Dr Richard Sullivan

Medical Oncologist

Deputy Chief Medical Officer

Auckland Hospital

Saturday, June 10, 2017

14:50 - 15:10 Maximising Patient Outcomes

Supported by:

TUAPAPA PŪKAHUKAHU LUNG FOUNDATION New Zealand

MSD

Pfizer

Lung Cancer

Maximising Patient Outcomes

Dr Richard Sullivan

Deputy CMO AucklandHospital

Director Cancer Auckland Hospital

Canopy Cancer Care

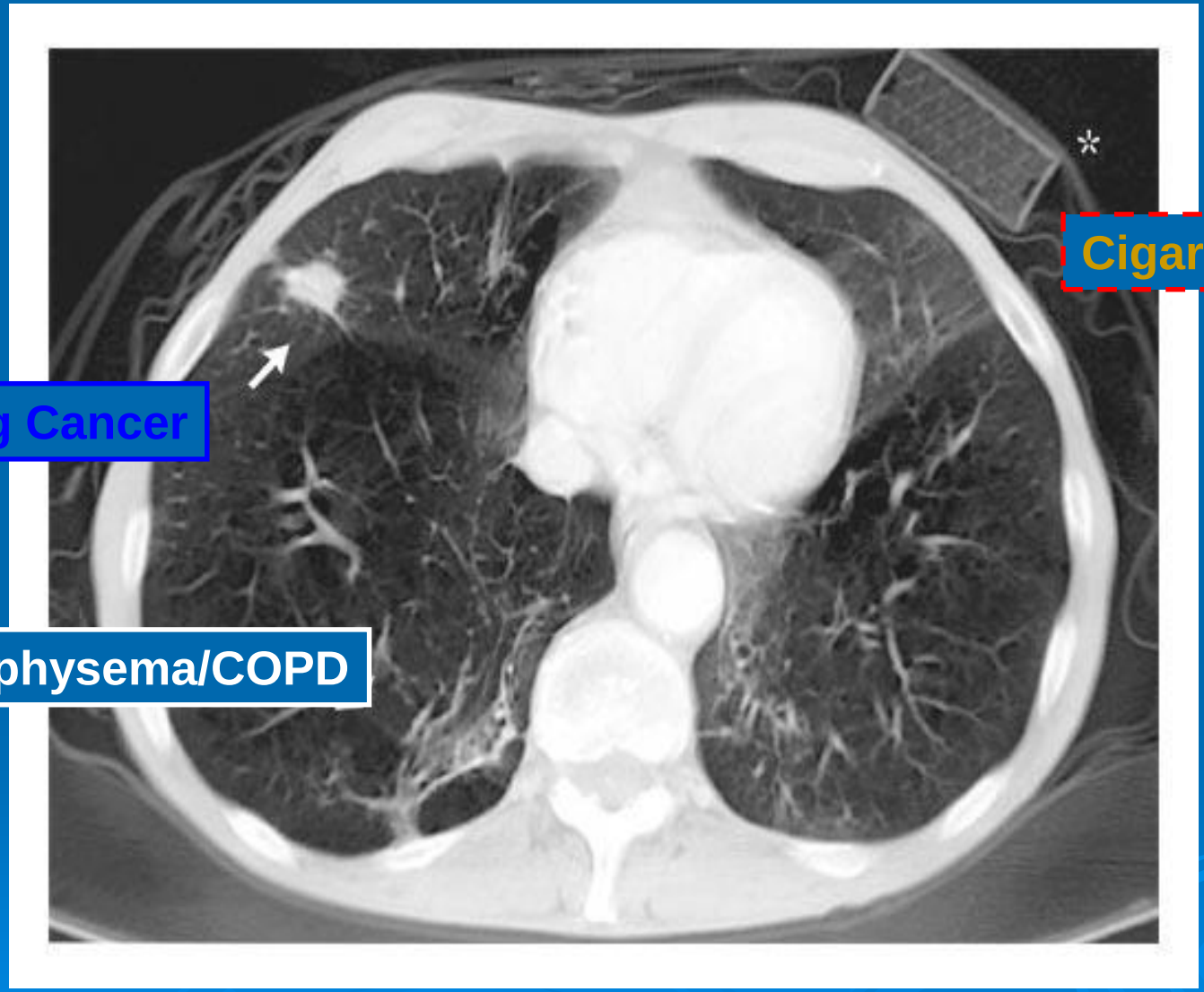
Director Northern Cancer Network

Medical Oncologist

Northern Cancer Network

TUAPAPA PŪKAHUKAHU
LUNG FOUNDATION
New Zealand

Risk Profile



Current options

- High quality care
- Surgery
- Stereotatic radiotherapy
- Targeted therapy
- Immune checkpoint therapy
- Chemotherapy
- Radiotherapy

Non-small Cell Lung Cancer: Metastatic Disease

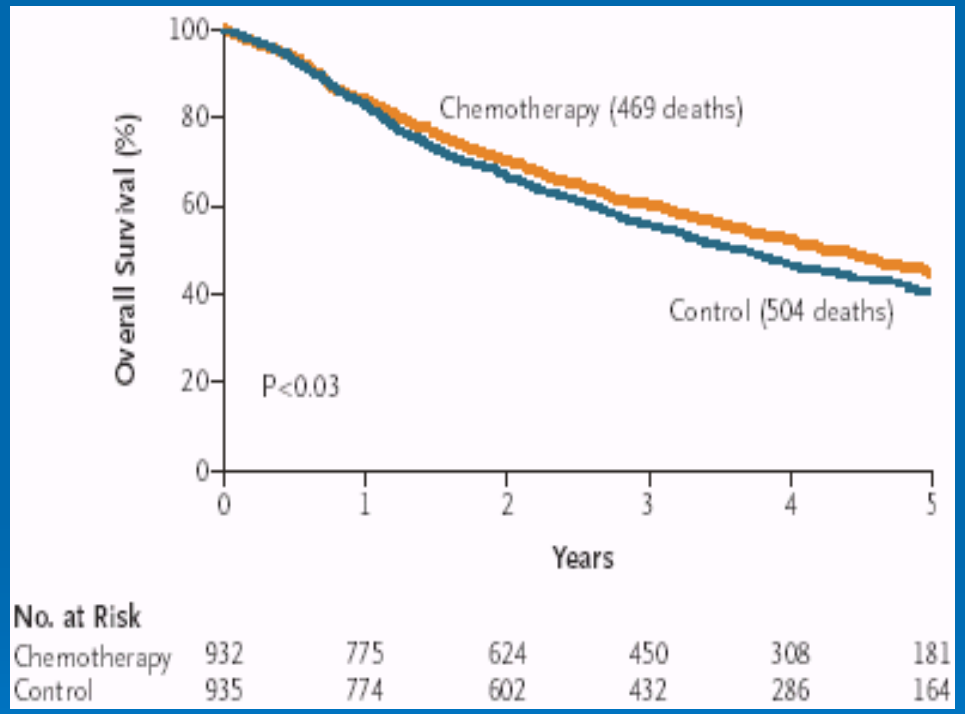
- Untreated patients have a median survival rate of 4 to 5 months
- Untreated only 15-20% of patients survive one year

Adjuvant Chemotherapy

- This translated into an absolute improvement in chances of long term survival of 5% at 5 years

Cisplatin-Based Adjuvant Chemotherapy in Patients with Completely Resected NSCLC: The IALT Trial

- Absolute 5-year survival benefit was 4.1% (*P* = 0.03)
- RT given to <25% pts
- Compliance achieved in 74% pts
- Chemo mortality <1%



The International Adjuvant Lung Cancer Trial Collaborative Group. New England Journal of Medicine 2004; 350:4 351-360.

Northern Cancer Network

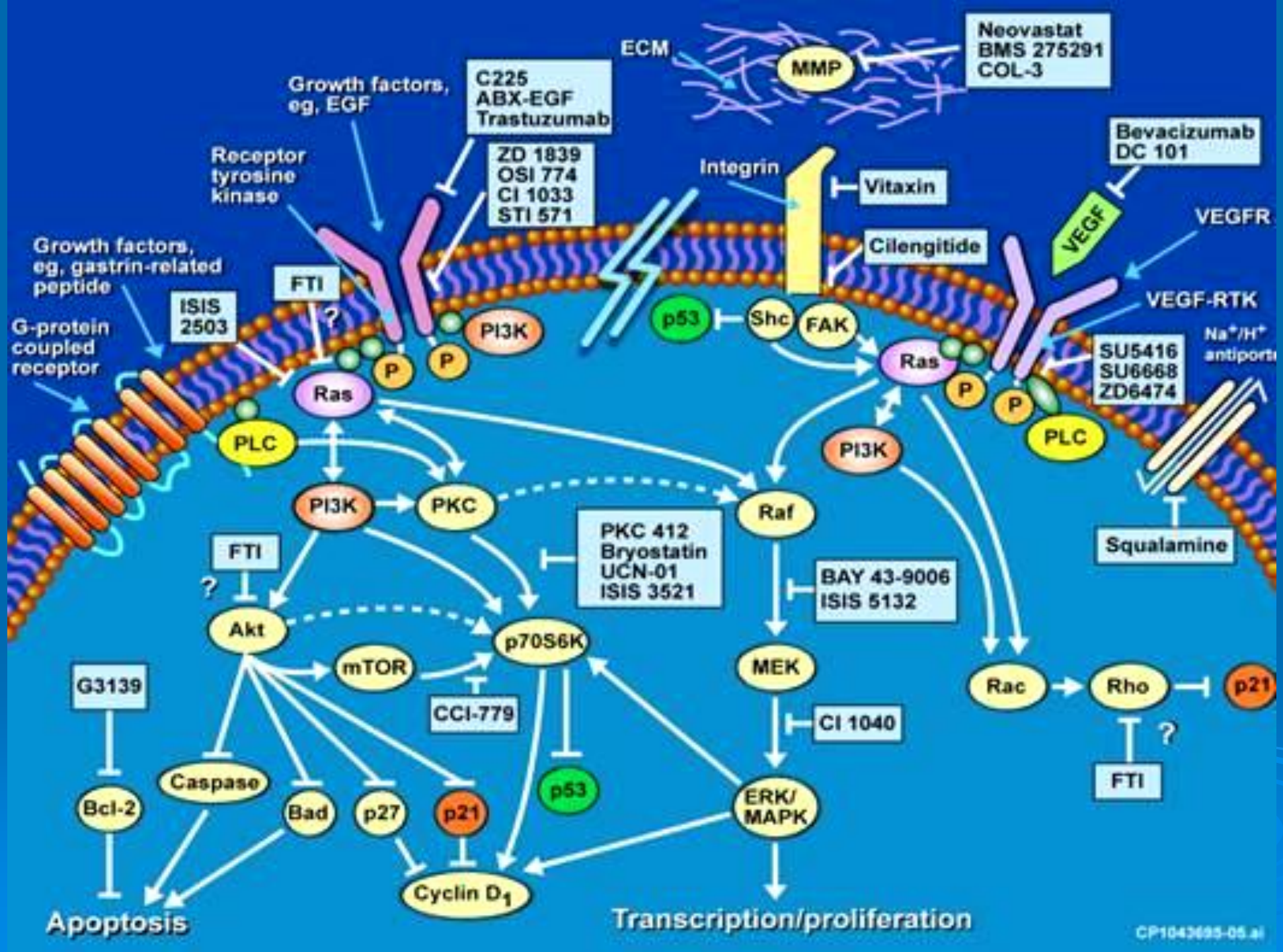
TUAPAPA PŪKAHUKAHU LUNG FOUNDATION New Zealand

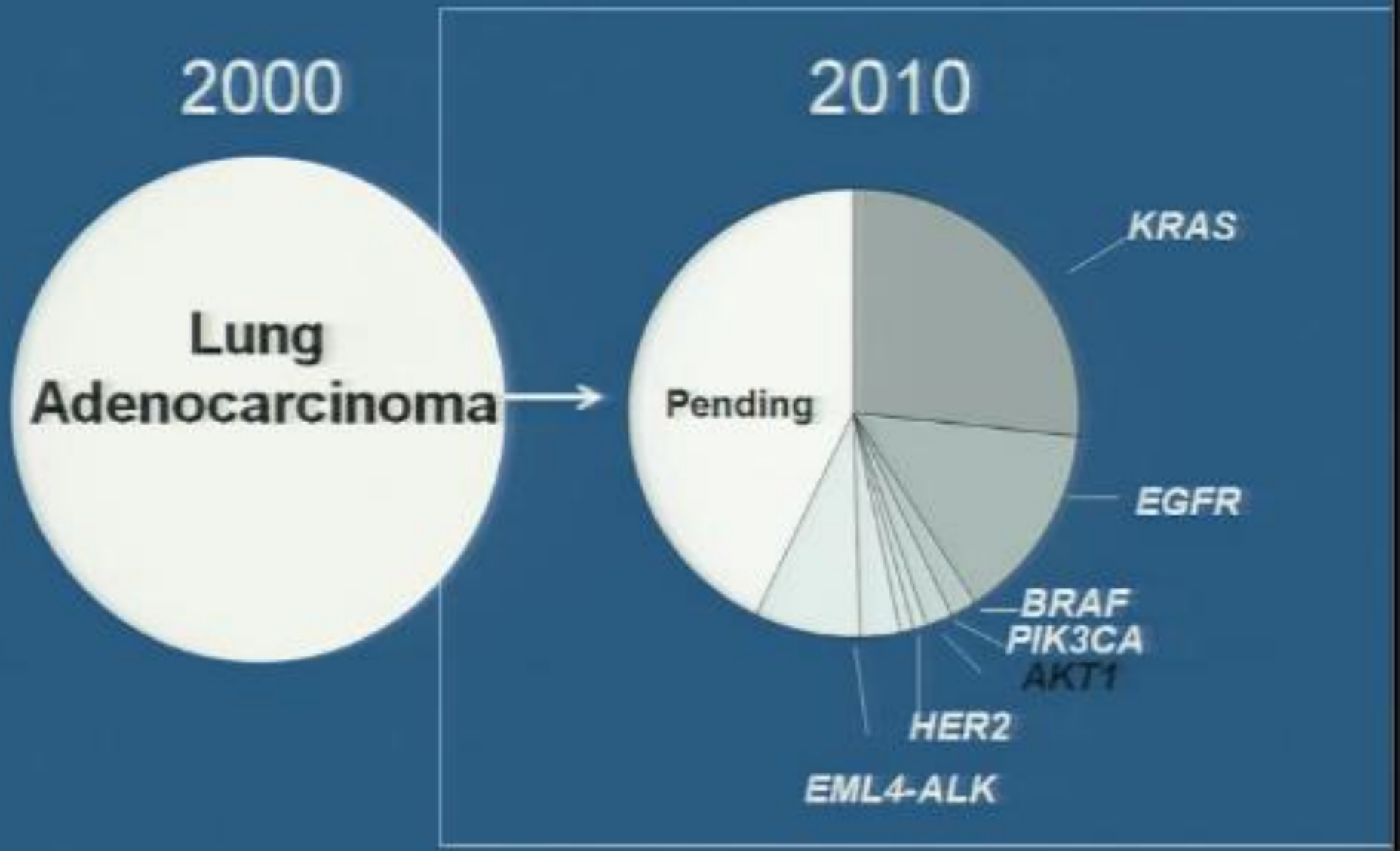
Modern Trials

- Recent trials have shown a clear Overall Survival benefit
  - 15% OS benefit in stage 2b resected Lung Cancer
- Adjuvant therapy for surgically resected stage 1B greater 4cm tumour,2a,2b and resected 3a accepted as providing clear survival benefit.

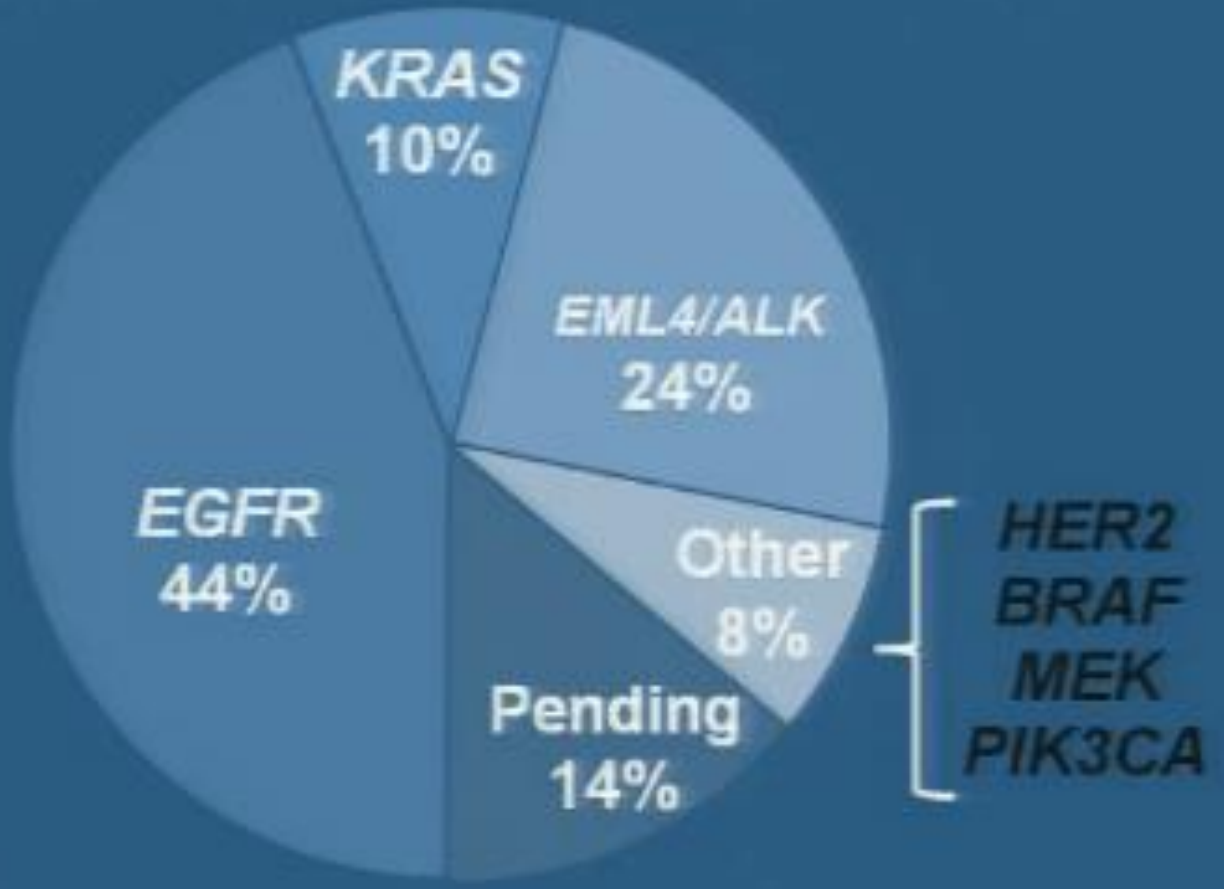
Targeted Therapy

- EGFR inhibition
- Erlotinib,Gefitinib,Icotinib,Afatinib,Osimertinib
- ALK
- Crizotinib,Ceratinib,Alectinib,Lorlatinib,Brigatinib
- ROS
- BRAF
- MET
- Her-2


ECM
MMP
Neovastat
BMS 275291
COL-3
Growth factors,
eg, EGF
C225
ABX-EGF
Trastuzumab
Receptor
tyrosine
kinase
ZD 1839
OSI 774
CI 1033
STI 571
Integrin
Vitaxin
Bevacizumab
DC 101
VEGF
VEGFR
Cilengitide
Growth factors,
eg, gastrin-related
peptide
FTI
ISIS
2503
G-protein
coupled
receptor
PI3K
P
p53
Shc
FAK
VEGF-RTK
Na+/H+
antiport
SU5416
SU6668
ZD6474
Ras
PLC
PKC
Raf
PKC 412
Bryostatin
UCN-01
ISIS 3521
Squalamine
BAY 43-9006
ISIS 5132
Akt
p70S6K
mTOR
CCI-779
MEK
CI 1040
G3139
Rac
Rho
p21
Caspase
Bcl-2
Bad
p27
p21
p53
ERK/
MAPK
Cyclin D1
Apoptosis
Transcription/proliferation

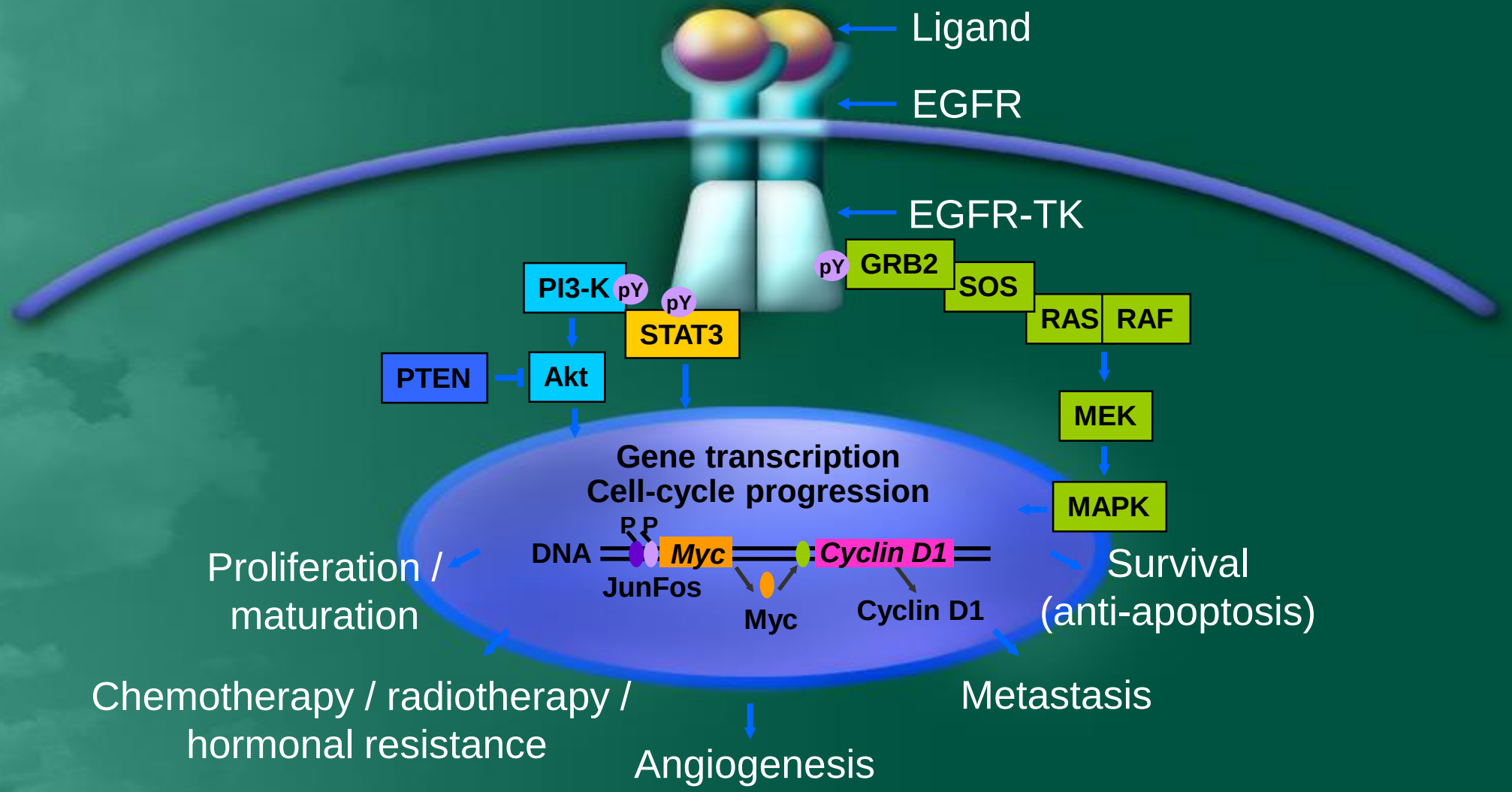

2000
2010
Lung
Adenocarcinoma
Pending
KRAS
EGFR
BRAF
PIK3CA
AKT1
HER2
EML4-ALK

Molecular Alterations in Never Smokers (22,000/yr)

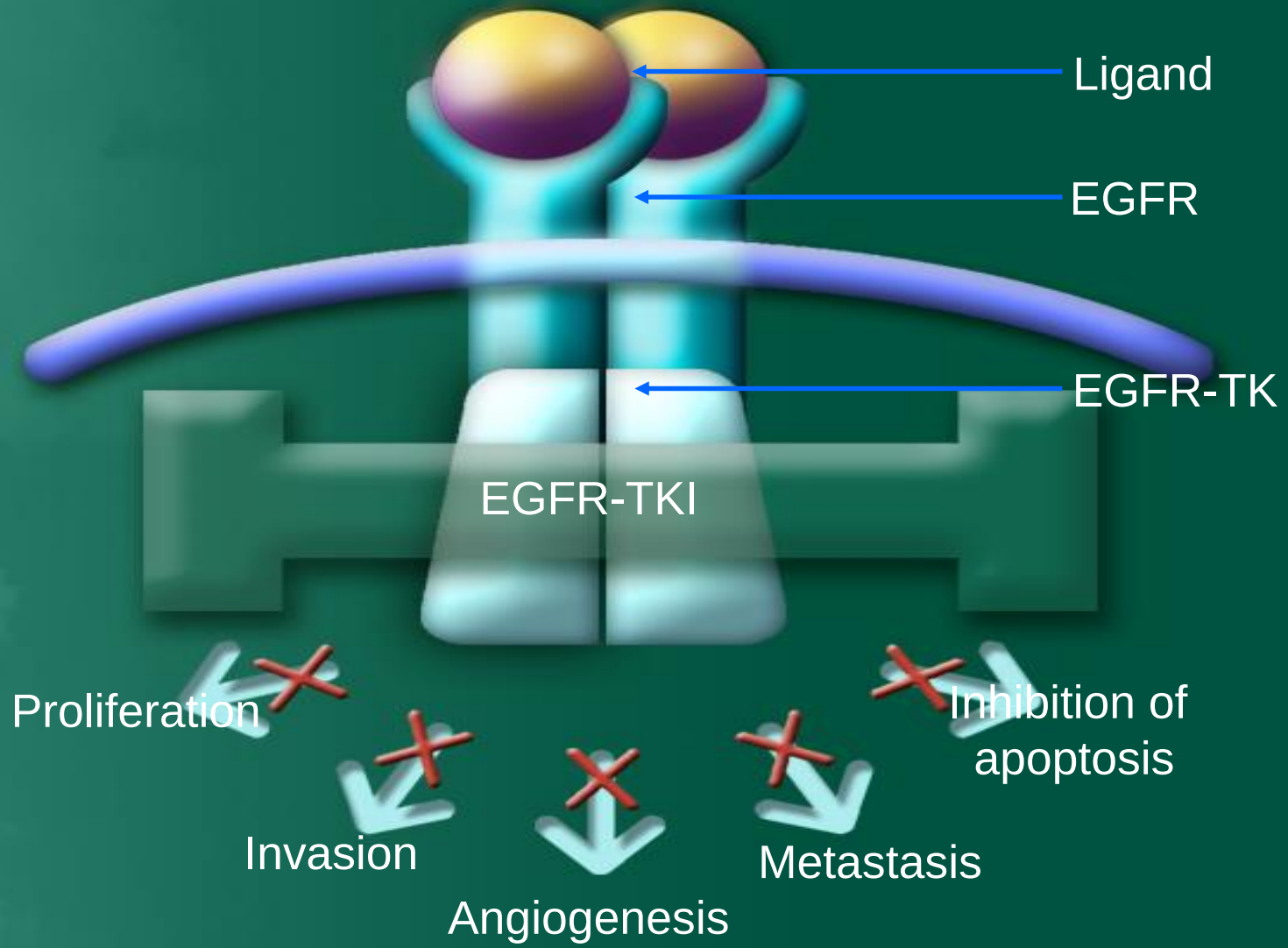


Pham J Clin Oncol 2006
Shaw J Clin Oncol 2009
Riely Clin Cancer Res 2008

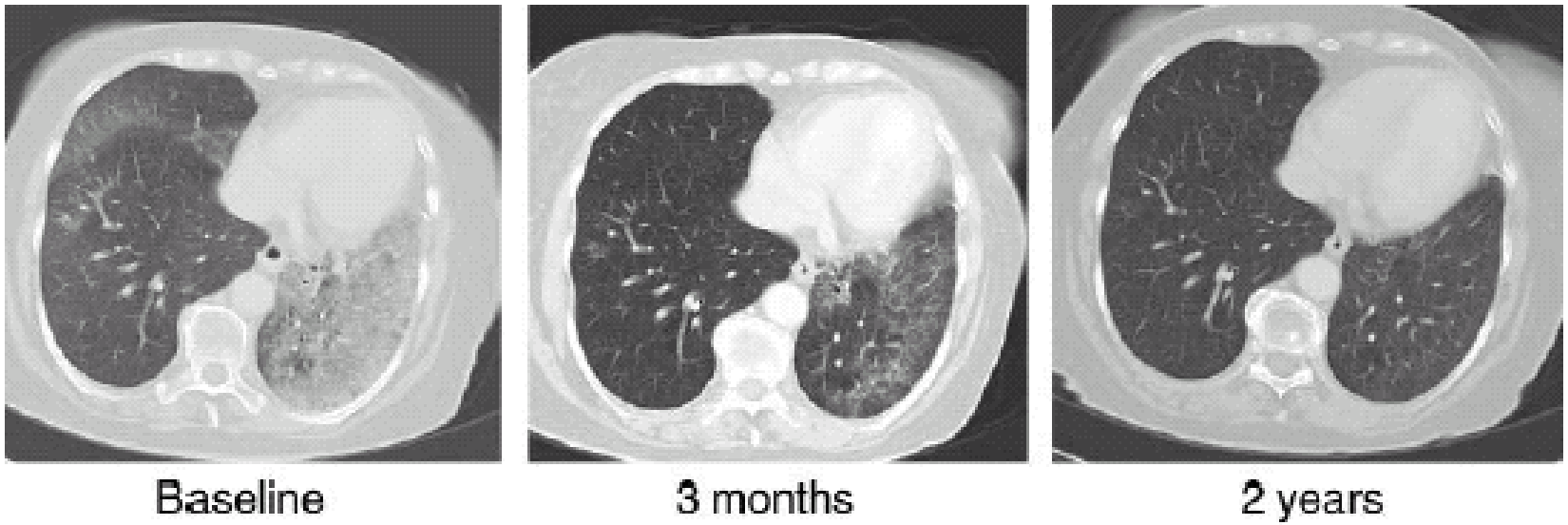
Activation of the EGFR: a pivotal driver of malignancy



EGFR inhibition by EGFR-TKI



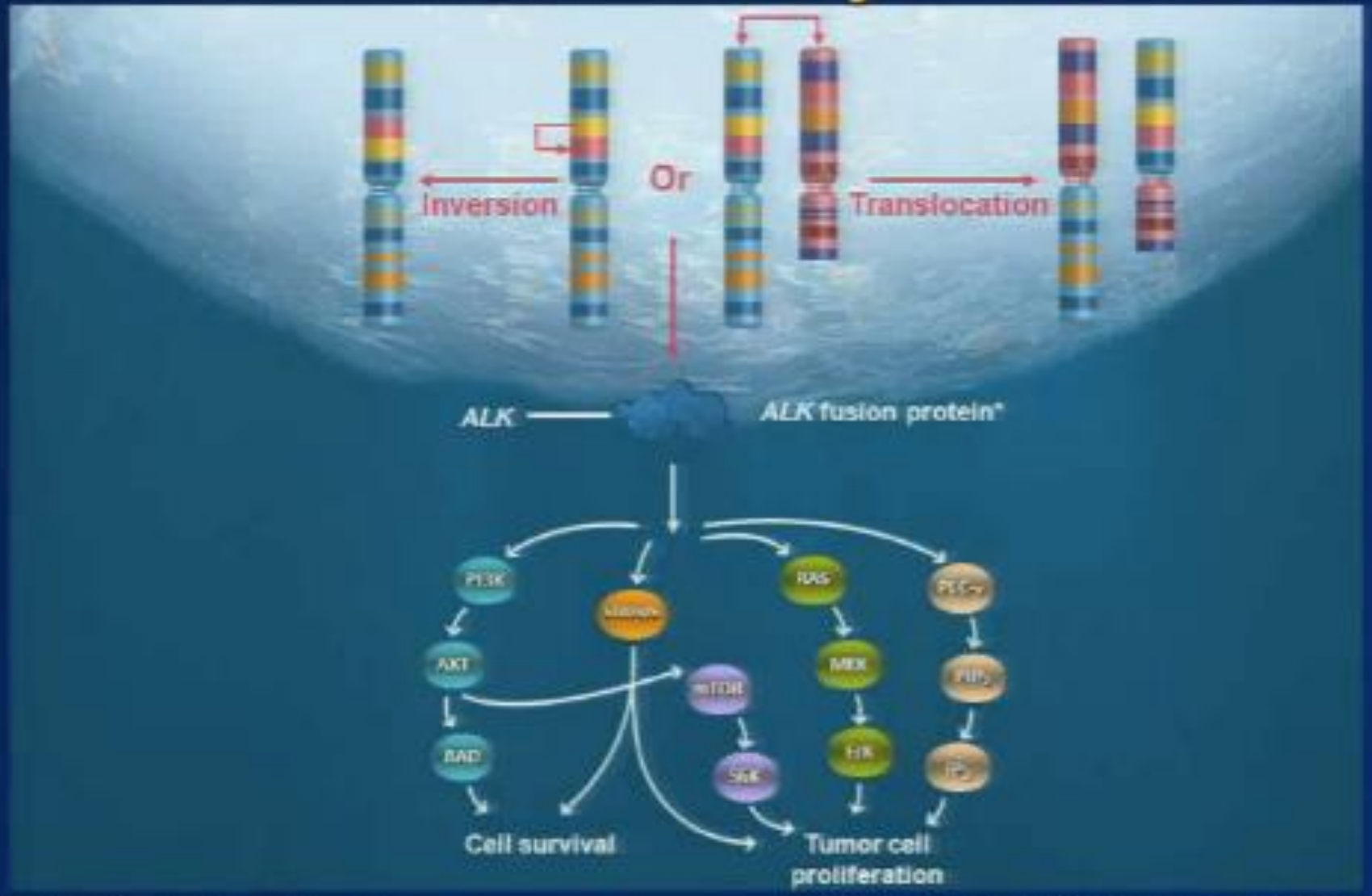
Activating Mutations in the Epidermal Growth Factor Receptor Underlies the Responsiveness of NSCLC to Gefitinib



Lazarus response. As shown by this series of CT scans, Iressa has been able to clear some patients' lung tumors, although it has proved effective only for a small minority. New results explain why some patients are more susceptible to the drug.

Lynch TJ et al. New England Journal of Medical 2004 350; 21 (20 May 2004)
Paez et al Science 2004 online; Marx J Science 2004 ; 304: 658-9

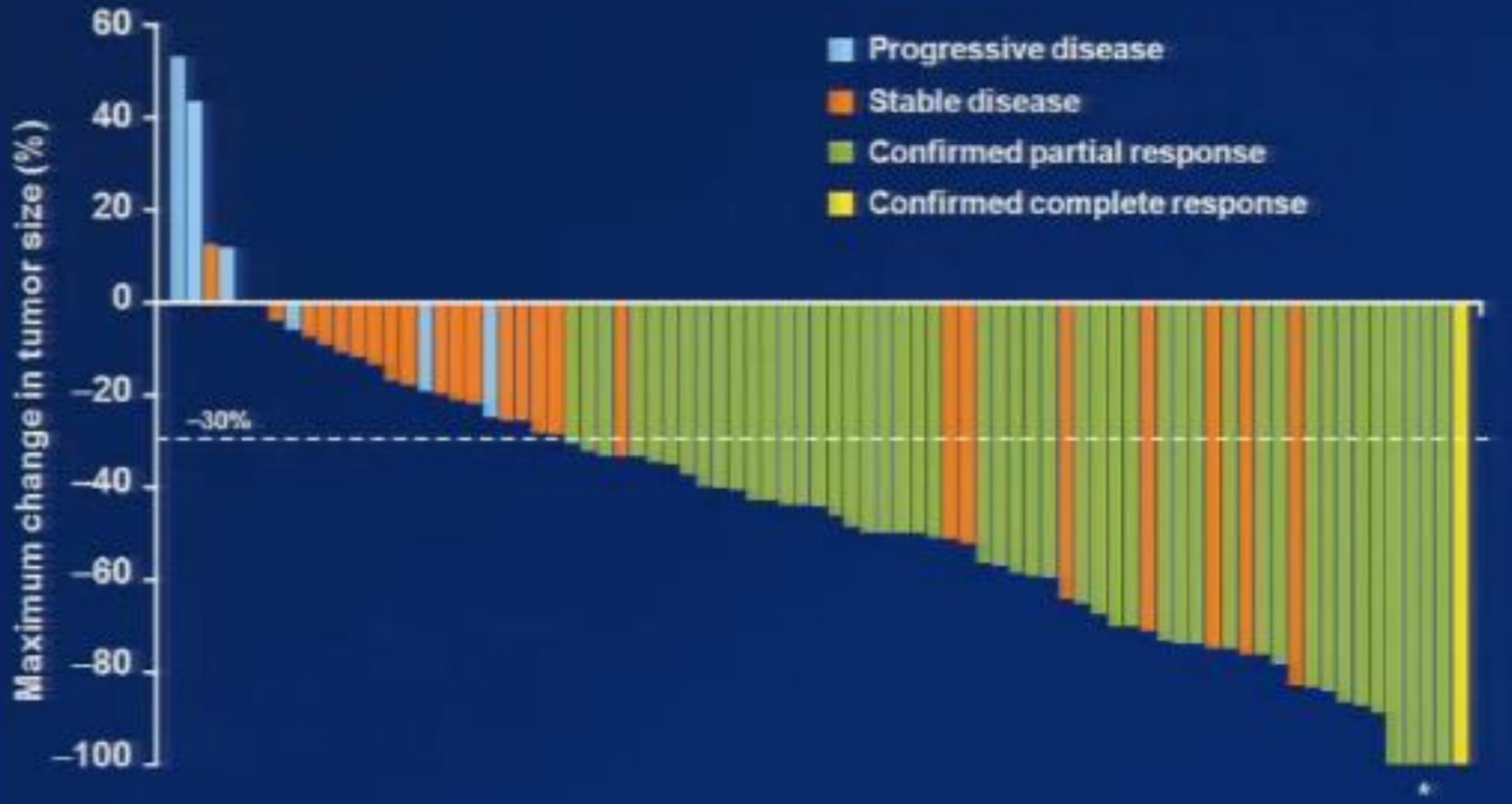
ALK Pathway



*Subcellular localization of the ALK fusion gene, while likely to occur in the cytoplasm, is not confirmed.[1,2]

1. Inamura K et al. J Thorac Oncol 2008;3:13–17.
2. Soda M et al. Proc Natl Acad Sci U S A 2008;105:19893–19897.
Figure based on: Chiarle R et al. Nat Rev Cancer 2008;8(1):11–23; Mosse YP et al. Clin Cancer Res 2009;15(18):5609–5614; and Data on file. Pfizer Inc.

Tumor Responses to Crizotinib for Patients with *ALK*-positive NSCLC

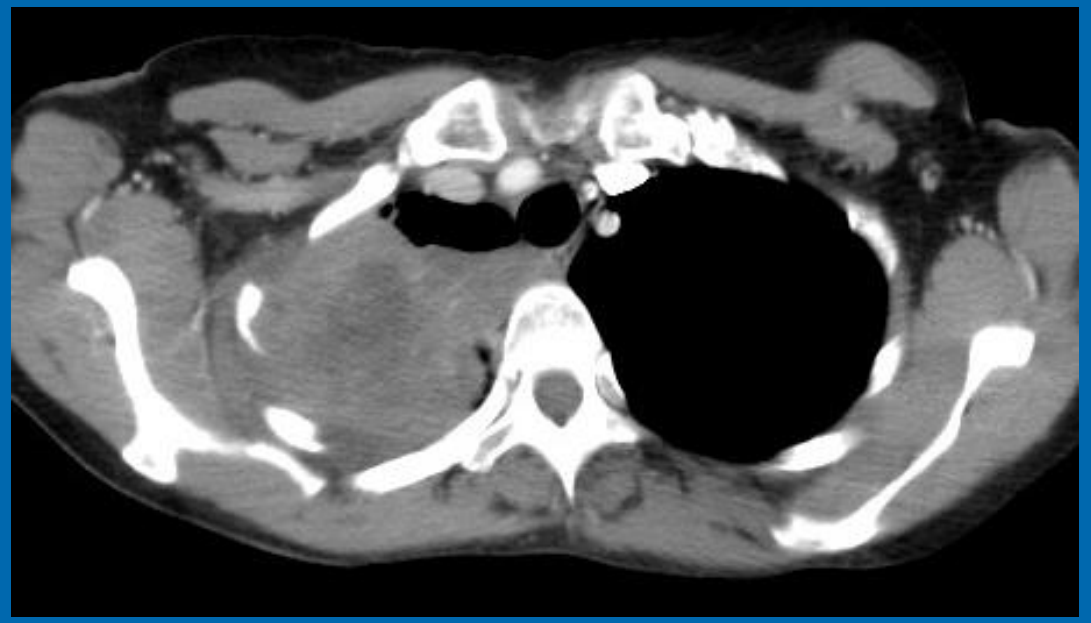


*Partial response patients with 100% change have non-target disease present

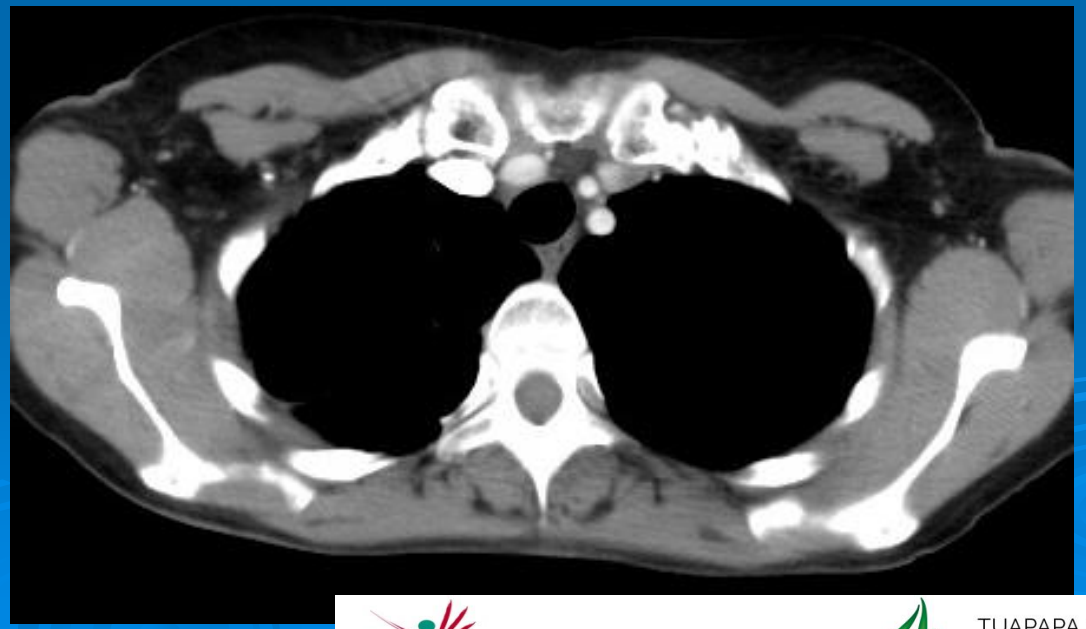
Pemetrexed

- Targeted chemotherpy
- Shown to be most effective chemotherapy for people with Advanced Adenocarcinoma of the lung

Baseline



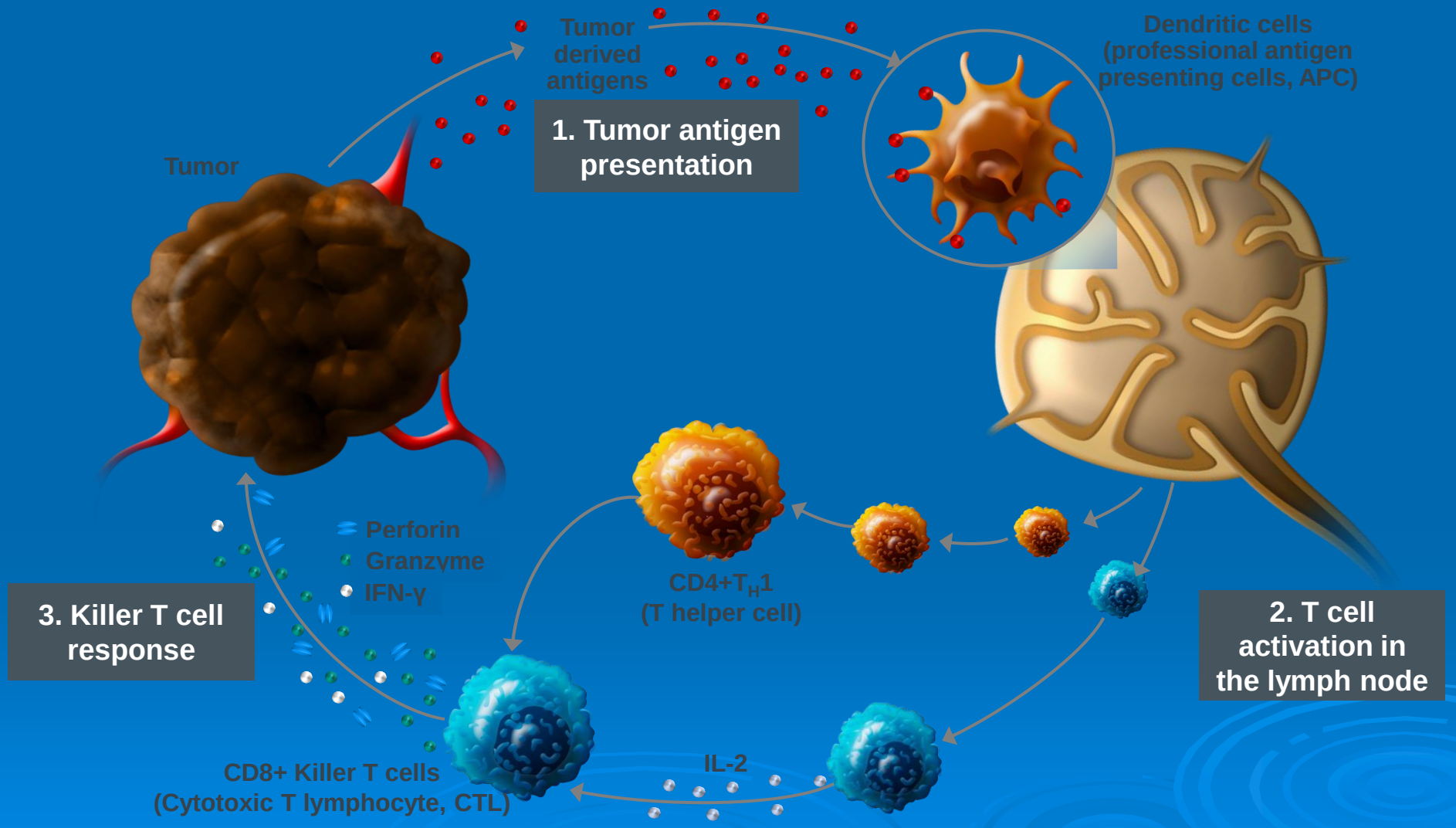
After chemo



Chemotherapy favourably alters the natural history of NSCLC

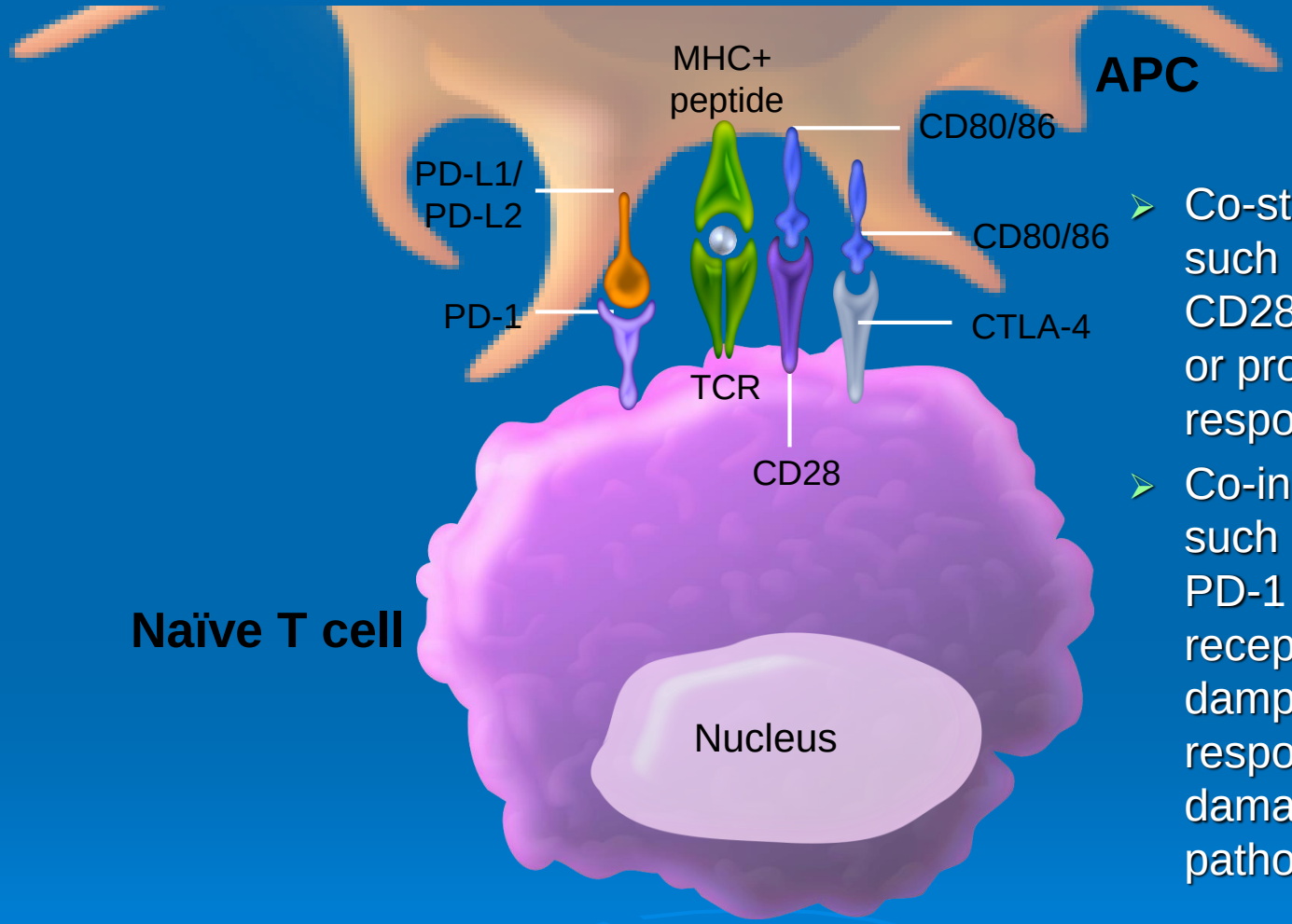
	Median survival (months)	One year survival (%)
Best supportive care	5.1	18
Cisplatin alone	6.7	25
Cisplatin plus old agent	7.6	31
Cisplatin plus new agent	13	50
Patients with EGFR /ALK/ROS Mutation treated	Excess of 40 months	Near 100%

Normal Immune Surveillance: Activation and Response[1-6]



1. Motz GT et al. *Immunity*. 2013;39:61–73. 2. Chen DS et al. *Immunity.* 2013;39:1–10. 3. Pardoll DM. *Nat Rev Cancer*. 2012;12:252–64. 4. Janeway CA, et al. *Immunobiology*. 6th ed. New York and London: Garland Science; 2004:341-342.
5. Liu CC et al. *N Engl J Med*. 1996 ;335:1651-1659. 6. Mellman I et al. *Nature*. 2011;480:480-489.

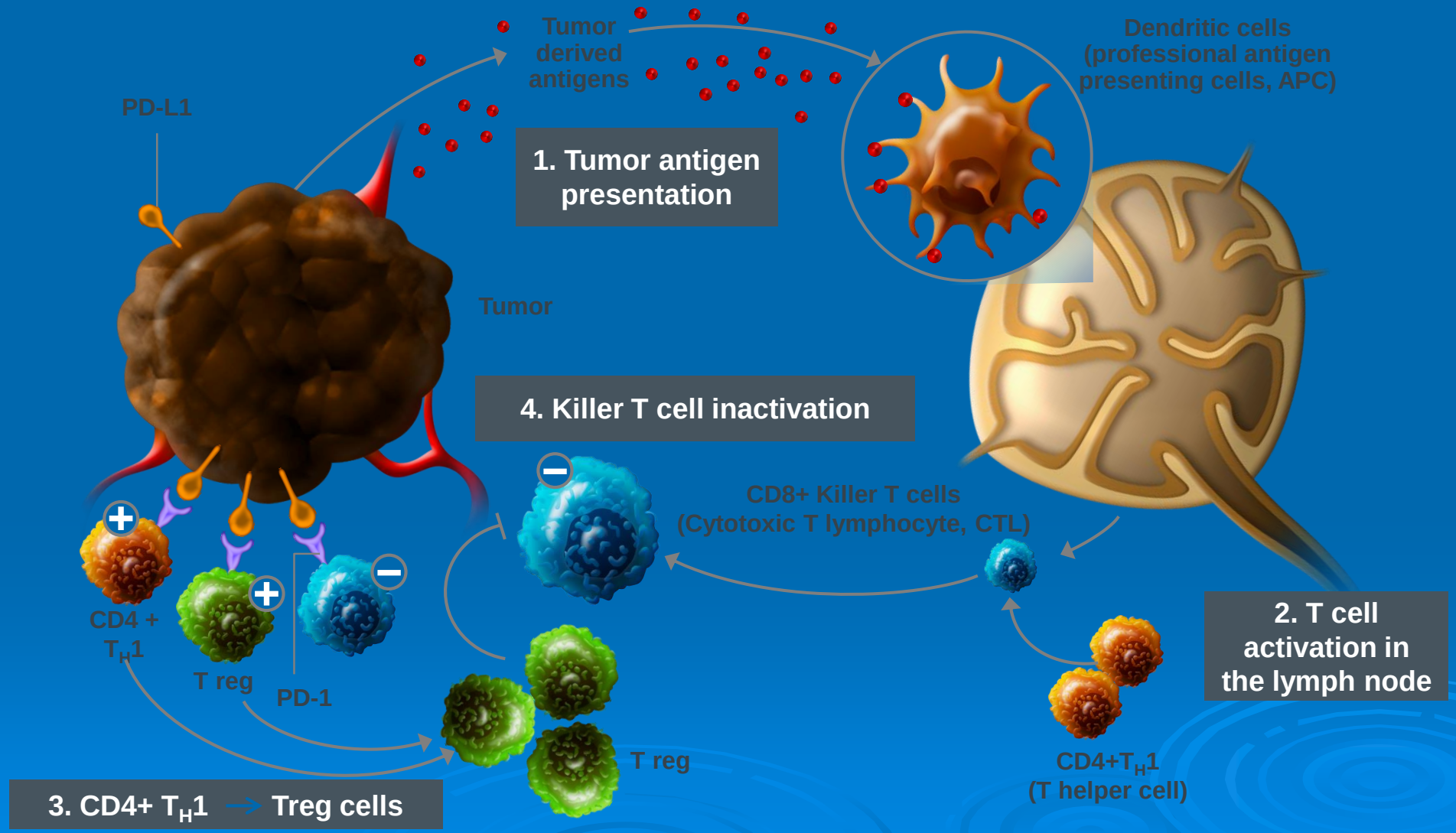
Regulation of T Cell Function: Multiple Co-stimulatory and Inhibitory Pathways[1,2]



- Co-stimulatory molecules such as CD80/86 and CD28 positively regulate or promote immune response
- Co-inhibitory molecules such as CTLA-4 and PD-1 (immune checkpoint receptors) normally dampen T cell-mediated responses to avoid damage to self during pathogenic infection

1. Adapted from Sznol M et al. *Clin Cancer Res.* 2013;19:1021–1034.
2. Pardoll DM. *Nat Rev Cancer.* 2012; 12:252–264.

Many Tumors Exploit the PD-1 Immune Checkpoint to Evade Immune Eradication[1-7]



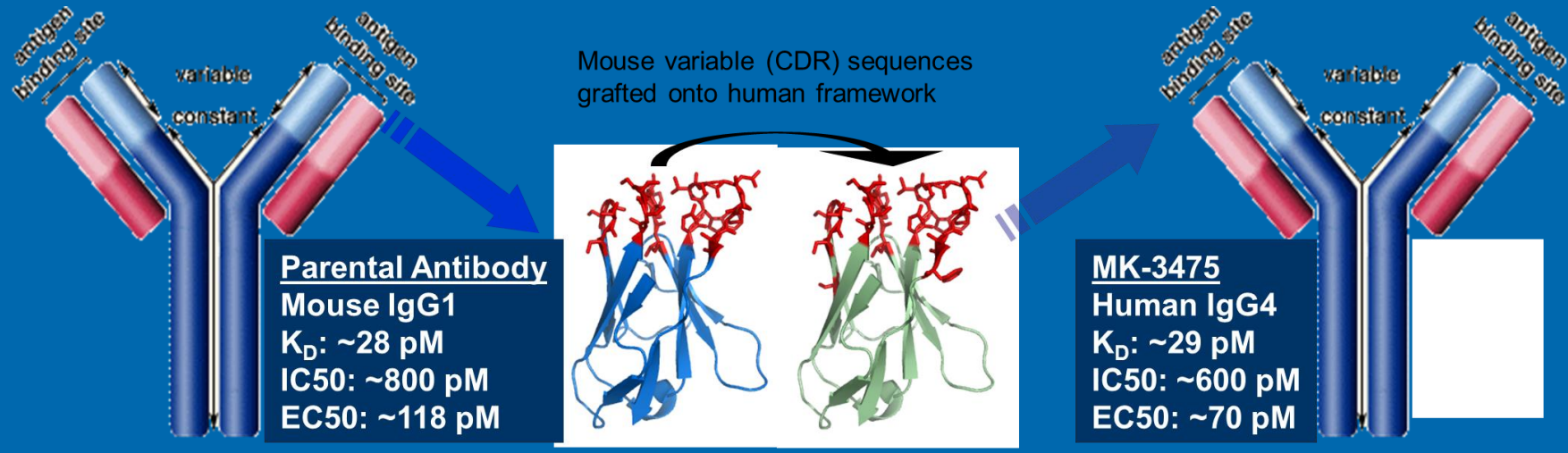
1. Zou W et al. *Nat Rev Immunol.* 2008;8:467–477. 2. Janeway CA, et al. *Immunobiology*. 6th ed. New York and London: Garland Science; 2004:635-637. 3. Chen DS et al. *Clin Cancer Res*. 2012;18:6580–6587. 4. Dong H et al. *Nat Med*. 2002;8:793–800. 5. Francisco LM et al. *J Exp Med*. 2009;206:3015–3029. 6. Amarnath S et al. *Sci Transl Med*. 2011:3:111ra120. 7. Mellman I et al. *Nature*. 2011;480:480-489.

PD-L1 Expression in Selected Tumor Types[1-6]

- PD-L1 is expressed in a number of tumor types:
  - Melanoma[1]
  - Glioma[2]
  - Lung[3]
  - Ovarian[4]
  - Urothelial[5]
  - Breast[6]

1. Hino R et al. *Cancer*. 2010;116:1757–66. 2. Wintterle S et al. *Cancer Res*. 2003;63:7462–7467.
3. Konishi J et al. *Clin Cancer Res*. 2004;10:5094–5100. 4. Hamanishi J et al. *Proc Natl Acad. Sci. USA* 2009;104:3360–3365.
5. Inman BA et al. *Cancer*. 2007;109:1499–1505. 6. Ghebeh H et al. *Neoplasia*. 2006;8:190–198.

MK-3475: An Anti-PD-1 Immunotherapy Exerting Dual Ligand Blockade (DLB) of the PD-1 Pathway[1,2]



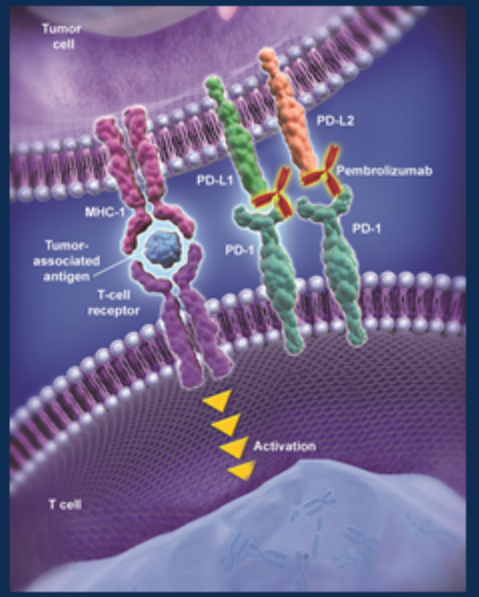
- Humanized IgG4- no cytotoxic (ADCC/CDC) activity
- Pharmacokinetics supportive of dosing every 2 weeks (Q2W) or every 3 weeks (Q3W)
- Half-life = ~21 days
- Low occurrence of anti-drug antibodies and no impact on pharmacokinetics

1. Robert C et al. EADO 2012. Poster P42.
2. Hamid O et al. *N Engl J Med*. 2013;369:134–144.

J Brahmer. ASCO 2017

Pembrolizumab and NSCLC

- Robust, durable antitumor activity and generally well tolerated in advanced NSCLC
  - As monotherapy for both treatment-naive and previously treated advanced, nonsquamous and squamous tumors that express PD-L1[1-5]
  - In combination with pemetrexed and carboplatin for treatment-naive, nonsquamous tumors[6]



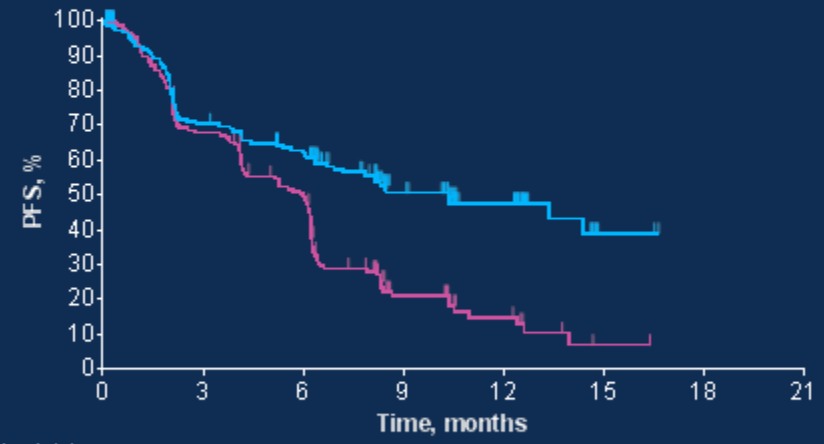
1. Garon EB et al. *N Engl J Med* 2015;372:2018-2028; 2. Chatterjee M et al. *Ann Oncol* 2016;27:1291-1298; 3. Hui R et al. *Ann Oncol* 2017;28:874-881; 4. Herbst RS et al. *Lancet* 2016;387:1540-1550. 5. Reck M et al. *N Engl J Med* 2016;375:1823-1833; 6. Langer CJ et al. *Lancet Oncol* 2016;17:1497-1508.

J Brahmer. ASCO 2017

KEYNOTE-024: Primary Analysis
(Median Follow-Up: 11.2 months)

Progression-Free Survival[a]

HR 0.50 (95% CI 0.37-0.68)
***P* < 0.001**

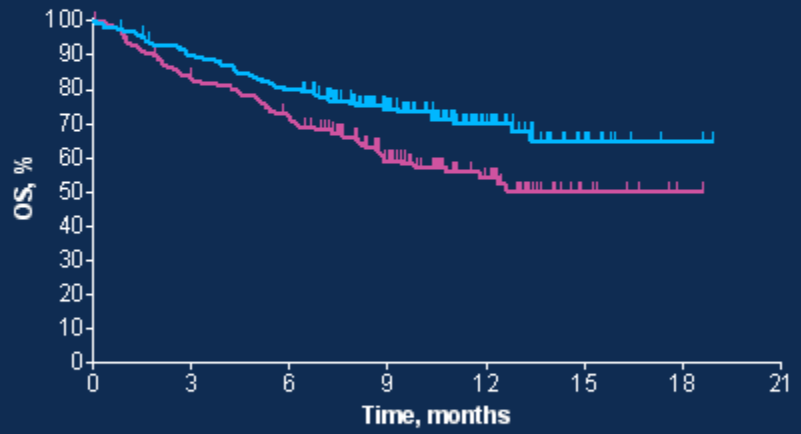


No. at risk

Pembro	154	104	89	44	22	3	1	0
Chemo	151	99	70	18	9	1	0	0

Overall Survival

HR 0.60 (95% CI 0.41-0.89)
***P* = 0.005**



No. at risk

Pembro	154	136	121	82	39	11	2	0
Chemo	151	123	106	64	34	7	1	0

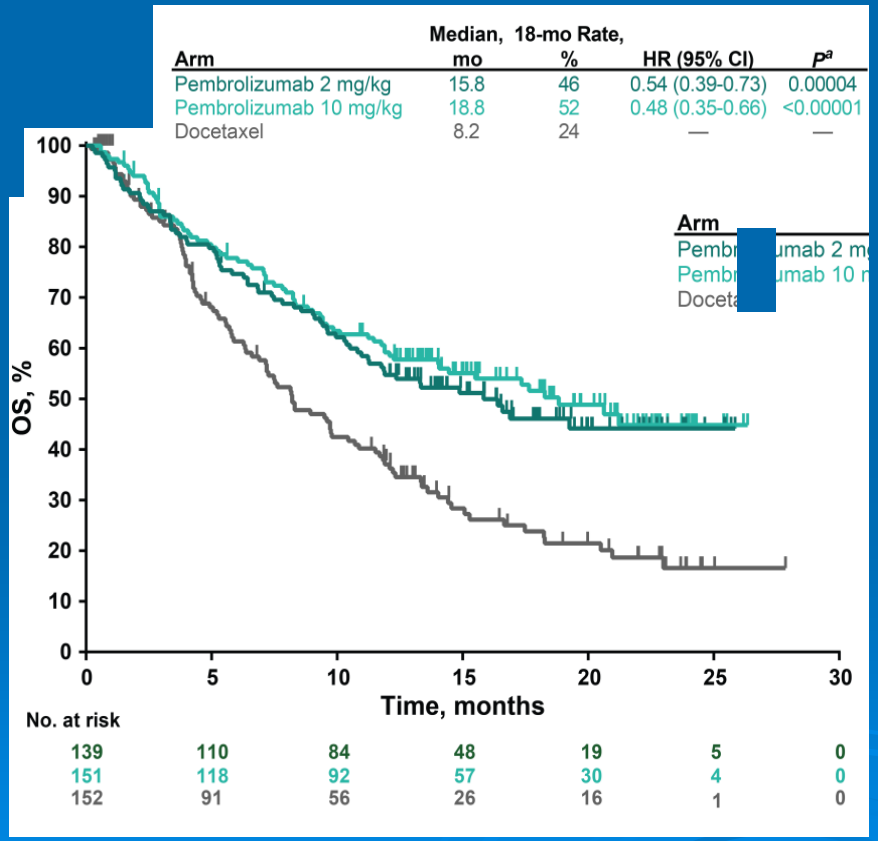
[a]RECIST v1.1 by blinded, independent central review.
Reck M et al. *N Engl J Med* 2016;375:1823-33.
Data cutoff: May 9, 2016.

Kaplan-Meier estimates of OS

- With an additional 6 months of follow-up, OS continued to be superior with pembrolizumab 2 mg/kg and 10 mg/kg versus docetaxel in both the TPS ≥50% and ≥1% populations

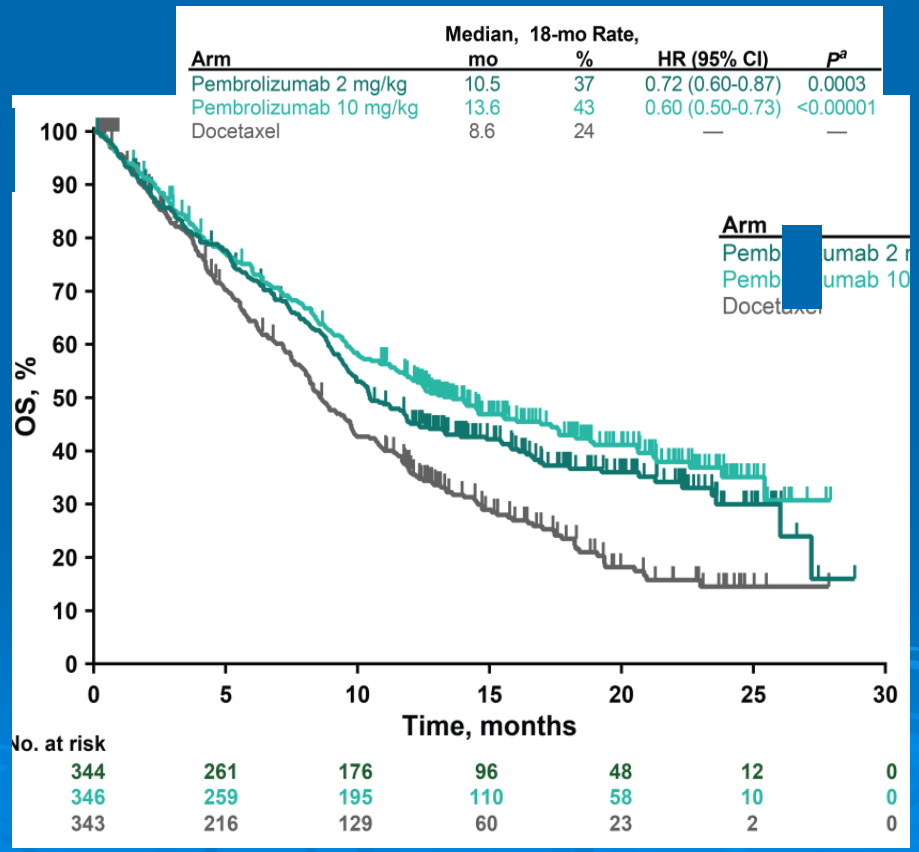
PD-L1 TPS ≥50%

Arm	Median, mo	18-mo Rate, %	HR (95% CI)	P[a]
Pembrolizumab 2 mg/kg	15.8	46	0.54 (0.39-0.73)	0.00004
Pembrolizumab 10 mg/kg	18.8	52	0.48 (0.35-0.66)	<0.00001
Docetaxel	8.2	24	—	—



PD-L1 TPS ≥1%

Arm	Median, mo	18-mo Rate, %	HR (95% CI)	P[a]
Pembrolizumab 2 mg/kg	10.5	37	0.72 (0.60-0.87)	0.0003
Pembrolizumab 10 mg/kg	13.6	43	0.60 (0.50-0.73)	<0.00001
Docetaxel	8.6	24	—	—



[a]No formal statistical comparison of the difference between treatment arms was performed; therefore, *P* values are nominal only.

Confirmed Best Overall Response (RECIST v1.1)

Patients Completing 24 months of Pembrolizumab (N = 47)

Best Overall Response	n	%
Complete response	3	6
Partial response	39	83
Stable disease	5	11
Progressive disease	0	0
No assessment/Not evaluable	0	0
Median duration of response, months (range)		Not reached (2+–31+)

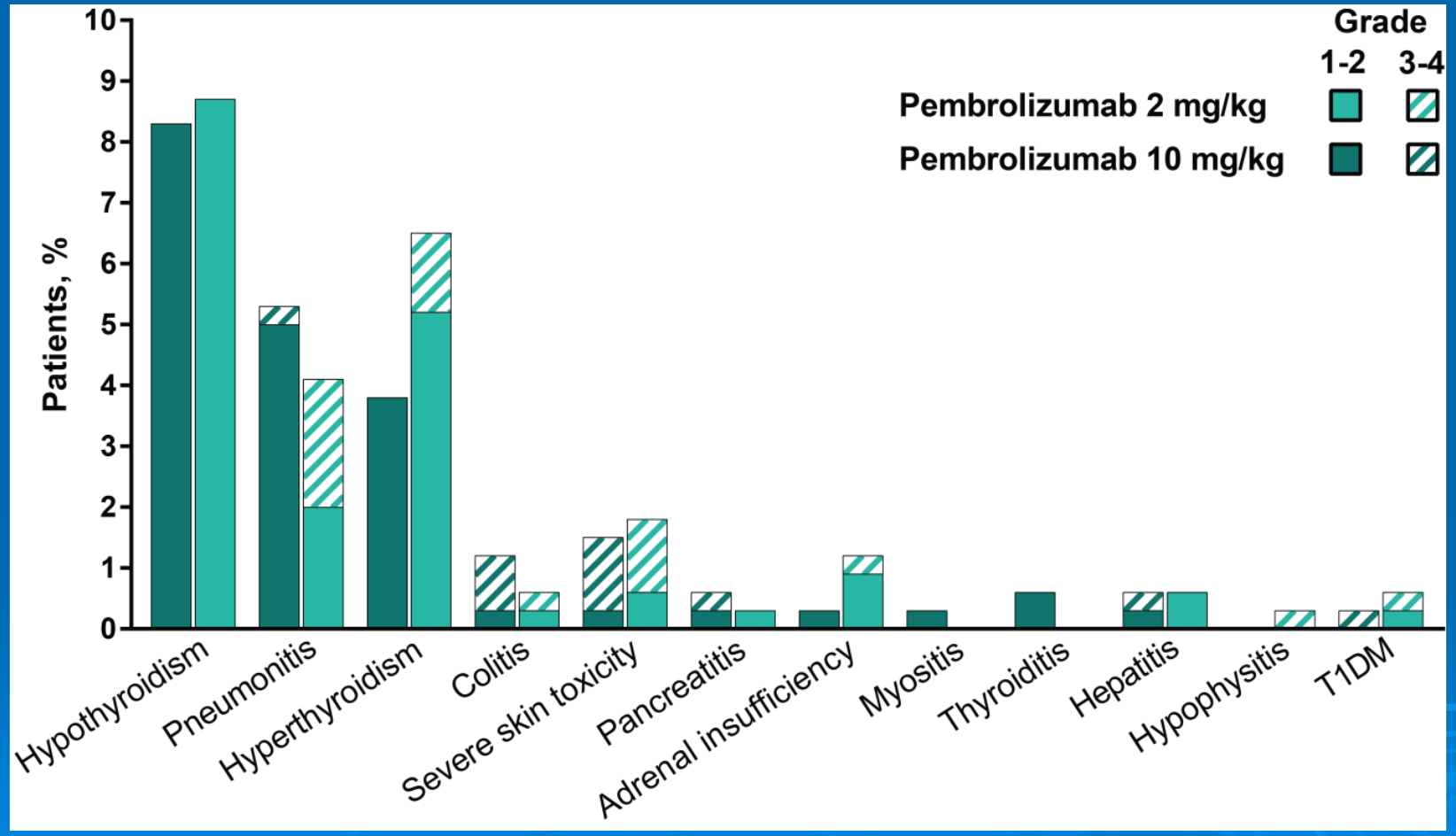
- **Objective response rate: 89%**
- **Clinical benefit rate (CR + PR + SD ≥6 months): 100%**
- **Median time to response: 2 months (range, 2-24 months)**
- **72% of responses were ongoing**

Data cutoff date: September 30, 2016.

Northern Cancer Network

TUAPAPA PŪKAHUKAHU LUNG FOUNDATION New Zealand

Incidence of Immune-Mediated Adverse Events Observed in ≥2 Patients in the Pembrolizumab Arms in the PD-L1 TPS ≥1% Population



T1DM=type 1 diabetes mellitus.

Northern Cancer Network

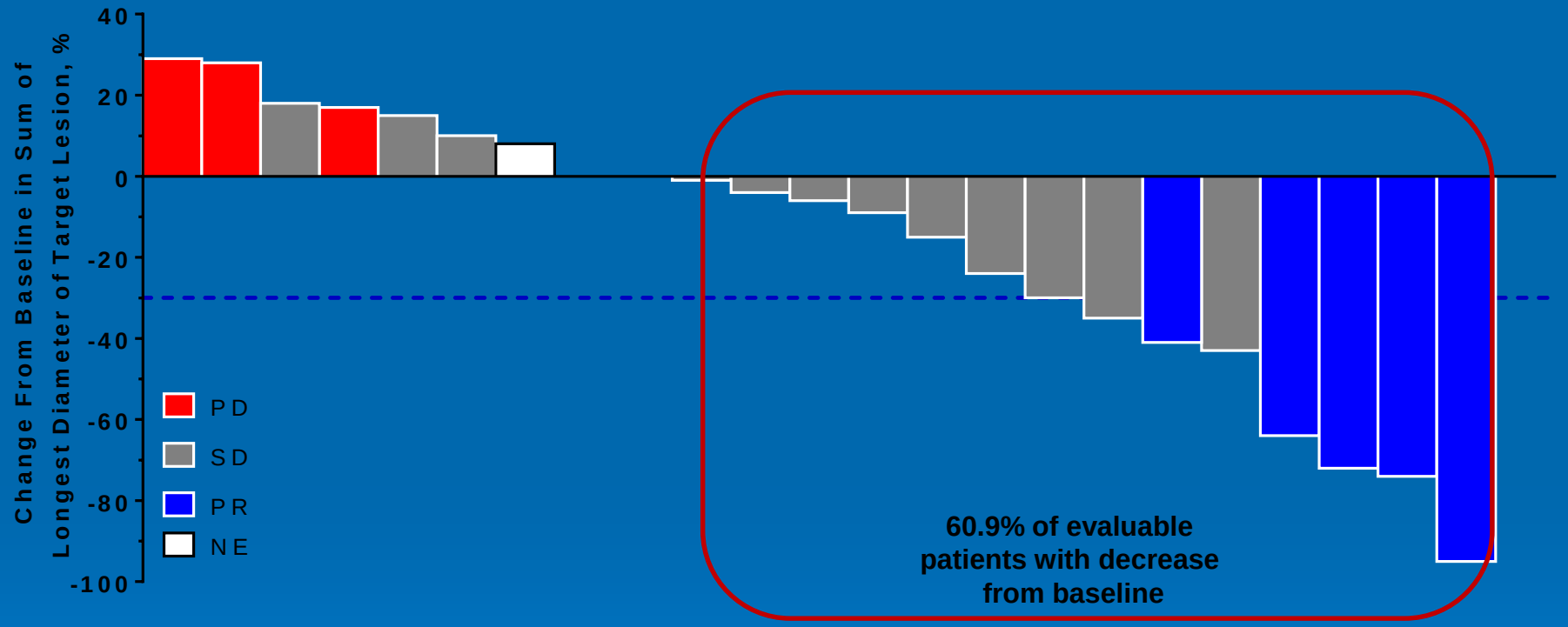
TUAPAPA PŪKAHUKAHU
LUNG FOUNDATION
New Zealand

Mesothelioma

Northern Cancer Network

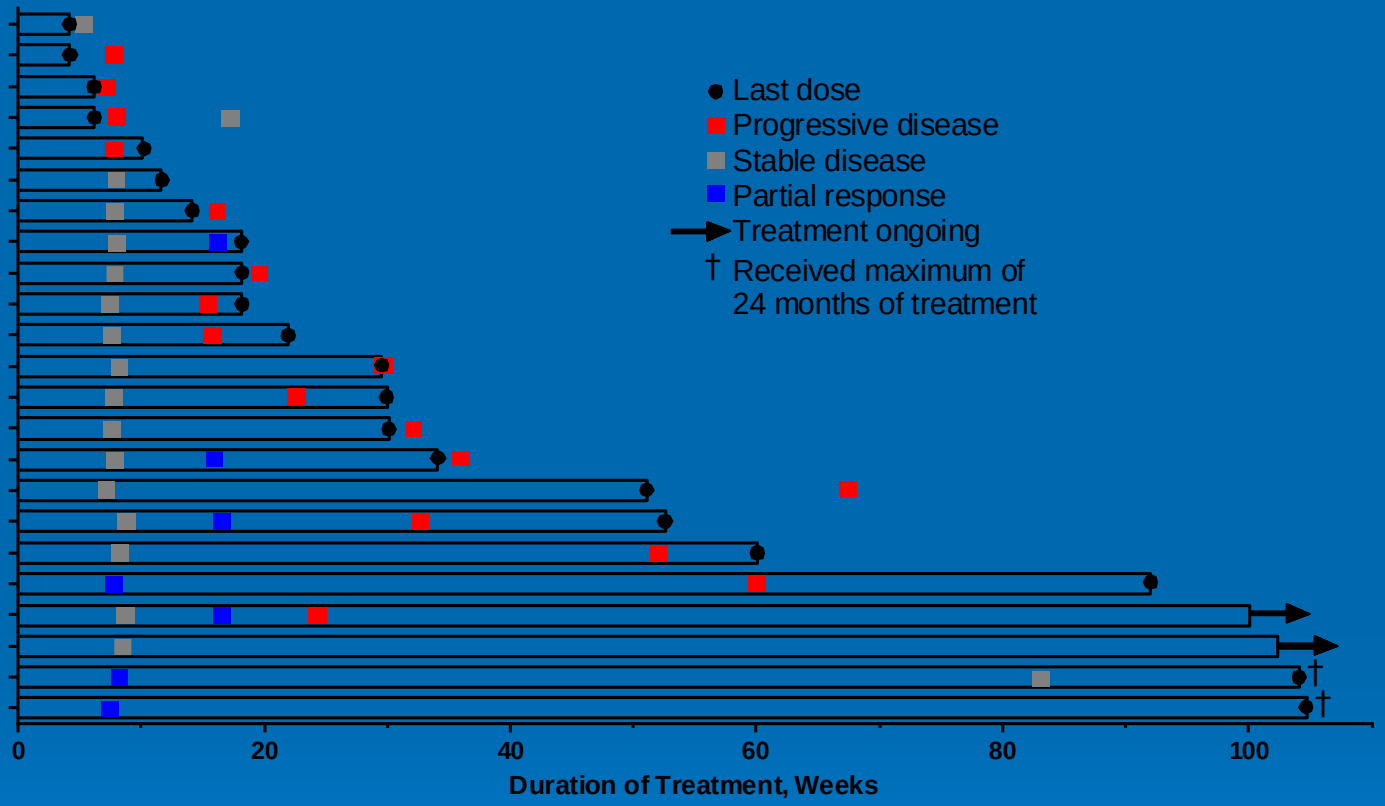
TUAPAPA PŪKAHUKAHU
LUNG FOUNDATION
New Zealand

Pembrolizumab - Change From Baseline in Tumor Size
(RECIST v1.1, investigator review)



Bar lengths are best target lesion changes, bar colors are best overall responses.
Data cutoff date: June 20, 2016.

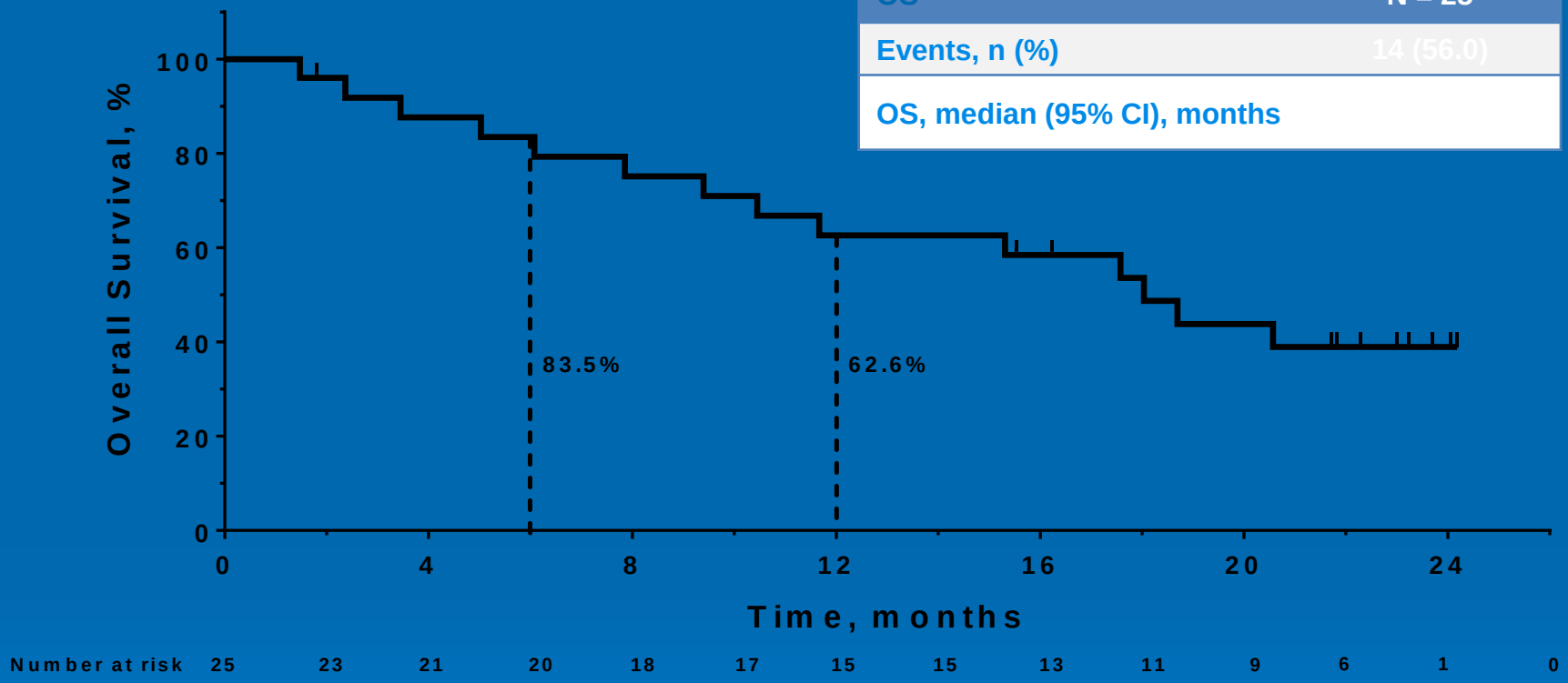
Treatment Duration and Duration of Response (RECIST v1.1, investigator review)



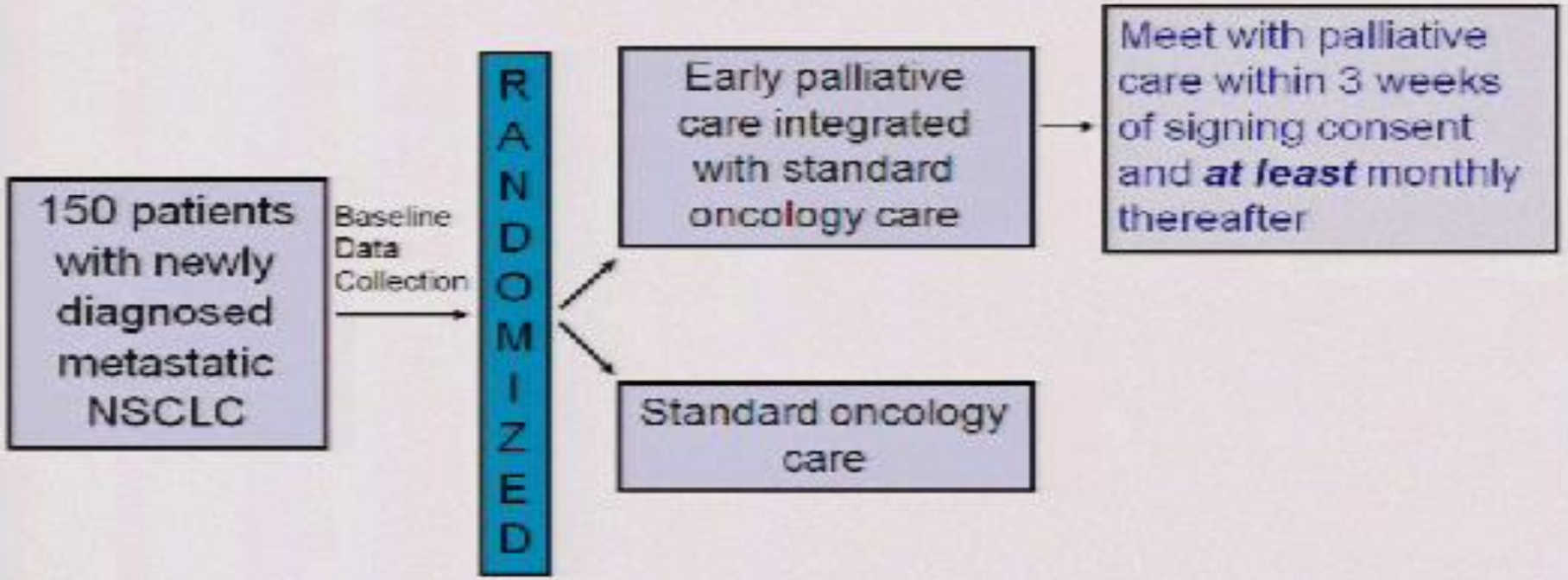
The length of each bar corresponds to the duration of treatment.
Response symbols represent time to first report and not best overall.
Data cutoff date: June 20, 2016.

Overall Survival

OS	N = 25
Events, n (%)	14 (56.0)
OS, median (95% CI), months	



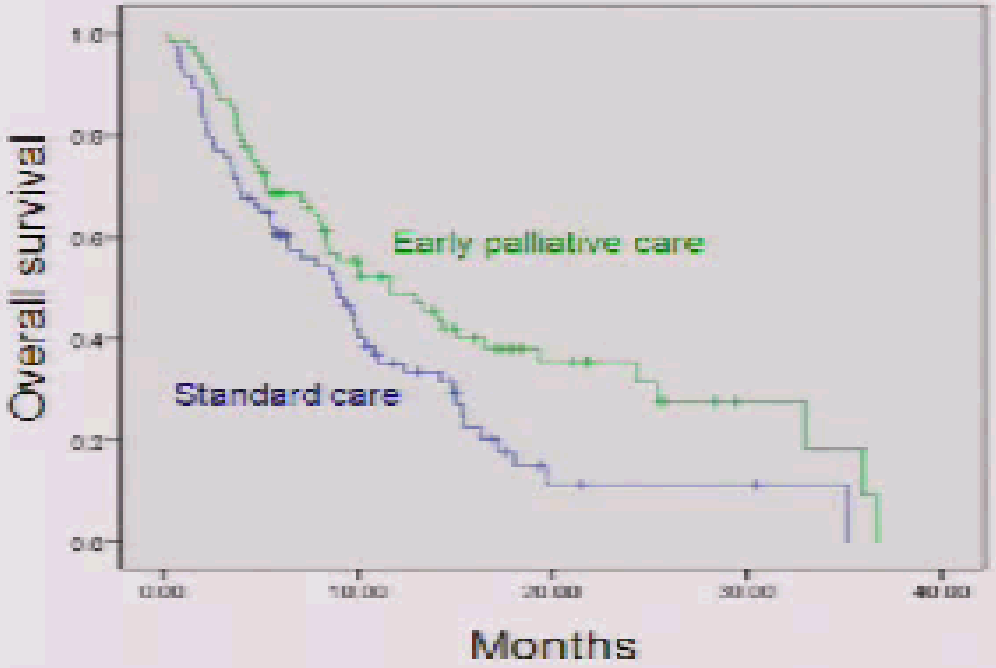
Study Design



Effect of early palliative care (PC) on quality of life (QOL), aggressive care at the end stage IV NSCLC patients: Results of a phase III randomized trial.

Moderator: Jennifer S. Temel

Survival Analysis



Median Survival
Early palliative care 11.6 mo
Standard care 8.9 mo
p=0.02

Controlling for age, gender and PS, adjusted HR=0.59 (0.40-0.88), p=0.01