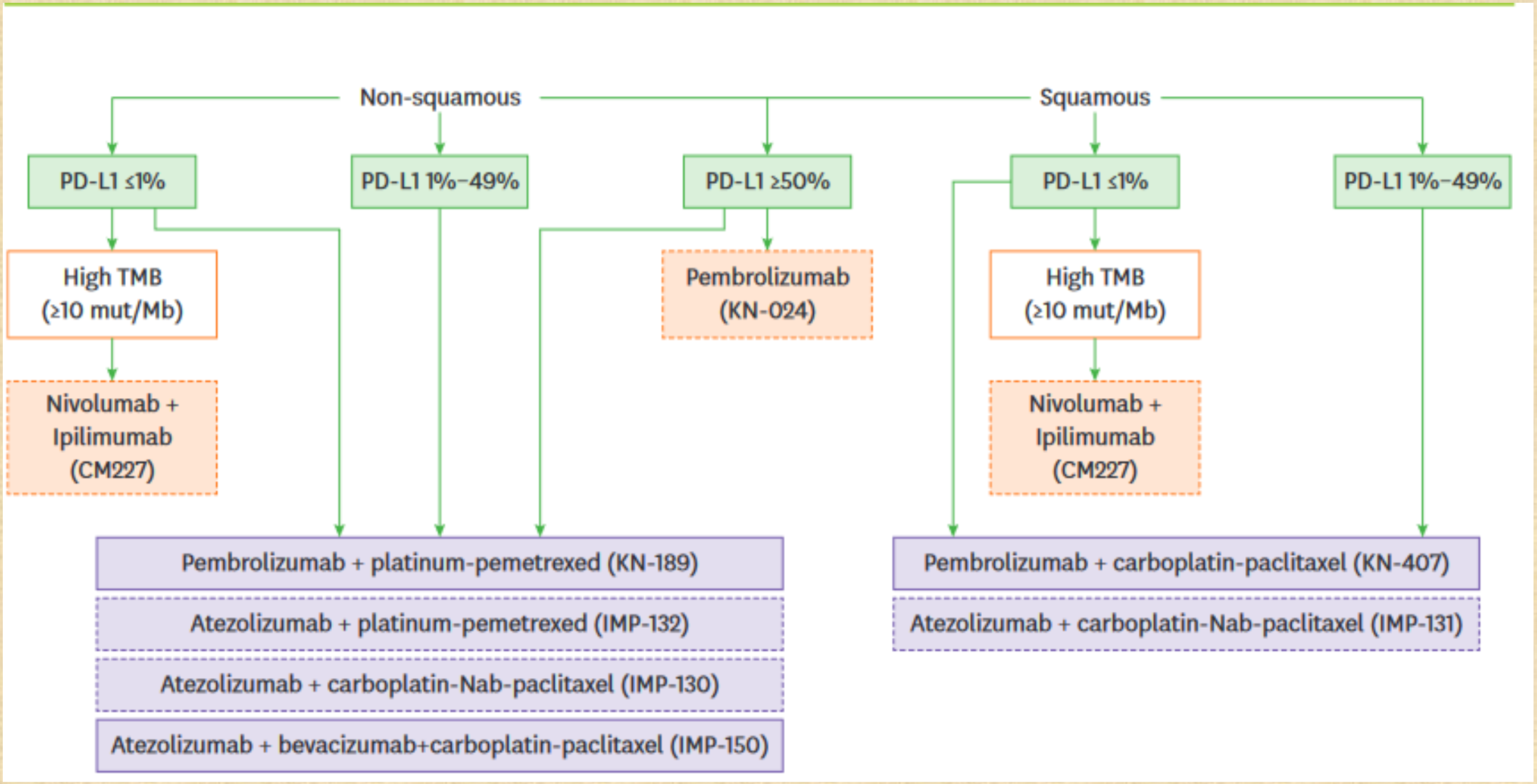
A

First-Line Treatment



B


Second-Line & Beyond Treatment
Non-Squamous NSCLC**
Squamous NSCLC*
Nivolumab
(CheckMate 017* & 057**)
Atezolizumab
(OAK & POPLAR)
Pembrolizumab
(KEYNOTE-010)


Non-squamous
Squamous
PD-L1 ≤1%
PD-L1 1%–49%
PD-L1 ≥50%
PD-L1 ≤1%
PD-L1 1%–49%
High TMB (≥10 mut/Mb)
Pembrolizumab (KN-024)
High TMB (≥10 mut/Mb)
Nivolumab + Ipilimumab (CM227)
Nivolumab + Ipilimumab (CM227)
Pembrolizumab + platinum-pemetrexed (KN-189)
Atezolizumab + platinum-pemetrexed (IMP-132)
Atezolizumab + carboplatin-Nab-paclitaxel (IMP-130)
Atezolizumab + bevacizumab+carboplatin-paclitaxel (IMP-150)
Pembrolizumab + carboplatin-paclitaxel (KN-407)
Atezolizumab + carboplatin-Nab-paclitaxel (IMP-131)

TIMELINE: FDA APPROVAL FOR LUNG CA

Drug	Manufacturer	FDA approval	Indication	Companion diagnostic
Nivolumab	Bristol-Myers Squibb (Princeton, New Jersey)	March 2015	Second-line advanced stage NSCLC (squamous cell carcinoma)	None required
Nivolumab	Bristol-Myers Squibb	October 2015	Second-line advanced stage NSCLC (nonsquamous cell carcinoma)	None required
Pembrolizumab	Merck (Kenilworth, New Jersey)	October 2015	Second-line advanced stage NSCLC	PD-L1 IHC >1% TPS*
Atezolizumab	Genentech/Roche (San Francisco, California)	April 2016	Second-line advanced stage NSCLC	None required
Pembrolizumab	Merck	October 2016	First-line advanced stage NSCLC	PD-L1 IHC >50% TPS
Pembrolizumab with carboplatin/ pemetrexed	Merck	May 2017	First-line advanced stage NSCLC (nonsquamous cell carcinoma)	None required

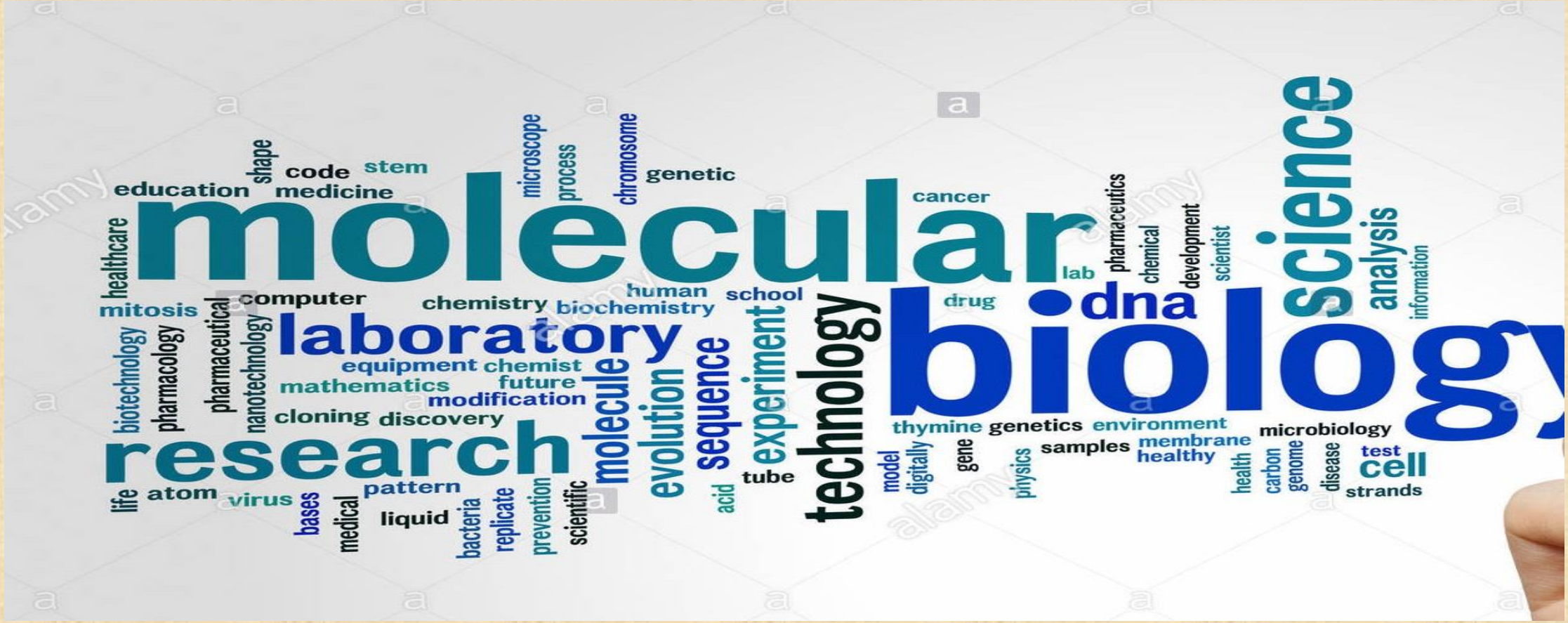
FDA, US Food and Drug Administration; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; PD-1, programmed cell death 1; PD-L1 programmed cell death ligand 1; TPS, tumor proportion score.

Summary of PD-1/PD-L1 Immune Checkpoint Inhibitors Approved for Advanced NSCLC

	Nivolumab[1] (Anti–PD-1)	Pembrolizumab[2] (Anti–PD-1)	Atezolizumab[3] (Anti–PD-L1)
Dose/schedule	240 mg every 2 wks; 480 mg every 4 wks	200 mg every 3 wks	1200 mg every 3 wks
Requirement for PD-L1 expression/approved settings	No; second line or later	▪ First-line monotherapy if ≥ 50% PD-L1 expression ▪ First line in combination with chemotherapy* ▪ After chemotherapy if ≥ 1% PD-L1 expression	No; second line or later
PD-L1 IHC assay	Dako 28-8[4]	Dako 22C3[5]	Ventana SP142[6]
Definition of PD-L1 positive	PD-L1(+): ≥ 1% Strong(+): ≥ 5%	PD-L1(+): ≥ 1% Strong(+): ≥ 50%	PD-L1(+): ≥ 50% TC or ≥ 10% IC

"THERE ARE NO SUCH THINGS AS INCURABLE, THERE ARE ONLY THINGS FOR WHICH MAN HAS NOT FOUND A CURE."

FUTURE IS MOLECULAR BIOLOGY



THANK YOU FOR YOUR TIME