# NUOVE SFIDE CLINICHE
## NELL'ERA DELL'IMMUNOTERAPIA
## DEL CARCINOMA DEL **POLMONE**

13-14 MARZO 2017

**Desenzano del Garda**

HOTEL ACQUAVIVA DEL GARDA

# Presentazione linee terapeutiche successive, quando introdurre l'immunoterapia?

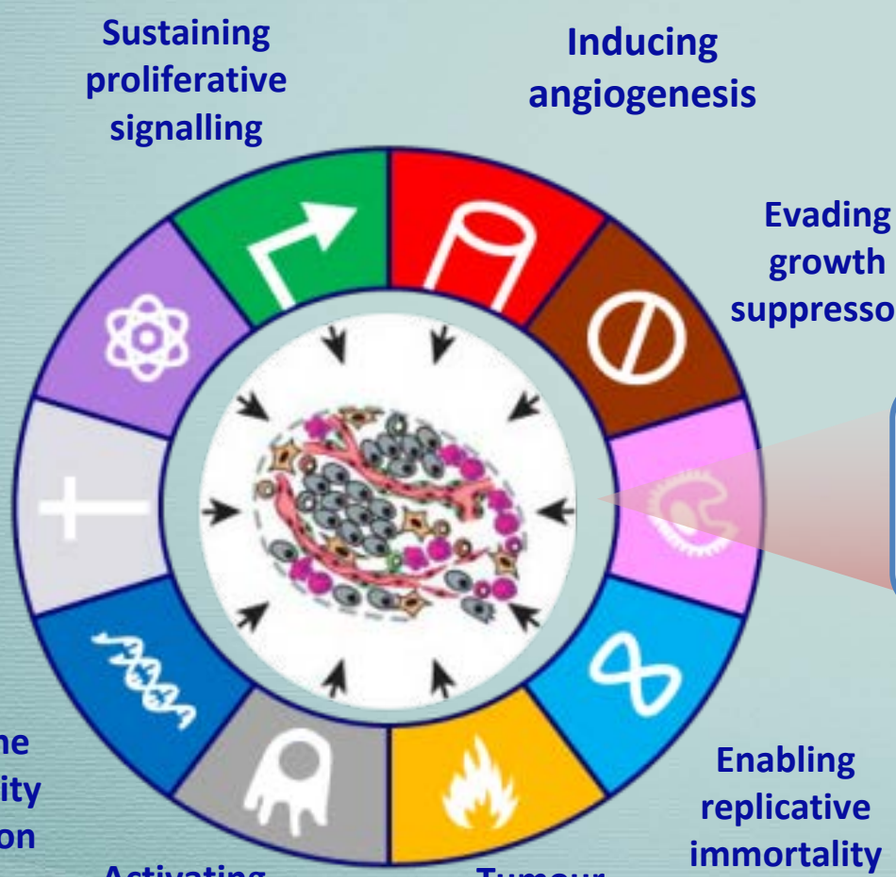
Dr.ssa Elisa Roca
Dirigente Medico - Referente Oncologia Toracica
Oncologia Medica - Spedali Civili di Brescia

# Summary

- Immunoterapy
- Clinical studies
- Patients selection
- Future
- Conclusions

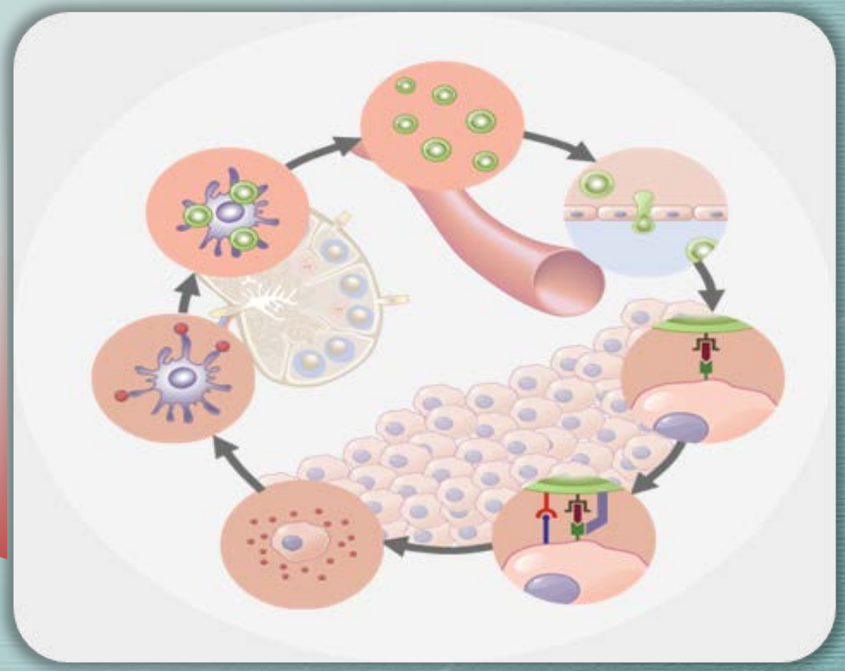
# Immunoterapy

## Avoiding immune destruction is a hallmark of cancer




**Avoiding immune destruction[1]**

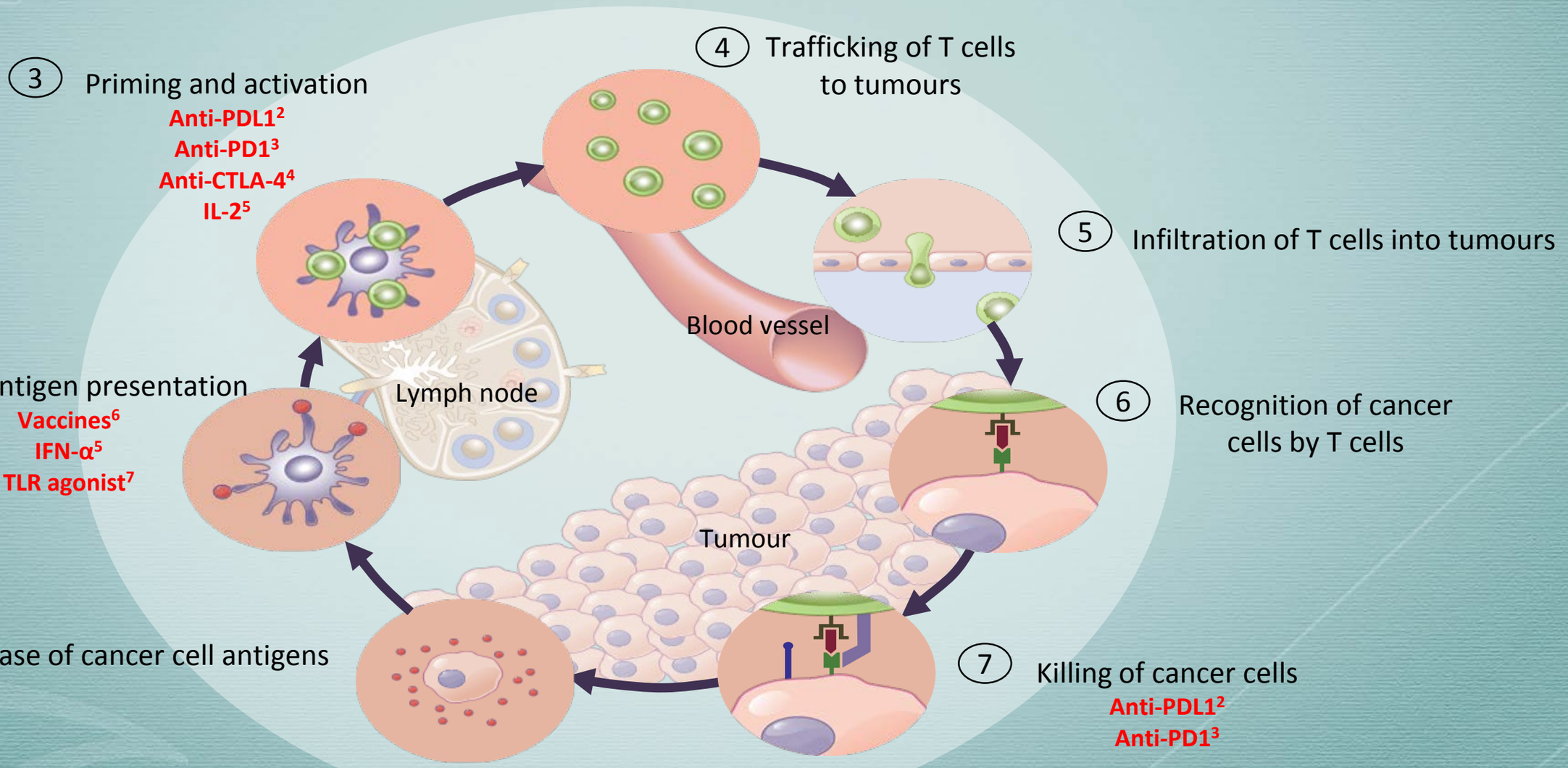
### Cancer immunity cycle[2]



1. Hanahan & Weinberg. Cell 2011 2. Chen & Mellman. Immunity 2013

# Immunoterapy

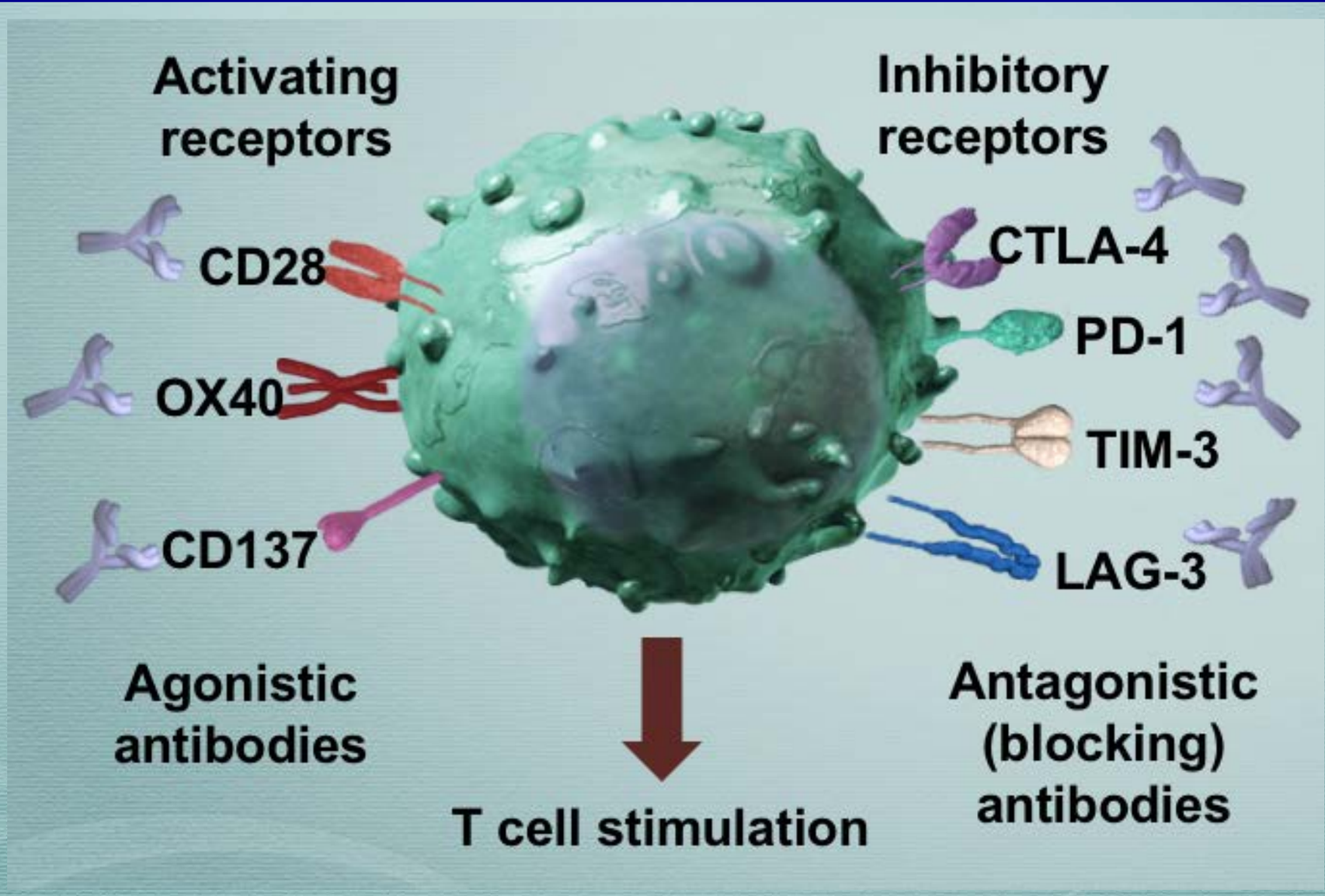
## Immunotherapy in NSCLC can target several steps in the cancer immunity




1. Chen and Mellman. Immunity 2013; 2. Soria, et al. ECC 2013; 3. Brahmer, et al. ASCO 2014 4. Lynch, et al. JCO 2012; 5. Jansen, et al. J Immunother 1992; 6.Vansteenkiste, et al. JCO 2013 7. Manegold, et al. JCO 2008

# Immunoterapy

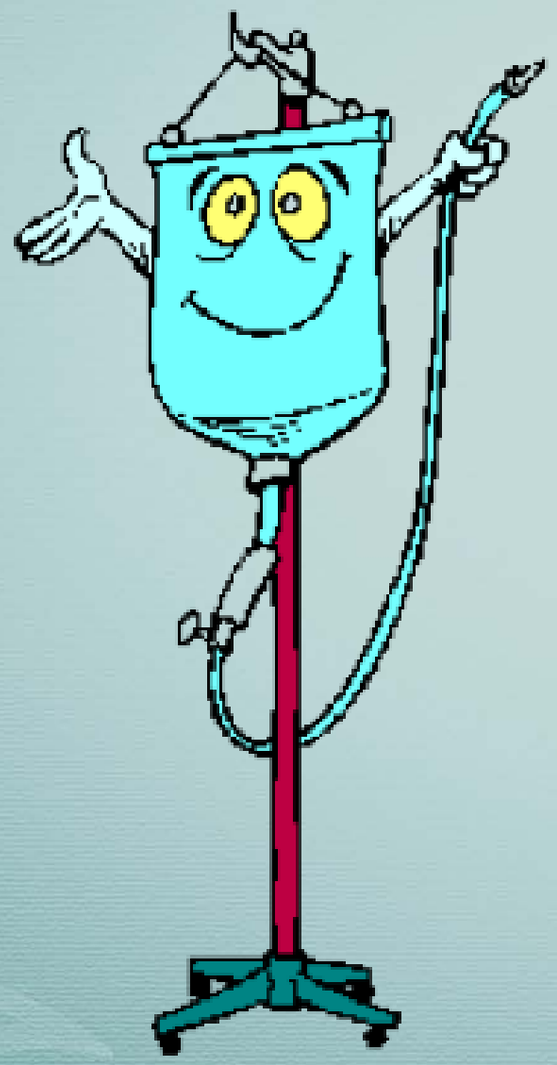
Regulating the T cell immune response




Adapted from Mellman I, et al. *Nature.* 2011:480;481–489; Pardoll DM. *Nat Rev Cancer.* 2012;12:252–264.

# Immunoterapy

## Standard Chemotherapy

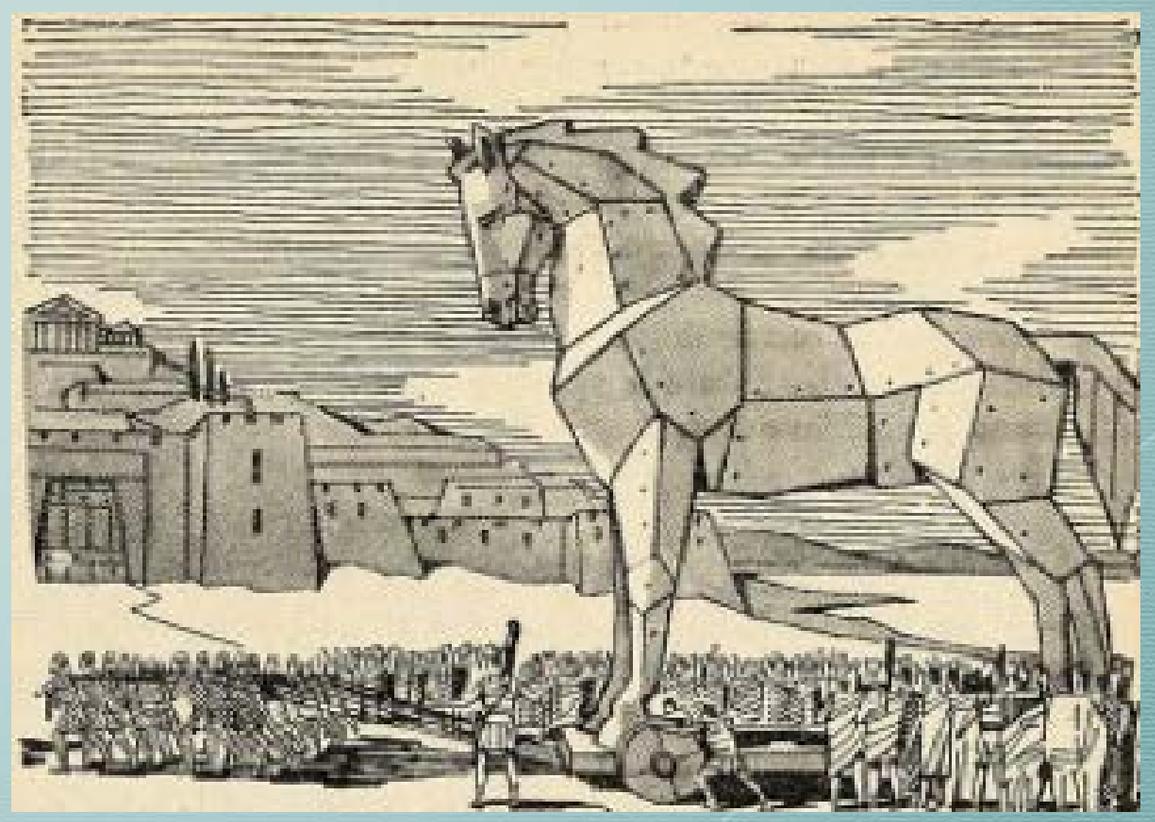


## Target Therapy

# Immunoterapy

**Standard Chemotherapy**

**Immunotherapy**



# IMMUNOTHERAPY:

## Using The Body To Fight Cancer

# Clinical Studies

| Therapeutic | Lead company | Antibody type |
|---|---|---|
| **Anti-PDL1** | | |
| Atezolizumab | Roche | Engineered IgG1 (no ADCC) |
| Durvalumab | AstraZeneca | Modified IgG1 (no ADCC) |
| Avelumab | Merck Serono | IgG1 (humanized) |
| BMS-936559 | Bristol-Myers Squibb | IgG4 (humanised) |
| **Anti-PD1** | | |
| Nivolumab | Bristol-Myers Squibb | IgG4 |
| Pembrolizumab | MercK Sharp Dome | IgG4 (humanised) |
| AMP-224 | GlaxoSmithKline | PD-L2 IgG1 Fc fusion |
| Pidilizumab (CT-011) | CureTech | IgG1 (humanised) |

# Clinical Studies

- CheckMate 017
- CheckMate 057
- Keynote 010
- POLAR
- OAK
- Atlantic

# Clinical Studies

## CheckMate 017

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer

Julie Brahmer, M.D., Karen L. Reckamp, M.D., Paul Baas, M.D., Lucio Crinò, M.D., Wilfried E.E. Eberhardt, M.D., Elena Poddubskaya, M.D., Scott Antonia, M.D., Ph.D., Adam Pluzanski, M.D., Ph.D., Everett E. Vokes, M.D., Esther Holgado, M.D., Ph.D., David Waterhouse, M.D., Neal Ready, M.D., Justin Gainor, M.D., Osvaldo Arén Frontera, M.D., Libor Havel, M.D., Martin Steins, M.D., Marina C. Garassino, M.D., Joachim G. Aerts, M.D., Manuel Domine, M.D., Luis Paz-Ares, M.D., Martin Reck, M.D., Christine Baudelet, Ph.D., Christopher T. Harbison, Ph.D., Brian Lestini, M.D., Ph.D., and David R. Spigel, M.D.

N Engl J Med 2015;373:123-35.
DOI: 10.1056/NEJMoa1504627

# Clinical Studies

## CheckMate 017

- **Stage IIIb/IV SQ NSCLC**
- **1 prior platinum doublet-based chemotherapy**
- **ECOG PS 0–1**
- **Pre-treatment (archival or fresh) tumor samples required for PD-L1 analysis**

**N = 272**

Randomize 1:1

**Nivolumab**
3 mg/kg IV Q2W
until PD or unacceptable toxicity
n = 135

**Docetaxel**
75 mg/m$^2$ IV Q3W
until PD or unacceptable toxicity
n = 137

- **Primary Endpoint:**
  – OS
- **Additional Endpoints:**
  – Investigator-assessed ORR
  – Investigator-assessed PFS
  – Correlation between PD-L1 expression and efficacy
  – Safety
  – Quality of life (LCSS)

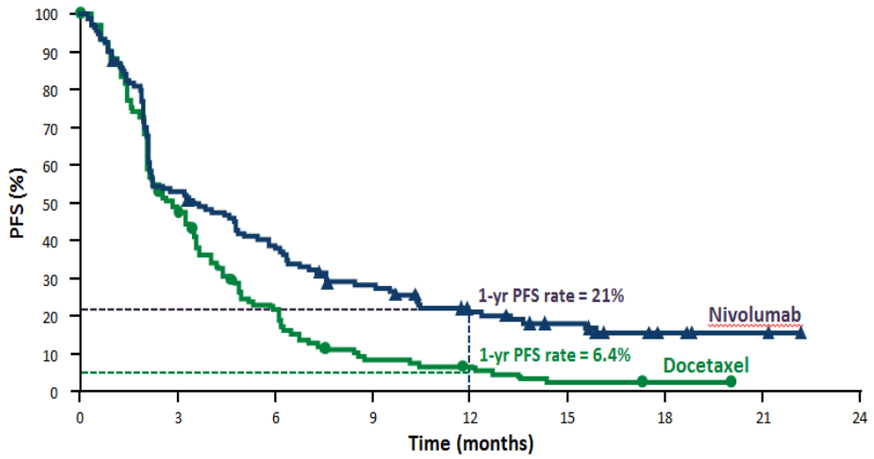
LCSS = Lung cancer symptom scale

Spigel et al, ASCO 2015; Brahmer et al, NEJM 2015

# Clinical Studies

## CheckMate 017

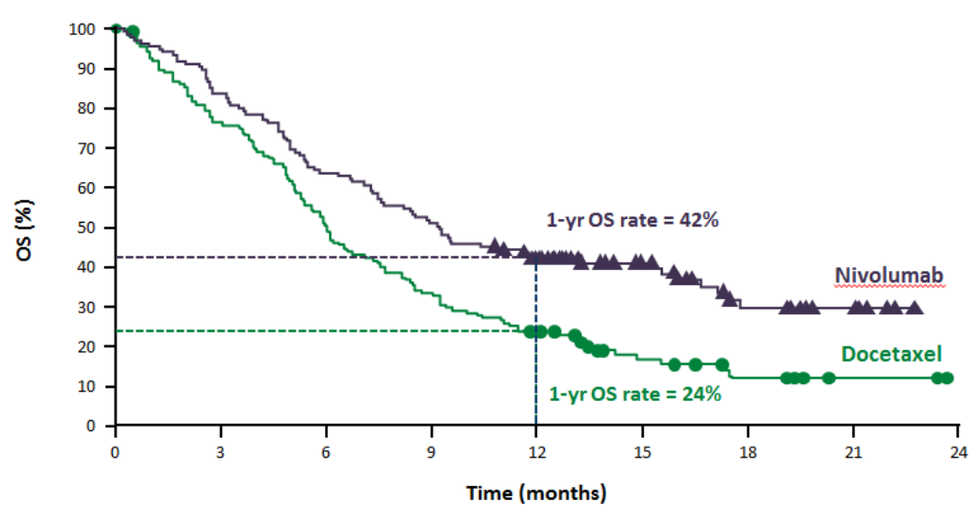
### PFS




| Number of Patients at Risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Nivolumab | 135 | 68 | 48 | 33 | 21 | 15 | 6 | 2 | 0 |
| Docetaxel | 137 | 62 | 26 | 9 | 6 | 2 | 1 | 0 | 0 |

PFS per investigator.

### OS




| Number of Patients at Risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Nivolumab | 135 | 113 | 86 | 69 | 52 | 31 | 15 | 7 | 0 |
| Docetaxel | 137 | 103 | 68 | 45 | 30 | 14 | 7 | 2 | 0 |

| | Nivolumab n = 135 | Docetaxel n = 137 |
|---|---|---|
| **mPFS, mo (95% CI)** | **3.5** (2.1, 4.9) | **2.8** (2.1, 3.5) |

**HR = 0.62** (95% CI: 0.47, 0.81); ***P* = 0.0004**

| | Nivolumab n = 135 | Docetaxel n = 137 |
|---|---|---|
| **mOS mo,** (95% CI) | **9.2** (7.3, 13.3) | **6.0** (5.1, 7.3) |
| **# events** | 86 | 113 |

**HR = 0.59** (95% CI: 0.44, 0.79), ***P* = 0.00025**

Spigel et al, ASCO 2015; Brahmer et al, NEJM 2015

# Clinical Studies

## CheckMate 017

**CONCLUSIONS**

Among patients with advanced, previously treated squamous-cell NSCLC, overall survival, response rate, and progression-free survival were significantly better with nivolumab than with docetaxel, regardless of PD-L1 expression level. (Funded by Bristol-Myers Squibb; CheckMate 017 ClinicalTrials.gov number, NCT01642004.)

N Engl J Med 2015;373:123-35.
DOI: 10.1056/NEJMoa1504627

# Clinical Studies

## CheckMate 057

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer

H. Borghaei, L. Paz-Ares, L. Horn, D.R. Spigel, M. Steins, N.E. Ready, L.Q. Chow, E.E. Vokes, E. Felip, E. Holgado, F. Barlesi, M. Kohlhäufl, O. Arrieta, M.A. Burgio, J. Fayette, H. Lena, E. Poddubskaya, D.E. Gerber, S.N. Gettinger, C.M. Rudin, N. Rizvi, L. Crinò, G.R. Blumenschein, Jr., S.J. Antonia, C. Dorange, C.T. Harbison, F. Graf Finckenstein, and J.R. Brahmer

N Engl J Med 2015;373:1627-39.
DOI: 10.1056/NEJMoa1507643

# Clinical Studies

## CheckMate 057

- **Stage IIIB/IV non-SQ NSCLC**
- **Pre-treatment (archival or recent) tumor samples required for PD-L1**
- **ECOG PS 0–1**
- **Failed 1 prior platinum doublet**
- **Prior maintenance therapy allowed[a]**
- **Prior TKI therapy allowed for known *ALK* translocation or *EGFR* mutation**

**N = 582**

Randomize 1:1

**Nivolumab**
3 mg/kg IV Q2W
until PD or
unacceptable toxicity
n = 292

**Docetaxel**
75 mg/m$^2$ IV Q3W
until PD or
unacceptable toxicity
n = 290

- **Primary Endpoint**
  – OS
- **Additional Endpoints**
  – ORR[b]
  – PFS[b]
  – Safety
  – Efficacy by tumor PD-L1 expression
  – Quality of life (LCSS)

**Patients stratified by prior maintenance therapy and line of therapy (second- vs third-line)**

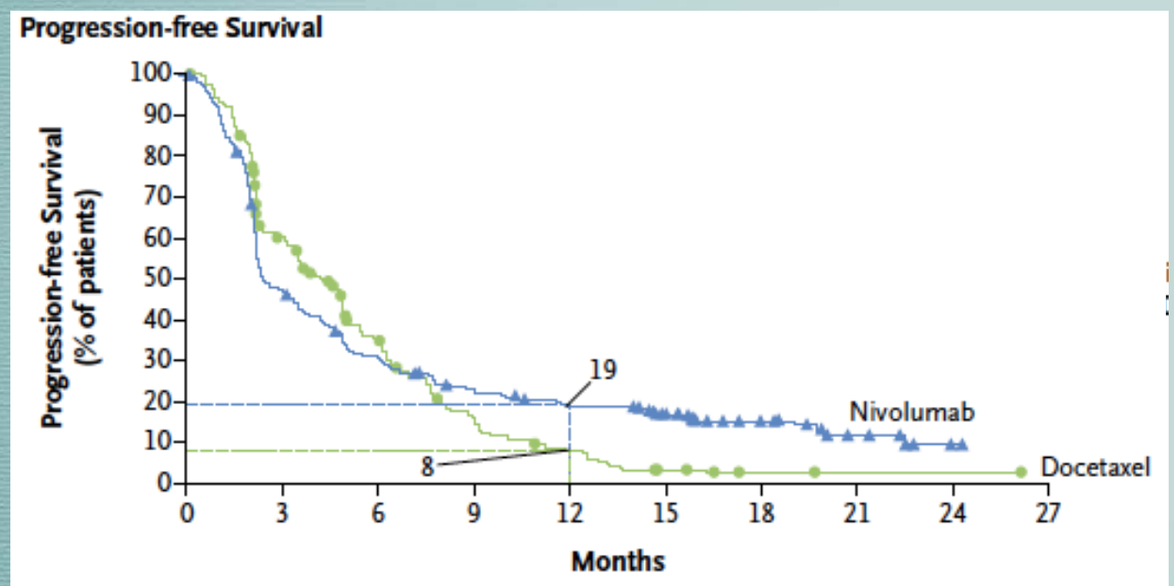
[a] Maintenance therapy included pemetrexed, bevacizumab, or erlotinib (not considered a separate line of therapy); [b] Per RECIST v1.1 criteria as determined by the investigator.

Spigel et al, ASCO 2015; Brahmer et al, NEJM 2015

# Clinical Studies

## CheckMate 057

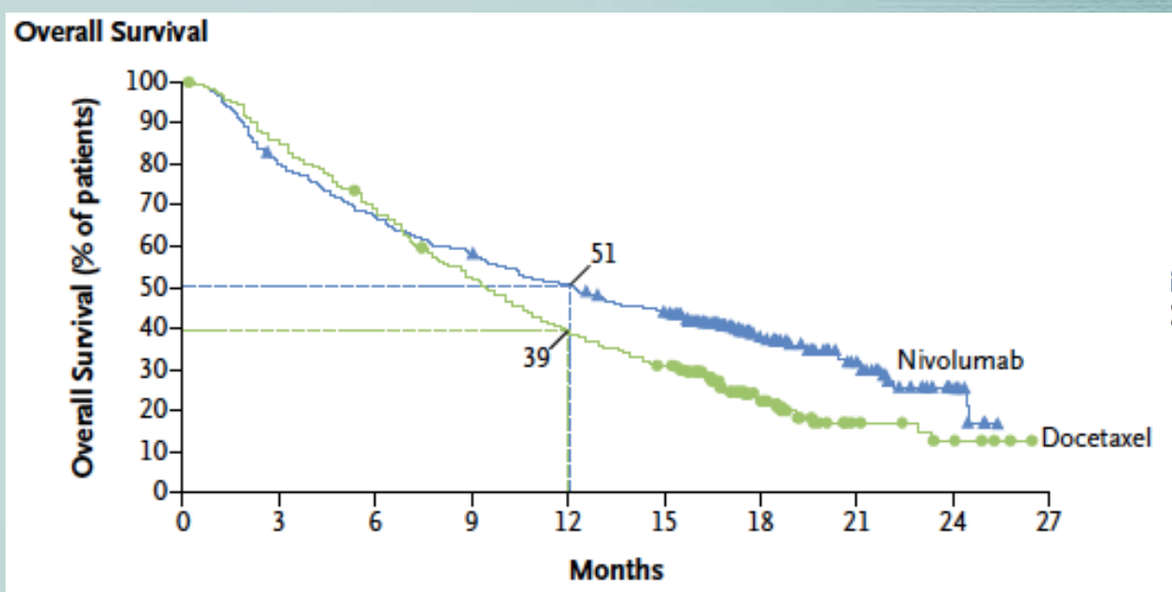
### PFS




| | Nivolumab (n = 292) | Docetaxel (n = 290) |
|---|---|---|
| **mPFS, mo** | 2.3 | 4.2 |

**HR = 0.92 (95% CI: 0.77, 1.11); *P* = 0.3932**

### OS




| | Nivolumab (n = 292) | Docetaxel (n = 290) |
|---|---|---|
| **mOS, mo** | 12.2 | 9.4 |

**HR = 0.73 (96% CI: 0.59, 0.89); *P* = 0.0015**

Spigel et al, ASCO 2015; Brahmer et al, NEJM 2015

# Clinical Studies

## CheckMate 057


**CONCLUSIONS**

Among patients with advanced nonsquamous NSCLC that had progressed during or after platinum-based chemotherapy, overall survival was longer with nivolumab than with docetaxel. (Funded by Bristol-Myers Squibb; CheckMate 057 ClinicalTrials.gov number, NCT01673867.)



N Engl J Med 2015;373:1627-39.
DOI: 10.1056/NEJMoa1507643

# Clinical Studies

## Keynote 010

# Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial

*Roy S Herbst, Paul Baas, Dong-Wan Kim, Enriqueta Felip, José L Pérez-Gracia, Ji-Youn Han, Julian Molina, Joo-Hang Kim, Catherine Dubos Arvis, Myung-Ju Ahn, Margarita Majem, Mary J Fidler, Gilberto de Castro Jr, Marcelo Garrido, Gregory M Lubiniecki, Yue Shentu, Ellie Im, Marisa Dolled-Filhart, Edward B Garon*

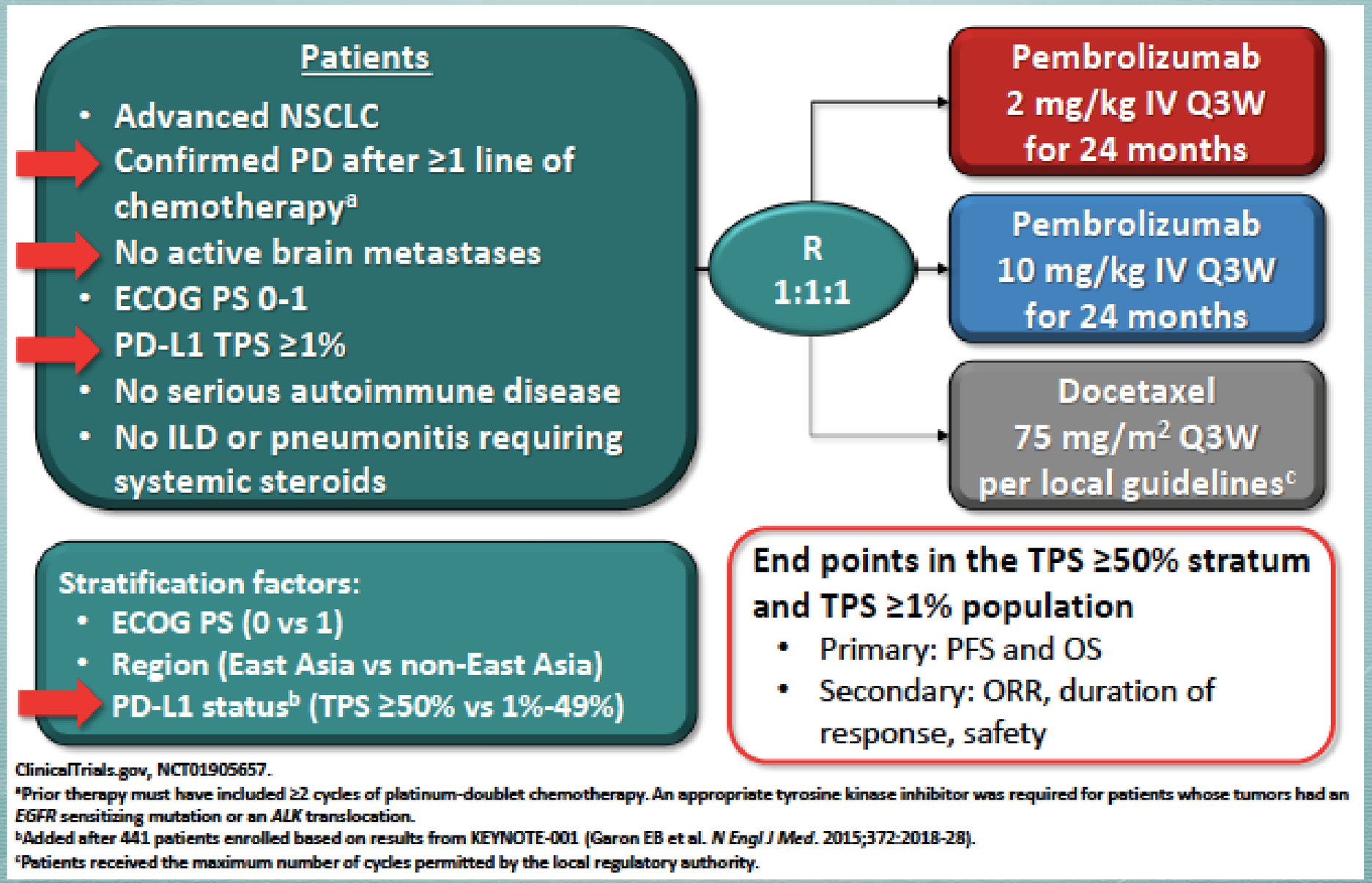
*Lancet* 2016; 387: 1540–50

Published Online
December 19, 2015
http://dx.doi.org/10.1016/S0140-6736(15)01281-7

See Comment page 1488

# Clinical Studies

## Keynote 010




ClinicalTrials.gov, NCT01905657.

[a]Prior therapy must have included ≥2 cycles of platinum-doublet chemotherapy. An appropriate tyrosine kinase inhibitor was required for patients whose tumors had an *EGFR* sensitizing mutation or an *ALK* translocation.

[b]Added after 441 patients enrolled based on results from KEYNOTE-001 (Garon EB et al. *N Engl J Med*. 2015;372:2018-28).

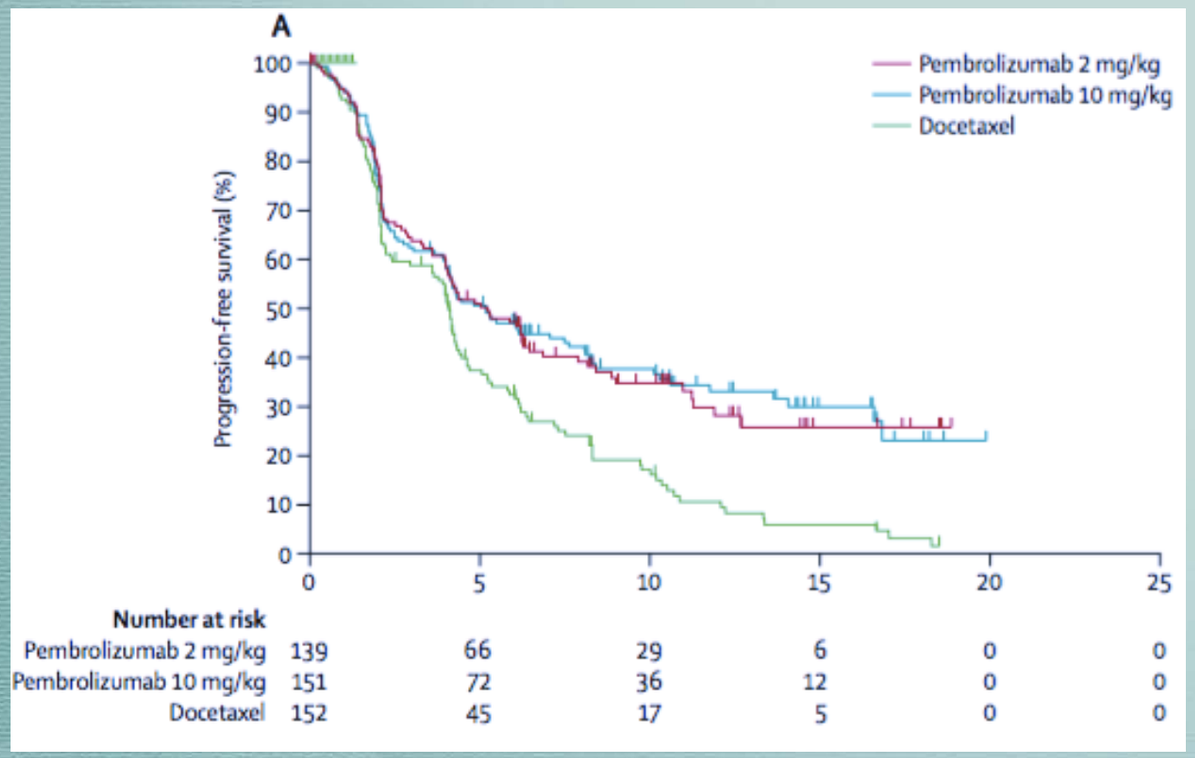
[c]Patients received the maximum number of cycles permitted by the local regulatory authority.

# Clinical Studies

## Keynote 010

### PFS

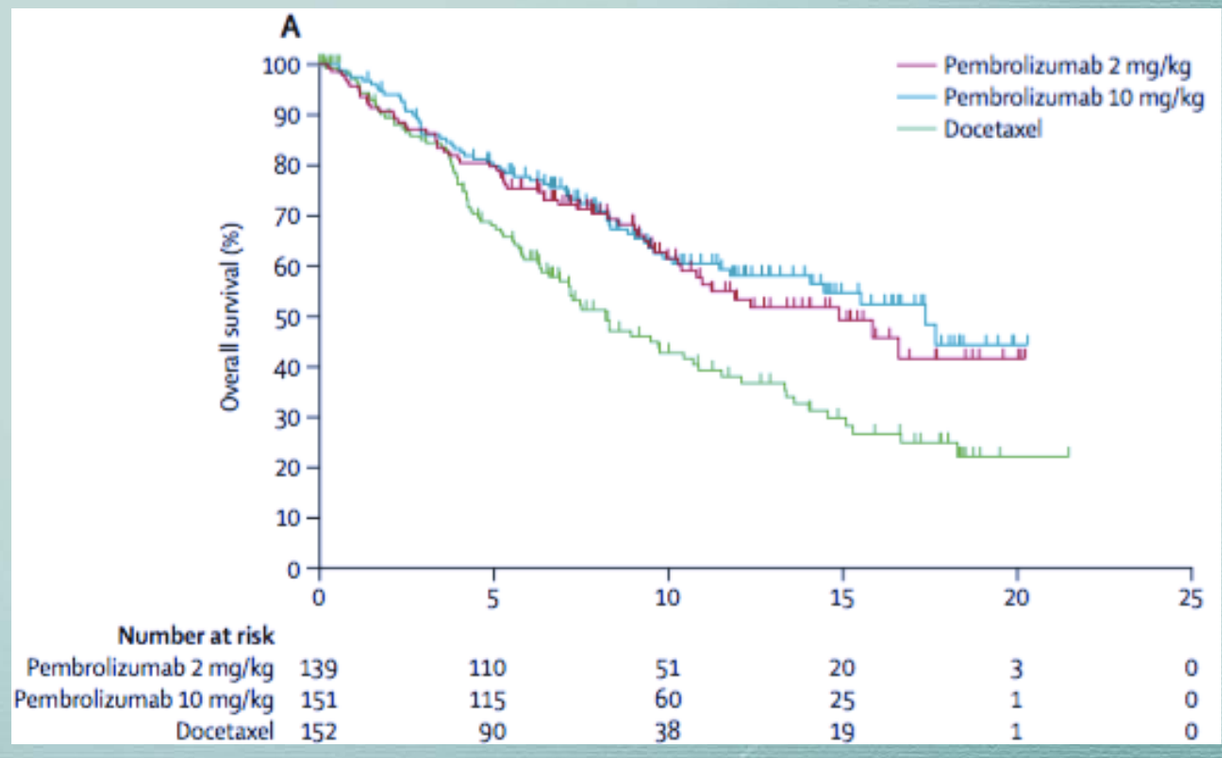
PD-L1 score 50% or greater




| Number at risk | | | | | | |
|---|---|---|---|---|---|---|
| Pembrolizumab 2 mg/kg | 139 | 66 | 29 | 6 | 0 | 0 |
| Pembrolizumab 10 mg/kg | 151 | 72 | 36 | 12 | 0 | 0 |
| Docetaxel | 152 | 45 | 17 | 5 | 0 | 0 |

### OS

PD-L1 score 50% or greater




| Number at risk | | | | | | |
|---|---|---|---|---|---|---|
| Pembrolizumab 2 mg/kg | 139 | 110 | 51 | 20 | 3 | 0 |
| Pembrolizumab 10 mg/kg | 151 | 115 | 60 | 25 | 1 | 0 |
| Docetaxel | 152 | 90 | 38 | 19 | 1 | 0 |

Herbst R et al, Lancet 2015

# Clinical Studies

## Keynote 010

**Interpretation** Pembrolizumab prolongs overall survival and has a favourable benefit-to-risk profile in patients with previously treated, PD-L1-positive, advanced non-small-cell lung cancer. These data establish pembrolizumab as a new treatment option for this population and validate the use of PD-L1 selection.

**Funding** Merck & Co.

*Lancet* 2016; 387: 1540–50

Published Online
December 19, 2015
http://dx.doi.org/10.1016/
S0140-6736(15)01281-7

See Comment page 1488

# Clinical Studies

## POPLAR

### Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial

*Louis Fehrenbacher, Alexander Spira, Marcus Ballinger, Marcin Kowanetz, Johan Vansteenkiste, Julien Mazieres, Keunchil Park, David Smith, Angel Artal-Cortes, Conrad Lewanski, Fadi Braiteh, Daniel Waterkamp, Pei He, Wei Zou, Daniel S Chen, Jing Yi, Alan Sandler, Achim Rittmeyer, for the POPLAR Study Group**

*Lancet* 2016; 387: 1837–46

Published Online
March 9, 2016
http://dx.doi.org/10.1016/S0140-6736(16)00587-0

# Clinical Studies

## POPLAR

**Metastatic or locally advanced NSCLC (2L/3L)**
**Disease progression on a prior platinum therapy**
**N = 287**

**Stratification Factors**
- **PD-L1 IC expression (0 vs 1 vs 2 vs 3)[a]**
- **Histology (squamous vs non-squamous)**
- **Prior chemotherapy regimens (1 vs 2)**

**R**
**1:1**

**Atezolizumab**
**1200 mg IV q3w**
**until loss of clinical benefit**

Docetaxel
75 mg/m$^2$ IV q3w
until disease progression

**Primary study objective:**
- **Estimate OS in PD-L1 selected and ITT populations**

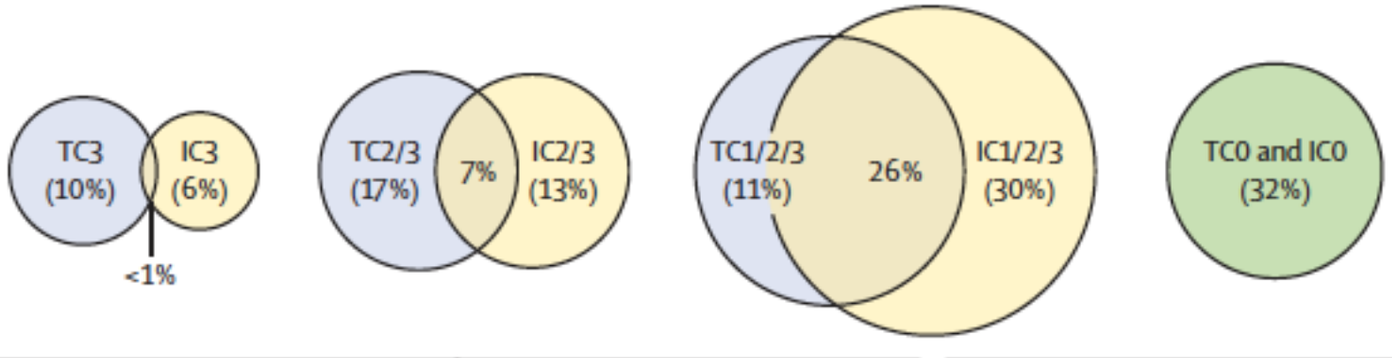
Secondary study objectives:
- Evaluate PFS, ORR and DOR in PD-L1 selected and ITT populations
- Evaluate safety

- [a]Archival or fresh tissue required for pre-dose testing.

Interim analysis is based on 153 events with a minimum follow-up 10 months

# Clinical Studies

## POPLAR




| PD-L1 tumour cell scoring | | PD-L1 tumour-infiltrating immune cell scoring | |
|---|---|---|---|
| Score | Percentage of PD-L1-expressing cells | Score | Percentage of PD-L1-expressing cells |
| TC3 | ≥50% | IC3 | ≥10% |
| TC2 | ≥5% and <50% | IC2 | ≥5% and <10% |
| TC1 | ≥1% and <5% | IC1 | ≥1% and <5% |
| TC0 | <1% | IC0 | <1% |

| Overall prevalence | |
|---|---|
| Subgroup | Proportion |
| TC3 or IC3 | 16% |
| TC2/3 or IC2/3 | 37% |
| TC1/2/3 or IC1/2/3 | 68% |
| TC0 and IC0 | 32% |

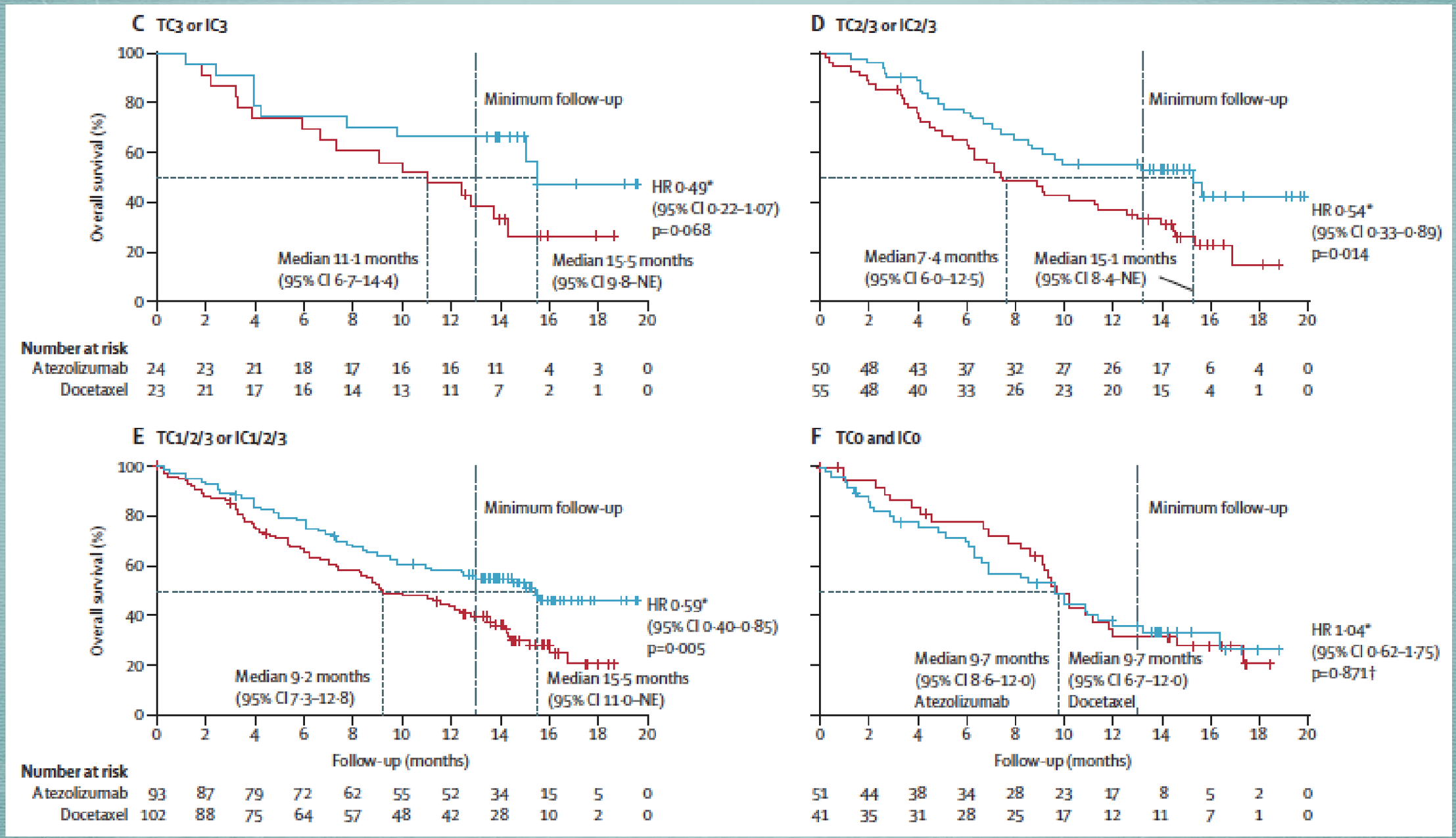
***Figure 1:*** **Programmed death ligand 1 (PD-L1) scoring criteria, prevalence, and overlap between PD-L1 expression on tumour cells and tumour-infiltrating immune cells**

Percentages in Venn diagrams represent the prevalence of PD-L1 expression in non-overlapping subgroups.

*Lancet* 2016; 387: 1837–46
Published Online
March 9, 2016
http://dx.doi.org/10.1016/S0140-6736(16)00587-0

# Clinical Studies

## POPLAR




*Lancet* 2016; 387: 1837–46
Published Online
March 9, 2016
http://dx.doi.org/10.1016/
S0140-6736(16)00587-0

# Clinical Studies

## POPLAR

**Interpretation** Atezolizumab significantly improved survival compared with docetaxel in patients with previously treated NSCLC. Improvement correlated with PD-L1 immunohistochemistry expression on tumour cells and tumour-infiltrating immune cells, suggesting that PD-L1 expression is predictive for atezolizumab benefit. Atezolizumab was well tolerated, with a safety profile distinct from chemotherapy.

**Funding** F Hoffmann-La Roche/Genentech Inc.

*Lancet* 2016; 387: 1837–46

Published Online
March 9, 2016
http://dx.doi.org/10.1016/
S0140-6736(16)00587-0

# Clinical Studies

## OAK

**Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial**

*Achim Rittmeyer, Fabrice Barlesi, Daniel Waterkamp, Keunchil Park, Fortunato Ciardiello, Joachim von Pawel, Shirish M Gadgeel, Toyoaki Hida, Dariusz M Kowalski, Manuel Cobo Dols, Diego L Cortinovis, Joseph Leach, Jonathan Polikoff, Carlos Barrios, Fairooz Kabbinavar, Osvaldo Arén Frontera, Filippo De Marinis, Hande Turna, Jong-Seok Lee, Marcus Ballinger, Marcin Kowanetz, Pei He, Daniel S Chen, Alan Sandler, David R Gandara, for the OAK Study Group**

*Lancet* 2017; 389: 255–65

Published Online
December 12, 2016
http://dx.doi.org/10.1016/S0140-6736(16)32517-X

# Clinical Studies

## OAK

**Locally Advanced or Metastatic NSCLC**

- 1–2 prior lines of chemo including at least 1 platinum based
- Any PD-L1 status

**N = 1,225 enrolled[a]**

**Stratification factors**

- PD-L1 expression
- Histology
- Prior chemotherapy regimens

R 1:1

**Atezolizumab 1200 mg IV q3w** → **PD or loss of clinical benefit**

**Docetaxel 75 mg/m² q3w** → **PD**

**Primary Endpoints (first 850 enrolled patients):**

- OS in the ITT population
- OS in patients with PD-L1 expression on ≥ 1% TC or IC

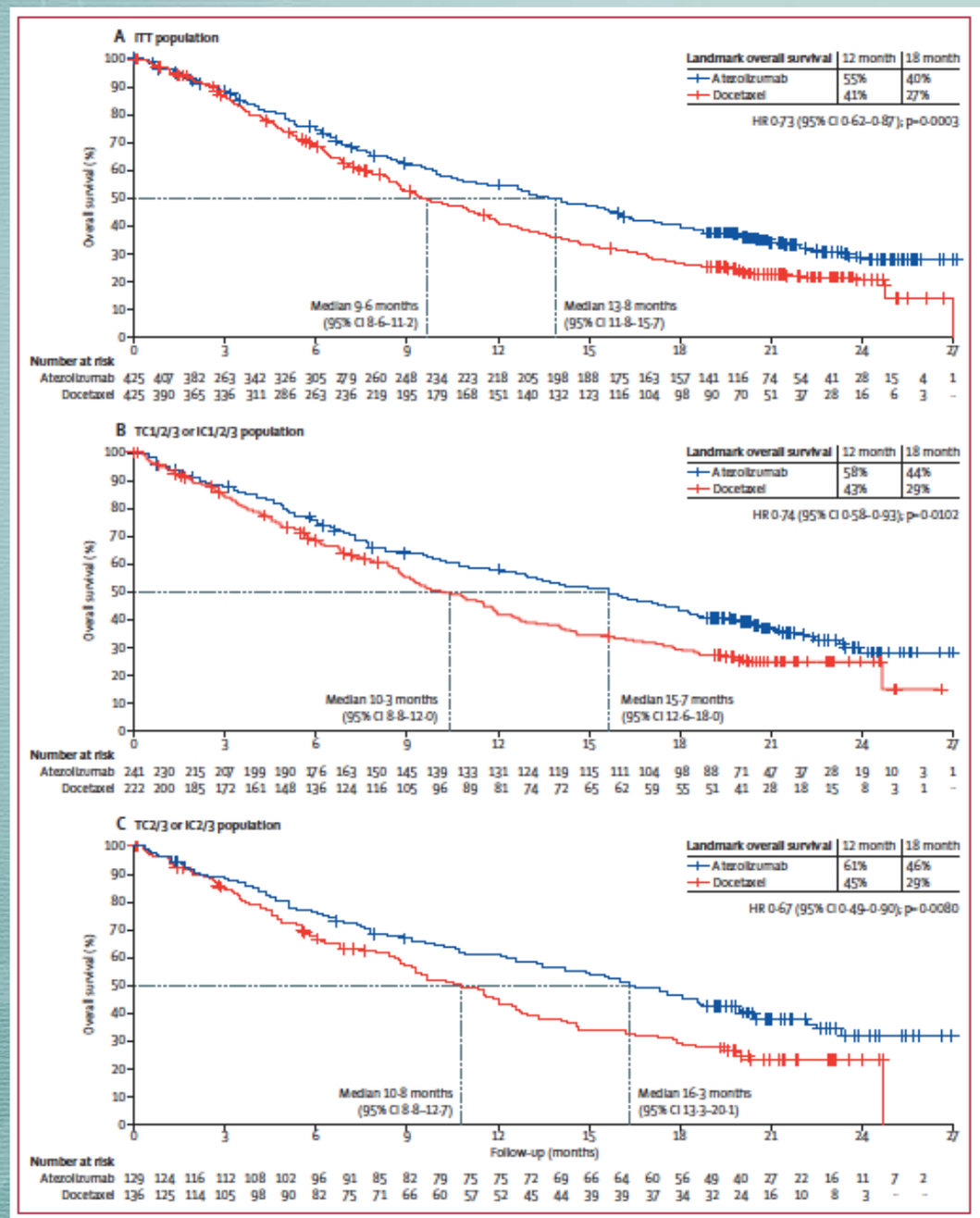
**Secondary Endpoints: ORR, PFS, DoR, Safety**

[a]A prespecified analysis of the first 850 patients provided sufficient power to test the co-primary endpoints of OS in the ITT and TC1/2/3 or IC1/2/3 subgroup (≥ 1% PD-L1 expression).
TC, tumor cells; IC, tumor-infiltrating immune cells.

Barlesi et al. ESMO 2016

# Clinical Studies

## OAK




*Lancet* 2017; 389: 255–65

Published Online
December 12, 2016
http://dx.doi.org/10.1016/S0140-6736(16)32517-X

# Clinical Studies

## OAK

**Interpretation** To our knowledge, OAK is the first randomised phase 3 study to report results of a PD-L1-targeted therapy, with atezolizumab treatment resulting in a clinically relevant improvement of overall survival versus docetaxel in previously treated non-small-cell lung cancer, regardless of PD-L1 expression or histology, with a favourable safety profile.

**Funding** F. Hoffmann-La Roche Ltd, Genentech, Inc.

*Lancet* 2017; 389: 255–65

Published Online
December 12, 2016
http://dx.doi.org/10.1016/
S0140-6736(16)32517-X

# Clinical Studies

## ATLANTIC

- NSCLC patients (Stage IIIB/IV)
- ≥2 prior systemic treatment regimens including 1 platinum-based CT
- Recent (≤3 months) tumour biopsy and archived tumour tissue block for PD-L1 testing

**N=1980 screened**

**Protocol amendment restricted selection to pts with PD-L1 high tumours***

Durvalumab i.v. 10 mg/kg q2w up to 12 months

**Cohort 1 (n=111)**
*EGFR* mutation/*ALK* alteration
PD-L1 high (≥25% tumour cells)

**Cohort 2 (n=265)**
*EGFR*/*ALK* wild-type
PD-L1 high (≥25% tumour cells) and PD-L1 low/negative

**Cohort 3 (n=68)**
*EGFR*/*ALK* wild-type
PD-L1 high (≥90% tumour cells)

Cohorts were independent;
Cohorts 2 and 3 enrolled sequentially

**Primary endpoint:**
- ORR†

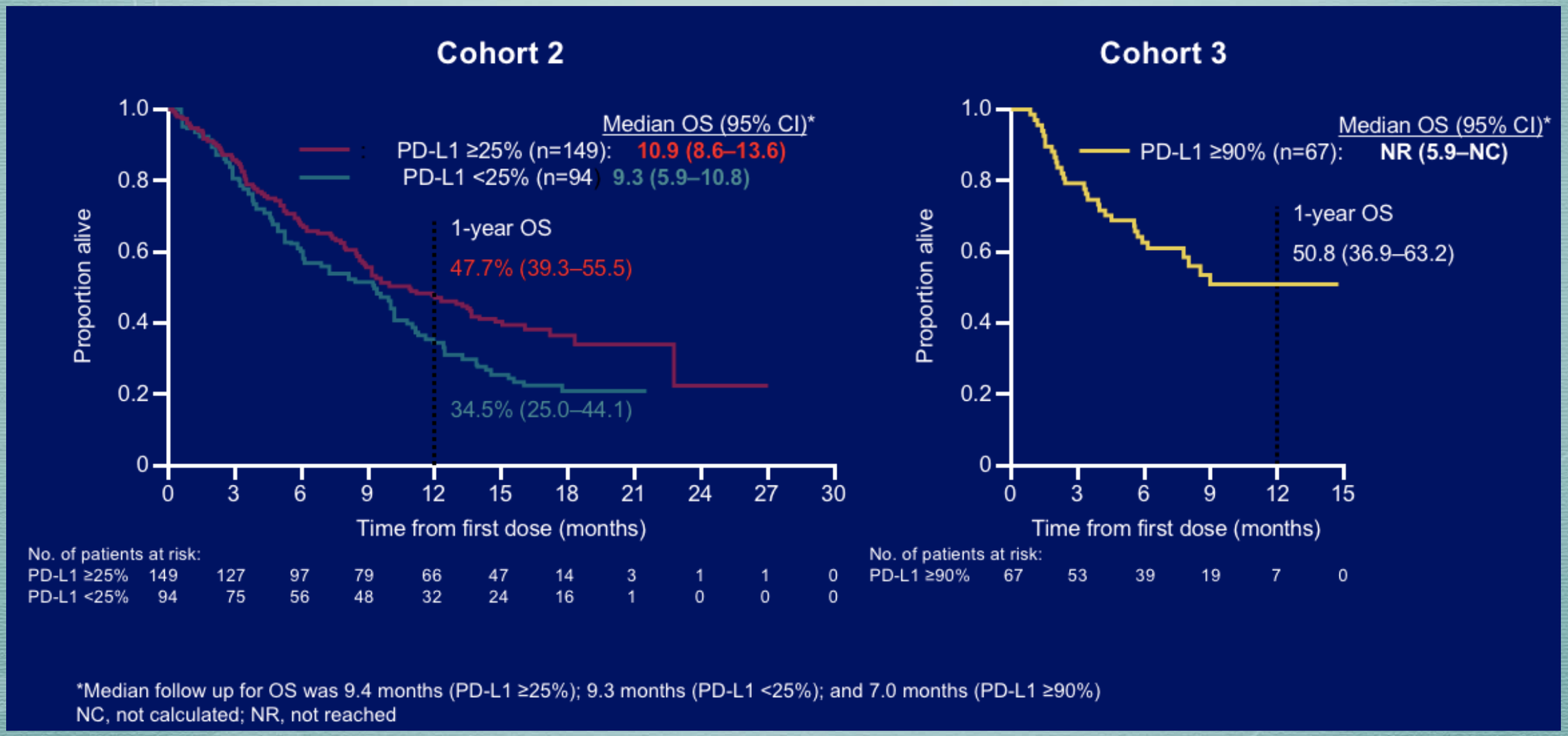
**Secondary endpoints:**
- DoR, PFS, DCR, OS
- Safety
- PK
- Immunogenicity

*PD-L1 expression levels assessed by immunohistochemistry (**VENTANA** PD-L1 [SP263] Assay); †ORR by independent central review (RECIST v1.1)
CT, chemotherapy; DCR, disease control rate; DoR, duration of response

Garassino et al. IASLC 2016

# Clinical Studies

## ATLANTIC




*Median follow up for OS was 9.4 months (PD-L1 ≥25%); 9.3 months (PD-L1 <25%); and 7.0 months (PD-L1 ≥90%)
NC, not calculated; NR, not reached

Garassino et al. IASLC 2016

# Clinical Studies

## ATLANTIC

- Durvalumab was active and led to durable responses in a heavily pretreated metastatic NSCLC population
  - Higher PD-L1 expression appeared to be associated with higher response rate
  - 1-year OS was 48% in patients with PD-L1 ≥25% and 51% in those with PD-L1 ≥90%

- Most AEs were low grade and manageable

- Results are consistent with other anti-PD-1/PD-L1 therapies in metastatic NSCLC

Garassino et al. IASLC 2016

# Clinical Studies

## ATLANTIC



ClinicalTrials.gov
A service of the U.S. National Institutes of Health
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### A Global Study to Assess the Effects of MEDI4736 in Patients With Locally Advanced or Metastatic Non Small Cell Lung Cancer (ATLANTIC)

This study is ongoing, but not recruiting participants.

**Sponsor:**
AstraZeneca

**Information provided by (Responsible Party):**
AstraZeneca

**ClinicalTrials.gov Identifier:**
NCT02087423

First received: March 4, 2014
Last updated: February 11, 2017
Last verified: February 2017
History of Changes



### Purpose

A study to assess the Effects of MEDI4736 in Patients With Locally Advanced or Metastatic Non Small Cell Lung Cancer in terms of efficacy, safety and tolerability

| Condition | Intervention | Phase |
|---|---|---|
| Non-Small Cell Lung Cancer | Drug: MEDI4736 | Phase 2 |

Study Type: Interventional
Study Design: Intervention Model: Single Group Assignment
Masking: No masking
Primary Purpose: Treatment

Official Title: A Phase II,Non-comparative,Open Label, Multi-centre, International Study of MEDI4736, in Patients With Locally Advanced or Metastatic Non Small Cell Lung Cancer (Stage IIIB-IV) Who Have Received at Least 2 Prior Systemic Treatment Regimens Including 1 Platinum-based Chemotherapy Regimen

# Patient Selection

# Patient Selection

- **Clinical Factors:**
  - Gender
  - Age / Smoking status
  - Histology

- **Genetic Factors:**
  - Specific mutations
  - Mutational load

- **Immunological Factors:**
  - PD-L1
  - Tumor microenvironment

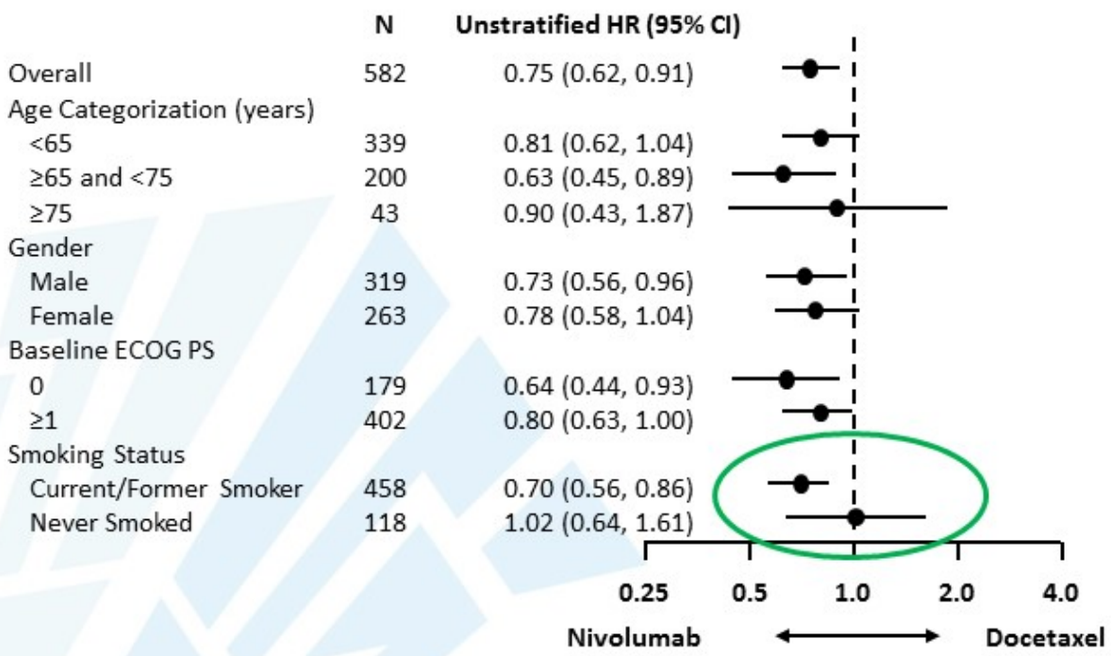
# Patient Selection

## Clinical Factors:

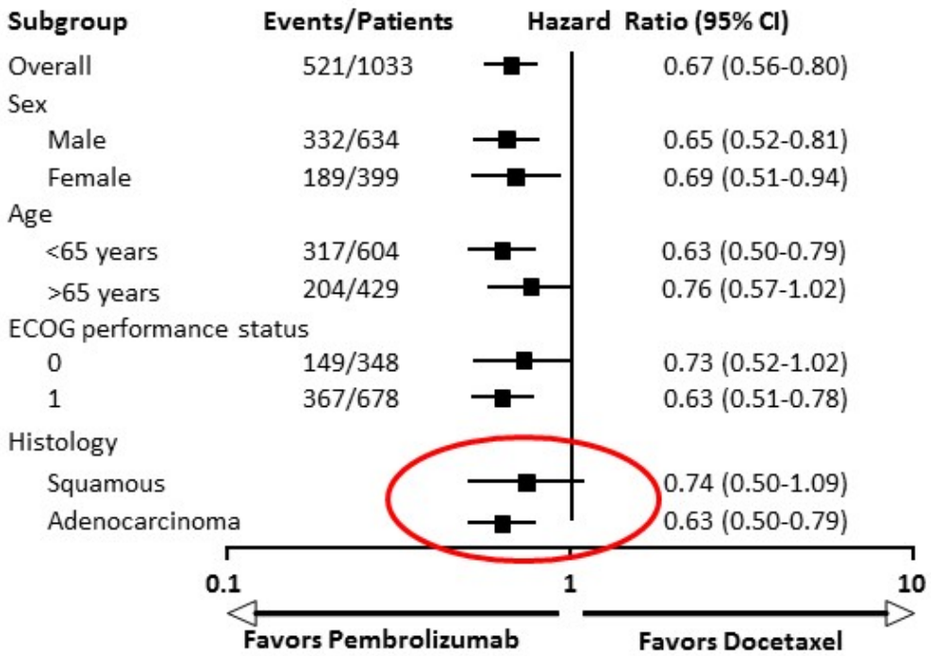
### Lung cancer immunotherapy

### > effect of age, gender, PS, smoking, histology: anti PD-1 datasets

**Ph3 Nivolumab (NSQ) [*ChM 057*]**




**Ph3 Pembrolizumab [*KN 010*]**





Borghaei et al, N Engl J Med 373:1627-1639, 2015
Herbst et al, Lancet 387:1540-150, 2016

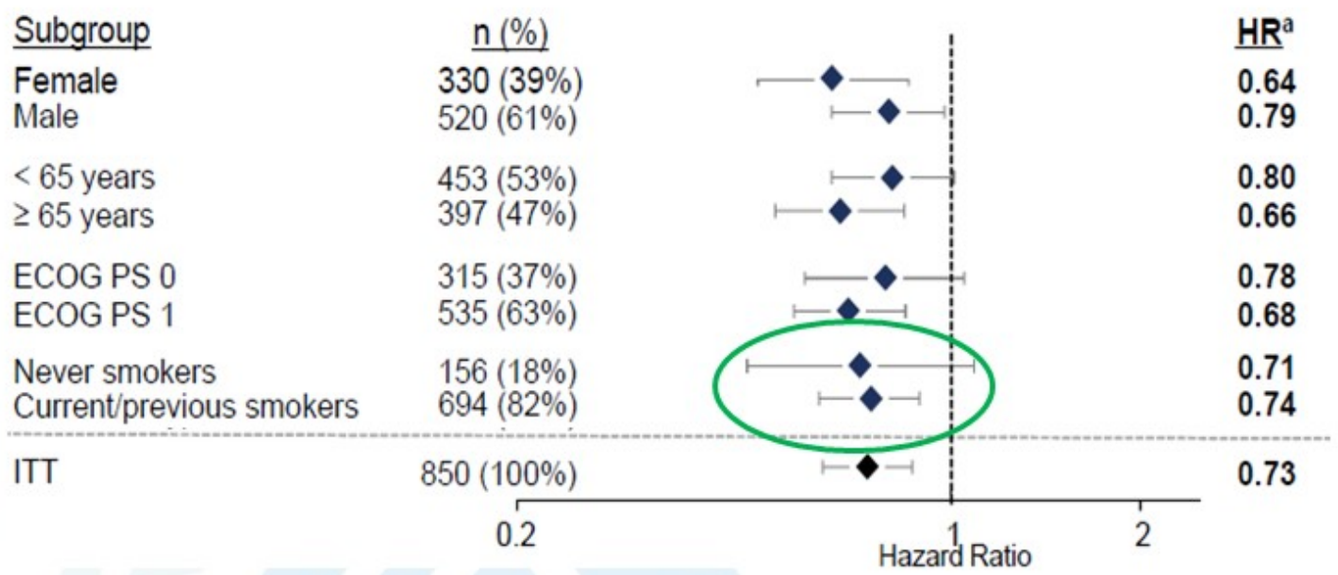
# Patient Selection

## Clinical Factors:

### Lung cancer immunotherapy

### > effect of age, gender, PS, smoking, histology: anti PD-L1 datasets

**Ph3 Atezolizumab [*OAK*]**




**Ph1/2 Durvalumab [*study 1108*]**

| RECIST response (ORR) | |
|---|---|
| **Histology** | |
| Squamous | 31/146 (21.2%) |
| Non-squamous | 19/139 (13.7%) |
| **Tobacco use** | |
| Former/current smoker | 47/240 (19.6%) |
| Never smoker | 3/45 (6.7%) |

Barlesi et al, ESMO 2016
Antonia et al, ESMO 2016


Respiratory Oncology Unit
Univ. Hospital Leuven
Leuven Lung Cancer Group
http://www.LLCG.be

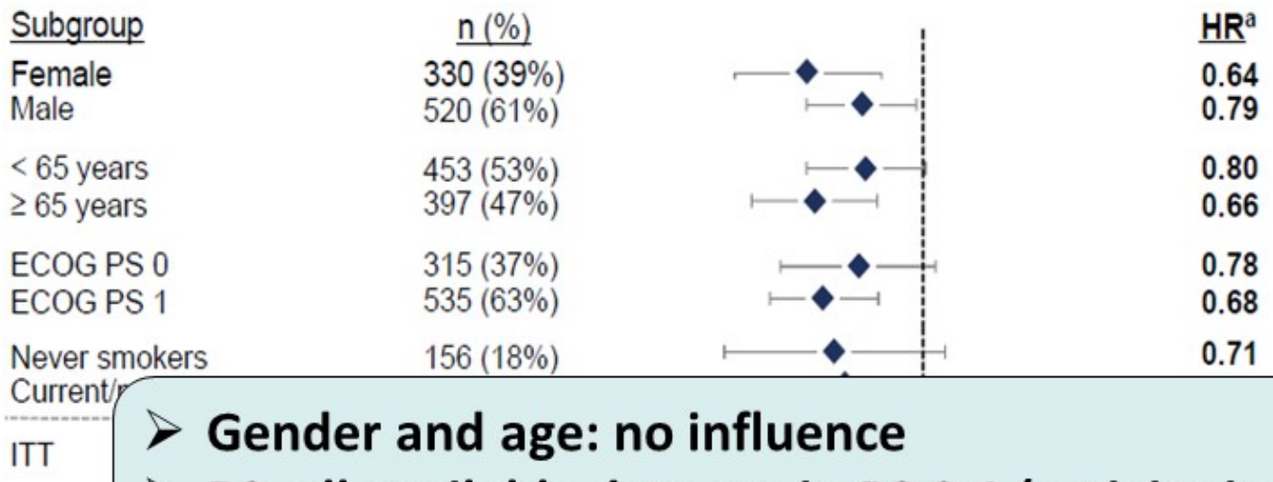
# Patient Selection

## Clinical Factors:

### Lung cancer immunotherapy

### > effect of age, gender, PS, smoking, histology

**Ph3 Atezolizumab [*OAK*]**

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| Squamous | 31/146 (21.2%) |
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| **Tobacco use** | |
| Former/current smoker | 47/240 (19.6%) |

- **Gender and age: no influence**
- **PS: all available data are in PS 0-1 (activity in PS 2 to be explored)**
- **Smoking history in general associated with better response & more outcome benefit**

Barlesi et al, ESMO 2016
Antonia et al, ESMO 2016

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# Patient Selection

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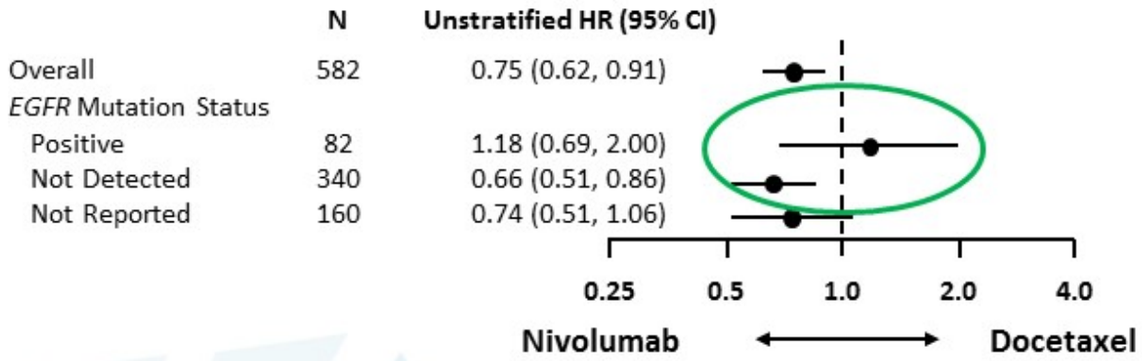
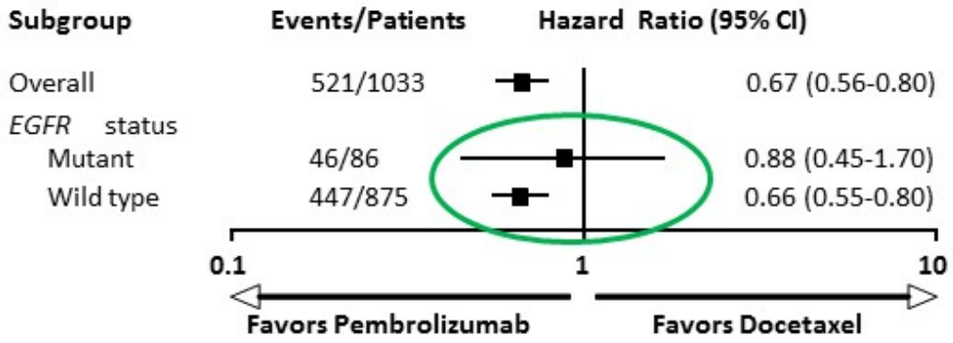
- **Immunological Factors:**
  - PD-L1
  - Tumor microenvironment

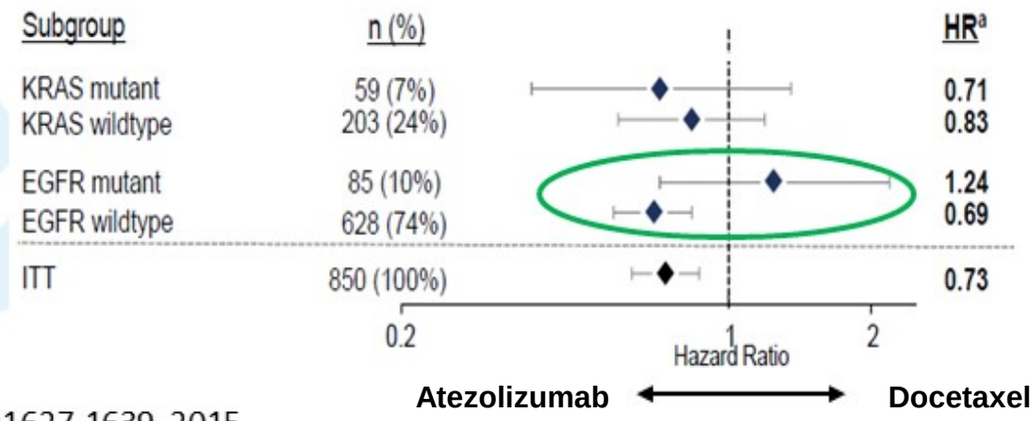
# Patient Selection

## Genetic Factors:

### Lung cancer immunotherapy
### > specific mutations





Borghaei et al, N Engl J Med 373:1627-1639, 2015
Herbst et al, Lancet 387:1540-150, 2016
Barlesi et al, ESMO 2016

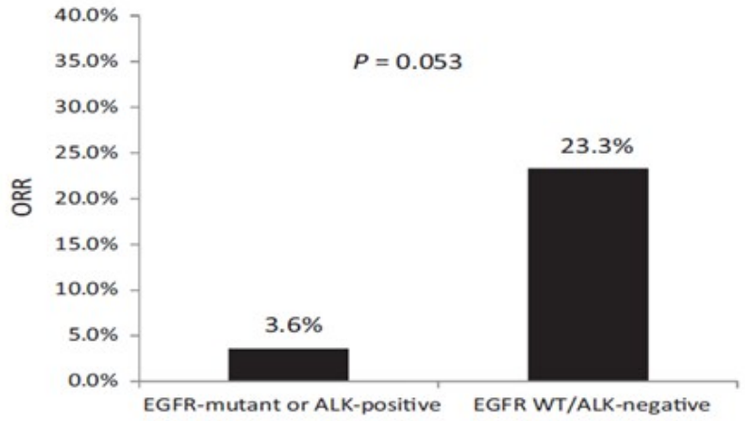
# Patient Selection

## Genetic Factors:

### Lung cancer immunotherapy

### > specific mutations

Gainor et al,
Clin Cancer Res 22: 4585–4593, 2016



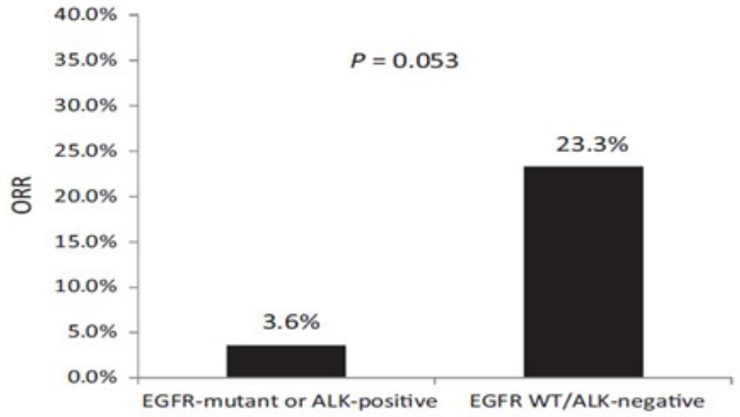

| | EGFR-mutant | | | ALK-rearranged | | |
|---|---|---|---|---|---|---|
| | Pre-TKI (*N* = 62) | Post-TKI (*N* = 63) | *P*[a] | Pre-Criz (*N* = 19) | Post-Criz (*N* = 12) | *P*[a] |
| PD-L1 positive | | | | | | |
| PD-L1$^+$ (≥50%) | 7 (11%) | 9 (14%) | 0.727 | 5 (26%) | 2 (17%) | 1.000 |
| PD-L1$^+$ (≥5%) | 10 (16%) | 18 (29%) | 0.119 | 9 (47%) | 3 (25%) | 0.500 |
| CD8$^+$ TILs (IHC)[b] | | | | | | |
| 0 | 17 (35%) | 18 (42%) | 0.847 | 2 (15%) | 4 (44%) | * |
| 1+ | 29 (60%) | 20 (47%) | | 8 (62%) | 5 (56%) | |
| 2+ | 2 (4.2%) | 5 (12%) | | 3 (23%) | 0 (0%) | |
| 3+ | 0 (0%) | 0 (0%) | | 0 (0%) | 0 (0%) | |
| Concurrent PD-L1 expression & CD8$^+$ TILs (IHC) | | | | | | |
| PD-L1$^+$ (≥50%) & high CD8$^+$ TILs (grade 2–3) | 1/48 (2.1%) | 1/43 (2.3%) | 1.000 | 0/13 (0%) | 0/9 (0%) | * |
| PD-L1$^+$ (≥5%) & high CD8$^+$ TILs (grade 2–3) | 1/48 (2.1%) | 5/43 (11.6%) | 0.219 | 0/13 (0%) | 0/9 (0%) | |

# Patient Selection

## Genetic Factors:

### Lung cancer immunotherapy
### > specific mutations

Gainor et al,
Clin Cancer Res 22: 4585–4593, 2016

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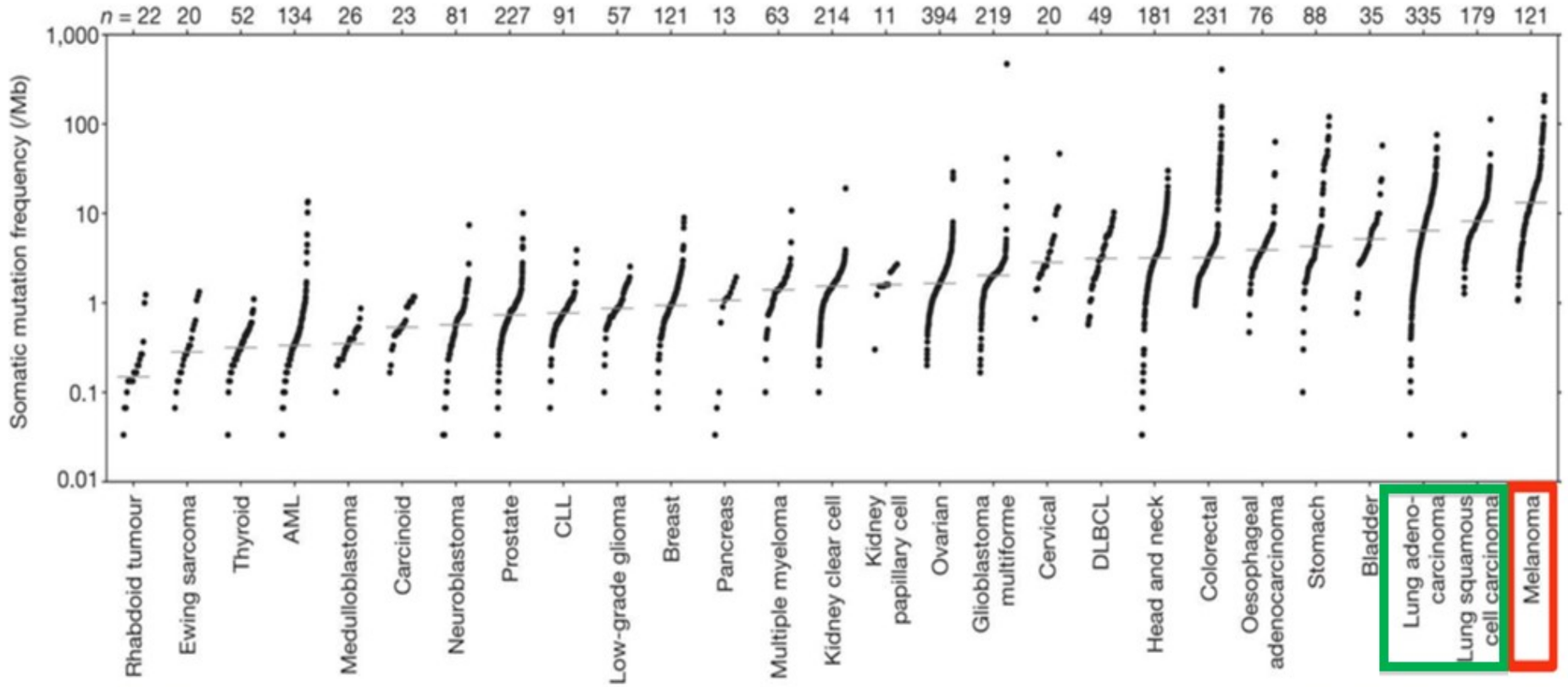
| 0 | | | | | | |
| 1+ | | | | | | |
| 2+ | | | | | | |
| 3+ | | | | | | |
| Concurrent | | | | | | |
| PD-L1$^+$ (≥50%) & high CD8$^+$ TILs (grade 2–3) | 1/48 (2.1%) | 1/43 (2.3%) | 1.000 | 0/13 (0%) | 0/9 (0%) | * |
| PD-L1$^+$ (≥5%) & high CD8$^+$ TILs (grade 2–3) | 1/48 (2.1%) | 5/43 (11.6%) | 0.219 | 0/13 (0%) | 0/9 (0%) | |

- **EGFR mutated / ALK translocated tumors:**
  **lower response rate and less outcome benefit**

# Patient Selection

## Genetic Factors:

### Lung cancer immunotherapy
### > mutational load



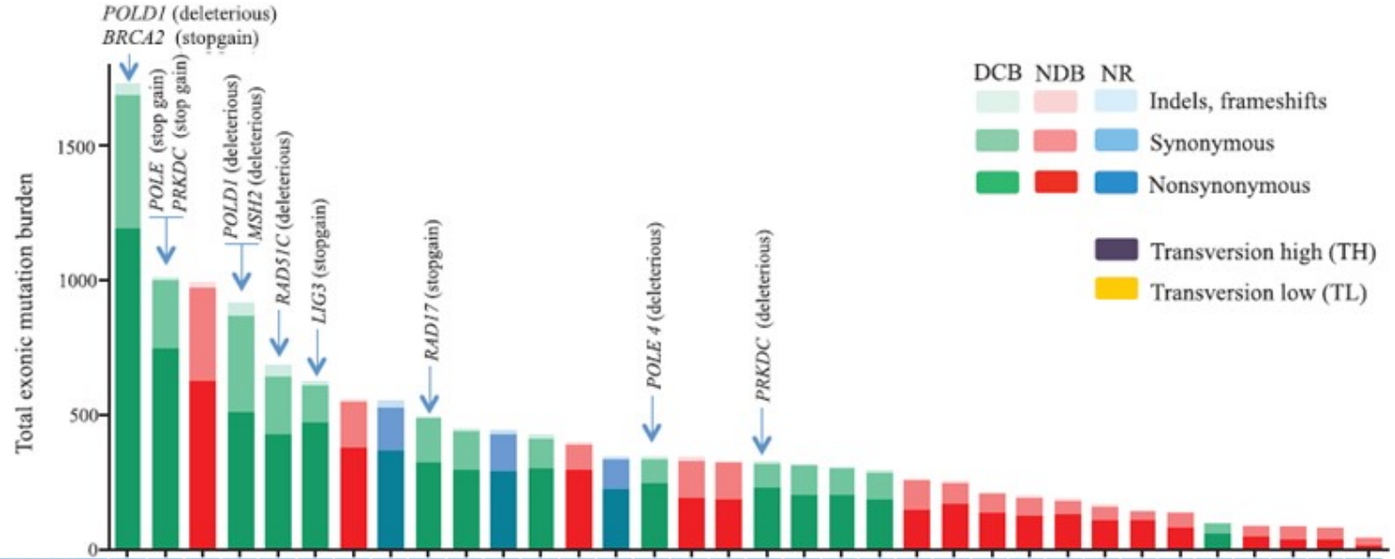

Lawrence et al, Nature 499:214-218, 2013

# Patient Selection

## Genetic Factors:

### Lung cancer immunotherapy

### > mutational load and response to anti-PD-1




| Study ID | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cohort | V | D | D | V | V | D | V | V | D | D | V | D | D | V | V | V | D | D | V | V | D | D | D | V | V | V | D | V | V | V | D | V | D | D |
| Objective Response | PR | PR | PD | SD | PR | PR | PD | SD | PR | PR | PR | SD | PD | PR | SD | PD | PD | PR | PR | PR | SD | SD | PD | PD | PD | PD | PD | SD | SD | PR | SD | PD | PD | SD |
| PFS (months) | 8 | 14 | 2 | 8 | 14 | 16 | 2 | 4 | 15 | 13 | 4 | 8 | 2 | 4 | 8 | 3 | 3 | 10 | 27 | 10 | 8 | 7 | 2 | 2 | 1 | 2 | 2 | 4 | 6 | 8 | 4 | 2 | 2 | 6 |
| Ongoing response | ++ | ++ | | | ++ | ++ | | ++ | | ++ | ++ | | | ++ | ++ | | | ++ | ++ | ++ | | | | | | | | | | | | | | |
| Smoking signature | TH | TH | TH | TL | TH | TH | TL | TH | TH | TH | TH | TH | TH | TH | TH | TL | TL | TH | TL | TL | TH | TL | TH | TL | TL | TL | TL | TL | TL | TL | TL | TL | TL | TL |

Rizvi et al, Science 348:124-128, 2015

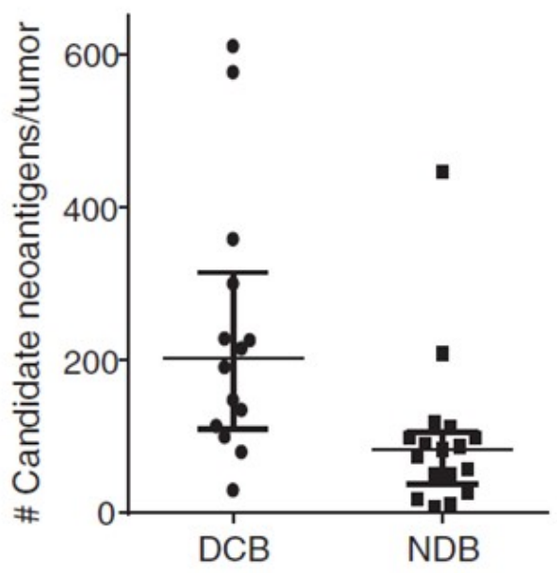
Johan Vansteenkiste, WCLC. 2016

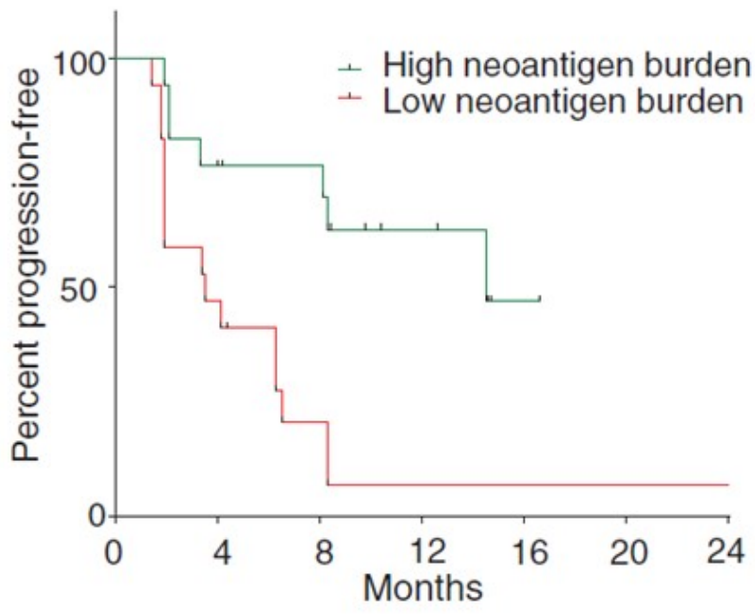
# Patient Selection

## Genetic Factors:

### Lung cancer immunotherapy

> mutational load and response to anti-PD-1




Rizvi et al, Science 348:124-128, 2015

# Patient Selection

- **Clinical Factors:**
  - Gender
  - Age / Smoking status
  - Histology

- **Genetic Factors:**
  - Specific mutations
  - Mutational load

- **Immunological Factors:**
  - PD-L1
  - Tumor microenvironment

# Patient Selection

## Immunological Factors:

### Lung cancer immunotherapy

> defining expectations with anti PD-1/PD-L1 therapy

**PD-L1 immunohistochemistry**

Is it **THE** biomarker?

Is it **A** biomarker?

Is it **NO** biomarker?

# Patient Selection

## Immunological Factors:

### Lung cancer immunotherapy

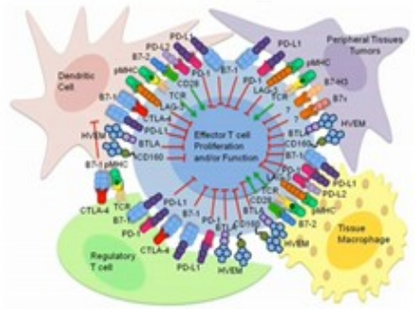
### > defining expectations with anti PD-1/PD-L1 therapy

- **EGFRmut ≈ EGFR-TKI**
  - Related to tumor only
  - "Simple" mechanism

  - Yes/No phenomenon
  - Stable over time

**THE biomarker**

- **PD-L1 IHC ≈ anti-PD-1/PD-L1**
  - Related to tumor & environment
  - Complex mechanism




  - Continuous phenomenon
  - Inducible

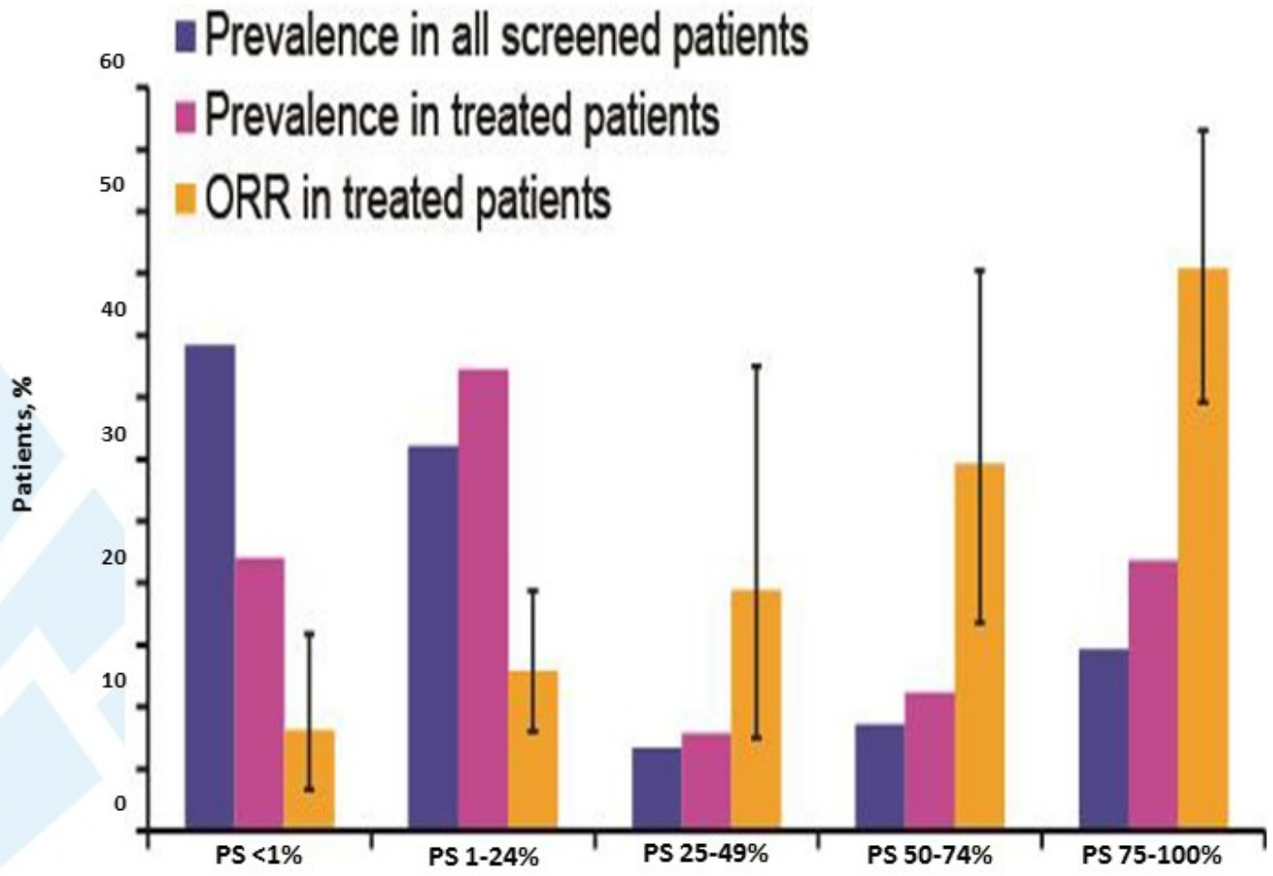
**?**

# Patient Selection

## Immunological Factors:

### Biomarker PD-L1

> ph1 Pembrolizumab study [*KEYNOTE 001*]



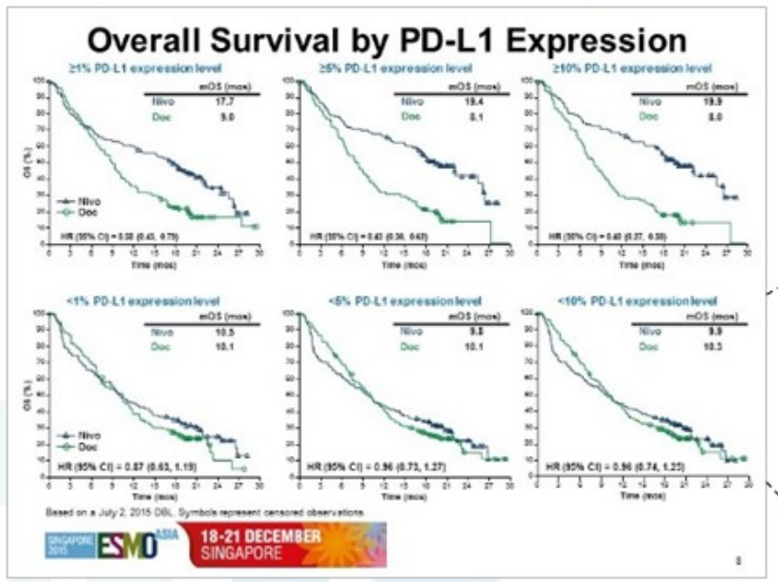

Garon et al, N Engl J Med 372:2018-2028, 2015 Suppl Material

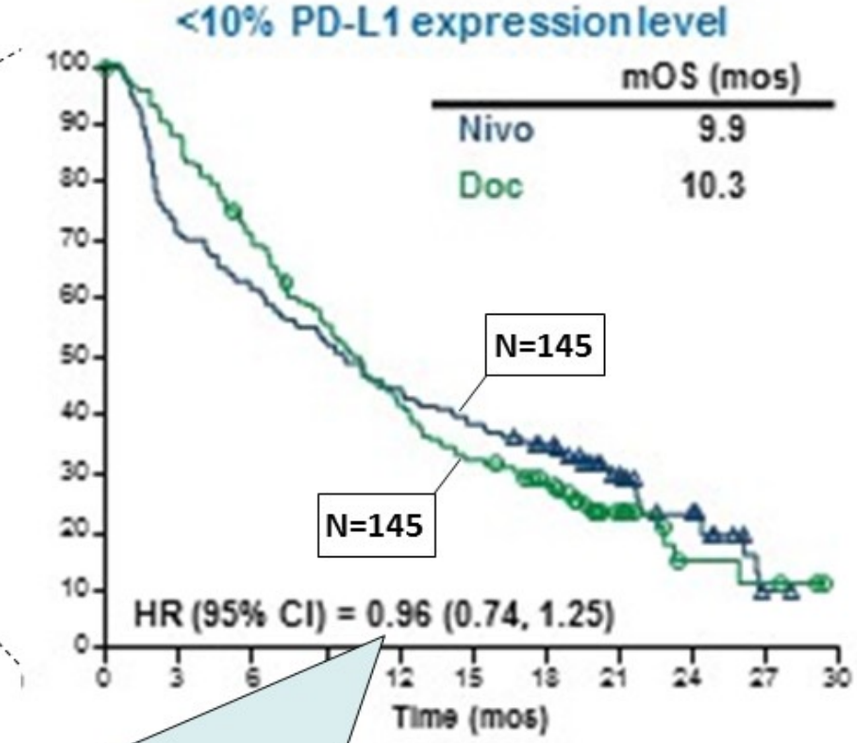
# Patient Selection

## Immunological Factors:

### Lung cancer immunotherapy

### > ph3 Nivolumab nsq-NSCLC study [*Checkmate 057*]:




Horn et al, ESMO-ASIA 2015

- **OS is the same with nivolumab and docetaxel [HR 0.96]**

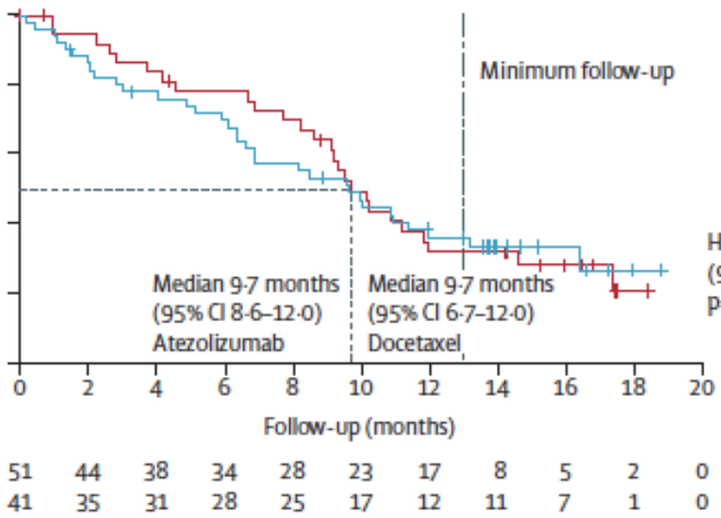
# Patient Selection

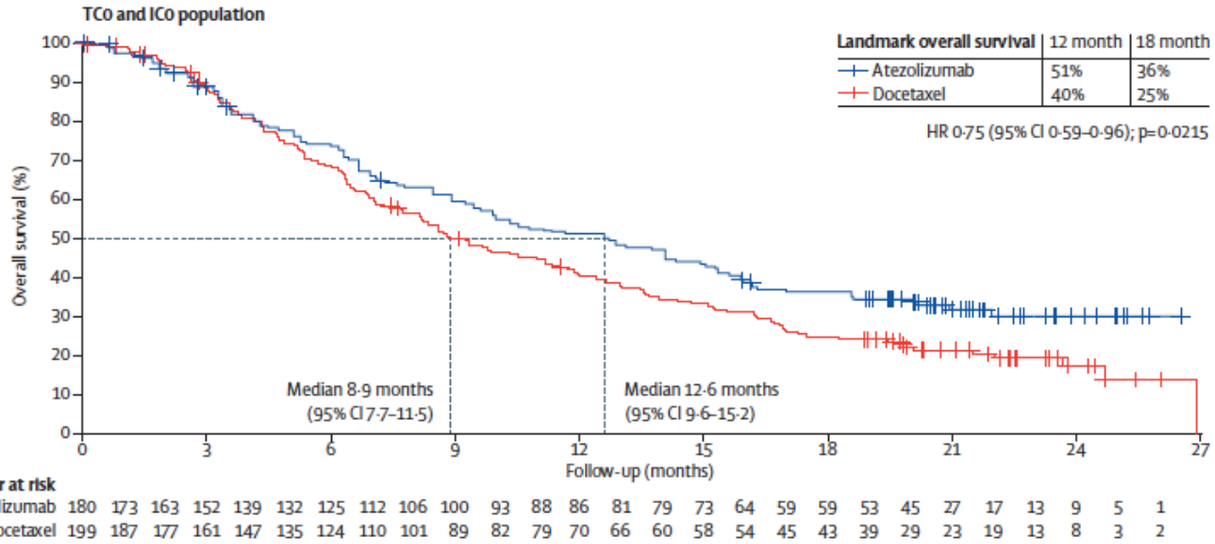
## Immunological Factors:

### Lung cancer immunotherapy

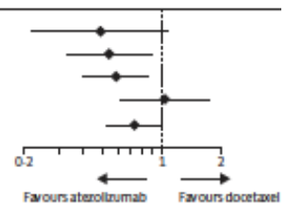
### > ph2R and ph3 Atezolizumab studies [*POPLAR-OAK*]

**F** TC0 and IC0

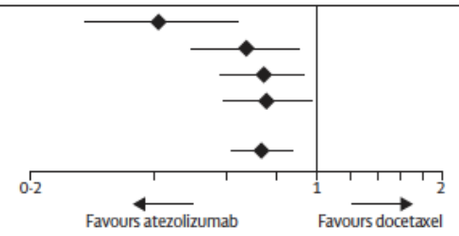



| | n (%) | HR* | 95% CI | p value | Median overall survival (months [95% CI]) | |
|---|---|---|---|---|---|---|
| | | | | | Atezolizumab (n=144) | Docetaxel (n=143) |
| TC3 or IC3 | 47 (16%) | 0·49 | 0·22–1·07 | 0·068 | 15·5 (9·8–NE) | 11·1 (6·7–14·4) |
| TC2/3 or IC2/3 | 105 (37%) | 0·54 | 0·33–0·89 | 0·014 | 15·1 (8·4–NE) | 7·4 (6·0–12·5) |
| TC1/2/3 or IC1/2/3 | 195 (68%) | 0·59 | 0·40–0·85 | 0·005 | 15·5 (11·0–NE) | 9·2 (7·3–12·8) |
| TC0 and IC0 | 92 (32%) | 1·04 | 0·62–1·75 | 0·871 | 9·7 (6·7–12·0) | 9·7 (8·6–12·0) |
| Intention to treat | 287 | 0·73 | 0·53–0·99 | 0·040 | 12·6 (9·7–16·4) | 9·7 (8·6–12·0) |




| | n (%) | Median overall survival (months) | | HR (95% CI) |
|---|---|---|---|---|
| | | Atezolizumab | Docetaxel | |
| TC3 or IC3 | 137 (16) | 20·5 | 8·9 | 0·41 (0·27–0·64) |
| TC2/3 or IC2/3 | 265 (31) | 16·3 | 10·8 | 0·67 (0·49–0·90) |
| TC1/2/3 or IC1/2/3 | 463 (54) | 15·7 | 10·3 | 0·74 (0·58–0·93) |
| TC0 and IC0 | 379 (45) | 12·6 | 8·9 | 0·75 (0·59–0·96) |
| ITT | 850 (100) | 13·8 | 9·6 | 0·73 (0·62–0·87) |



# Patient Selection

## Immunological Factors:

### Lung cancer immunotherapy

> ph1/2R Durvalumab [*study 1108 expansion*]

| | High PD-L1 (n=154) | Low PD-L1 (n=116) | Total (n=287) |
|---|---|---|---|
| RECIST response (ORR) | 39/154 (25.3%) | 7/115 (6.1%) | 50/285 (17.5%) |
| Treatment setting | | | |
| First line | 14/49 (28.6%) | 1/9 (11.1%) | 16/59 (27.1%) |
| Second line | 12/46 (26.1%) | 1/24 (4.2%) | 15/80 (18.8%) |
| ≥ Third line | 13/59 (22.0%) | 5/82 (6.1%) | 19/146 (13.0%)–19.6 |

Antonia et al, ESMO 2016

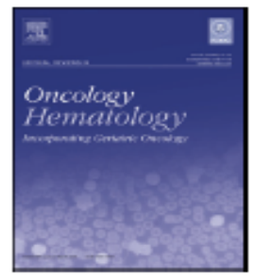
# Patient Selection

Critical Reviews in Oncology/Hematology 109 (2017) 35–41

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc



## New perspectives in the second-line treatment of non squamous NSCLC patients: Results from a large Italian Lung Cancer Working Group

Diego Cortinovis[a], Vanesa Gregorc[b], Maria Rita Migliorino[c], Maria Ida Abate[a], Anna Manzo[d], Umberto Malapelle[e], Alessandro Morabito[d,*], on behalf of The Italian Lung Cancer Working Group[1]

[a] SC Oncologia Medica asst, Monza H S Gerardo, Italy
[b] Department of Medical Oncology, IRCCS Ospedale San Raffaele, Milan, Italy
[c] UOSD Pneumologia Oncologica, Azienda Ospedaliera San Camillo-Forlanini, Roma, Italy
[d] SC Thoracic Medical Oncology Istituto Nazionale Tumori, "Fondazione G. Pascale"—IRCCS, Napoli, Italy
[e] Dipartimento di Sanità Pubblica, Università degli Studi di Napoli Federico II, Italy

# Patient Selection



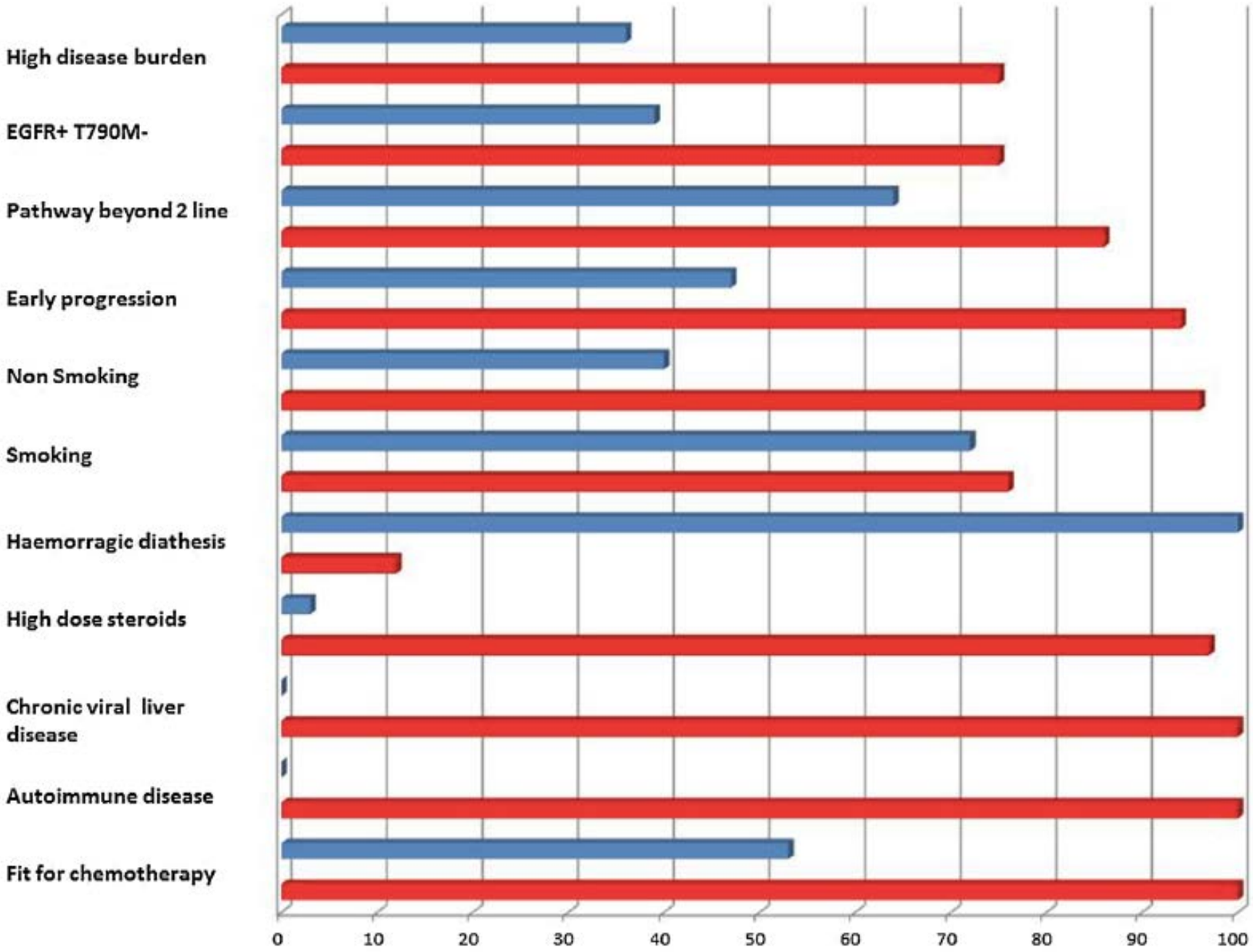



**Fig. 1.** Preferences of Panellists. Red: preference for angiogenesis inhibitor + docetaxel. Blue: preference for immunotherapy. The sum could not be 100%. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

# Patient Selection



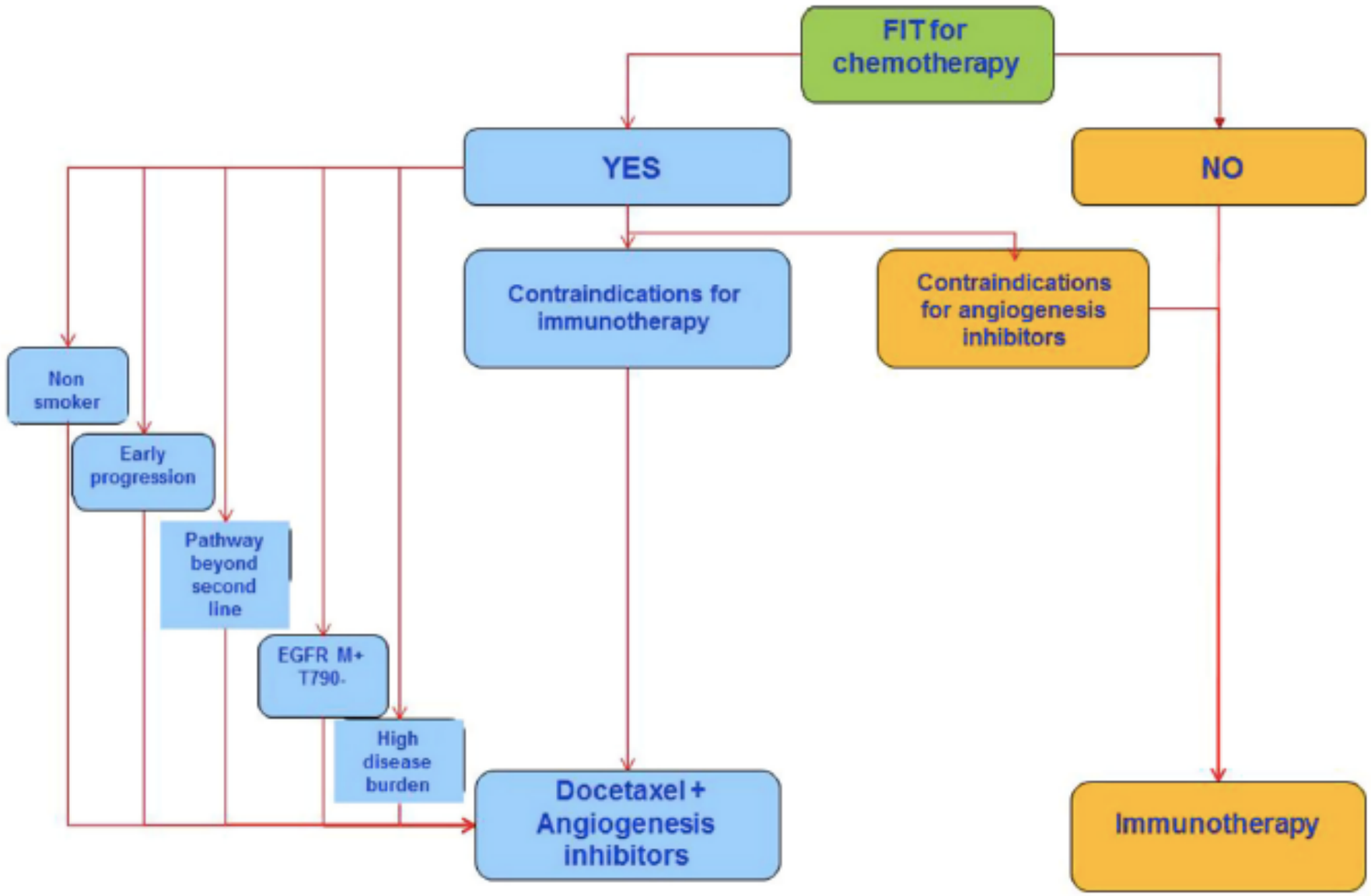



**Fig. 2.** Decision-making tree for second-line treatment of non-squamous NSCLC.

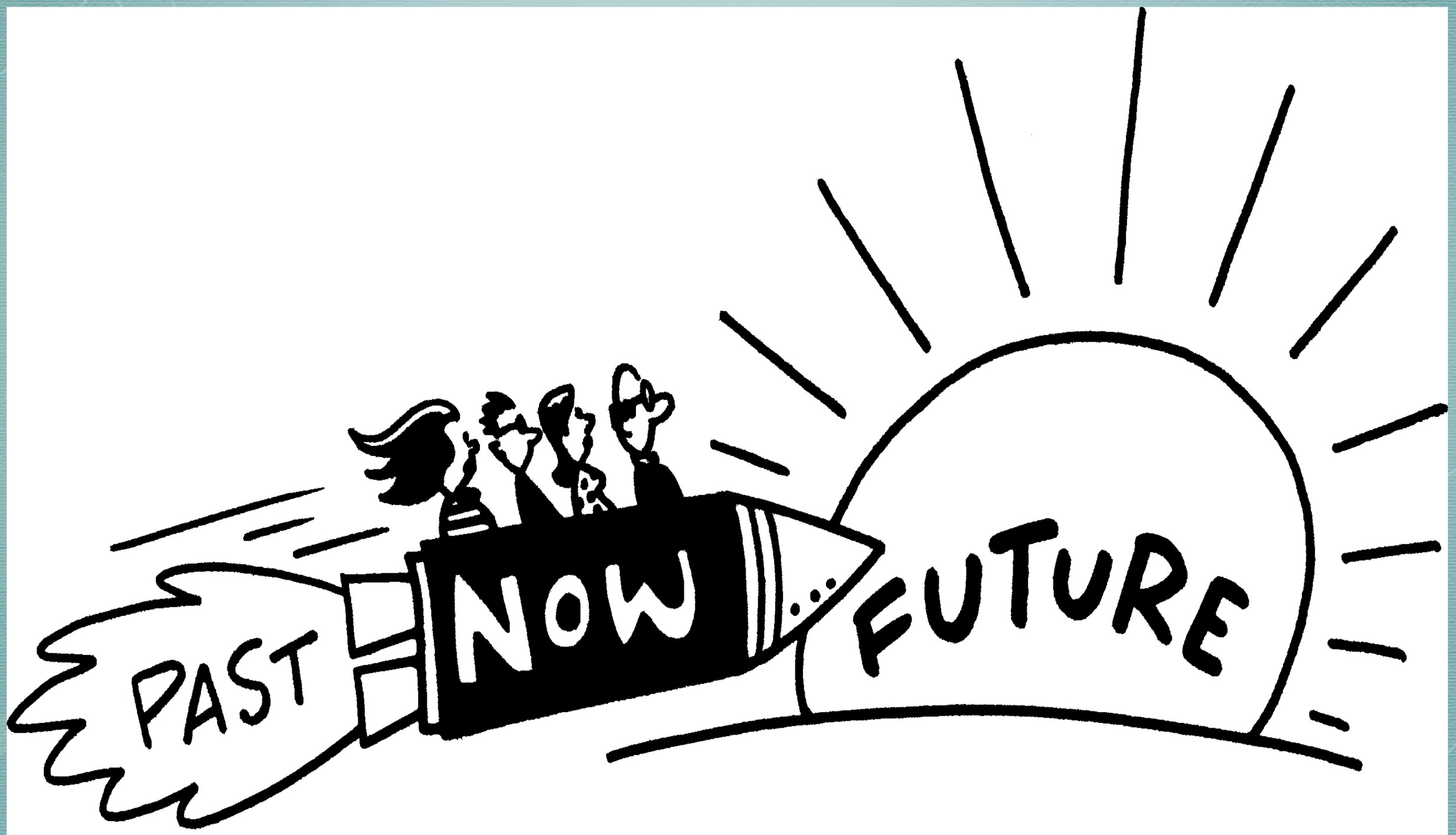
# Patient Selection

**Key points**

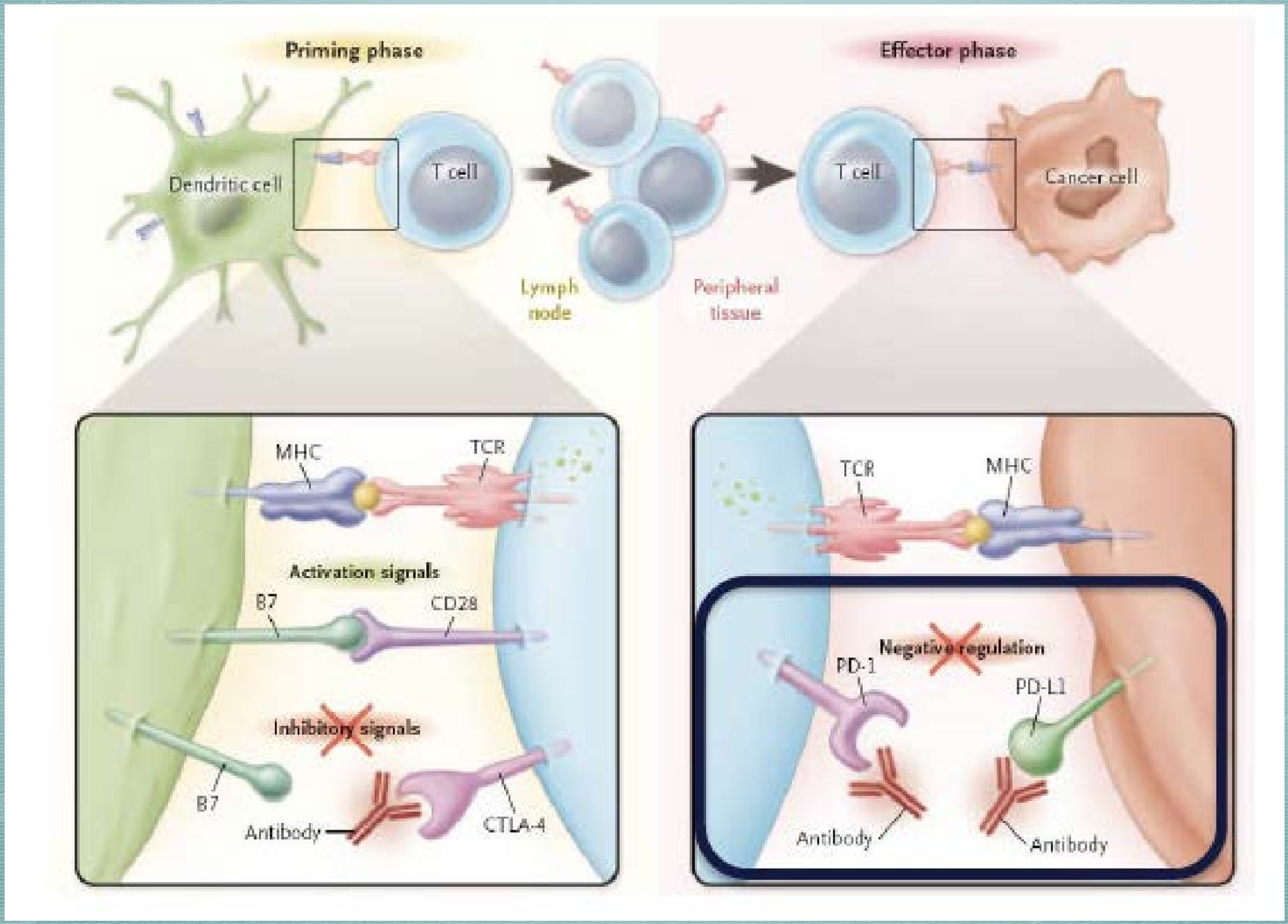
1. In non squamous NSCLC second line therapies improved median OS to 12 months thanks to the advent of antiangiogenic agents and immune check-point inhibitors
2. No established predictive factors allow the right selection of these agents in clinical practice
3. The chance to obtain the best results is associated to the employment of all drugs considered active
4. The clinical criteria that should be considered in the definition of a shared therapeutic decision in the second line setting should be: fit for chemotherapy, conditions contraindicating the use of angiogenesis inhibitors or immunotherapy, non-smoker status, early progression, therapeutic pathway expected beyond second line, EGFR mutation positive with T790 M negative resistant to TKIs and platinum based chemotherapy, high disease burden.

Cortinovis et al, Clinical reviews in Oncology/Immunology, 2017

# Future



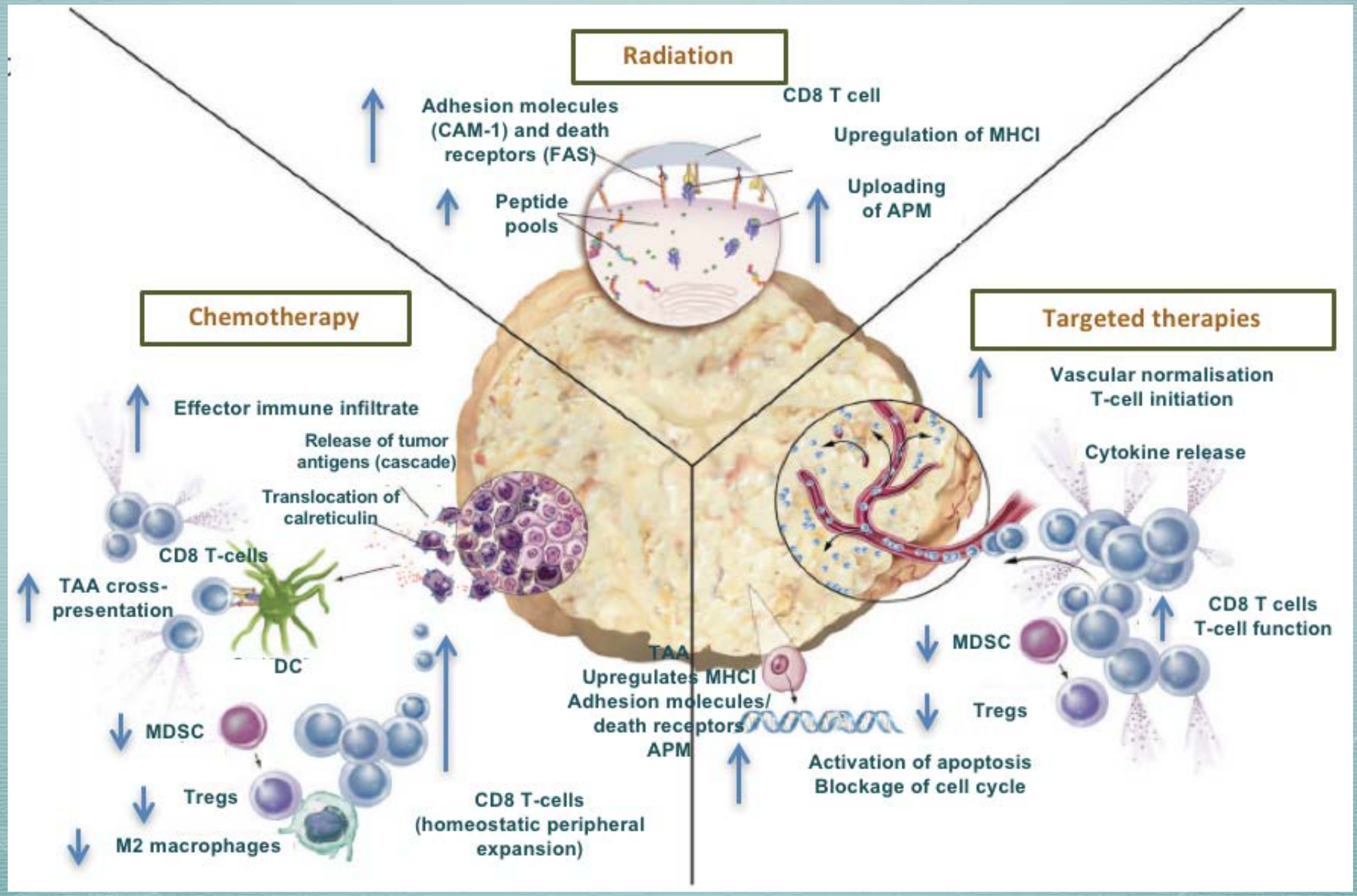
# Future




Rivas a et al, NEJM. 2012

# Future

## Rationale for Investigating Opportunities to Combine Immunotherapy With Other Therapeutic Modalities




APM = antigen processing machinery; TAA = tumor-associated antigen.

1. Adapted from Hodge JW. *Semin Oncol.* 2012;39:323–339; 2. Drake CG. *Ann Oncol.* 2012;23(suppl 8):viii41–viii46; 3. Ménard C, et al. *Cancer Immunol Immunother.* 2008;57:1579–1587; 4. Hannani D, et al. *Cancer J.* 2011;17:351–358; 5. Ribas A at al. *Curr Opin Immunol.* 2013:25:291–296.

# Future

- The impact that the new immunotherapy treatments may have on NSCLC outcomes is very exciting
- Checkpoint inhibition including PD-1 and its ligands PD-L1/PD-L2 have shown encouraging results
- Nivolumab and pembrolizumab, both PD-1 inhibitors, have recently received European licences as treatment in metastatic NSCLC
- There is hope that immunotherapy may be able to improve results in the adjuvant setting too
- Many new drugs and targeted treatments have developed in the last 10 years, which have added incremental benefits
- In the world post sequencing of the human genome, the challenge is to find relevant genes that may help us to more appropriately target our therapies
- The idea that one treatment fits all has faded. Most cancers now are being seen as many subgroups with different drivers of the oncogenic process

# Conclusions

KEEP
CALM
AND
TAKE
CONCLUSION

# Conclusions

## PD-1/PD-L1 Inhibitors in pretreated NSCLC

| | CheckMate 017 phase 3[125] | | CheckMate 057 phase 3[126] | | KEYNOTE-010 phase 3[127] | | | POPLAR phase 2[128] | | Durvalumab phase 1b[129] | Avelumab phase 1b[130] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Nivolumab | Docetaxel | Nivolumab | Docetaxel | Pembrolizumab 2 mg/kg | Pembrolizumab 10 mg/kg | Docetaxel | Atezolizumab | Docetaxel | Durvalumab | Avelumab |
| Patients (n) | 135 | 137 | 292 | 290 | 345 | 346 | 343 | 144 | 143 | 198 | 184 |
| Response rate (%) | | | | | | | | | | | |
| All patients | 20 | 9 | 19 | 12 | 18 | 19 | 9 | 15 | 15 | 16 | 14 |
| PD-L1 positive | 21 | 8 | 36 | 13 | 30 | 29 | 8 | 38 | 13 | 27 | 16 |
| PD-L1 negative | 15 | 12 | 10 | 14 | NA | NA | NA | 8 | 10 | 5 | 10 |
| Median progression-free survival (months) | | | | | | | | | | | |
| All patients | 3·5 | 2·8 | 2·3 | 4·2 | 3·9 | 4·0 | 4·0 | 2·7 | 3·0 | NA | 2·9 |
| PD-L1 positive | 4·8 | 3·1 | 5·0 | 3·8 | 5·0 | 5·2 | 4·1 | 2·8 | 3·0 | NA | 3·0 |
| PD-L1 negative | 4·2 | 2·9 | 2·1 | 4·2 | NA | NA | NA | 1·7 | 4·1 | NA | 1·4 |
| Median overall survival (months) | | | | | | | | | | | |
| All patients | 9·2 | 6·0 | 12·2 | 9·4 | 10·4 | 12·7 | 8·5 | 12·6 | 9·7 | NA | 8·9 |
| PD-L1 positive | 10 | 6·4 | 19·4 | 8·1 | 14·9 | 17·3 | 8·2 | 15·5 | 9·2 | NA | 8·4 |
| PD-L1 negative | 8·5 | 6·1 | 9·8 | 10·1 | NA | NA | NA | 9·7 | 9·7 | NA | 4·6 |
| Histology | SCC | SCC | Non-SCC | Non-SCC | All comers | All comers | All comers | All comers | All comers | All comers | All comers |
| Setting | Second line | Second line | Second line | Second line | Second line | Second line | Second line | Second line | Second line | Pre-treated | Pre-treated |
| PD-L1 expression | | | | | | | | | | | |
| Positive | ≥5% | ≥5% | ≥5% | ≥5% | Highly positive ≥50%; positive ≥1% | Highly positive ≥50%; positive ≥1% | Highly positive ≥50%; positive ≥1% | Tumour cell 1–3 or tumour-infiltrating immune cells 1–3 | | ≥25% | ≥1% |
| Negative | <5% | <5% | <5% | <5% | <1% (not included) | <1% (not included) | <1% (not included) | Tumour cell 0 and tumour-infiltrating immune cells 0 | | <25% | <1% |

Percentages rounded. PD-1=programmed death-1. PD-L1=programmed death ligand-1. SCC=squamous cell cancer. NA=not available.

*Table 4*: Trials of anti-PD-1/PD-L1 inhibitors in patients with advanced NSCLC who were pre-treated with chemotherapy

Hirsch et al. Lancet 2015

# Conclusions

## Summary of phase III studies of immunotherapy in previously treated patients

| | **CheckMate 017**[1] Nivolumab vs docetaxel | **CheckMate 057**[1] Nivolumab vs docetaxel | **KEYNOTE-010**[2] Pembrolizumab (2mg/kg or 10mg/kg) vs docetaxel | **OAK**[3] Atezolizumab vs docetaxel |
|---|---|---|---|---|
| **Phase of study** | III | III | II/III | III |
| **PD-L1 selected** | No | No | Yes (TPS* ≥1%) | No |
| **Study size, n** | 272<br>(135 vs 137) | 582<br>(292 vs 290) | 1,033<br>(344 vs 346 vs 343) | 1,225<br>(425 vs 425)* |
| **Histology** | Squamous | Non-squamous | All-comers | All-comers |
| **Line of therapy, %**<br>2L<br>3L<br>>3L<br>Other/unknown | <br>100<br>0<br>0<br>0 | <br>88<br>11<br><1<br>0 | <br>69<br>20<br>9<br><1 | <br>75<br>25<br>0<br>0 |
| **Subsequent CIT (immunotherapy arm vs chemo arm), %** | <1 vs 2 | 1 vs 2 | 0.6 vs 1.7 vs 13.1 | 4.5 vs 17.2 |
| **Crossover from chemo arm to study immunotherapy, %** | 4 | 6 | Not permitted | Not permitted |
| **Median OS, months**<br>**HR vs docetaxel (p value)** | 9.2 vs 6.0<br>0.62 (p=0.0004) | 12.2 vs 9.5<br>0.75 (p<0.001) | 10.4 vs 12.7 vs 8.5<br>2mg/kg: 0.71 (p=0.0008)<br>10mg/kg: 0.61 (p<0.0001) | 13.8 vs 9.6<br>0.73 (p=0.0003) |

* *850 in primary population
NR = not reached

# Take Home Messages

"one size fits all"…fits no one

# Take Home Messages

## Therapeutic Sequence

# Take Home Messages

## Personalized therapy

# Grazie per l'attenzione