Immunotherapy for Lung Cancer

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Presenter Disclosure

- **Faculty:** David Dawe, MD FRCPC

- **Relationships with commercial interests in last 12 months:**
  - **Grants/Research Support:** None
  - **Speakers Bureau/Honoraria:** Merck and AstraZeneca Advisory Boards
  - **Consulting Fees:** None
  - **Other:** None

Mitigating Potential Bias

- I have referred only to immunotherapy treatments with randomized controlled trial evidence
- I have listed all immunotherapy agents available
- I have used generic names (except on one slide)
- I have created these slides myself, with no input from Pharma

Objectives

At the end of the workshop, participants will be able to:

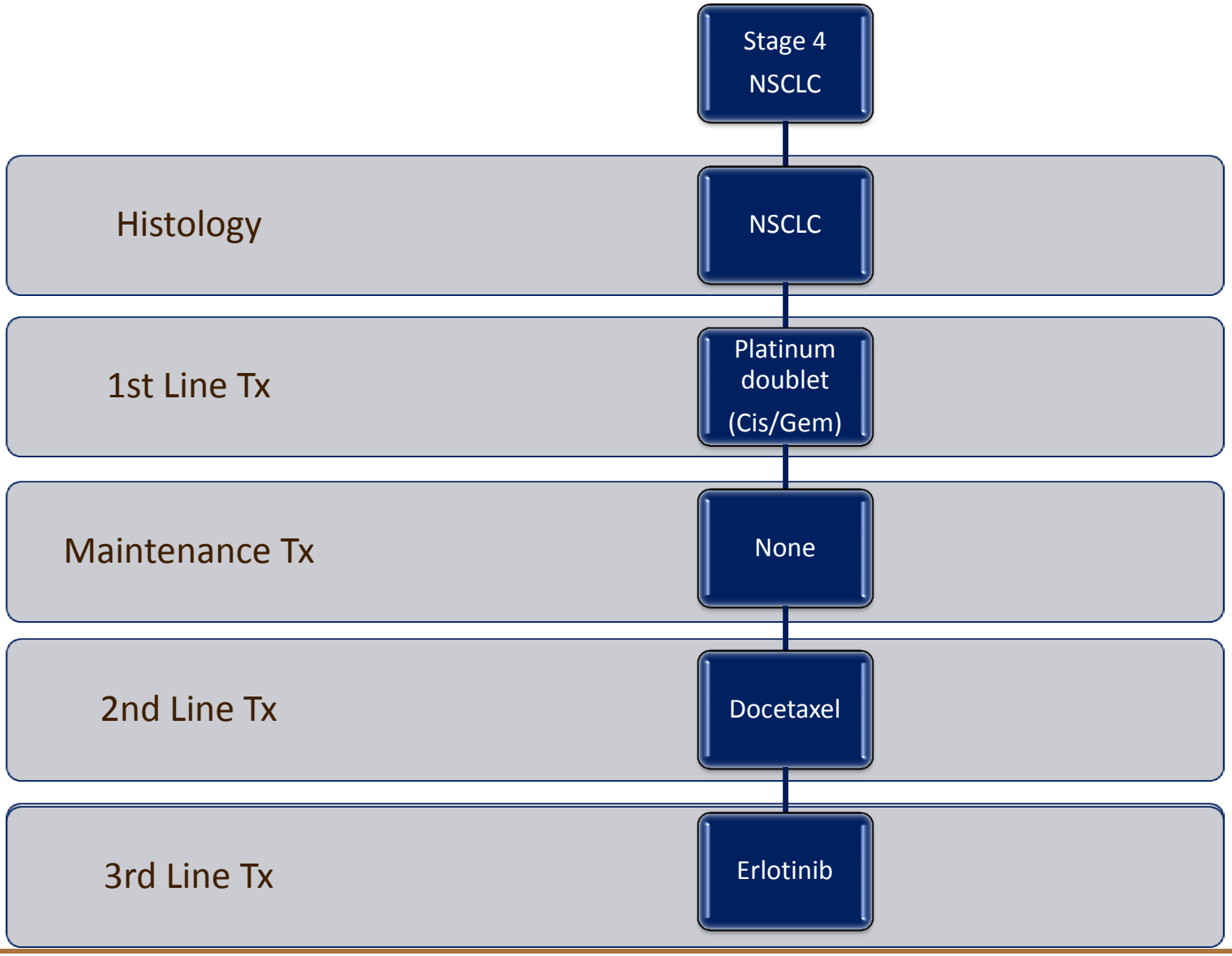
- Understand the mechanism of immuno-oncology agents
- Describe where immunotherapy fits within the treatment of NSCLC
- Identify the most common side effects
- Describe management approaches for immune related side effects, including when to call the oncologist

How do we define lung cancer?

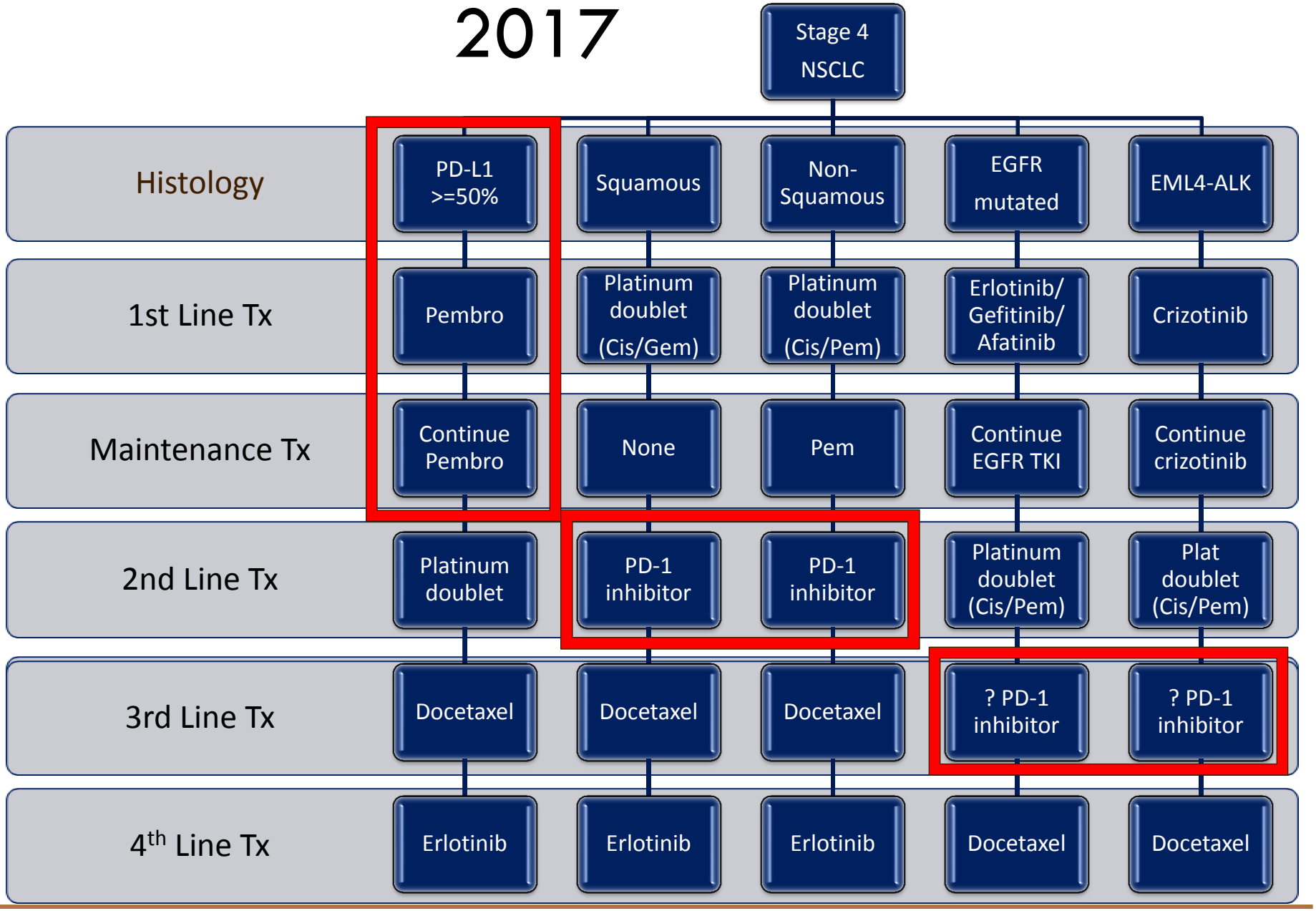
- Non-small cell lung cancer (85%)
  - Adenocarcinoma (50%)
  - Squamous cell (20%)
  - Large cell (10%)
- Small cell carcinoma (15%)
- Mesothelioma

- Remember, ~15% of lung cancers occur in non-smokers – usually adenocarcinomas

2005


Stage 4 NSCLC
Histology
NSCLC
1st Line Tx
Platinum doublet (Cis/Gem)
Maintenance Tx
None
2nd Line Tx
Docetaxel
3rd Line Tx
Erlotinib

2017


Stage 4 NSCLC
Histology
PD-L1 >=50%
Squamous
Non-Squamous
EGFR mutated
EML4-ALK
1st Line Tx
Pembro
Platinum doublet (Cis/Gem)
Platinum doublet (Cis/Pem)
Erlotinib/ Gefitinib/ Afatinib
Crizotinib
Maintenance Tx
Continue Pembro
None
Pem
Continue EGFR TKI
Continue crizotinib
2nd Line Tx
Platinum doublet
PD-1 inhibitor
PD-1 inhibitor
Platinum doublet (Cis/Pem)
Plat doublet (Cis/Pem)
3rd Line Tx
Docetaxel
Docetaxel
Docetaxel
? PD-1 inhibitor
? PD-1 inhibitor
4th Line Tx
Erlotinib
Erlotinib
Erlotinib
Docetaxel
Docetaxel

Evolving Beyond Cytotoxics

- Most new therapies over the last 5 years fall into the categories of targeted therapy and immunotherapy

- Targeted therapies
  - Interferes with a driver mutation

- Immunotherapy
  - Upregulate the immune system to fight cancer

Immunotherapy

- Invasive cancers have evaded the immune system during development
- If the immune system can be upregulated or cancer cells be made visible, your body can combat the cancer itself
- May avoid toxicity and provide a prolonged control or elimination of cancer cells

Immune Checkpoint Inhibitors

- CTLA-4
  - Ipilimumab (Yervoy)
  - Tremelimumab
- PD1
  - Nivolumab (Opdivo)
  - Pembrolizumab (Keytruda)
- PD-L1
  - Atezolizumab (Tecentriq)
  - Durvalumab (Imfinzi)
  - Avelumab (Bavencio)

PD-1 inhibitors

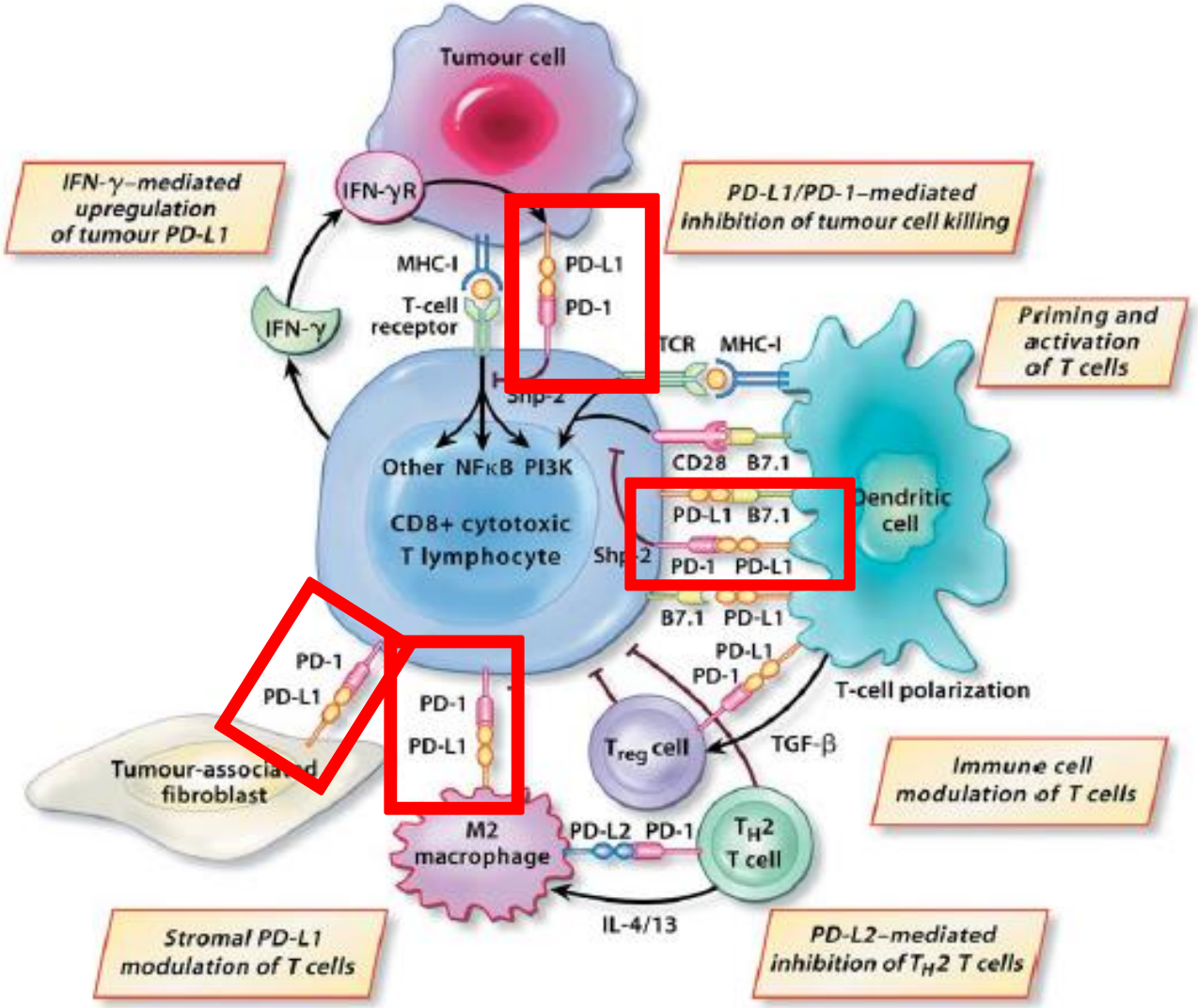
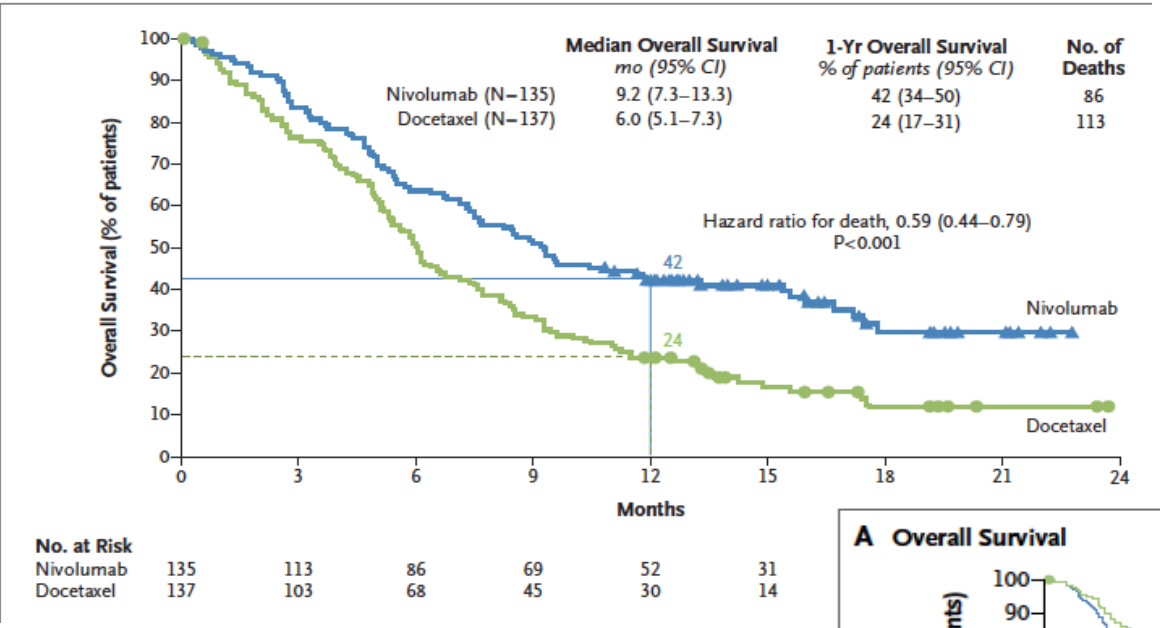


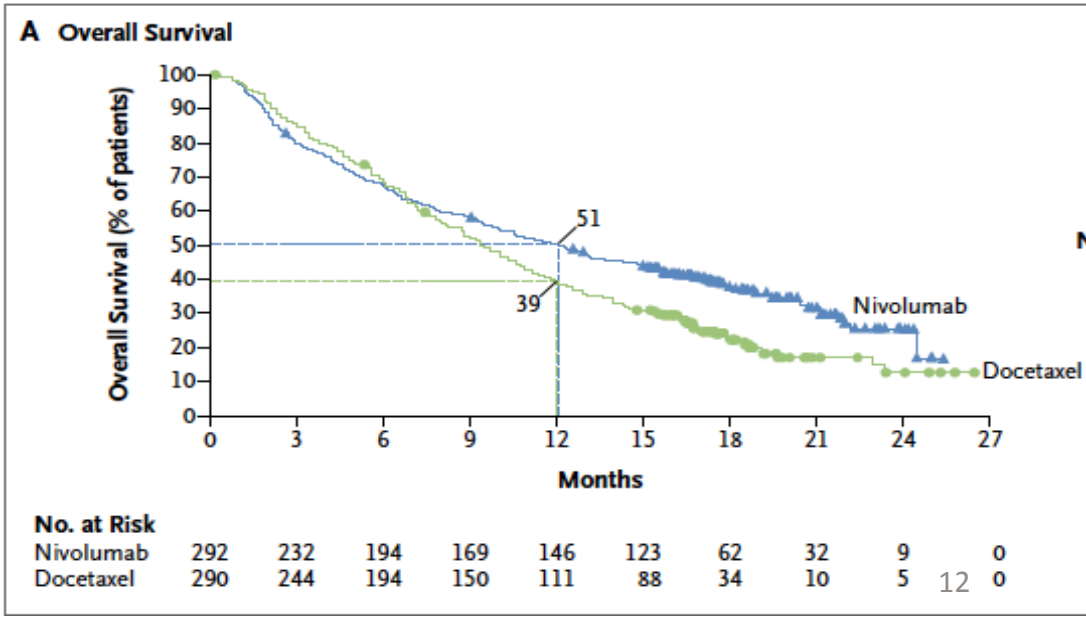
Figure 1. *Tumor immunology and the PD-1/PD-L1 pathway (modified after 11).*

ANTICANCER RESEARCH 35: 5745-5758 (2015)

Nivolumab 2nd line example



Squamous
HR 0.59 (0.44–0.79)
P<0.001
Median OS 9.2 v 6 mo



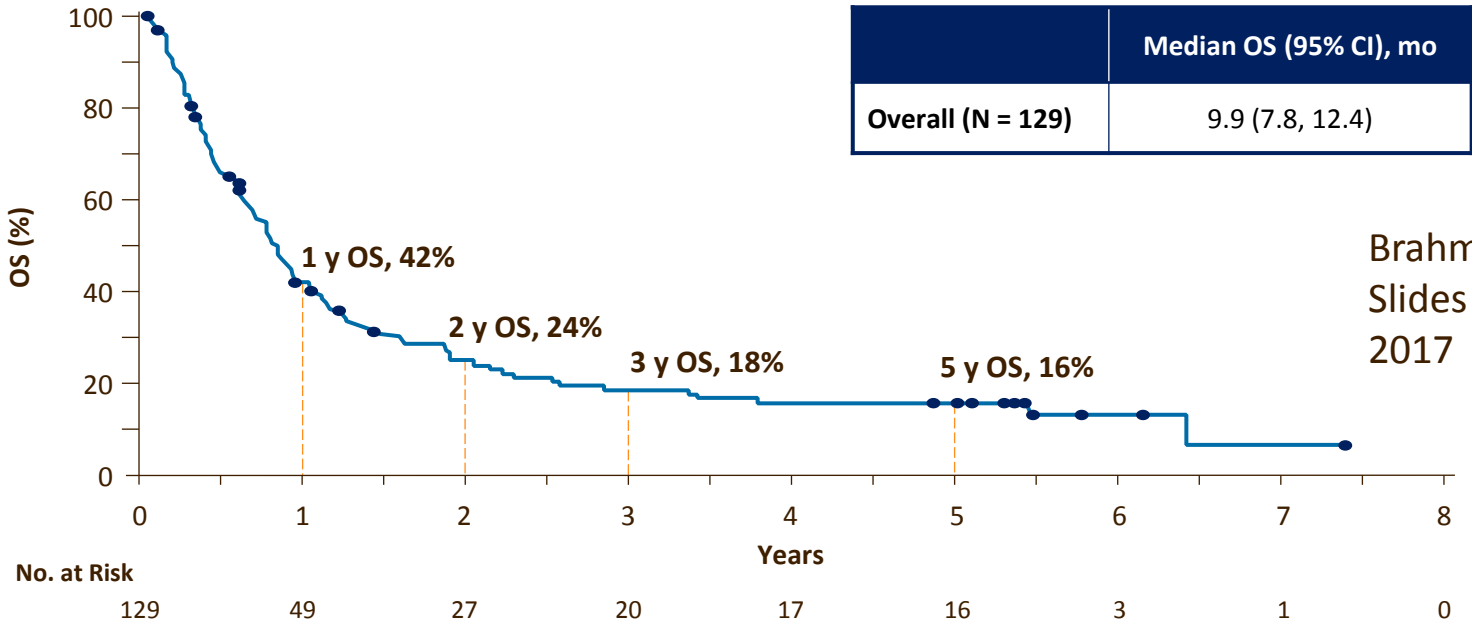
Non-squamous
HR 0.73 (0.59–0.89)
P=0.002
Median OS 12.2 v 9.4 mo

Immune Toxicity

	Squamous		Non-Squamous	
Side Effect	Any Grade N (%)	Grade 3+ N (%)	Any Grade N (%)	Grade 3+ N (%)
Hypothyroid	5 (4)	0 (0)	19 (7)	0 (0)
Diarrhea/Colitis	11 (8)	1 (1)	22 (8)	2 (1)
Hepatic	2 (2)	0 (0)	9 (3)	1 (<1)
Pneumonitis	7 (5)	1 (1)	8 (3)	3 (1)
Renal	4 (3)	1 (1)	5 (2)	0 (0)
Skin	12 (9)	0 (0)	27 (9)	1 (<1)
Infusion Reaction	1 (1)	0 (0)	8 (3)	0 (0)

Does it work?

- In people who's cancer has progressed after previous treatment with chemotherapy
  - Tumor shrinkage in 15-20%, some long-lasting
  - Improves length of life and quality of life
  - Good studies show this with 3 different drugs – 2 available in MB

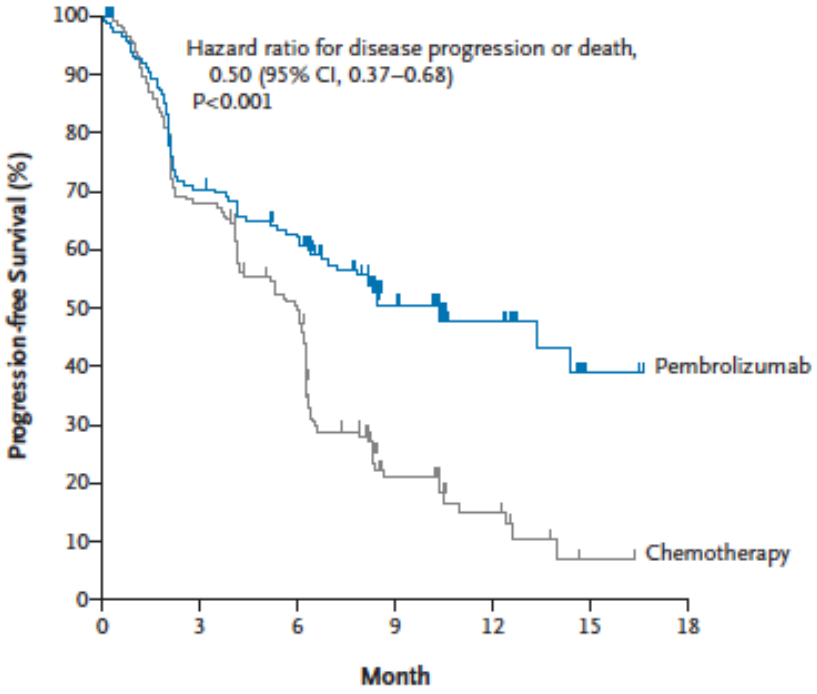


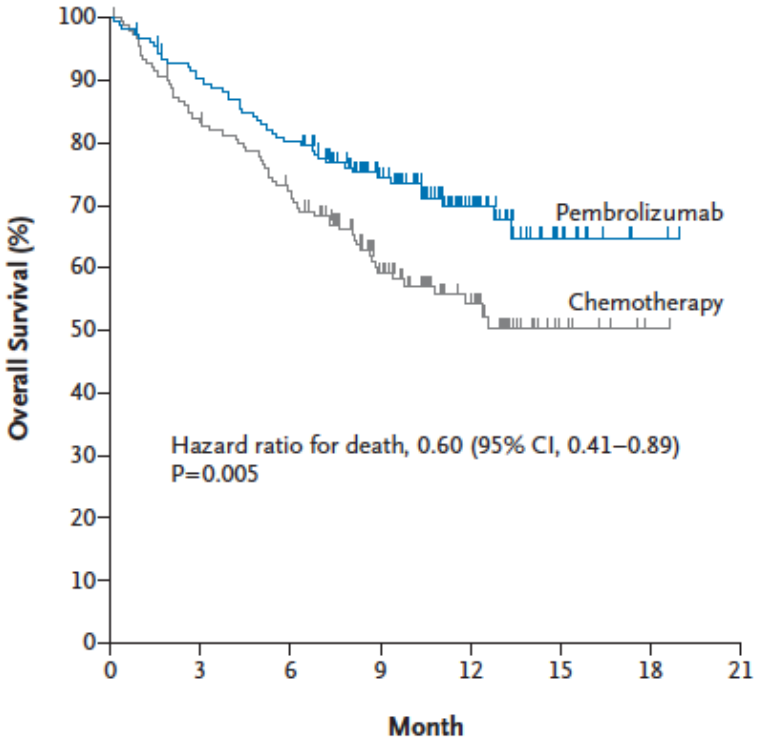
	Median OS (95% CI), mo
Overall (N = 129)	9.9 (7.8, 12.4)

Brahmer at al. Slides from AACR 2017

1st line Pembrolizumab

Only for those whose tumour has PD-L1 >=50%





Reck M. NEJM 2016

Toxicity

Table 3. Adverse Events in the As-Treated Population.*

Adverse Event	Pembrolizumab Group (N=154)		Chemotherapy Group (N=150)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
	number of patients (percent)			
Treatment-related†				
Any	113 (73.4)	41 (26.6)	135 (90.0)	80 (53.3)
Serious	33 (21.4)	29 (18.8)	31 (20.7)	29 (19.3)
Led to discontinuation	11 (7.1)	8 (5.2)	16 (10.7)	9 (6.0)
Led to death	1 (0.6)	1 (0.6)	3 (2.0)	3 (2.0)

Reck M. NEJM 2016

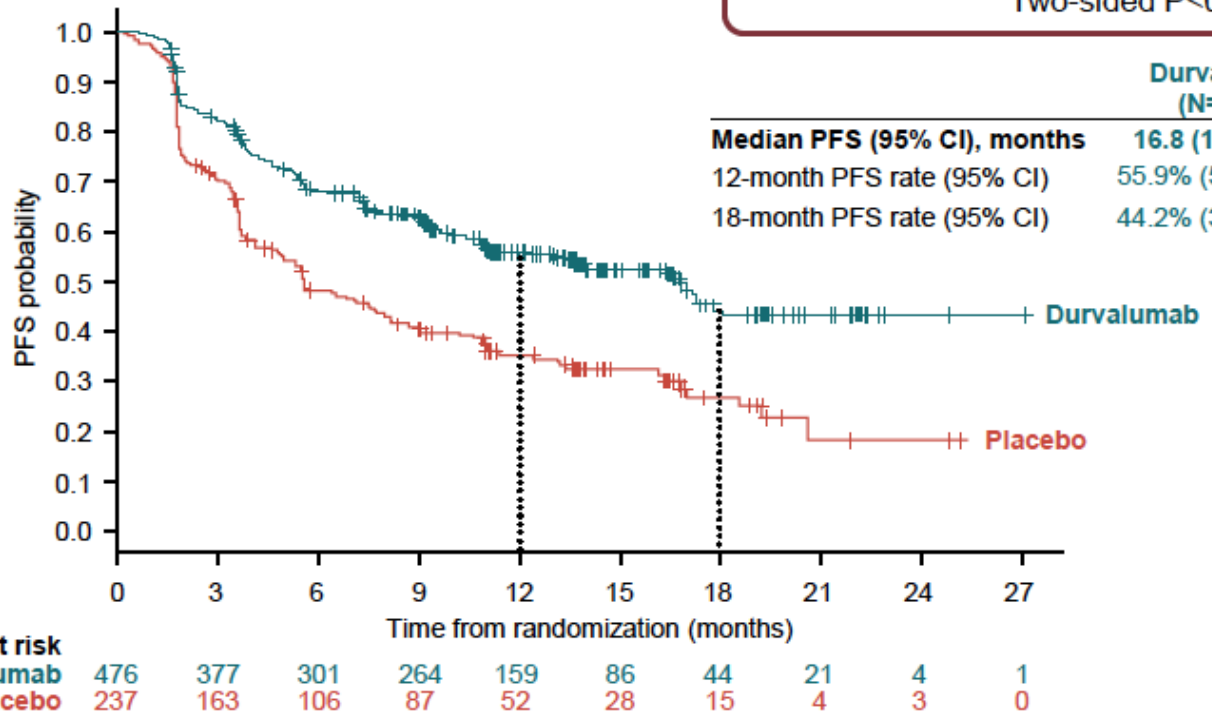
PACIFIC – Durvalumab Post-CRT

MADRID 2017 ESMO congress

PFS by BICR (Primary Endpoint; ITT)

Stratified hazard ratio, 0.52 (95% CI, 0.42–0.65)
Two-sided P<0.0001

	Durvalumab (N=476)	Placebo (N=237)
Median PFS (95% CI), months	**16.8 (13.0–18.1)**	**5.6 (4.6–7.8)**
12-month PFS rate (95% CI)	55.9% (51.0–60.4)	35.3% (29.0–41.7)
18-month PFS rate (95% CI)	44.2% (37.7–50.5)	27.0% (19.9–34.5)



NOT YET HEALTH CANADA APPROVED FOR THIS INDICATION

BICR, blinded independent central review; CI, confidence interval; ITT, intention-to-treat; PFS, progression-free survival

Paz-Ares. ESMO 2017 slides

Pneumonitis or Radiation Pneumonitis

Pneumonitis (grouped terms) or radiation pneumonitis, n (%)*	Durvalumab (N=475)	Placebo (N=234)
Any grade	161 (33.9)	58 (24.8)
Grade 3/4	16 (3.4)	6 (2.6)
Grade 5	5 (1.1)	4 (1.7)
Leading to discontinuation	30 (6.3)	10 (4.3)

- Very interesting trial with suggestion of benefit
- Manageable toxicity

- Ideally need to wait for overall survival data

Paz-Ares. ESMO 2017 slides

Immune Related Adverse Events (irAEs)

- Effective management of irAEs is based on:
  - Early recognition
  - Frequent monitoring
  - Use of corticosteroids (and/or other immunosuppressive therapies) combined with either delaying or discontinuing

- Patient Education
  - Note how they feel prior to starting treatment, any change advise patient to call
  - Treating early, may help them remain on therapy

Example I-O Drug Related Symptoms

Pulmonary **New or Worsening** **• Shortness of breath** **• Dyspnea on exertion** **• Decrease in pulse oximetry** **• Cough** **• Wheezing**	**Gastrointestinal** **• Any changes in normal bowel habits** **• Diarrhea** **• Blood or mucus in stool** **• Constipation** **• Stomach pain/cramps** **• Nausea** **• Vomiting** **• Weight loss**	**Endocrine** **• Headache** **• Fatigue/weakness** **• Severe dehydration** **• Shock** **• Behavioral changes** **• Electrolyte disturbances** **• Hypotension** **• Heart rate and rhythm abnormalities**
Hepatic • Liver function tests (LFTs) abnormalities, including elevations in AST, ALT, T. Bili • Jaundice	Eyes • Inflammation of the tissues of the eye (conjunctivitis, uveitis, iritis, episcleritis) • Visual field defects	Constitutional • Fever • Fatigue
Skin • Pruritus • Rash • Peeling • Skin excoriations	Neurological • Sensory neuropathy • Motor neuropathy	Renal • Creatinine abnormalities

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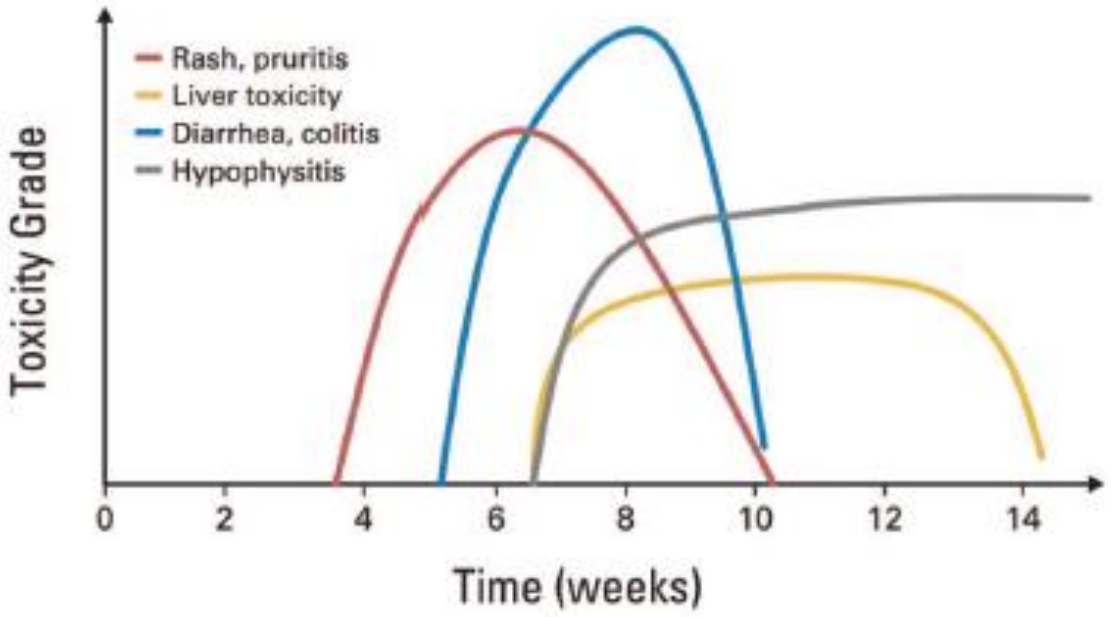
Timing

FIGURE 1. Kinetics of Appearance of Immune-Related Adverse Events



Postow MA. ASCO Education Book 2015

Toxicity Evaluation - CTCAE

In General	
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death due to the adverse event

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

National Cancer Institute CTCAE v4, 2009

General Rules for Immune-Related AEs

Grade	Management	Continue the study drug?
Low	Delay the dose (Steroids if persistent)	Resume I-O drug when AEs resolve to grade ≤ 1 or baseline
Moderate ~ High	Administer Corticosteroids ± Immunosuppressants (anti-TNF, mycophenolate, etc)	Discontinue I-O drug permanently (Delay in some situations)

Remember: Keep non-inflammatory causes in mind.
Don't assume! Don't delay treatment either!

Call the oncologist if unsure OR moderate-high grade!

Algorithm for Suspected GI Toxicity

Infectious causes to be ruled out! Opiates / narcotics may mask symptoms of perforation! No infliximab in case of perforation / sepsis!

Grade of Diarrhea/Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea: < 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated < 24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 305 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥ 7 stools per day over baseline; incontinence; IV fluids indicated ≥ 24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

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Take Home Messages

- Immune checkpoint inhibitors (immunotherapy) represent an exciting new treatment for lung cancer
- In specific settings, they are more effective than traditional chemotherapy

- While toxicity is less common than with cytotoxic chemo, these patients can still get serious toxicity
- Steroids are the mainstay of treatment for immune-related adverse events from immunotherapy!

- Early recognition and treatment is essential!

Any Questions?