Lung cancer Immunotherapy 2018 update

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Financial Disclosures: None

Objectives

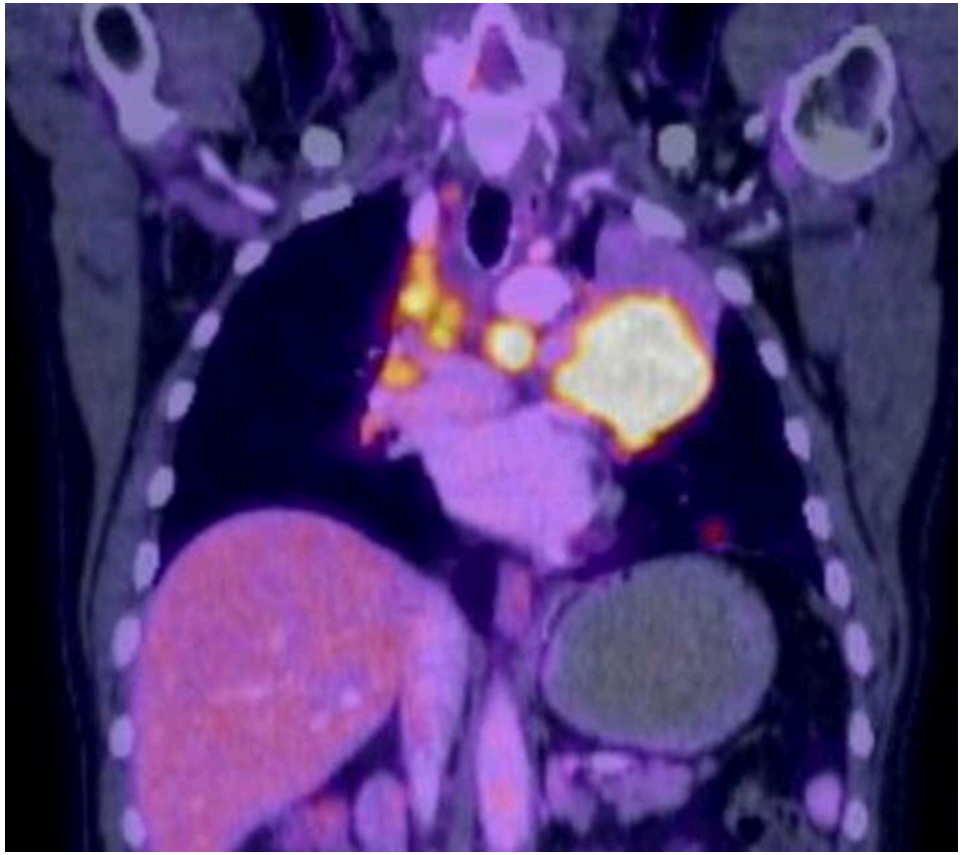
- How does immunotherapy work.
- Updates on trials for advanced non-small cell and small cell lung cancers.
- Predictors for response.
- Promising results for earlier stages.
- Managing side effects.

Case study

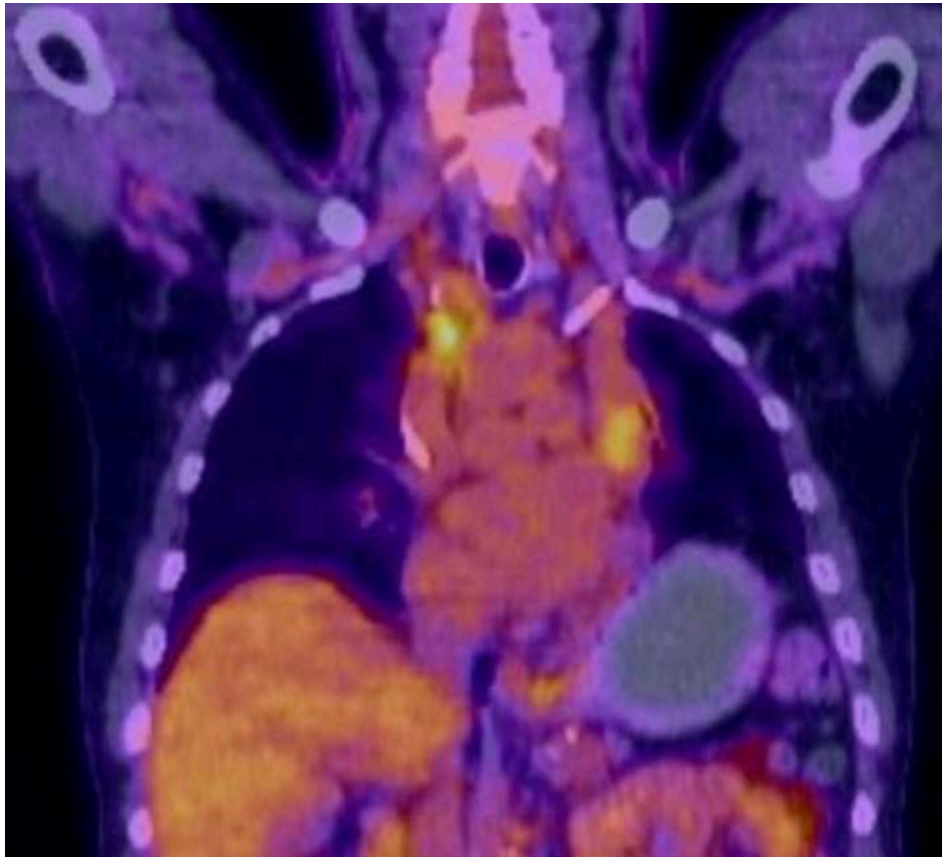
- 68 yo with HTN and COPD smoked 2 ppd for 35 years.
- Presented with dyspnea and cough/ mild hemoptysis. CXR showed **left hilar mass**.
- Bronchoscopy and mediastinoscopy confirmed **lung squamous cell carcinoma**.
- PET scan showed large left upper lobe lung mass with invasion of upper lobe bronchus, mediastinum. Hypermetabolic mediastinal, bilateral hilar, bilateral internal mammary chains. Biopsy from the latter showed squamous cell carcinoma. **PD-L1 100%. Stage IV**.

- He underwent **radiation to LUL** (part of clinical trial) and started on **pembrolizumab**.

Case study

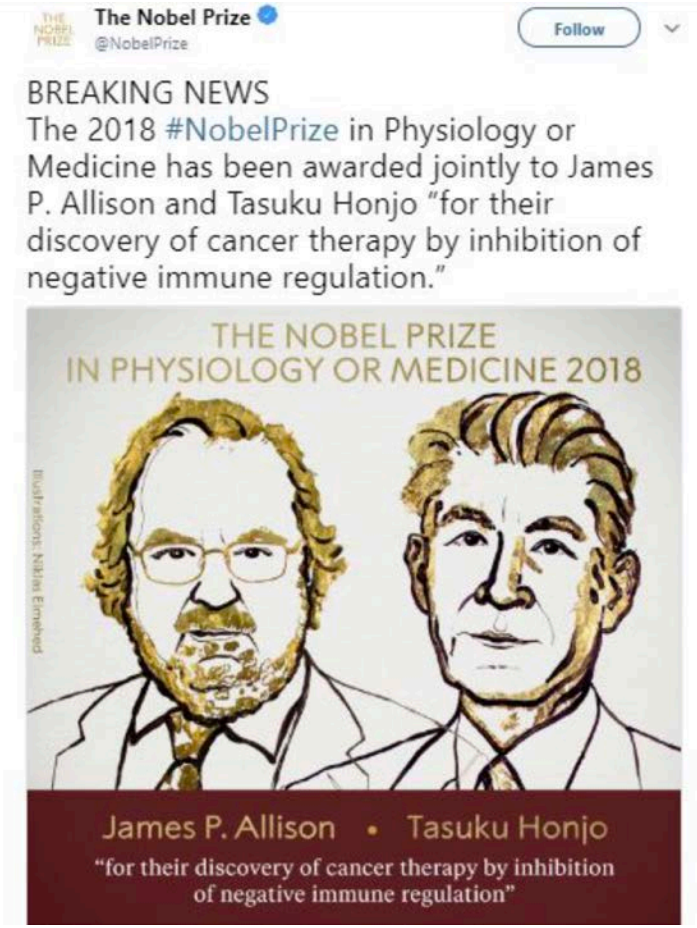


July 2017



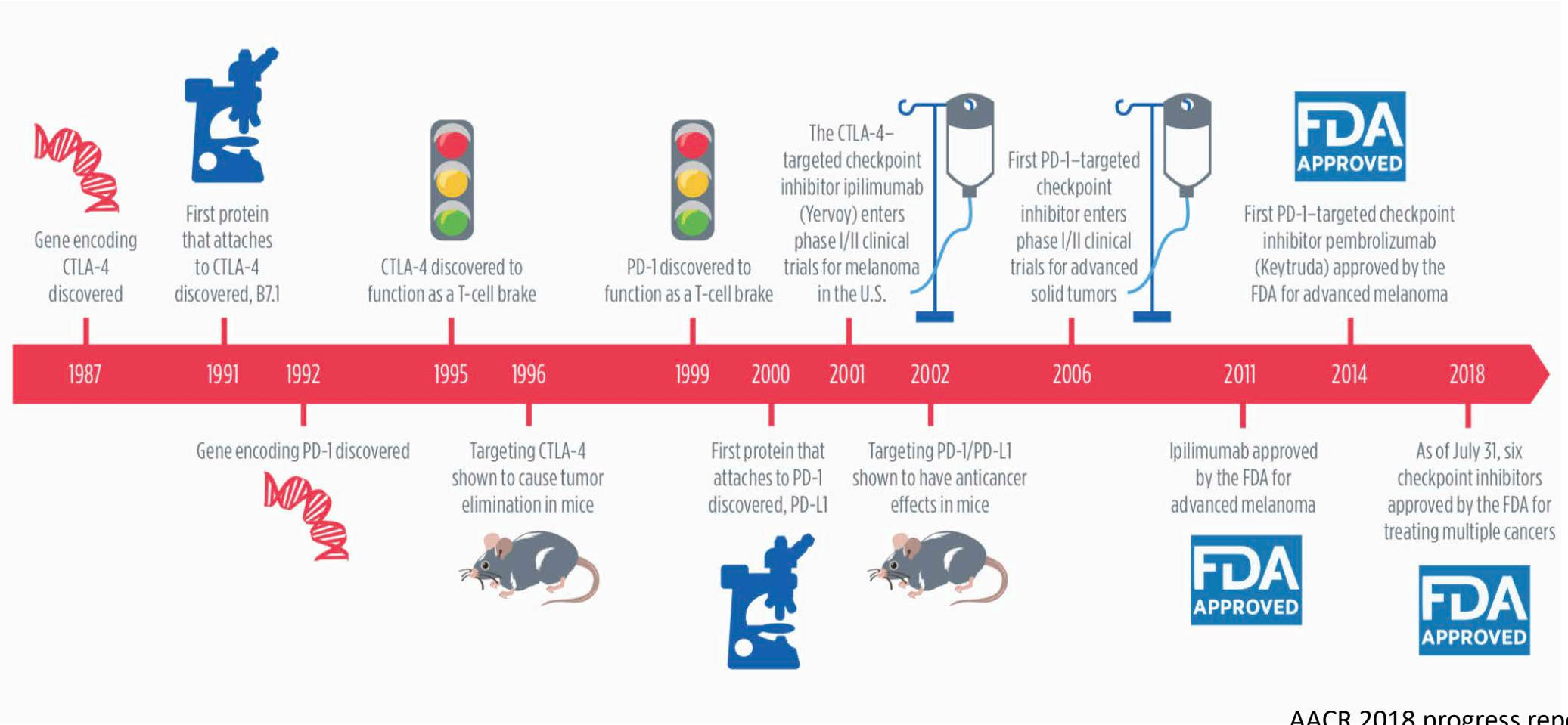
July 2018

Immunotherapy: A breakthrough in cancer therapy



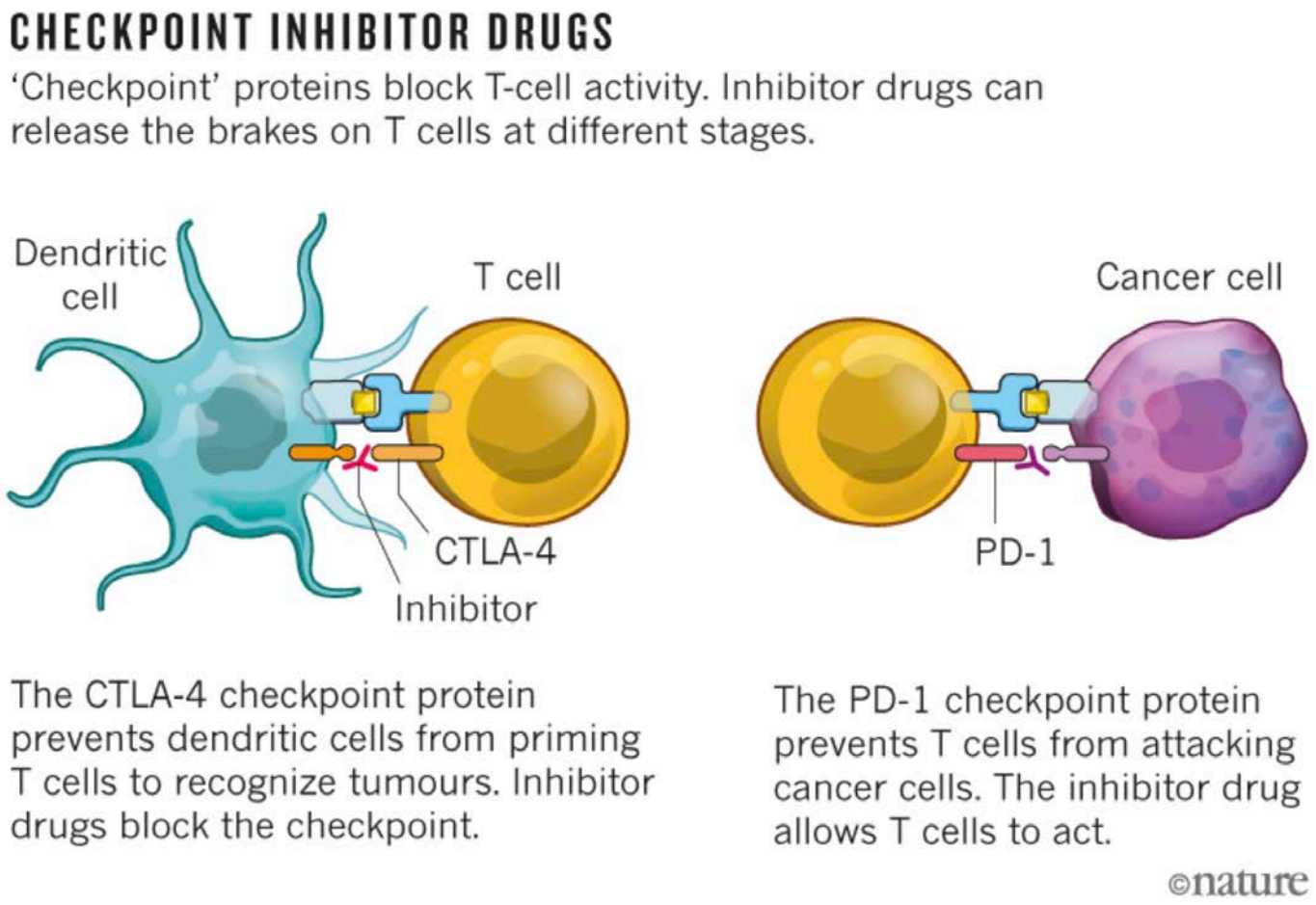
"I was like, 'Oh my God, it happened,'" Allison says to TIME. "I'm just in shock, I guess."

The journey

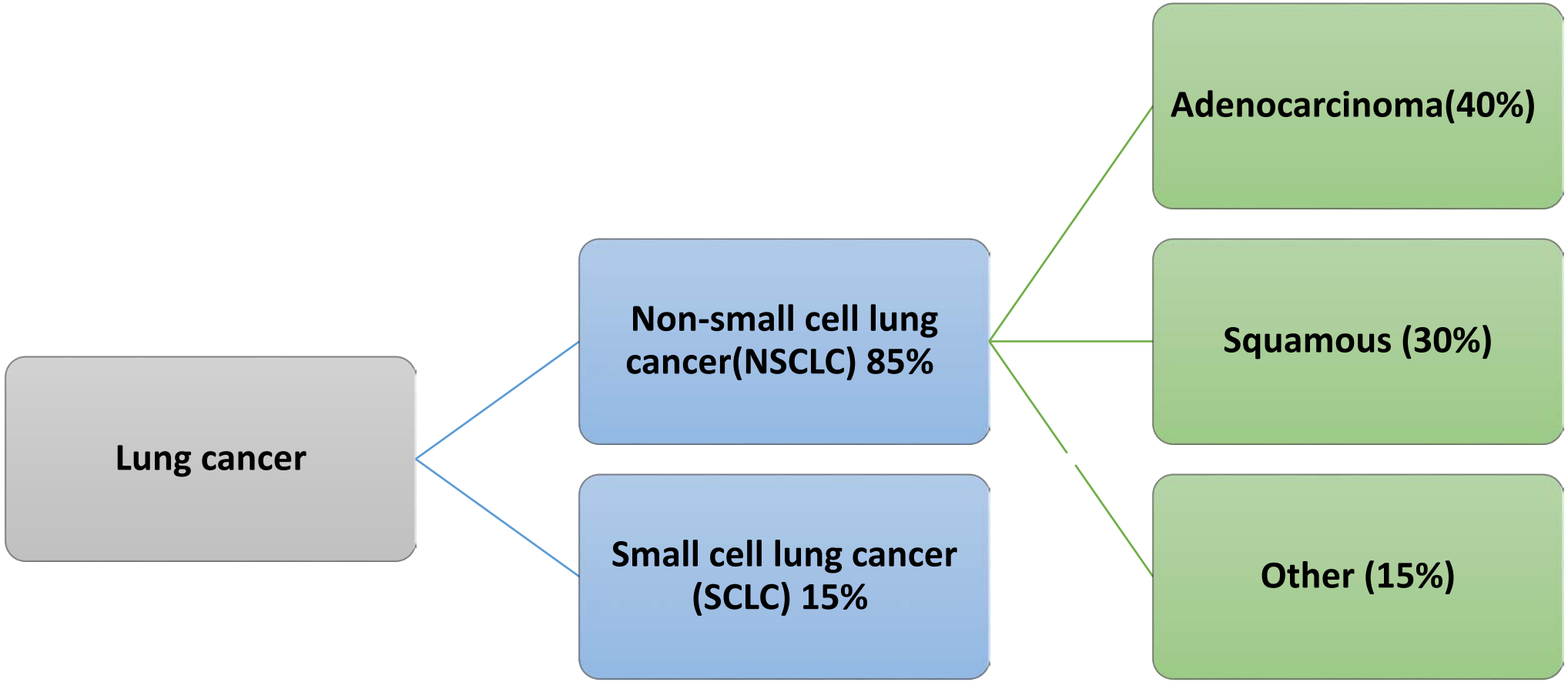


AACR 2018 progress report

Taking the brakes off



Lung Cancer by Histology



Lung cancer treatment: Overview

Stage I

Surgery +/- chemo for high risk patients

Localized radiation if can't have surgery

Stage II

Surgery then platinum doublet chemo

Stage III

IIIA Chemo-radiation --> surgery

IIIB and IIIC: Definitive chemo-radiation --> **Immunotherapy(IO)**

Stage IV

Depending on biomarkers

Biologics, **Immunotherapy,** Platinum doublet, or combination

SCLC

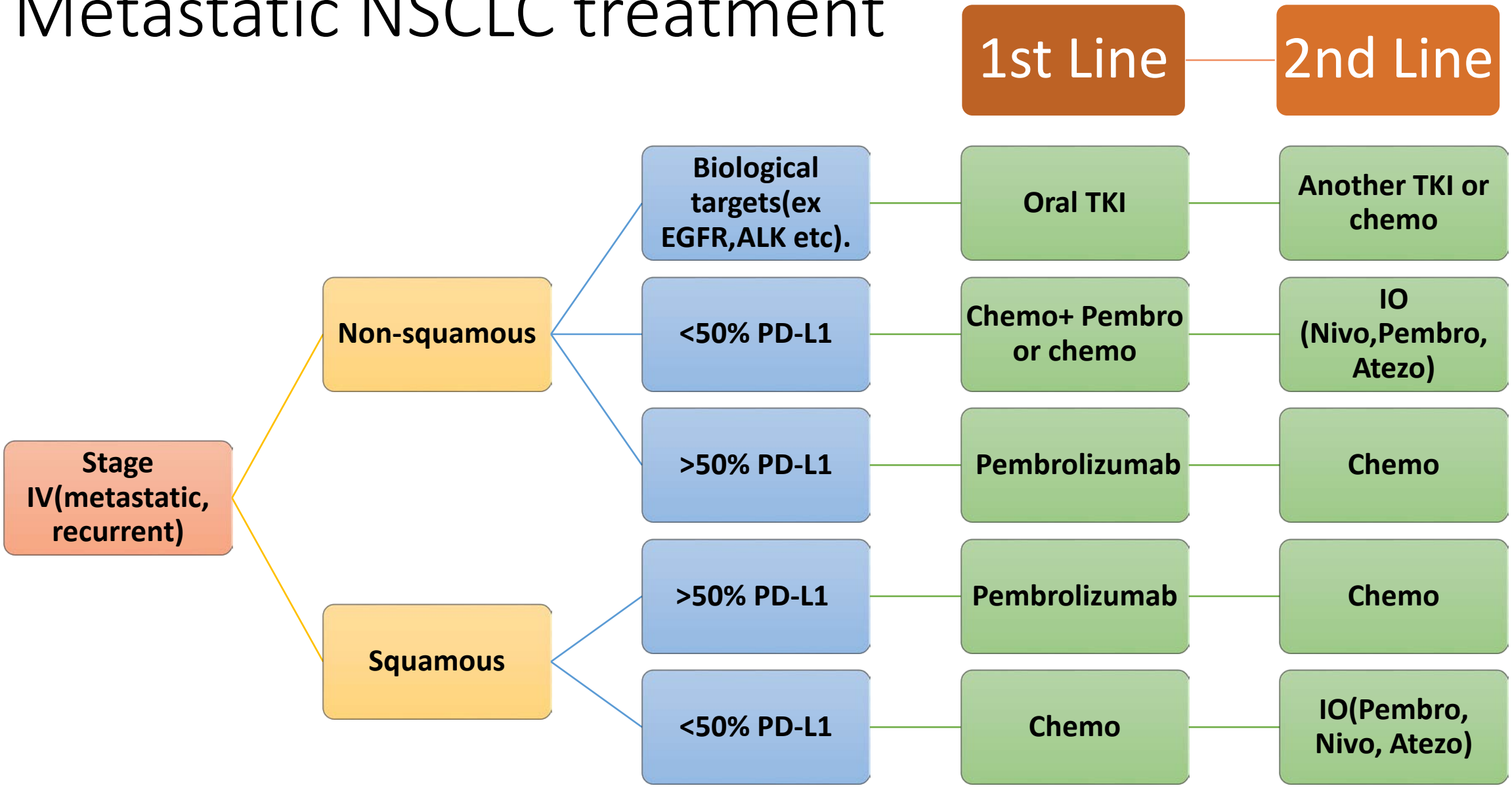
Limited Stage

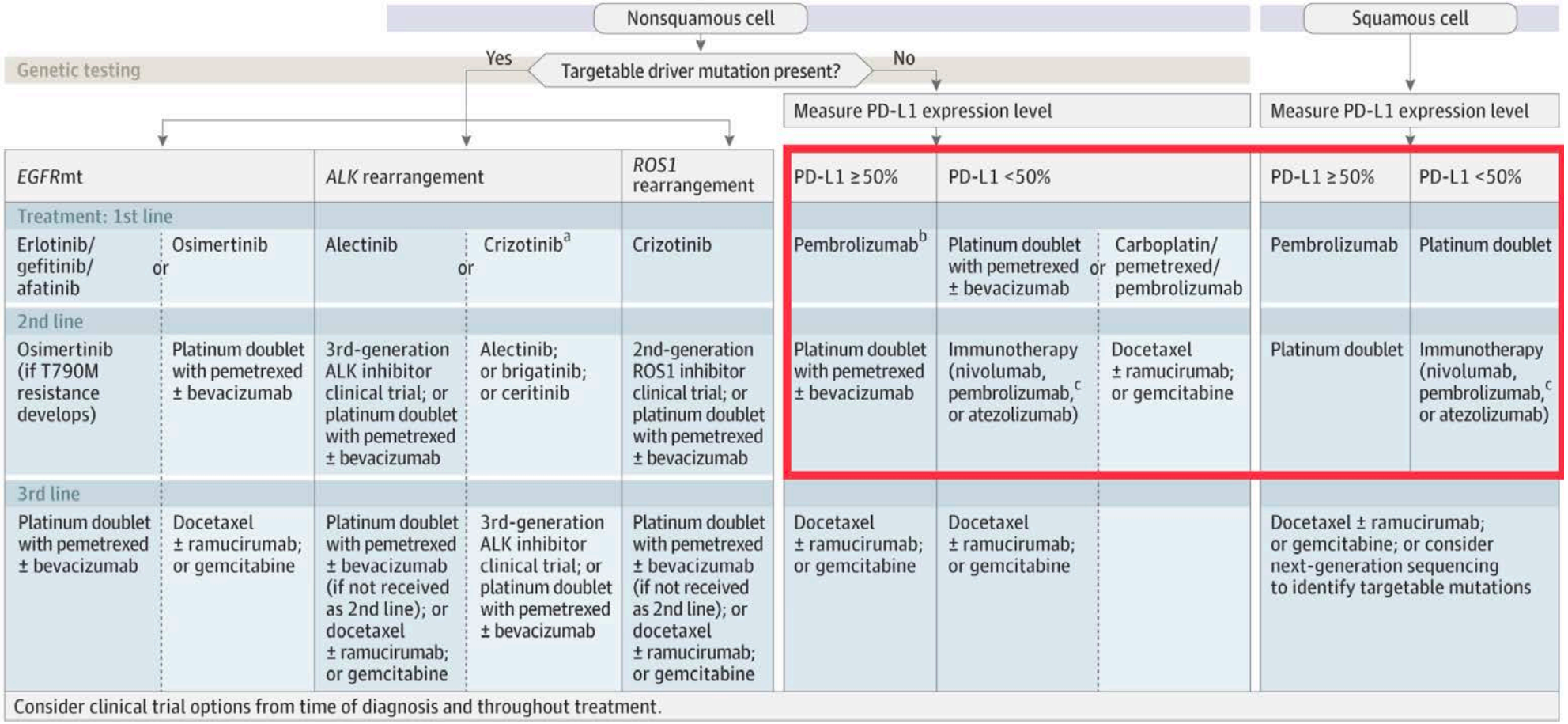
Chemoradiation: (Platinum+etoposide)

Extensive disease

Chemo alone: (Platinum+etoposide)

Metastatic NSCLC treatment





Abbreviations: PD-L1, programmed cell death 1 ligand 1; *EGFR*mt, *EGFR* mutated.

[a]If crizotinib treatment was started prior to FDA approval of alectinib for 1st-line treatment.

[b]Carboplatin/pemetrexed/pembrolizumab is also FDA approved in this setting.

[c]Pembrolizumab use requires PD-L1 >1%.

JAMA Oncol. 2018;4(4):569-570

Current immunotherapy FDA approvals

Non-small cell lung cancer

- 1st line Pembrolizumab PD-L1> 50%
- 1st line Pembrolizumab + pemetrexed/ carboplatin in non-squamous NSCLC

- 2nd line Pembrolizumab PD-L1 > 1 %
- 2nd line Nivolumab
- 2nd line Atezolizumab

- Stage III: Maintenance Durvalumab after chemo-radiation

Small cell lung cancer.

- 3rd line Nivolumab

Major Clinical Trials presented in 2018

- **NSCLC**
- 1st line chemo + immunotherapy combination in squamous? Keynote 407
- 1st line immunotherapy alone for PD-L1 < 50%? Keynote 042
- Other Biomarkers beside PD-L1 (i.e. TMB)? CheckMate 227
- Immunotherapy + VEGF based combinations? IMPower 150
- Update on previously reported trials. POPLAR, PACIFIC

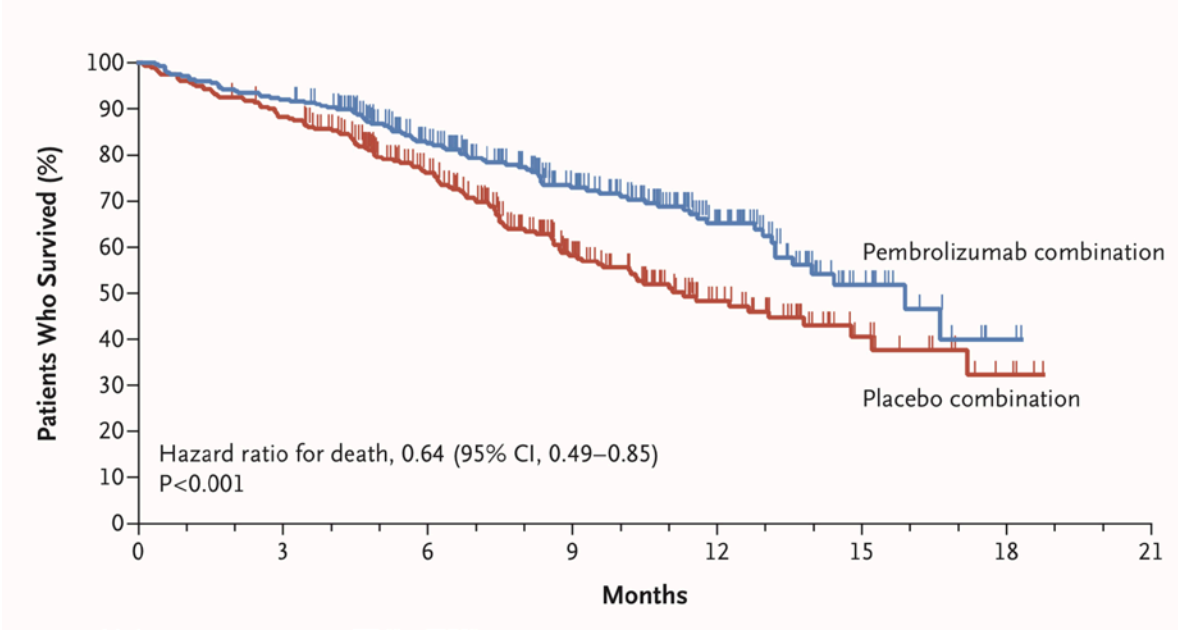
- **SCLC**
- 1st line immunotherapy + chemo in SCLC. IMpower 133

Keynote 407

1st line/ Squamous cell NSCLC

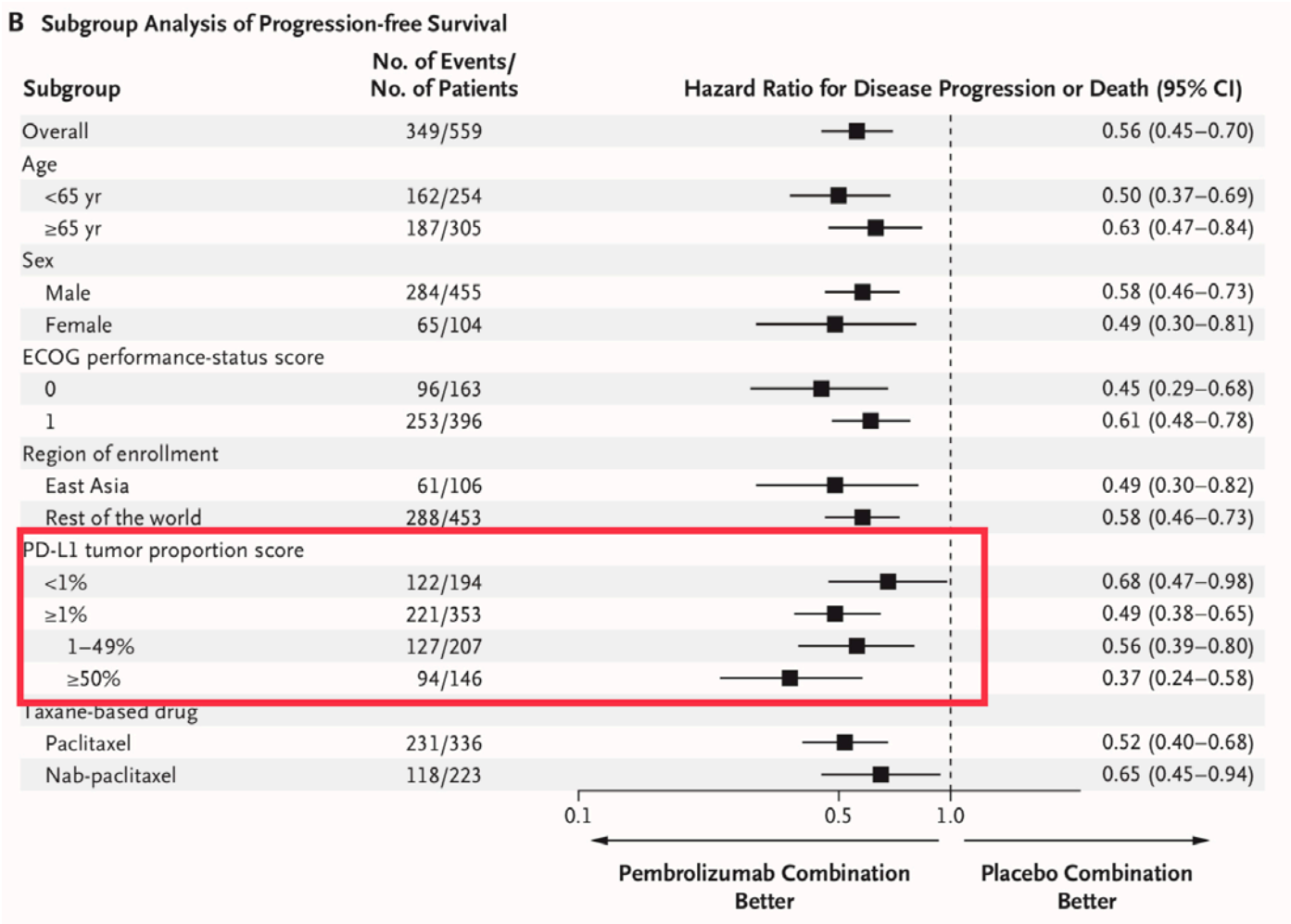
- **Pembrolizumab + platinum based chemo followed by pembro**
- **Platinum based Chemo followed by placebo**

- 559 pts
- Chemo: carboplatin and paclitaxel or nab-paclitaxel [Abraxane]
- Stratified by PD-L1 status, Geographic location, and Type of chemo
- Crossover allowed (42.5%)
- ORR 59.4% vs 38%,
- Median OS 15.9 vs 11.3 mo



Paz-Ares NEJM Sep 2018

Keynote 407



Paz-Ares NEJM Sep 2018

Keynote 042

1st line/ Non-squamous or squamous NSCLC

- **Pembrolizumab**
- **Platinum doublet**

- 1,274 pts
- PD-L1 >1%
- Chemo (Taxol/ carbo) or (pemetrexed plus carbo) depending on histology

	PD-L1 TPS					
	≥50%		≥20%		≥1%	
	Pembro N = 299	Chemo N = 300	Pembro N = 413	Chemo N = 405	Pembro N = 637	Chemo N = 637
OS						
HR (95% CI)	0.69 (0.56-0.85)		0.77 (0.64-0.92)		0.81 (0.71-0.93)	
P	.0003		.0020		.0018	
Median (95% CI), mo	20.0 (15.4-24.9)	12.2 (10.4-14.2)	17.7 (15.3-22.1)	13.0 (11.6-15.3)	16.7 (13.9-19.7)	12.1 (11.3-13.3)

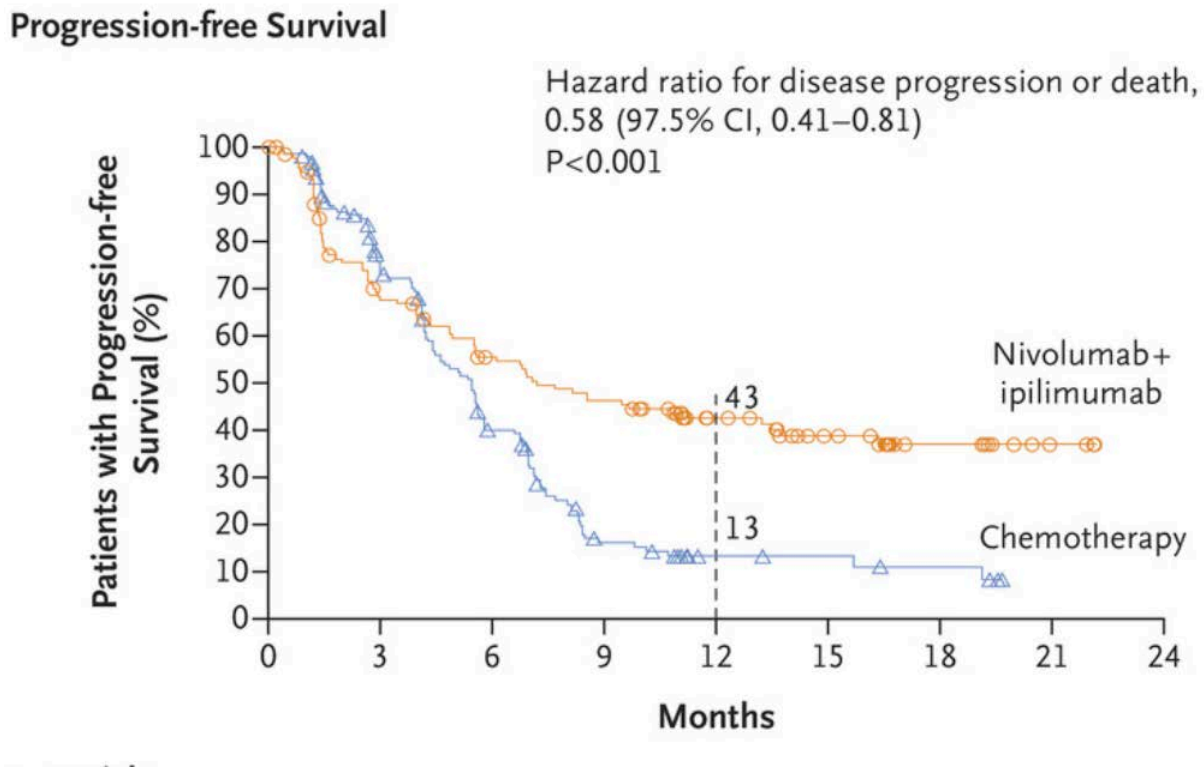
ASCO 2018 abstract LBA4

CheckMate 227

1st line/ squamous and non-squamous NSCLC

- **Nivolumab plus Ipilimumab**
- **Platinum based Chemo doublet**

• Exploratory analysis Pts with PD-L1 <1 % and high tumor mutational burden TMB (>10 mutations per megabase)



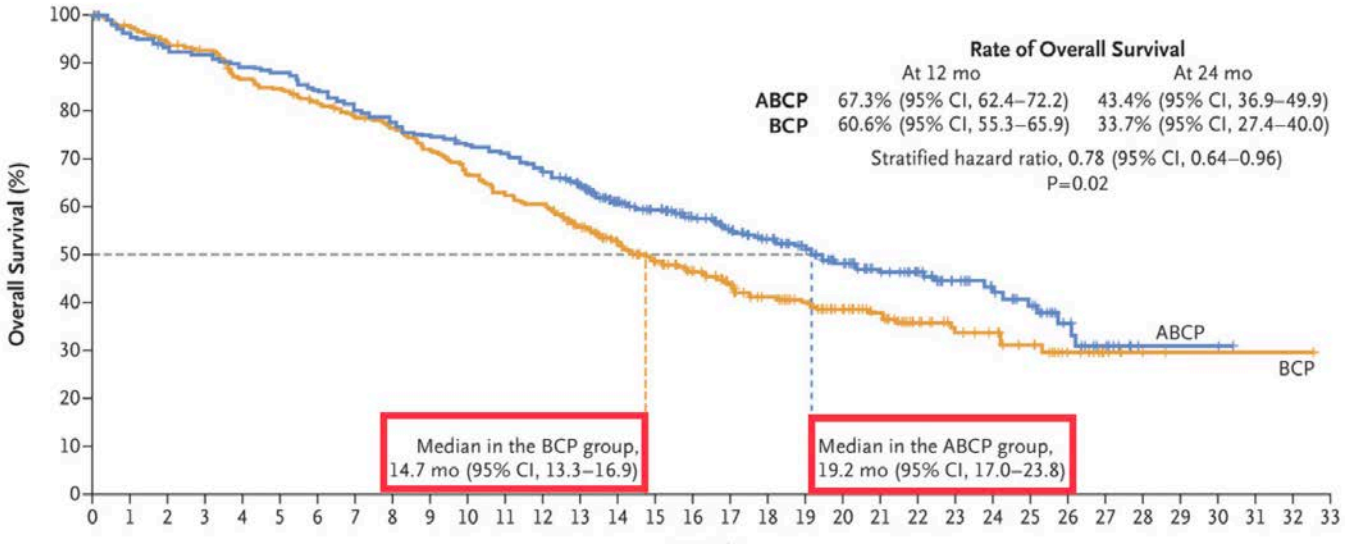
Hellmann NEJM May 2018

IMpower 150

1st line Non-squamous NSCLC

- **Atezolizumab + carbo + Taxol (ACP)**
- **Bevacizumab + carbo + Taxol (BCP)**
- **Atezo + BCP (ABCP)**

- 356 pts ABCP and 336 BCP

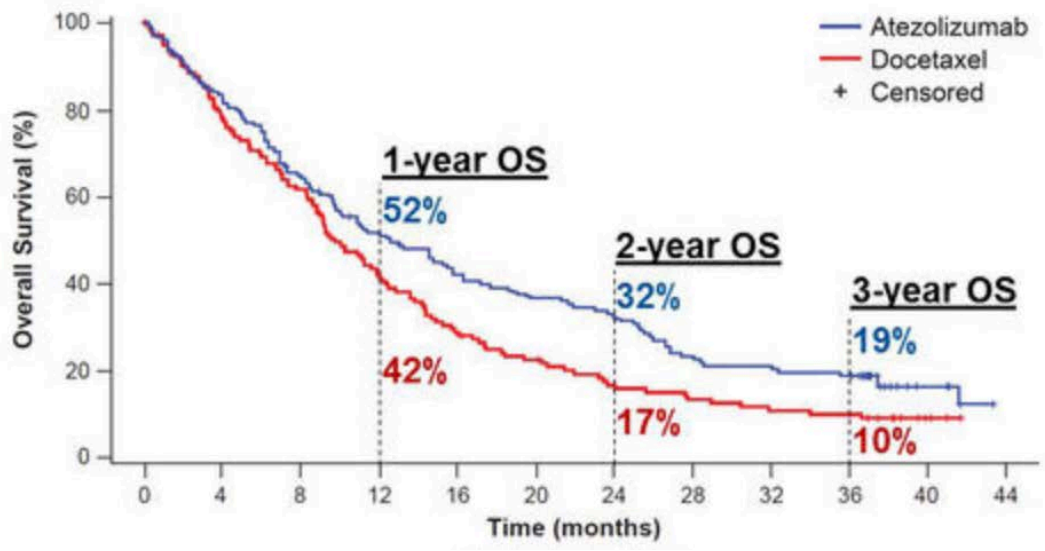


Socinski NEJM June 2018

POPLAR

2nd line squamous and non-squamous NSCLC

- **Atezolizumab**
- **Docetaxel**



- 287 pts
- Median duration of response 22.3 months vs 7.2 months.
- Long term survivors

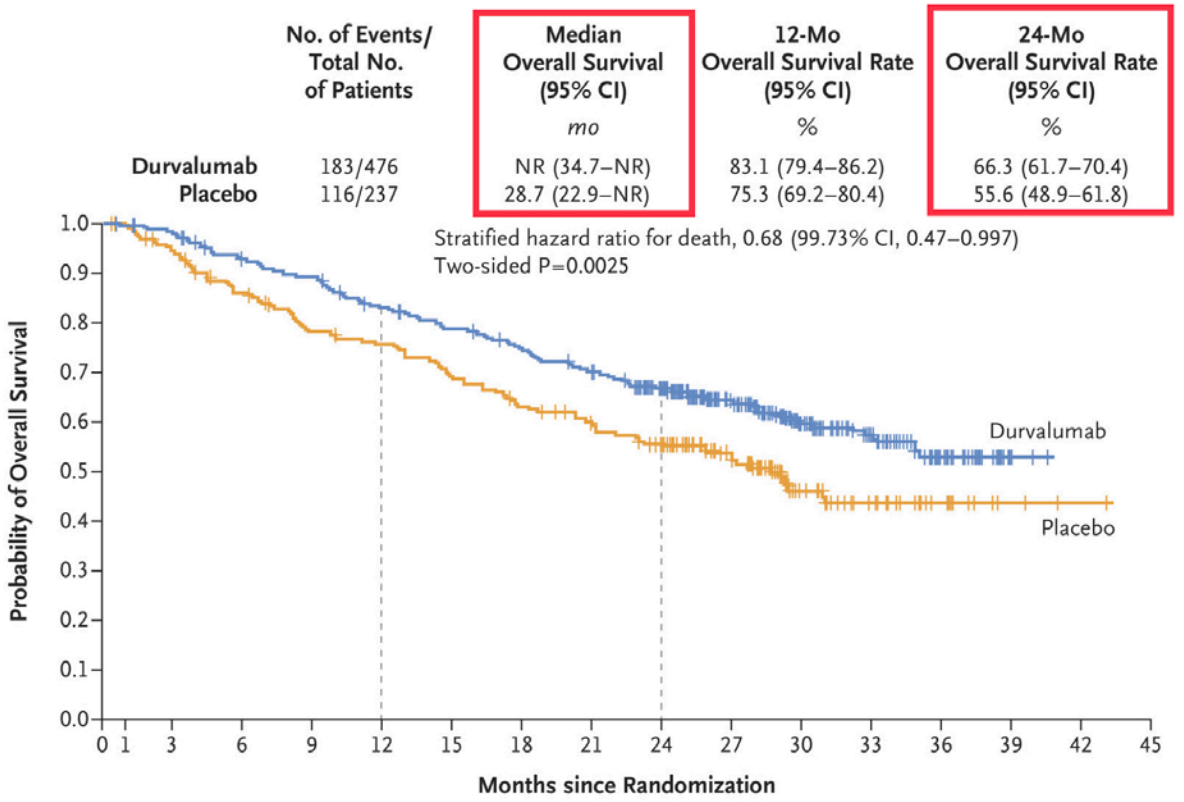
Mazieres ELCC 2018

PACIFIC

Stage III NSCLC After finishing definitive chemo-radiation

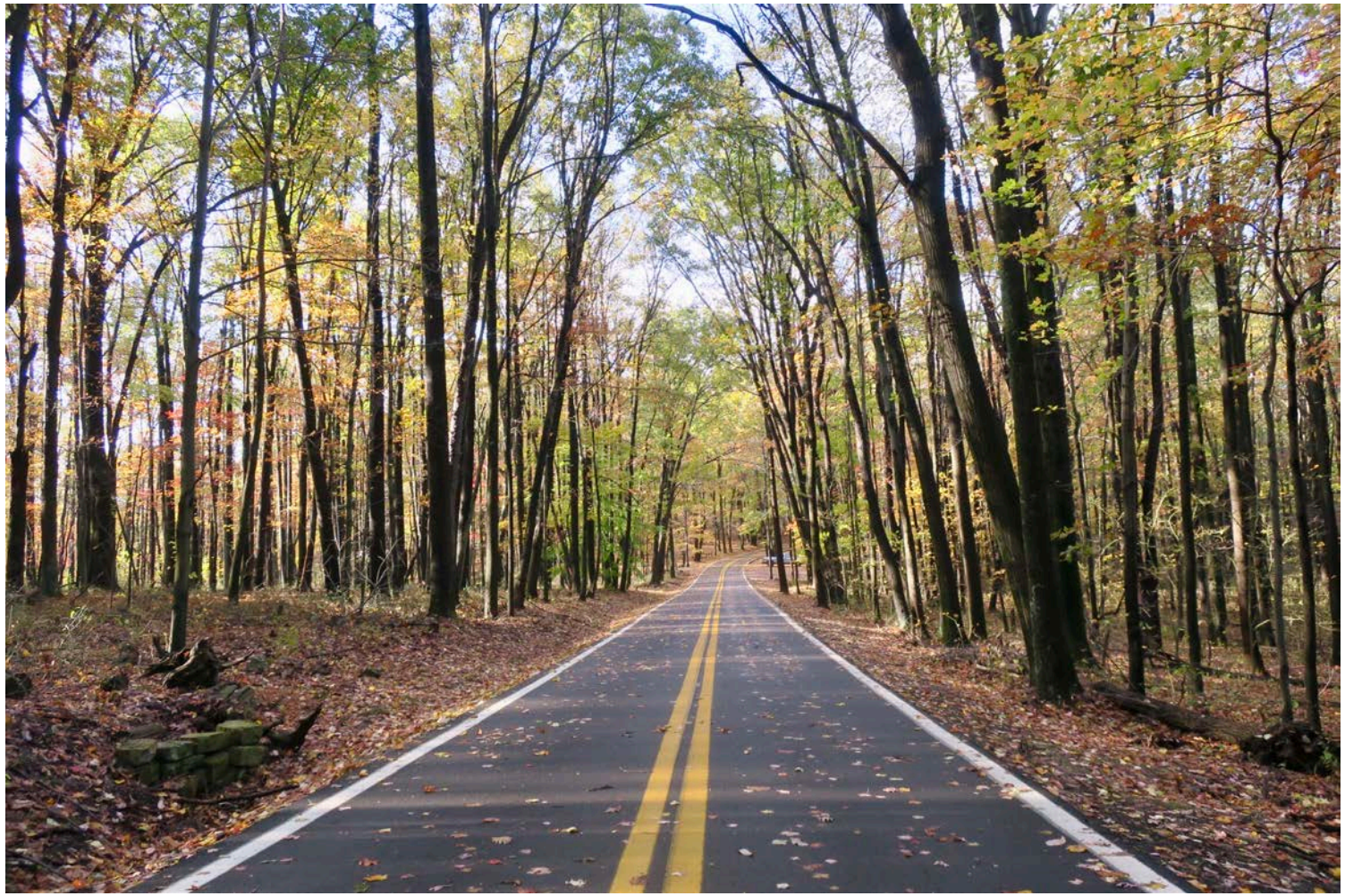
- **Durvalumab for 12 months**
- **Placebo**

- 713 pts (473 durvalumab and 236 placebo).
- Median follow-up 25.2 months
- Previously reported PFS 17.2 vs 5.6 months



Antonia S et al. NEJM Sep 2018.

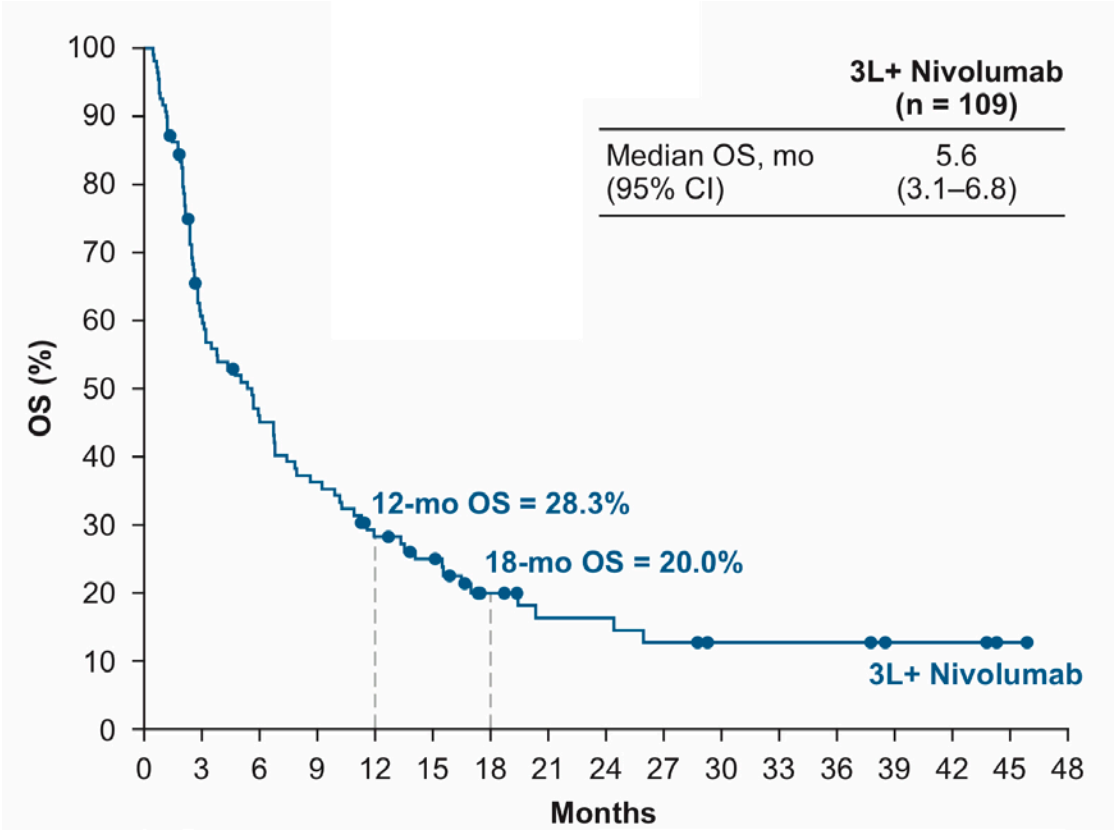
SCLC



CheckMate 032

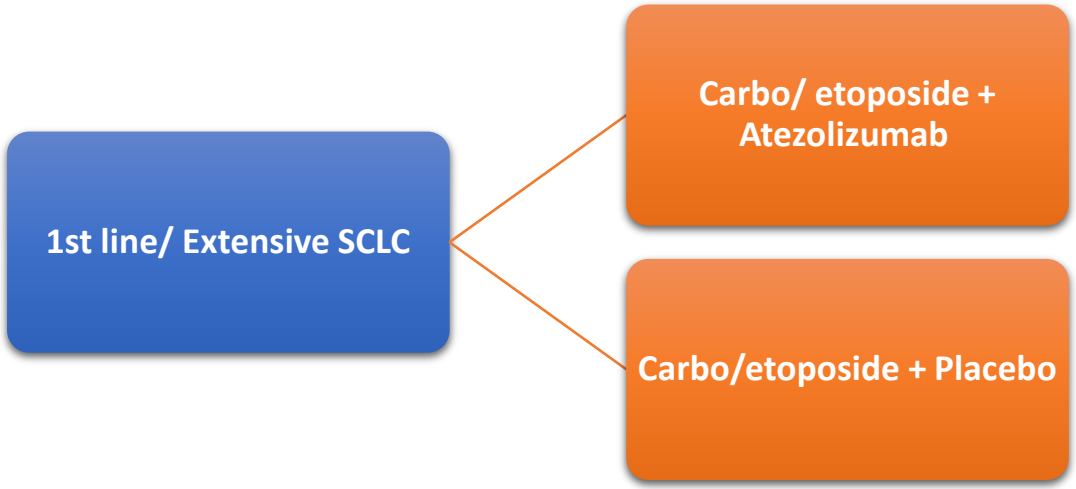
SCLC Progressed after 2 or more chemo — **Nivolumab**

- 109 pts
- Progressed on platinum based chemo and one more chemo
- Regardless of PD-L1

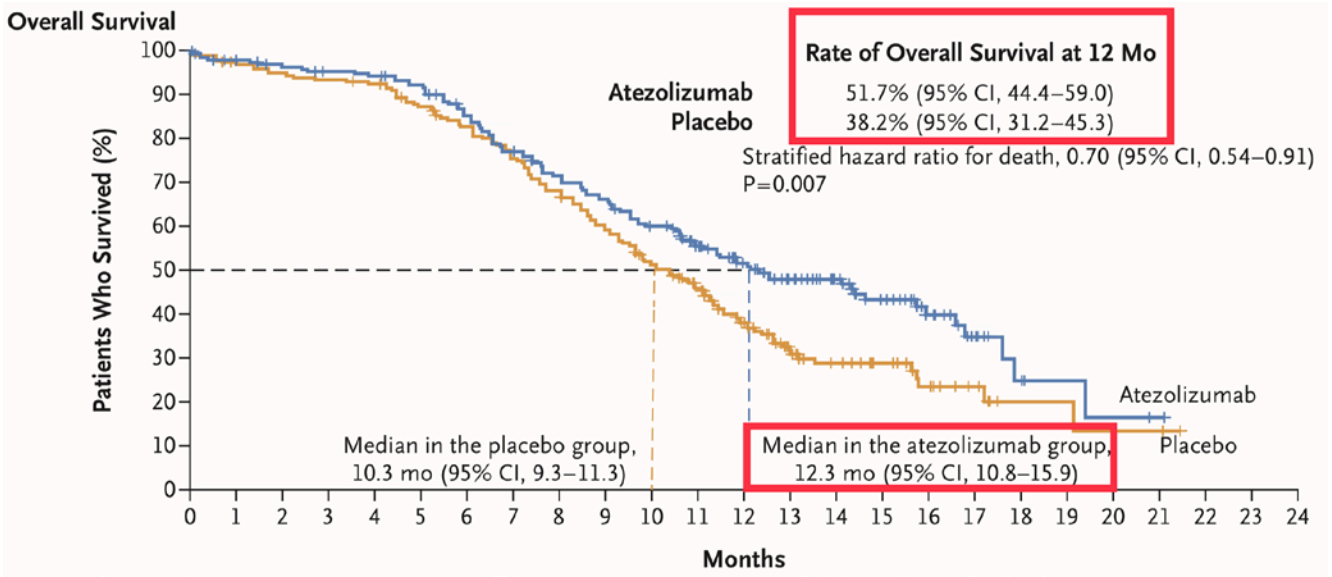


Ready et al. J Thorac Oncol Oct 2018.

IMpower133

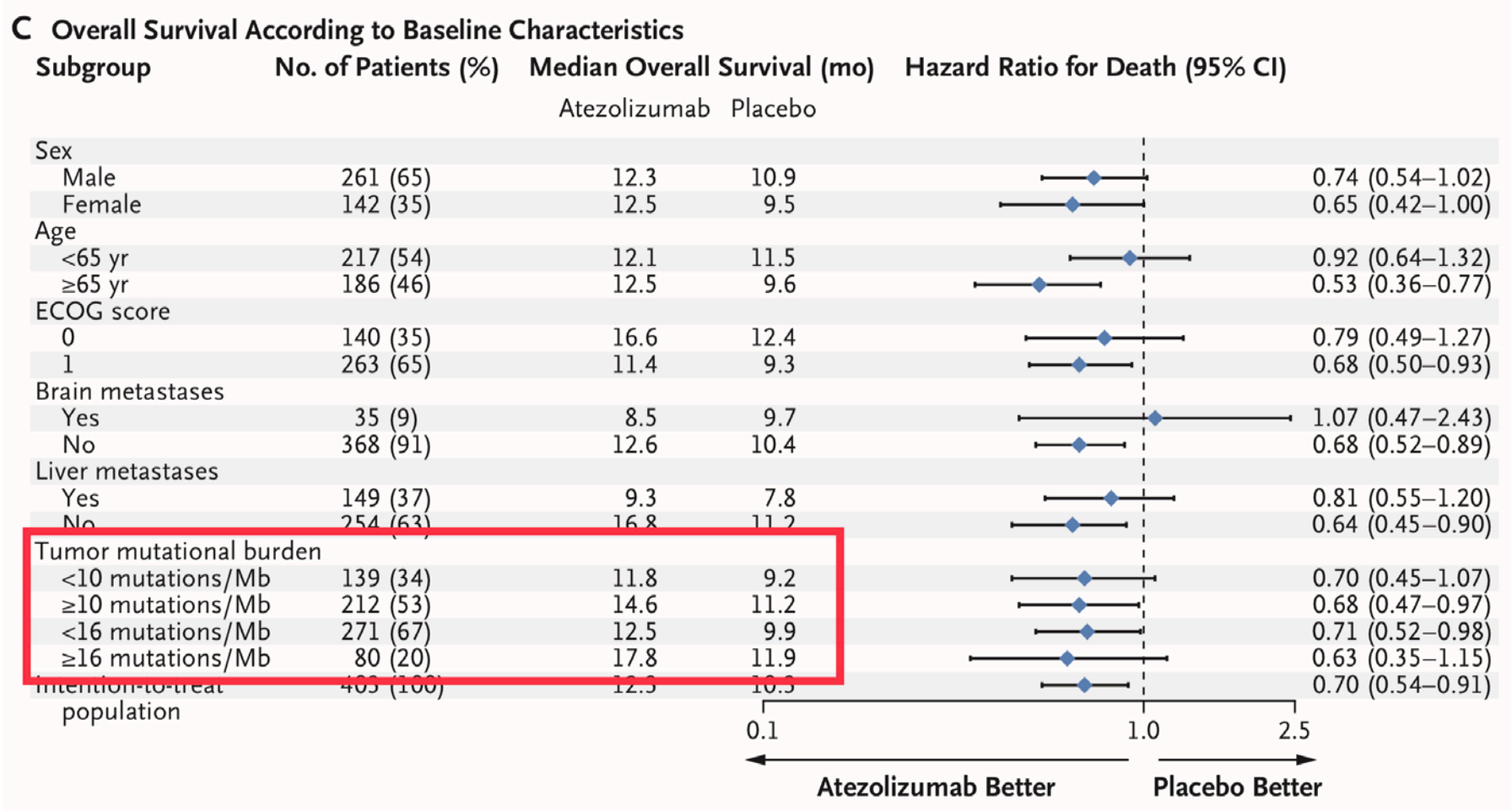


- 403 pts
- Induction with 4 cycles of platinum/ etoposide +/- Atezolizumab followed by maintenance with atezo or placebo



Horn et al. NEJM Sep 2018.

IMpower133



Horn et al. NEJM Sep 2018.

CheckMate 331

Bristol-Myers Squibb Announces Phase 3 CheckMate -331 Study Does Not Meet Primary Endpoint of Overall Survival with Opdivo Versus Chemotherapy in Patients with Previously Treated Relapsed Small Cell Lung Cancer

The New York Times

Wednesday, October 17, 2018

Possible near future immunotherapy approvals

Non-small cell lung cancer

- 1st line Pembrolizumab PD-L1> 50% (? Anyone with PD-L1>1%)
- 1st line Pembrolizumab + pemetrexed/ carboplatin in non-squamous NSCLC
  (? 1st line chemo + Pembrolizumab in squamous)
- ?1st line Nivolumab + Ipilimumab in high TMB
- ?1st line Chemo/Bevacizumab with Atezolizumab.

- 2nd line Pembrolizumab PD-L1 > 1 %
- 2nd line Nivolumab
- 2nd line Atezolizumab

- Maintenance Durvalumab after chemo-radiation

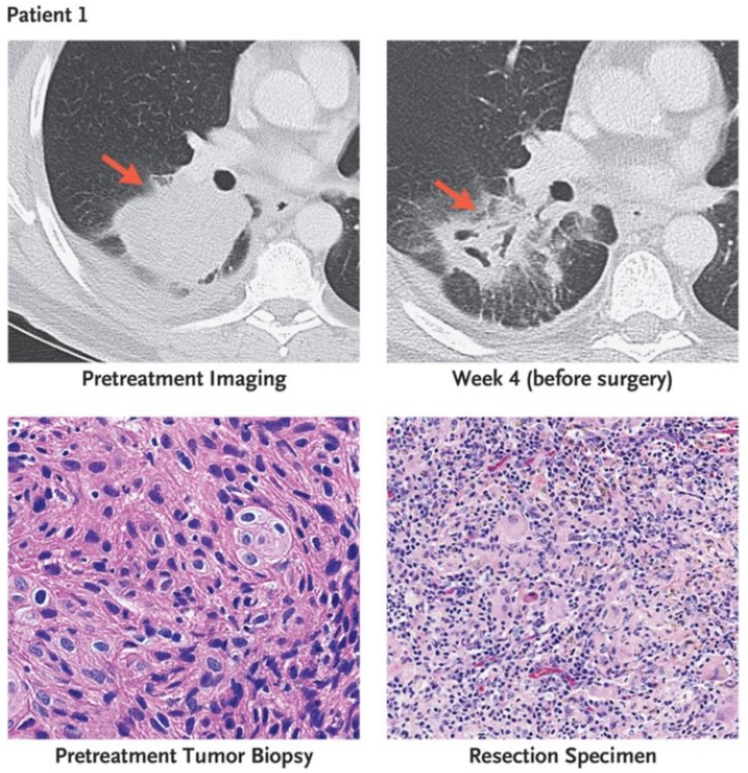
Small cell lung cancer.

- ?1st line Chemo+ Atezolizumab
- 3rd line Nivolumab

Neoadjuvant immunotherapy

- Safety and feasibility of neoadjuvant immunotherapy for resectable stage I-III NSCLC.
- Nivolumab every 2 weeks, with surgery 4 weeks after the first dose.
- Major pathologic response (<10% viable residual tumor) in 45% (9 of 20) with no delays in surgical resection.

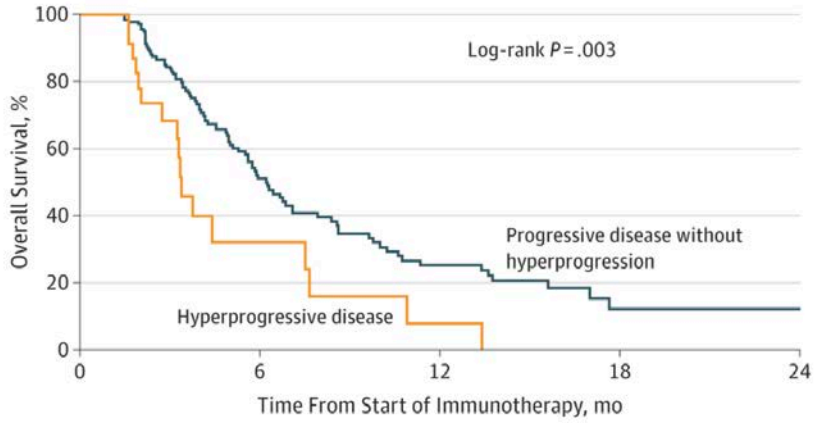
- Of the 9 patients with a major pathologic response, only 2 had a partial response on preoperative imaging.
- High correlation between pre-treatment tumor mutational burden (TMB) and major pathologic response to nivolumab (more than tumor PD-L1 expression).



Forde et al. NEJM May 2018.

HyperProgressive Disease (HPD)

- Retrospective French study. 406 pts treated with PD-1/PD-L1 inhibitors in second or later line treatment.
- HyperProgressive Disease (HPD) was defined as disease progression on the first CT scan during treatment with an absolute increase in Tumor Growth Rate exceeding 50%.



- 13.8% of pts vs 5.1 % historical chemo control group.
- Associated with more than two metastatic sites prior to treatment.

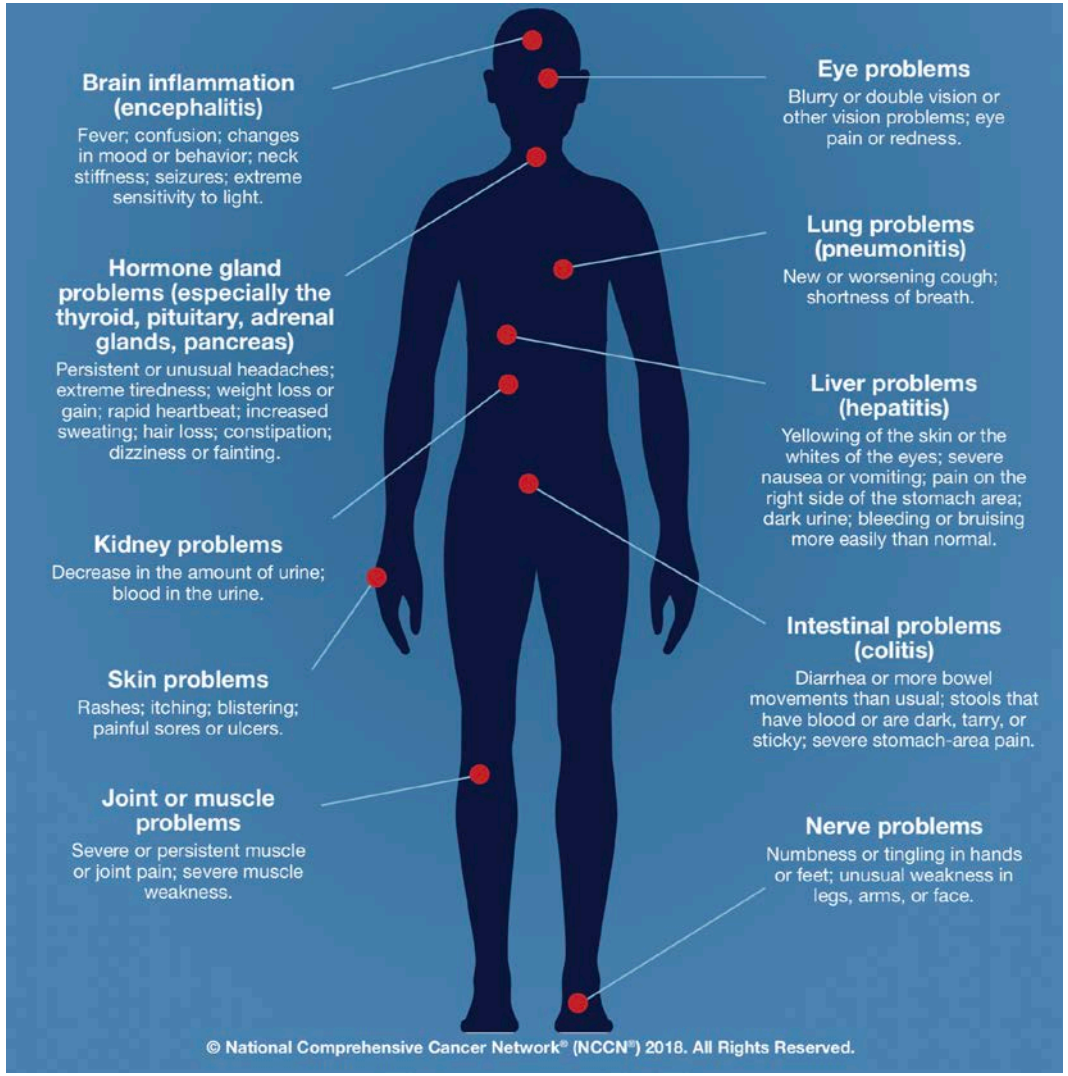
Ferrara et al. JAMA Oncol. Sep 2018

Adverse events

Table Recognizing the Side Effects of Immune Checkpoint Inhibitors

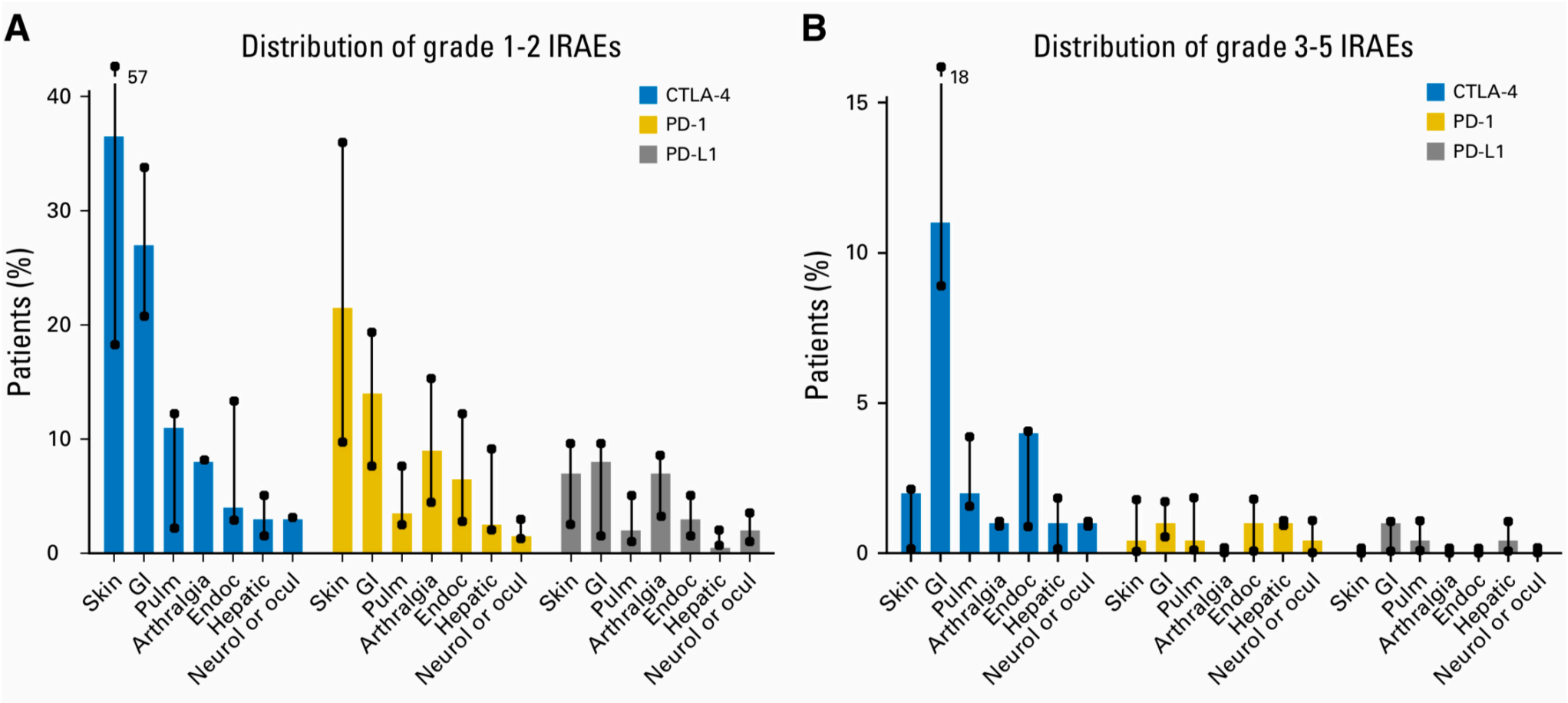
Body system/side effect	
Dermatologic events Bullous dermatoses Rash/inflammatory dermatitis Severe skin reactions	**Nervous system events** Myasthenia gravis Guillain-Barré syndrome Peripheral neuropathy Autonomic neuropathy Aseptic meningitis Encephalitis Transverse myelitis
Gastrointestinal events Colitis Hepatitis	**Hematologic events** Autoimmune hemolytic anemia Acquired thrombotic thrombocytopenic purpura Hemolytic uremic syndrome Aplastic anemia Lymphopenia Immune thrombocytopenia Acquired hemophilia
Pulmonary event Pneumonitis	**Cardiovascular events** Myocarditis Pericarditis Arrhythmias Impaired ventricular function with heart failure Vasculitis Venous thromboembolism
Endocrine events Diabetes Hyperthyroidism (primary) Hypophysitis Primary adrenal insufficiency	**Ocular events** Uveitis/iritis Episcleritis Blepharitis
Musculoskeletal system events Inflammatory arthritis Myositis Polymyalgia-like syndrome	
Renal system events Nephritis Symptomatic nephritis	

Source: Brahmer JR, et al. *J Clin Oncol*. 2018 Feb 14. Epub ahead of print.



Brahmer JCO June 2018
NCCN.com

Adverse Events



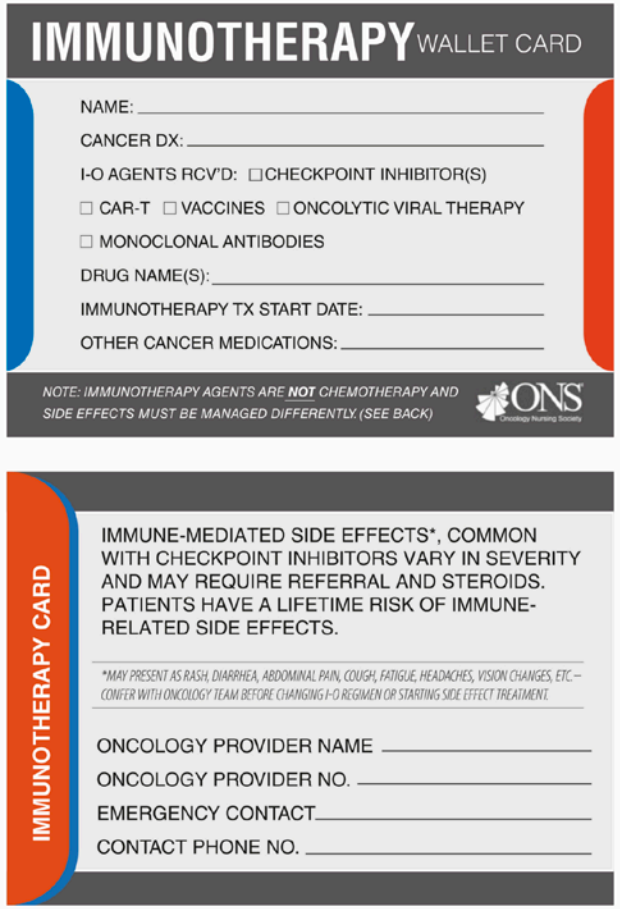
Brahmer JCO June 2018

Adverse events

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)
in partnership with the American Society of Clinical Oncology (ASCO)

Management of Immunotherapy-Related Toxicities

(Immune Checkpoint Inhibitor-Related Toxicities)



IMMUNOTHERAPY WALLET CARD

NAME: _____

CANCER DX: _____

I-O AGENTS RCV'D: ☐CHECKPOINT INHIBITOR(S)

☐ CAR-T ☐ VACCINES ☐ ONCOLYTIC VIRAL THERAPY

☐ MONOCLONAL ANTIBODIES

DRUG NAME(S): _____

IMMUNOTHERAPY TX START DATE: _____

OTHER CANCER MEDICATIONS: _____

*NOTE: IMMUNOTHERAPY AGENTS ARE **NOT** CHEMOTHERAPY AND SIDE EFFECTS MUST BE MANAGED DIFFERENTLY. (SEE BACK)*

ONS Oncology Nursing Society

IMMUNOTHERAPY CARD

IMMUNE-MEDIATED SIDE EFFECTS*, COMMON WITH CHECKPOINT INHIBITORS VARY IN SEVERITY AND MAY REQUIRE REFERRAL AND STEROIDS. PATIENTS HAVE A LIFETIME RISK OF IMMUNE-RELATED SIDE EFFECTS.

**MAY PRESENT AS RASH, DIARRHEA, ABDOMINAL PAIN, COUGH, FATIGUE, HEADACHES, VISION CHANGES, ETC.– CONFER WITH ONCOLOGY TEAM BEFORE CHANGING I-O REGIMEN OR STARTING SIDE EFFECT TREATMENT.*

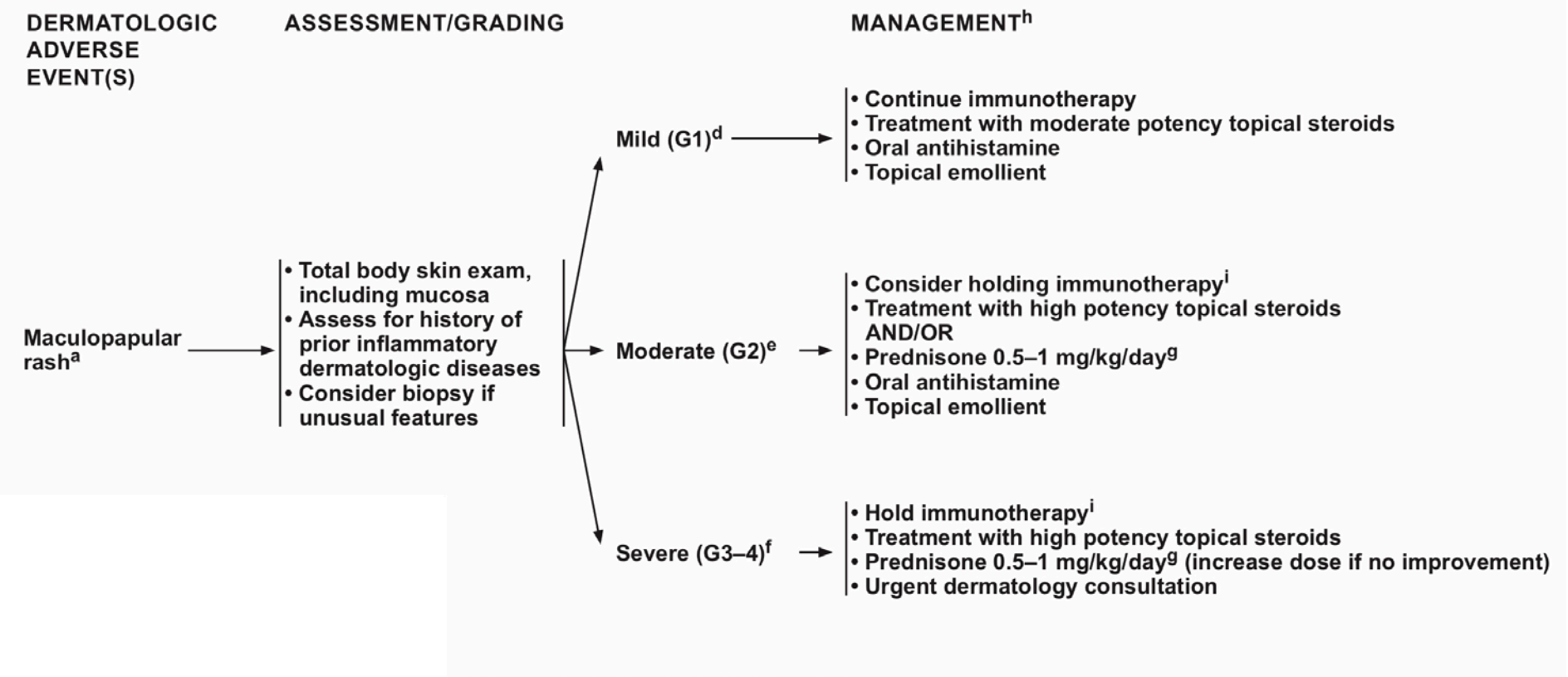
ONCOLOGY PROVIDER NAME _____

ONCOLOGY PROVIDER NO. _____

EMERGENCY CONTACT _____

CONTACT PHONE NO. _____

Example 1: Rash



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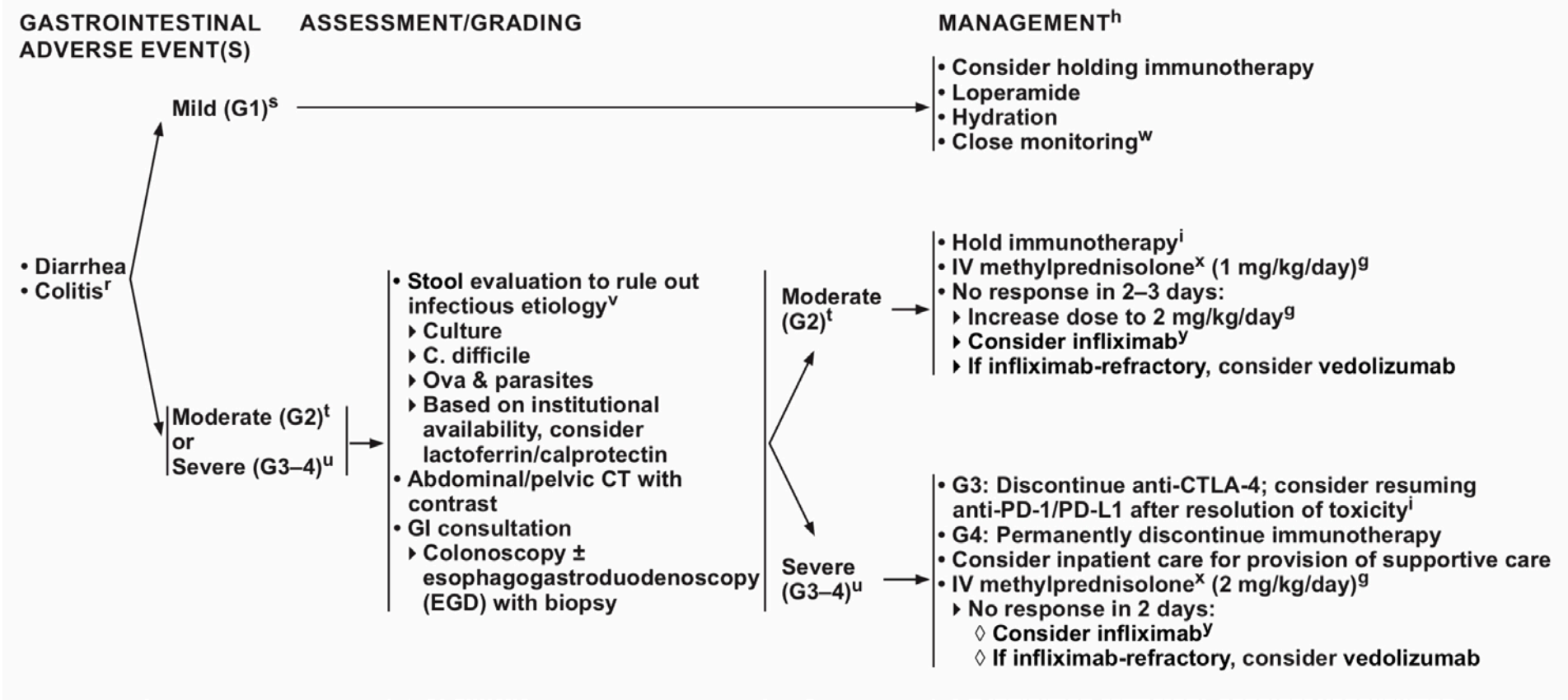
Example 2: Diarrhea/ Colitis



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Conclusions

- Immunotherapy therapeutic indications are expanding rapidly in the treatment of advanced lung cancer and have even replaced chemotherapy as first line therapy in many areas.
- PD-L1 expression and TMB are independent predictors of response to immunotherapy.

- It’s important to recognize and treat adverse reactions to immunotherapy promptly.
- Immunotherapy will likely play an important role in earlier stages of lung cancer.

Thank you

Questions???