Advances in the Management of Thoracic Malignancies:

Precision Medicine & Immunotherapy

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Questions

- What are current precision medicine targets in lung cancer?
- What is the abscopal effect?
- What are the kinetics of immune-related adverse events (irAEs)?
- What is the treatment of irAEs?

Outline

- Lung cancer
- What is Precision Medicine?
- PM in Lung CA
- Immunotherapy / Immuno-oncology
- Immune Related Adverse Events (irAEs)
- Remaining Issues

Outline

- **Lung cancer**
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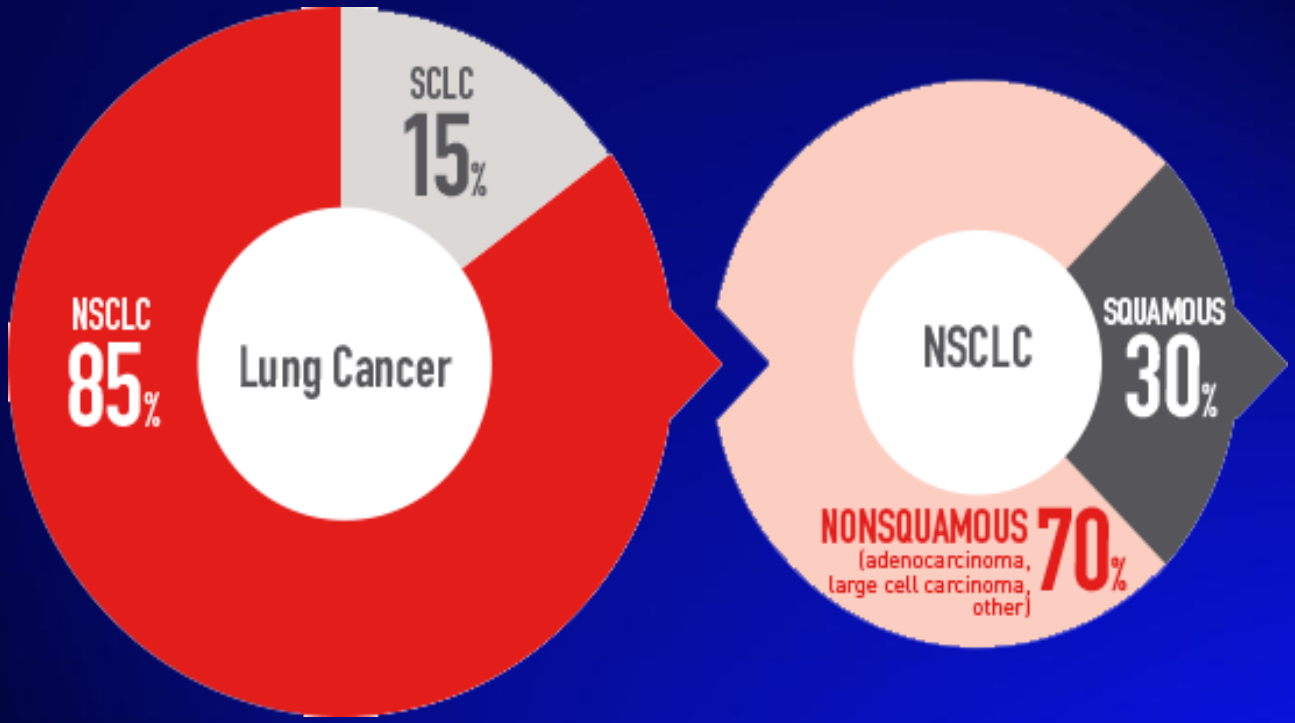
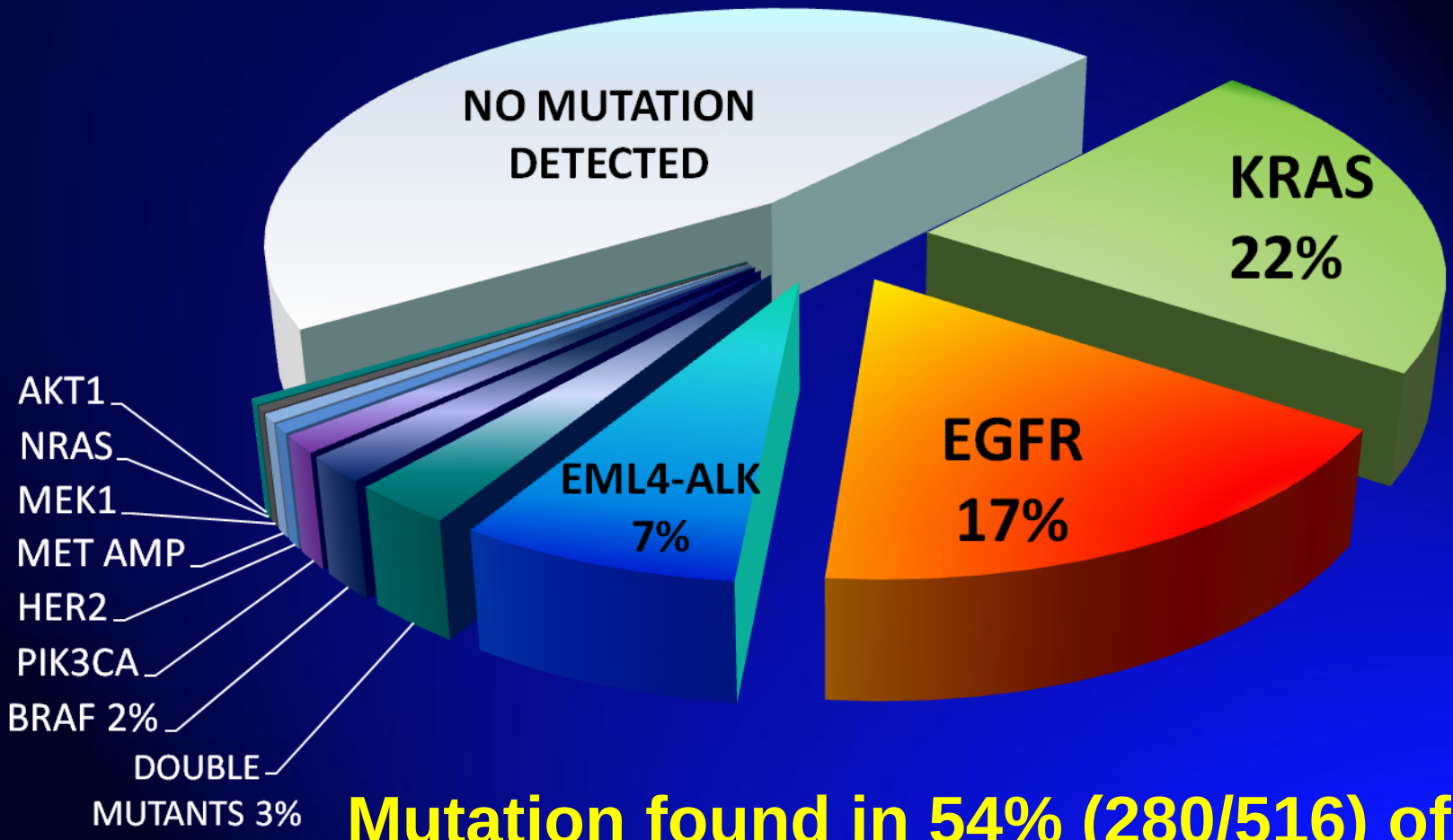
Lung Cancer



Lily Oncology - https://goo.gl/images/QPQgNL

Lung Cancer Mutation Consortium

Incidence of Single Driver Mutations



Mutation found in 54% (280/516) of tumors completely tested (CI 50-59%)

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What is Precision Medicine?

- If PM is defined broadly enough it can be equated with medicine in general and loses any real meaning.
- Also, PM applied at a systems or population level can be called “population health”.
- PM = molecularly-driven therapy choices (including immunotherapy based on biomarkers) applied to individuals.
- People have always tried to personalize therapy including evaluating the patient as a whole (holistic) and in context with age, co-morbidities, and family, we are now increasingly using molecular information to help define treatment.

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2004 EGFRi (1)

- 11/18/04 FDA approved erlotinib (Tarceva) for locally advanced or metastatic NSCLC after failure of at least one prior chemo Tx
- (2013 1L met NSCLC FDA approval)
- N=731 DB-RCT erlotinib vs placebo
- mOS
  - 6.7 mon erlotinib
  - 4.7 months placebo
  - HR 0.73, p = <0.001

https://www.cancer.gov/about-cancer/treatment/drugs/fda-erlotinib-hydrochloride

2004 EGFRi (2)

- mPFS
  - 9.9 weeks - erlotinib
  - 7.9 weeks - placebo
  - adjusted HR for progression was 0.59, p < 0.001
- **ORR 8.9 percent**
- median response duration was 34.3 weeks, ranging from 9.7 to 57.6+ weeks.
  - Two responses (0.9 percent, 95 percent CI: 0.1 to 3.4) were reported in the placebo group.
- This was in UNSELECTED pts by EGFR status
- An exploratory analysis of Epidermal Growth Factor Receptor (EGFR) protein expression status on treatment survival effect was performed; however, **EGFR status was known for only 33 percent of patients**. The EGFR expression was determined using the DAKO EGFR pharmDx™ kit. About half of the patients with known EGFR status were positive and half were negative.
- In the **EGFR positive** subgroup:

	OS (mon)
erlotinib	10.7
Placebo	3.8
HR	**0.65**, P 0.033

- No apparent erlotinib OS effect was observed in the EGFR negative subgroup
- **So, need to choose your targeted therapy based on biomarkers**

2014 (Four years ago!)

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2014
Non-Small Cell Lung Cancer

NCCN Guidelines Index
NSCLC Table of Contents
Discussion

TARGETED AGENTS FOR PATIENTS WITH GENETIC ALTERATIONS

Genetic Alteration (ie, Driver event)	Available Targeted Agents with Activity Against Driver Event in Lung Cancer
EGFR mutations	erlotinib,[1] gefitinib,[2] afatinib[3]
ALK rearrangements	crizotinib[4]
HER2 mutations	trastuzumab,[5] afatinib[6]
BRAF mutations	vemurafenib,[7] dabrafenib[8]
MET amplification	crizotinib[9]
ROS1 rearrangements	crizotinib[10]
RET rearrangements	cabozantinib[11]

[1]Sequist LV, Joshi VA, Janne PA, et al. Response to treatment and survival of patients with non-small cell lung cancer undergoing somatic EGFR mutation testing. Oncologist 2007;12:90-98.
[2]Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004;304:1497-1500.
[3]Sequist LV, Yang JC-H, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013;31:3327-3334.
[4]Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small cell lung cancer. N Engl J Med 2010;363:1693-1703.
[5]Cappuzzo F, Bemis L, Varella-Garcia M. HER2 mutation and response to trastuzumab therapy in non-small-cell lung cancer. N Engl J Med 2006;354:2619-2621.
[6]Mazieres J, Peters S, Lepage B, et al. Lung cancer that harbors an HER2 mutation: epidemiologic characteristics and therapeutic perspectives. J Clin Oncol 2013;31:1997-2003.
[7]Gautschi O, Pauli C, Strobel K, et al. A patient with BRAF V600E lung adenocarcinoma responding to vemurafenib. J Thorac Oncol 2012;7:e23-24.
[8]Planchard D, Mazieres J, Riely GJ, et al. Interim results of phase II study BRF113928 of dabrafenib in BRAF V600E mutation-positive non-small cell lung cancer (NSCLC) patients [abstract]. J Clin Oncol 2013;31(Suppl 15): Abstract 8009.
[9]Ou SH, Kwak EL, Siwak-Tapp C, et al. Activity of crizotinib (PF02341066), a dual mesenchymal-epithelial transition (MET) and anaplastic lymphoma kinase (ALK) inhibitor, in a non-small cell lung cancer patient with de novo MET amplification. J Thorac Oncol 2011;6:942-946.
[10]Bergethon K, Shaw AT, Ou SH, et al. ROS1 rearrangements define a unique molecular class of lung cancers. J Clin Oncol 2012;30:863-870.
[11]Drilon A, Wang L, Hasanovic A, et al. Response to cabozantinib in patients with RET fusion-positive lung adenocarcinomas. Cancer Discov 2013; 3:630-635.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Effective lung cancer treatment requires Precision Medicine

"I think we are in a precision medicine field, and lung cancer is a model of this and patients should not be treated until [an oncologist] has this information," Edward S. Kim, MD, chair of solid tumor oncology and investigational therapeutics at Levine Cancer Institute, told *HemOnc Today*. "It is part of the diagnostic workup."

[11/15/17] http://ow.ly/290030hF1vB

AHC Lung Panel

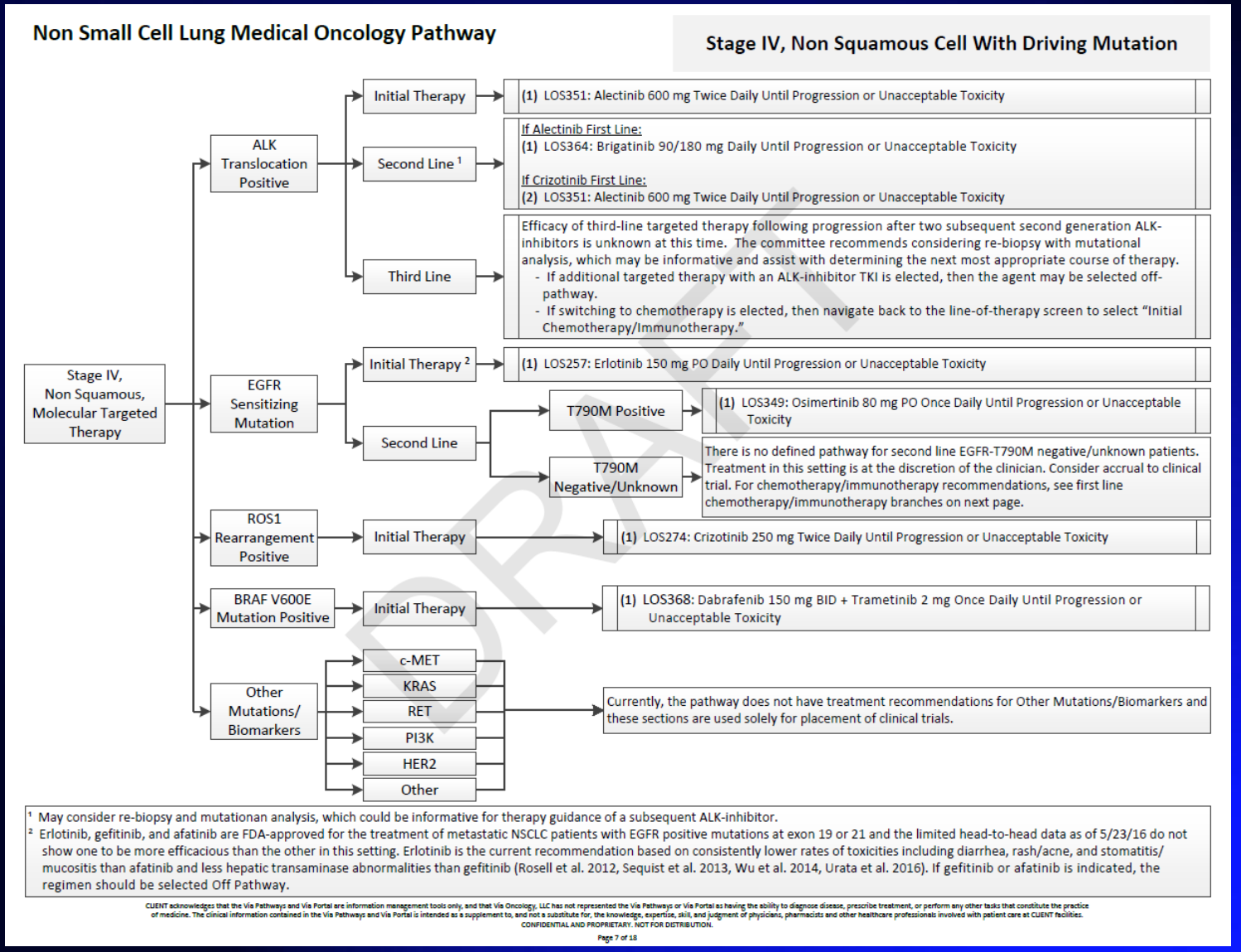
- < 2016 ad hoc orders
  - ~30% EGFR testing w/o systemic panels

Changed to testing on all lung CA path:

- 2016 EGFR, ALK, ROS1
- 2017 + PD-L1
- 2017 + BRAF (PCR) with BRAFi approval
- 12/13/17 NGS: ALK, ROS1, Ret, NTRK1, Met & EGFR, BRAF (PCR), PD-L1, HER2 IHC

2018

(additional PM pathways in development)

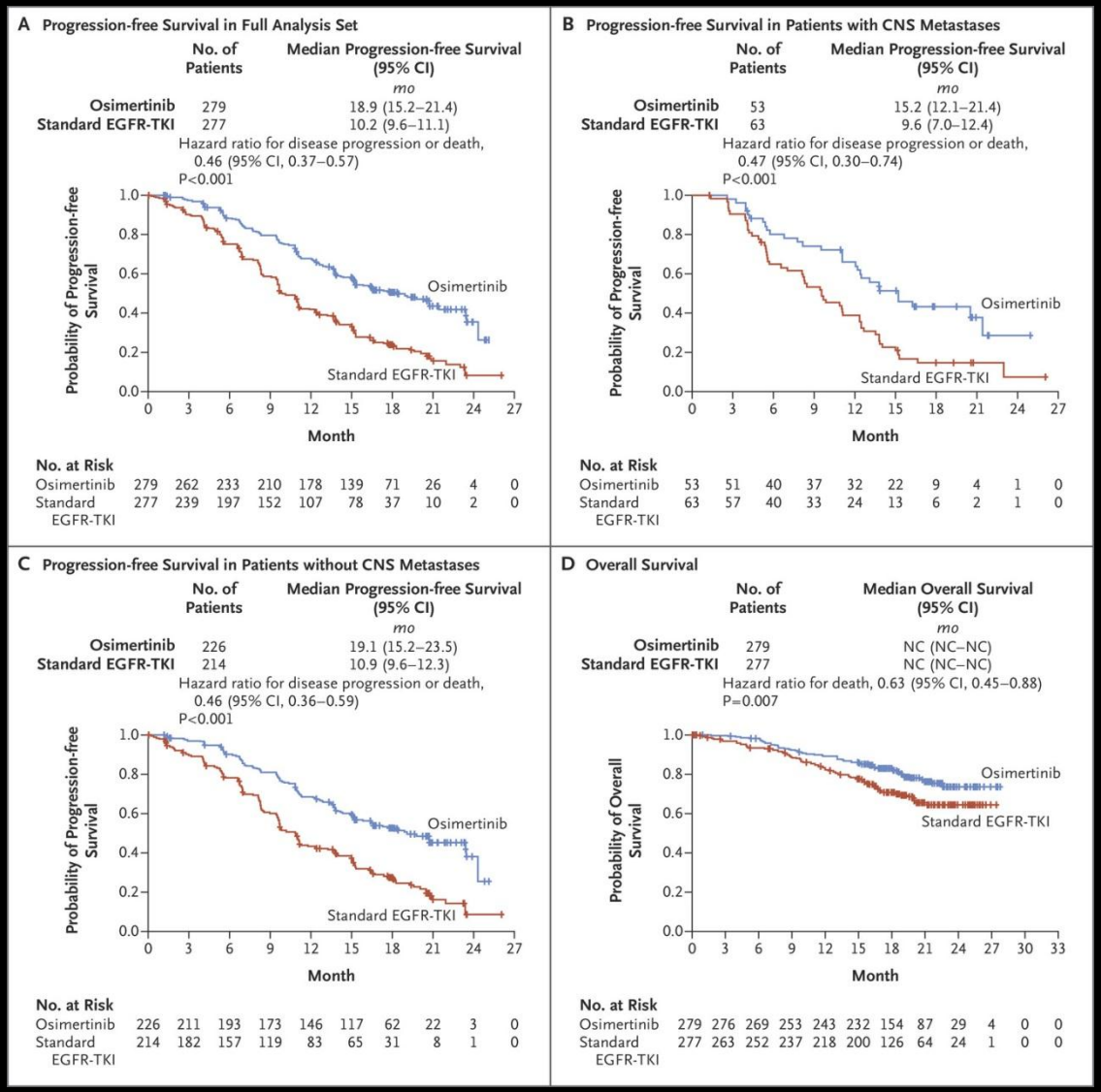


[1] May consider re-biopsy and mutationan analysis, which could be informative for therapy guidance of a subsequent ALK-inhibitor.

[2] Erlotinib, gefitinib, and afatinib are FDA-approved for the treatment of metastatic NSCLC patients with EGFR positive mutations at exon 19 or 21 and the limited head-to-head data as of 5/23/16 do not show one to be more efficacious than the other in this setting. Erlotinib is the current recommendation based on consistently lower rates of toxicities including diarrhea, rash/acne, and stomatitis/ mucositis than afatinib and less hepatic transaminase abnormalities than gefitinib (Rosell et al. 2012, Sequist et al. 2013, Wu et al. 2014, Urata et al. 2016). If gefitinib or afatinib is indicated, the regimen should be selected Off Pathway.

2018 - Improving on EGFRi PM

Osimertinib



Also,
Afatinib
1/16/18
FDA approval
EGFR G719X,
L861Q, & S768I

Soria J et al. N Engl J Med 2018;378:113-125.

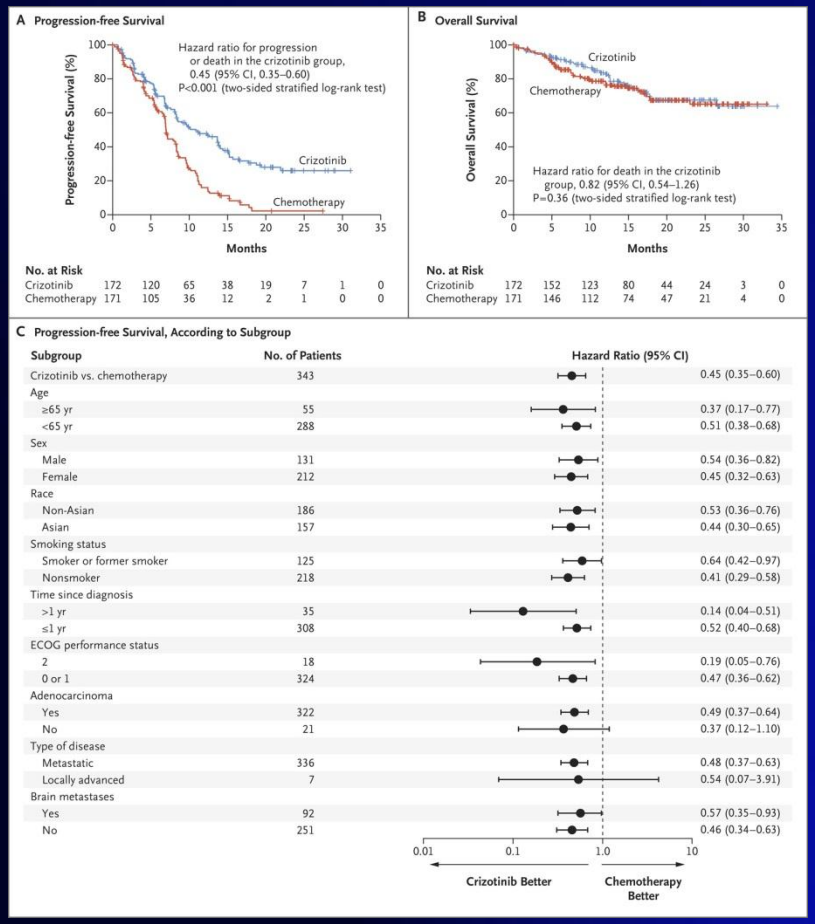
The NEW ENGLAND JOURNAL of MEDICINE

PM in Lung CA
(a sampling)

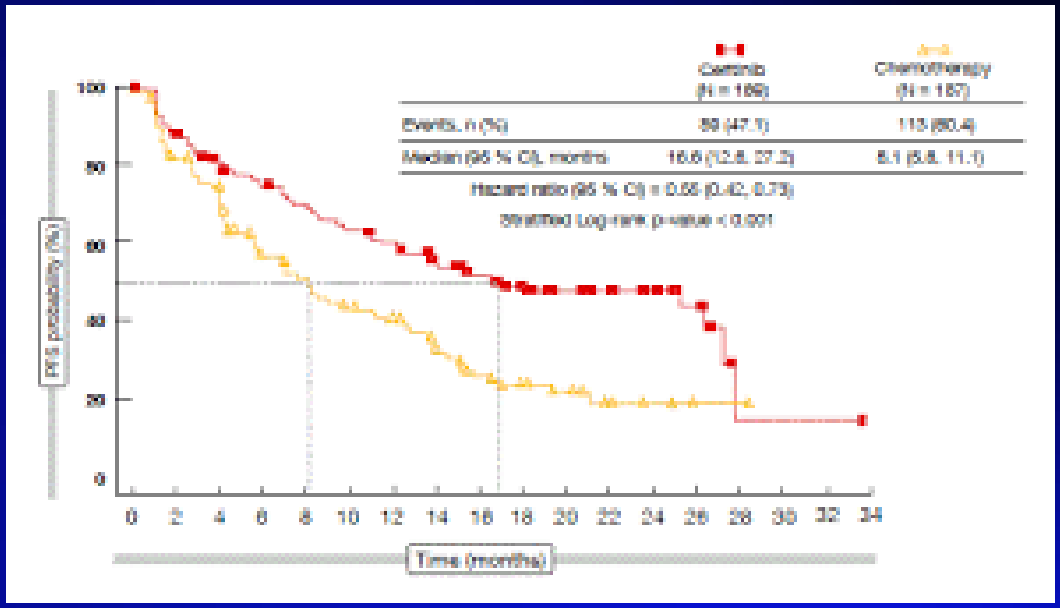
- EGFR
- ALK
- ROS1
- BRAF
- HER2
- MET
- RET

ALK

1L crizotinib vs Plat+pem
Solomon et al. NEJM 2014

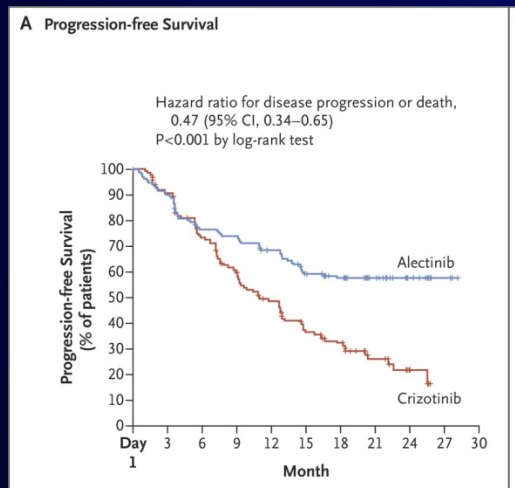


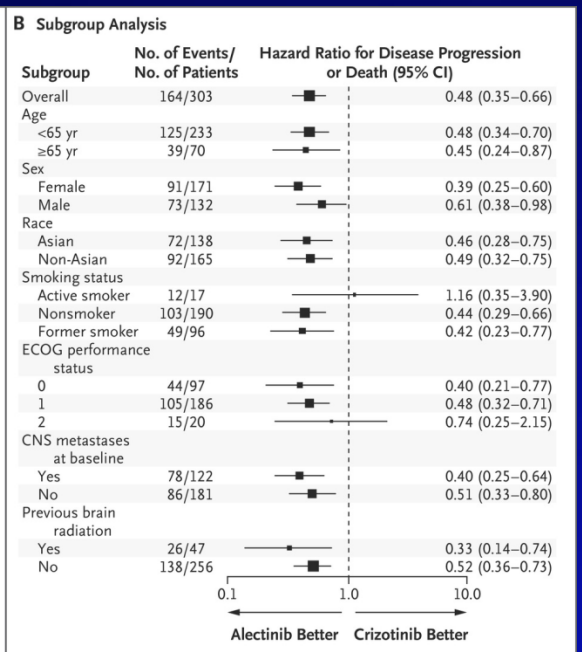
1L ceritinib vs Plat+pem
Soria et al. Lancet 2017

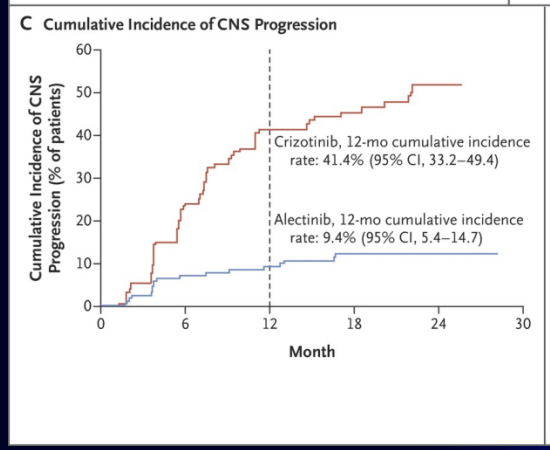


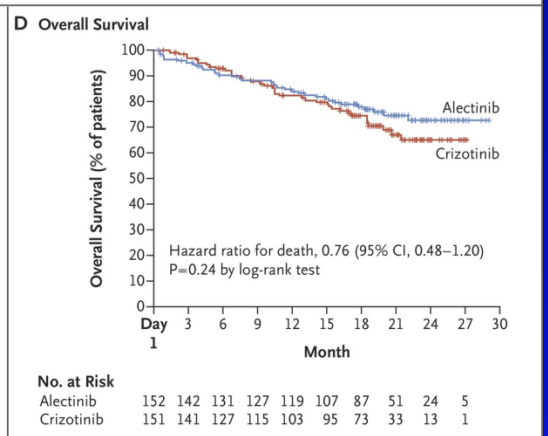
ALK - 1L Alectinib vs Crizotinib

Peters – NEJM 2017



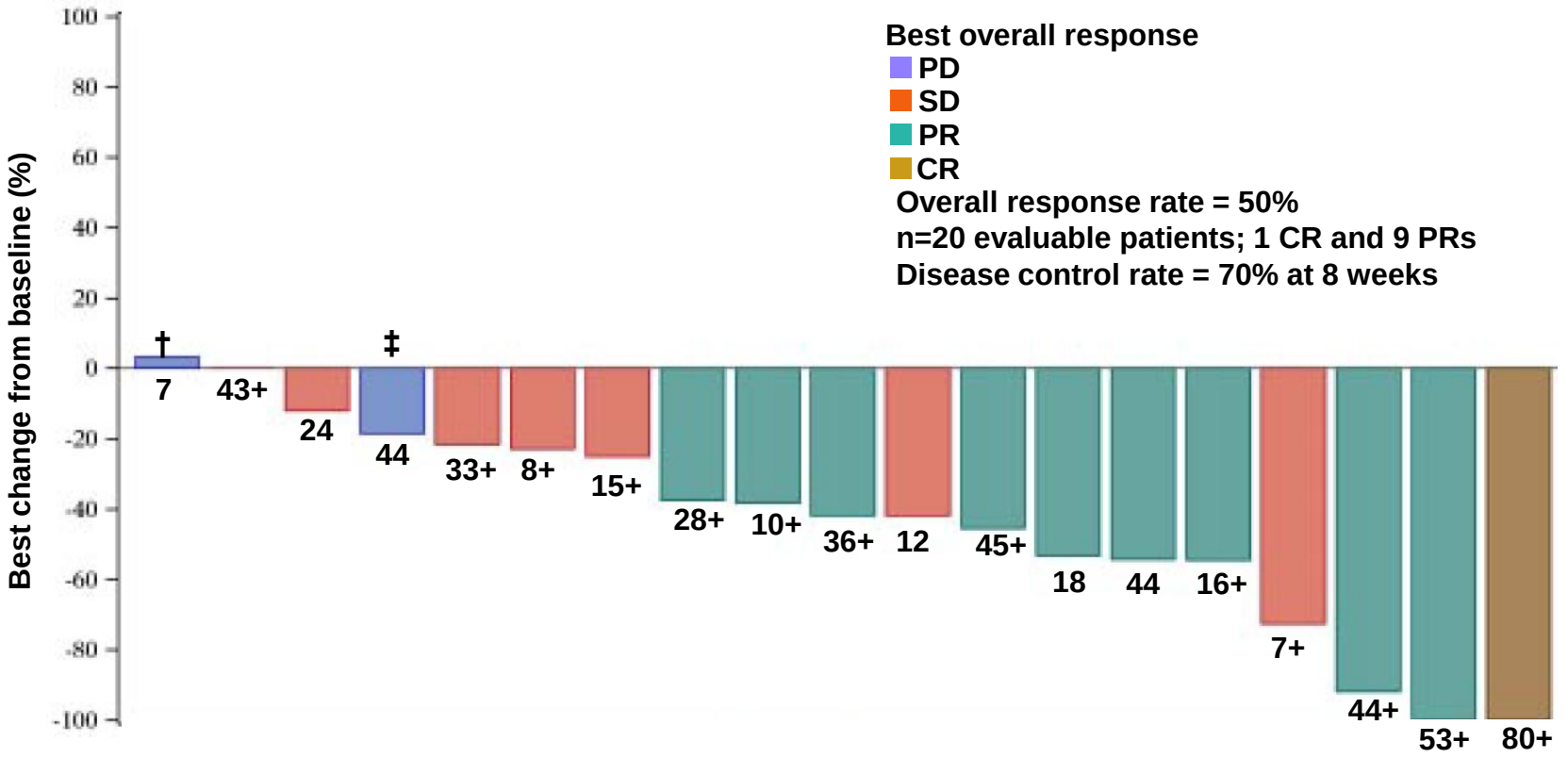






Comparing ALKi

Crizotinib in Advanced ROS1+ NSCLC*



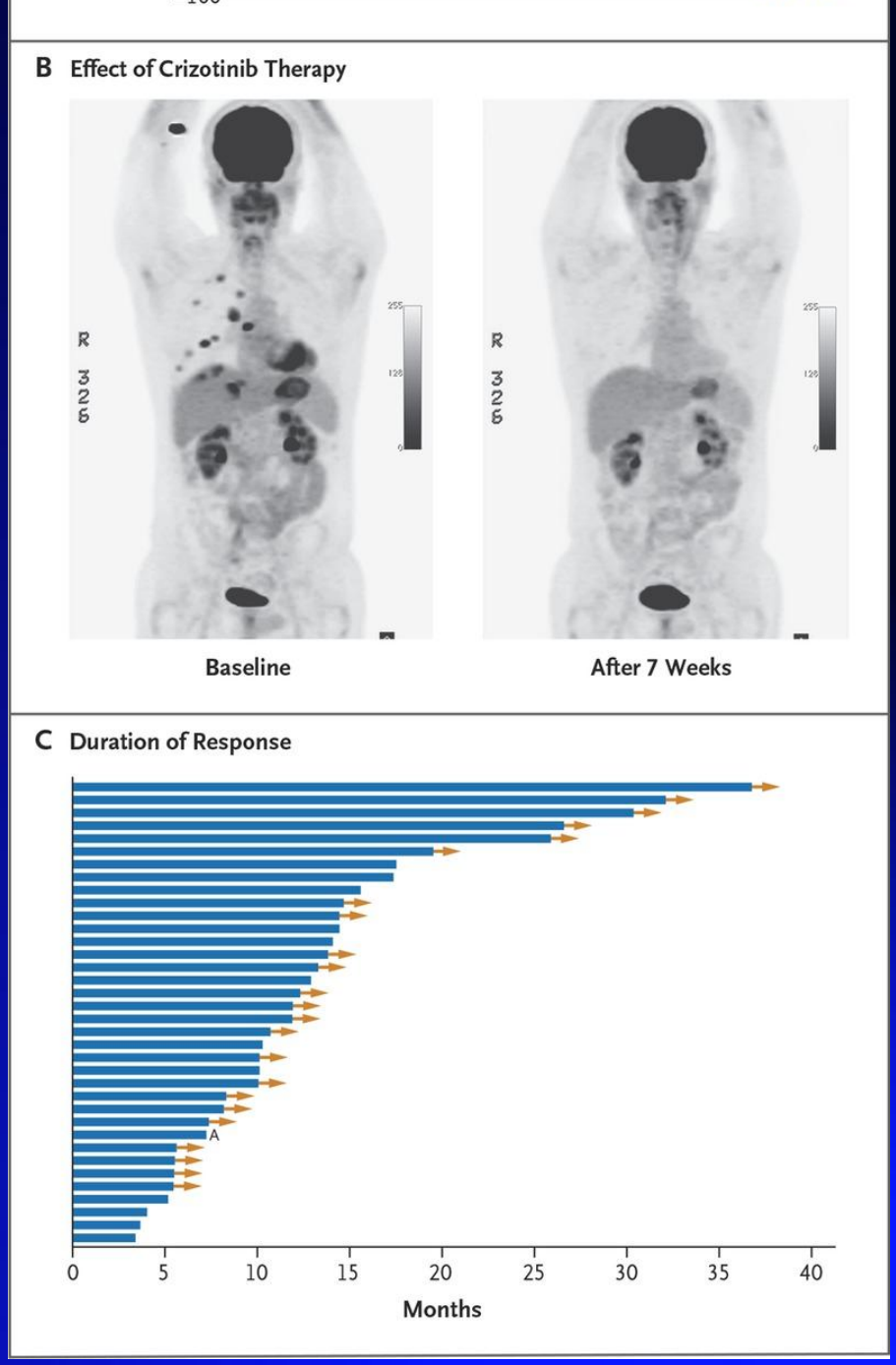
*Response-evaluable population excluding patients with early death/indeterminate response (n=19).
†Tumor ROS1 FISH-positive, but negative for ROS1 fusion gene expression. ‡Crizotinib held for >6 wks prior to first scans which showed PD. +, Treatment ongoing. For ongoing patients, duration of response/SD is the time from first documentation of tumor response/first dose to last available on treatment scan. For discontinued patients, duration is to the time of PD or death. Duration is in wks. Data in the database as of August 20, 2012.

Courtesy: Alice Shaw

Ou et al., ESMO 2012

ROS1

- Imaging
- Swimmers plot



Shaw et al. 2014 NEJM

BRAF

- Activating *BRAF*^{V600E} (Val600Glu) mutations ~1-2% of lung AdCA
- 6/22/17 FDA approved combination
  - dabrafenib (Tafinlar) - BRAFi
  - trametinib (Mekinist) - MEKi
- Oncomine Dx Target Test – NGS for:
  - BRAF, ROS1, and EGFR gene mutations
- AHC = PCR
- ORR, 1L = 64%

ESMO 2017: https://academic.oup.com/annonc/article/28/suppl_5/mdx440.054/4109966

HER2

Lung cancer patients with HER2 mutations treated with chemotherapy and HER2-targeted drugs: results from the European EUHER2 cohort.

Mazières et al. Ann Oncol 2016

- HER2 mutations 1-2% of lung adenocarcinomas.
- retrospective cohort study in European centers, n=38 centers, n=101 pts
- HER2 exon-20 insertion, treated with chemotherapy and/or HER2-targeted drugs.
- Concomitant EGFR mutations, ALK translocations, and ROS translocations were observed in 5, 1, and 1 patients, respectively.
- The median number of treatment lines was 3 (range: 1-11).
- The median overall survival was 24 months.
- Overall response rate (ORR) and the median progression-free survival (PFS) with conventional chemotherapy (excluding targeted therapies) were 43.5% and 6 months in first-line (n = 93), and 10% and 4.3 months in second-line (n = 52) therapies.
- Sixty-five patients received HER2-targeted therapies: trastuzumab = 57, neratinib = 14, afatinib = 9, lapatinib = 5, T-DM1 = 1.
- **ORR was 50.9%** and PFS was 4.8 months with **trastuzumab or T-DM1**.

MET

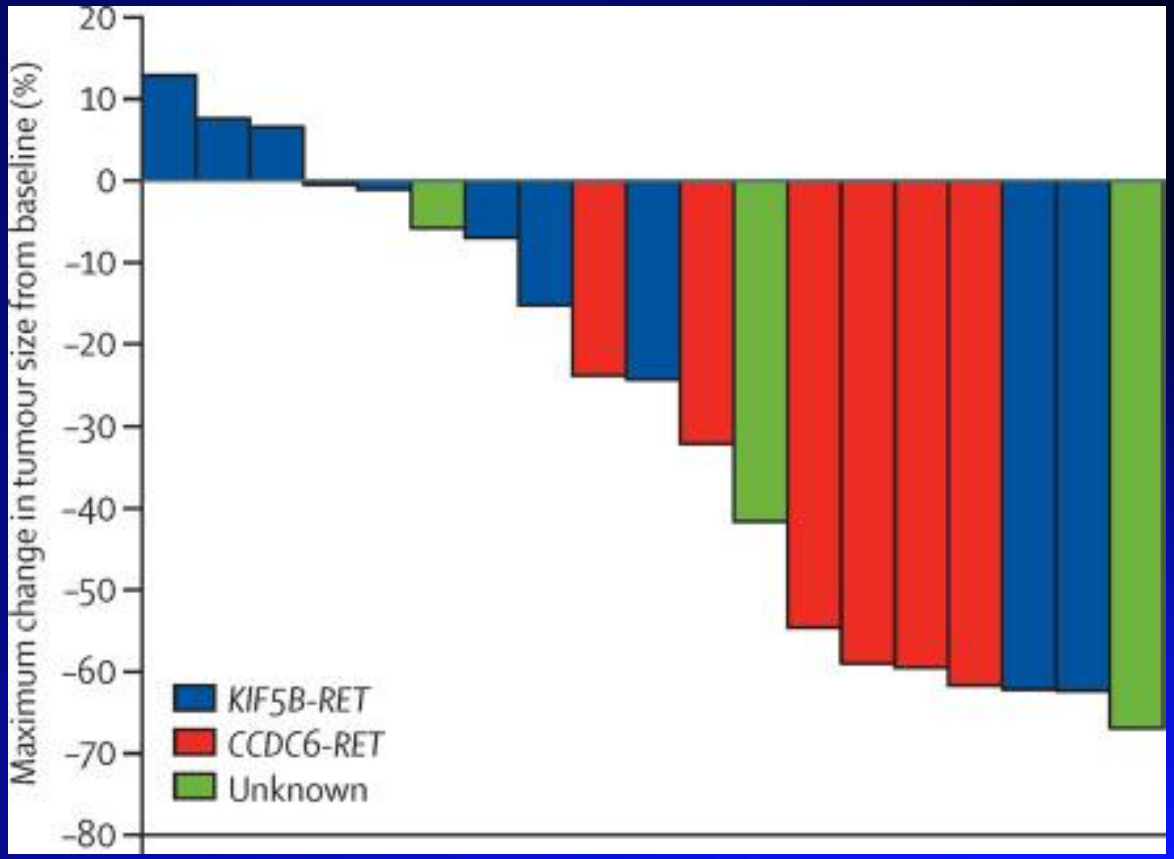
- *MET* alterations leading to exon 14 skipping occur in ~4% of lung carcinomas
- MET activation and sensitivity to MET inhibitors in vitro.
- Crizotinib, initially developed as a MET inhibitor, is approved for *ALK*-positive NSCLC
- PROFILE 1001
- N=18 pts
- **ORR 67%** (10/15 evaluable)

Efficacy & safety crizotinib in MET exon 14-altered NSCLC. Drilon et al. #ASCO16 Abs 108

http://ow.ly/Lu4m303LkfO

RET

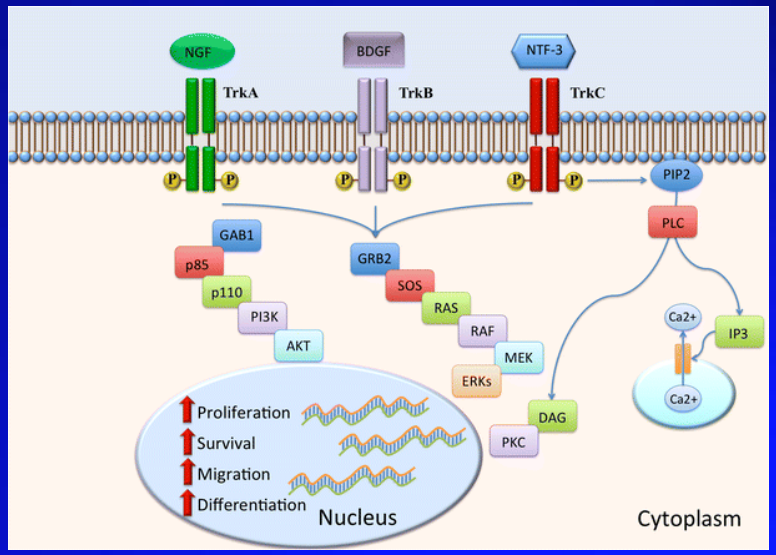
- Vandetanib
- n=19
- 2/7/2013 – 3/19/2015
- 53% ORR 9/17
- 47% ORR 9/19 ITT
- 90% DCR



Yoh et al. 2017 Lancet Resp Med - LURET

NTRK

- (neurotrophic) tropomyosin receptor kinase (Trk)
  - Protein: 3 TrkA, TrkB & TrkC receptors
  - Genes: NTRK1, NTRK2 and NTRK3
- entrectinib & LOXO-101 under clinical evaluation
- LOXO-101 phase I solid tumors ORR of 83% (5/6)
- 3% NSCLC NTRK alterations



Ricciuti et al. 2017 Med Oncol

Hong et al. AACR 2016

https://www.mycancergenome.org/content/disease/lung-cancer/ntrk1/315/

PM in Lung CA

Target	Drug	Line	ORR	Ref
EGFR	erlotinib	?	8.9%	unselected – PI 2004
	erlotinib	1L	65%	Rosell et al. Lancet Oncol - EURTAC
ALK	crizotinib	1L	74%	Solomon et al. 2014 NEJM
	ceritinib	1L	72.5%	Soria et al. Lancet 2017 – ASCEND 4
	alectinib	1L	82.9%	Peters et al. 2017 NEJM
ROS1	crizotinib	>1	72%	Shaw et al. 2014 NEJM
BRAF	dabra/tram	1L	64%	Planchard et al. 2017 JCO
HER2	traz, TDM1	~3	50.9%	Mazières et al. 2016 Ann Oncol
MET	meta analysis	??	67%	Drilon et al. 2016 ASCO - PROFILE001
RET	vandetanib	**>1**	53%	Yoh et al. 2017 Lancet R. M. - LURET

PM + Chemo

- During the early development of EGFR inhibitors, 4 large Phase RCTs combined erlotinib and gefitinib with first-line chemotherapy in unselected patients with NSCLC.
- **All these combination trials failed to show a survival benefit and were associated with increased toxicities**
- Intercalated erlotinib and showed an OS benefit of 3.1 months (18.3 versus 15.2 months) in the FAST-ACT2 study in an unselected population, but subgroup analysis demonstrated that the benefit was only in the *EGFR*-mutated population.
- The combination of pemetrexed and gefitinib has demonstrated a PFS benefit of 4.9 months (15.8 versus 10.9 months) in a phase II study of *EGFR*-mutated NSCLC (119).
- Combining chemotherapy upon progression on EGFR TKI therapy also did not demonstrate a benefit in the phase III IMPRESS trial (120).
- Combination of bevacizumab with erlotinib in an *EGFR*-mutated population demonstrated a PFS benefit of 6.3 months (16 versus 9.7 months), with OS data pending (121).
- The rational combination of cetuximab and afatinib appear to combine with favorable response rates, albeit with higher toxicity (23).

Imprecision in the Era of Precision Medicine in Non-Small Cell Lung Cancer [4/10/17] Sundar et al. Frontiers Medicine

http://ow.ly/ldS830ibVXj

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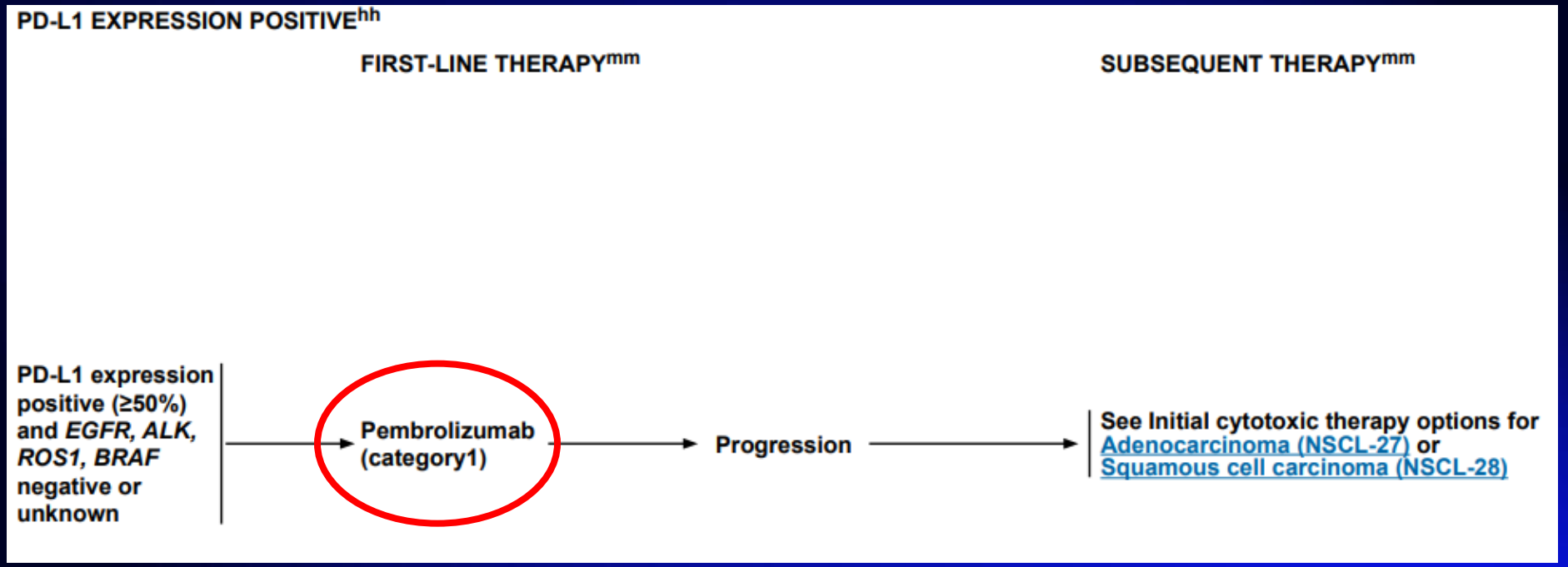
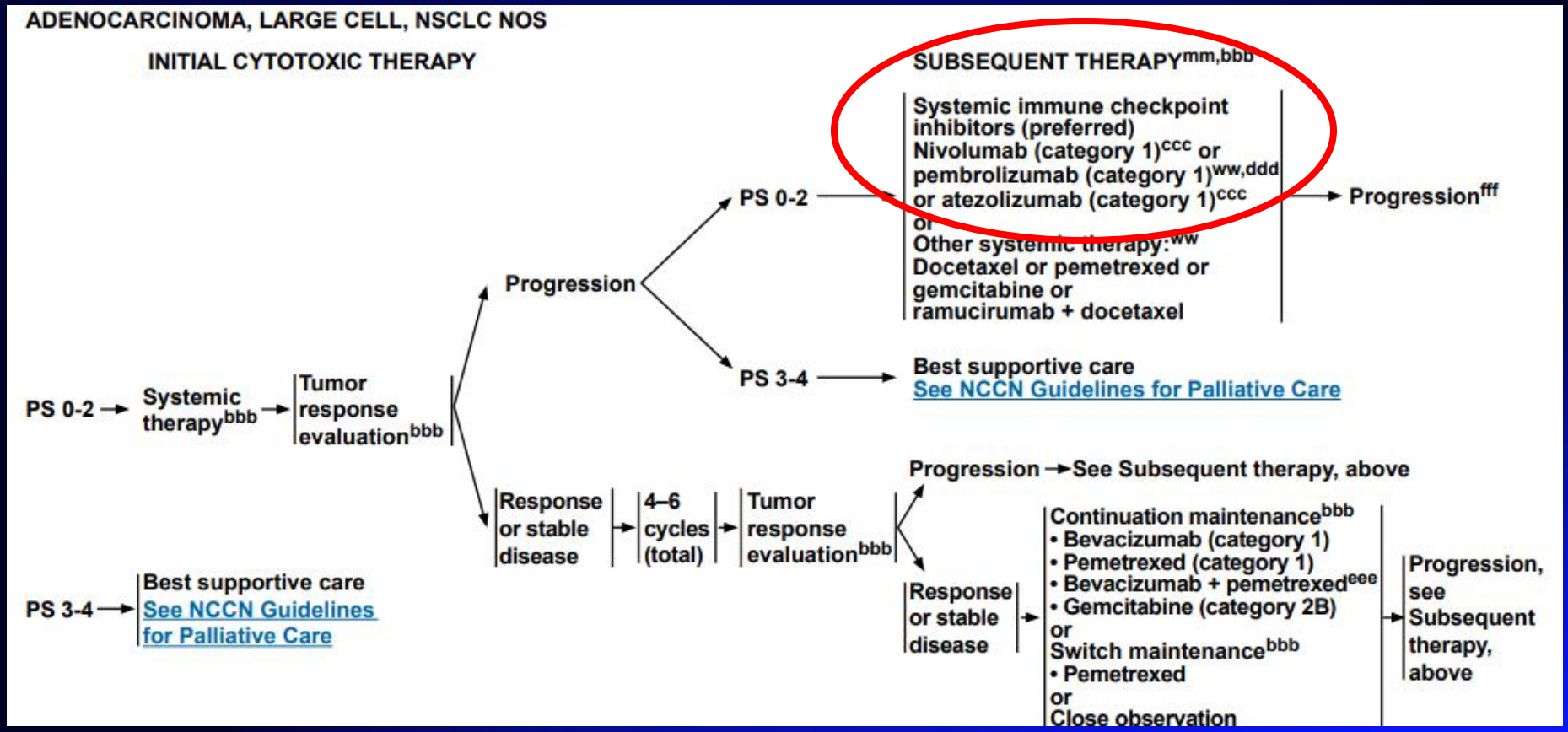
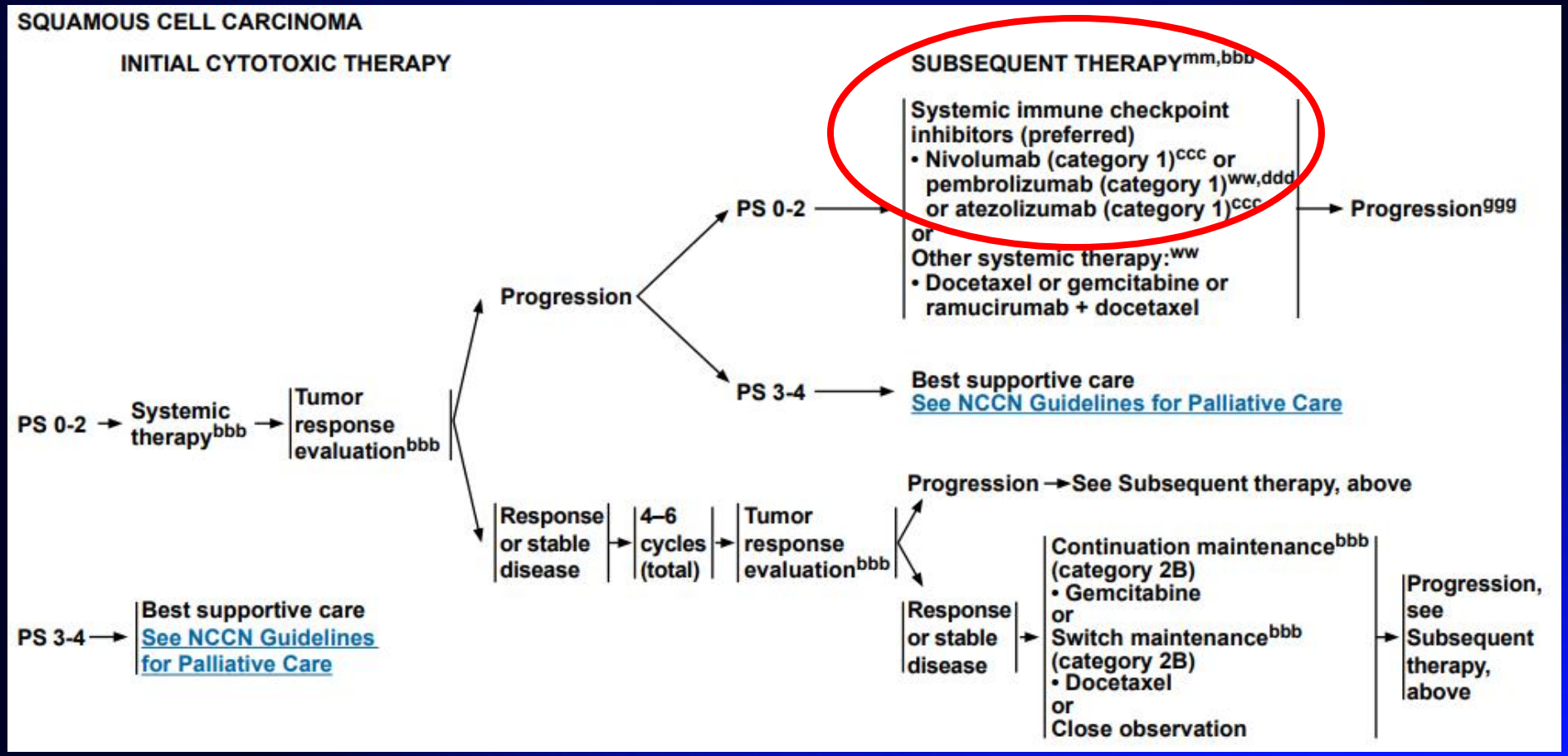
NCCN v2.2018
IO 1L Pembro



NCCN v2.2018 Ad
IO >1L – Nivo, pembro, Atezo



NCCN v2.2018 Sq
IO >1L – Nivo, pembro, Atezo



Immunotherapy

Assumes PM tx prior if EGFR or ALK alteration

- **Pembrolizumab**
  - 1L w/ Carbo/pemetrexed (AdCA) – PDL1 + or – combo ORR 55% vs 29% Carbo/pemet alone
  - 1L monoTx - tumor proportion score (TPS) ≥50%
  - >1L monoTx - PD-L1 TPS ≥1%
- **Nivolumab**
  - 2L PDL1 + or - & AdCA or Sq
- **Atezolizumab**
  - 2L PDL1 + or - & AdCA or Sq

Programmed Death-Ligand 1 (PD-L1) Immunohistochemistry Testing: A Review of Analytical Assays and Clinical Implementation in NSCLC [12/2017] Büttner et al. JCO http://ow.ly/bcvb30gTjFT

3 programmed death-1/programmed death-ligand 1 (PD-L1) inhibitors are currently approved for NSCLC.

Treatment with pembrolizumab in NSCLC requires PD-L1 IHC testing.

Nivolumab and atezolizumab are approved without PD-L1 testing, though US FDA-cleared complementary PD-L1 tests are available for both. PD-L1 IHC assays include

PD-L1 IHC 28-8 pharmDx (28-8)

PD-L1 IHC 22C3 pharmDx (22C3)

Ventana PD-L1 SP142 (SP142)

Ventana PD-L1 SP263 (SP263)

Differences in antibodies and IHC platforms have raised questions about comparability among these assays and their diagnostic use.

High concordance and interobserver reproducibility were observed with the 28-8, 22C3, and SP263 clinical trial assays for PD-L1 expression on tumor cell membranes, whereas lower PD-L1 expression was detected with SP142.

Immune-cell PD-L1 expression was variable and interobserver concordance was poor.

Inter- and intratumoral heterogeneity had variable effects on PD-L1 expression.

Conclusion

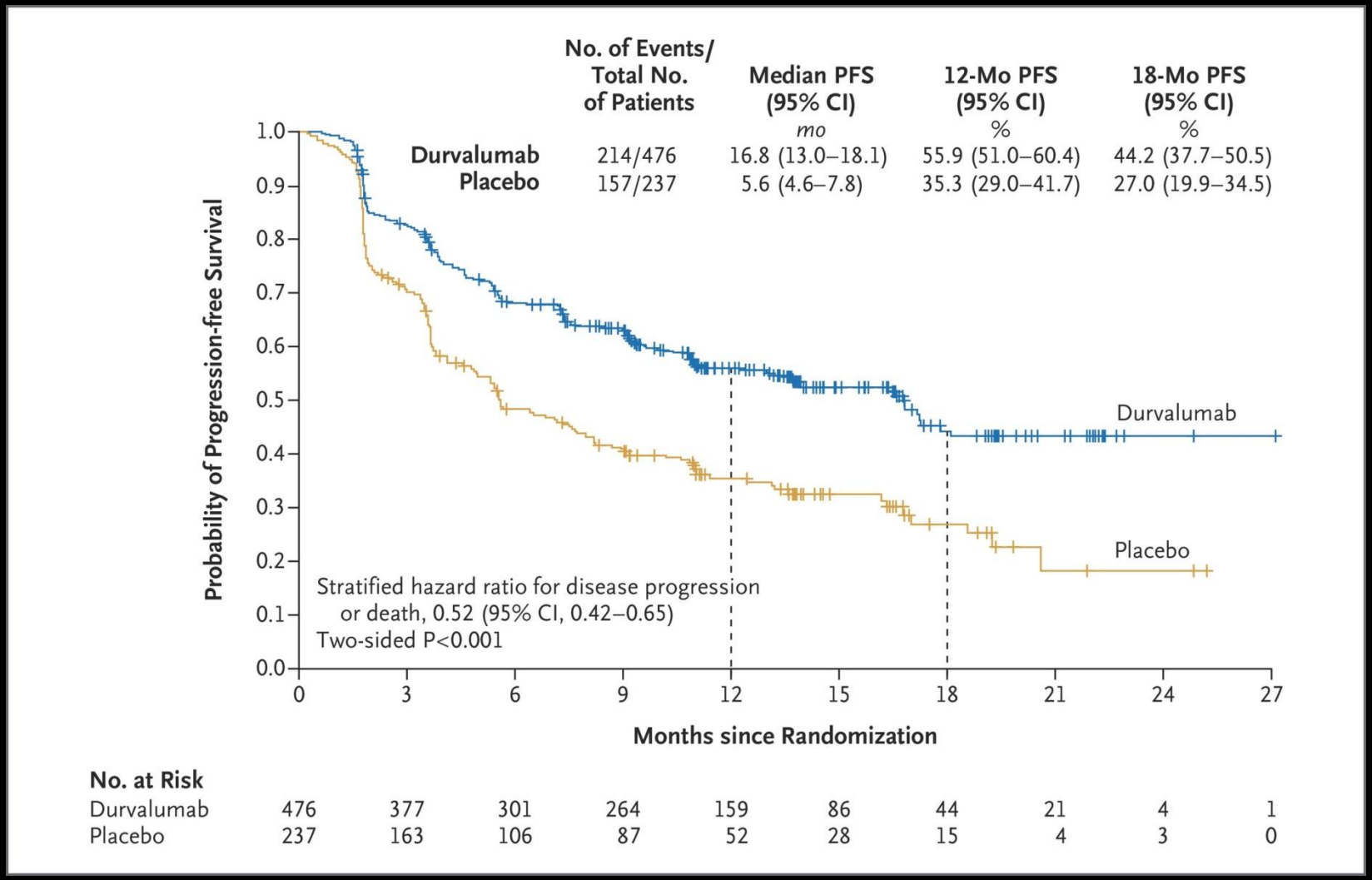
High concordance among 28-8, 22C3, and SP263 when assessing PD-L1 expression on tumor cell membranes suggests possible interchangeability of their clinical use for NSCLC but not for assessment of PD-L1 expression on immune cells. Development of LDAs requires stringent standardization before their recommendation for routine clinical use.

IO Stage III NSCLC

- PACIFIC trial
- Stage 3 NSCLC, n=713
- Durvalumab (anti–PDL1 Ab)
- PFS longer: 16.8 mon vs 5.6 mon, HR 0.52
- ORR 28.4% vs 16.0 %
- Med time to death or distant metastasis: 23.2 mon vs. 14.6 mon
- Safety was similar between the groups

Antonia et al. 2017 NEJM

Progression-free Survival in the Intention-to-Treat Population.



Antonia SJ et al. N Engl J Med 2017;377:1919-1929

SCLC – relapsed IO

ASCO 2017

	N	N+I
ORR	11%	25%
DCR	36%	49%
OS	4.1	7.9 mon

IASLC 2017 – high TMB

	TMB	N	N+I
ORR	low	5%	16%
	med	7%	22%
	high	21%	46%
1y OS	low	22%	23%
	med	26%	20%
	high	35%	62%

TMB = tumor mutation burden

Antonia et al. 2016 Lancet Oncol – Ph 1/2
Hellmann et al. 2017 ASCO Abstract 8503
Hellmann IASLC 2017 OA 07.03a http://ow.ly/kE2730ibURY

XRT and IO

- stereotactic body radiotherapy (SBRT) prior to pembrolizumab may help improve outcomes in patients with advanced solid tumors and multiple metastatic sites
- Well tolerated, and **abscopal** (out of field) responses were seen, suggesting further study is warranted for this treatment paradigm.

https://immunosym.org/daily-news/sbrt-could-augment-anti-pd-1-therapy-patients-metastatic-disease

Safety & clinical activity of pembrolizumab immunotherapy & multi-organ site ablative stereotactic body radiotherapy (iMOSART) in patients with advanced solid tumors [1/25/18] Lemons et al. #ImmunoOnc18 Abstract 20 http://ow.ly/sbG630i4Fez #ImmunoOnc #radonc #NCT02608385

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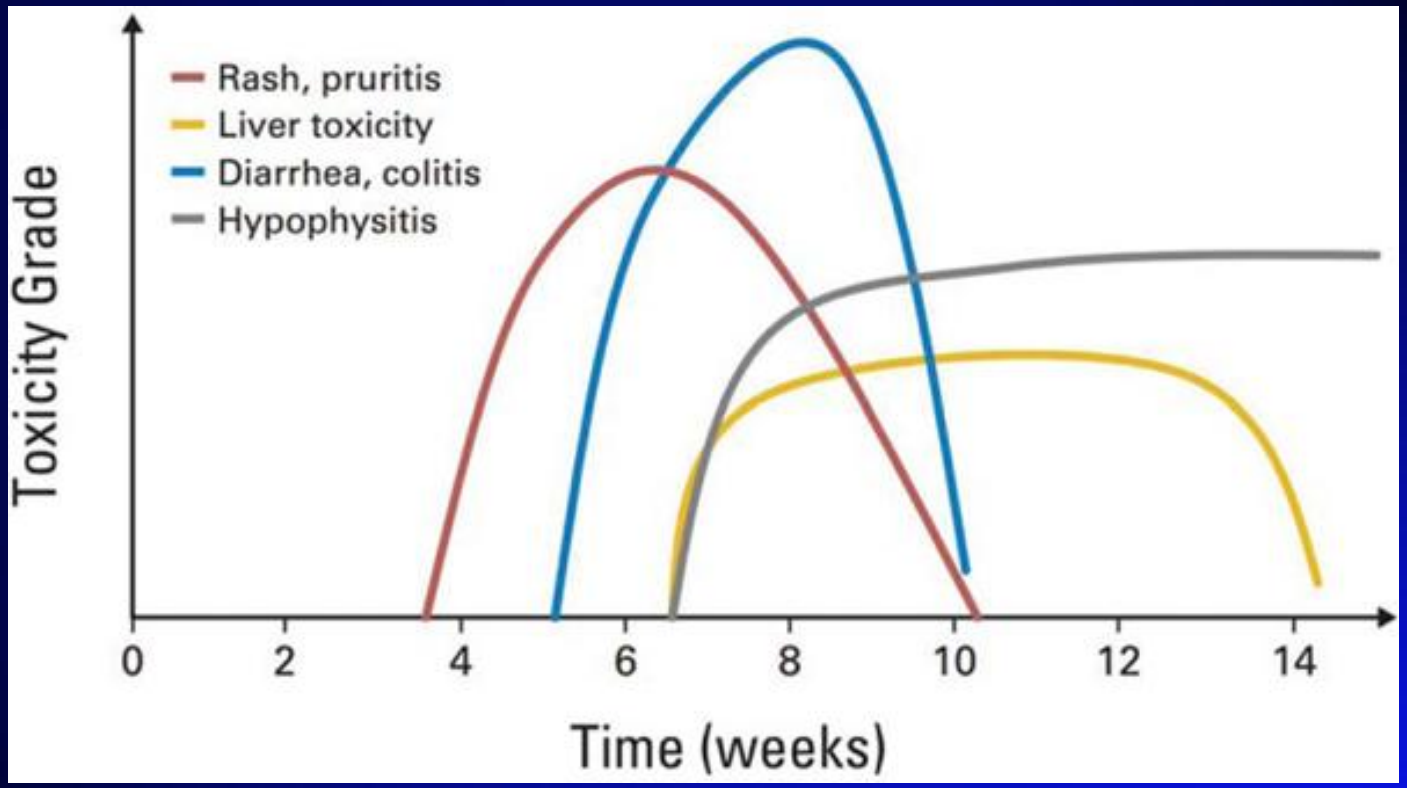
irAEs (1)



Immune-Related Adverse Events (irAE) Associated with Immune Checkpoint Blockade [1/11/18] Postow et al. NEJM http://ow.ly/WA8U30hJQPk

Managing immune checkpoint-blocking antibody side effects - Postow ASCO15 http://ow.ly/ysd9304fCS7

irAEs (2)

- Treatments w/ immunosuppressants
  - Corticosteroids
    - Systemic
    - Topical for rash
  - tumor necrosis factor-alpha antagonists
  - mycophenolate mofetil
  - other agents

irAE -> Efficacy = Controversial

"The correlation between efficacy of checkpoint-blocking antibodies and the occurrence of irAEs is controversial.[76,77] Patients can benefit from checkpoint-blocking antibodies without developing irAEs. Any potential association between PD-1/PD-L1–blockade and irAEs will be hard to determine as the incidence of significant irAEs is low."

irAEs Assoc w/ Nivolumab Efficacy in NSCLC

[9/21/17] Haratani et al. JAMA Onc
http://ow.ly/5gAW30fMbnj

- **Question:** Are irAEs associated with outcome of nivolumab in NSCLC?
- **Findings:** Multi-institutional medical record review including 134 patients with advanced or recurrent NSCLC treated with nivolumab monotherapy, landmark and multivariable analyses showed that immune-related adverse events were significantly associated with a better treatment outcome.

Outline

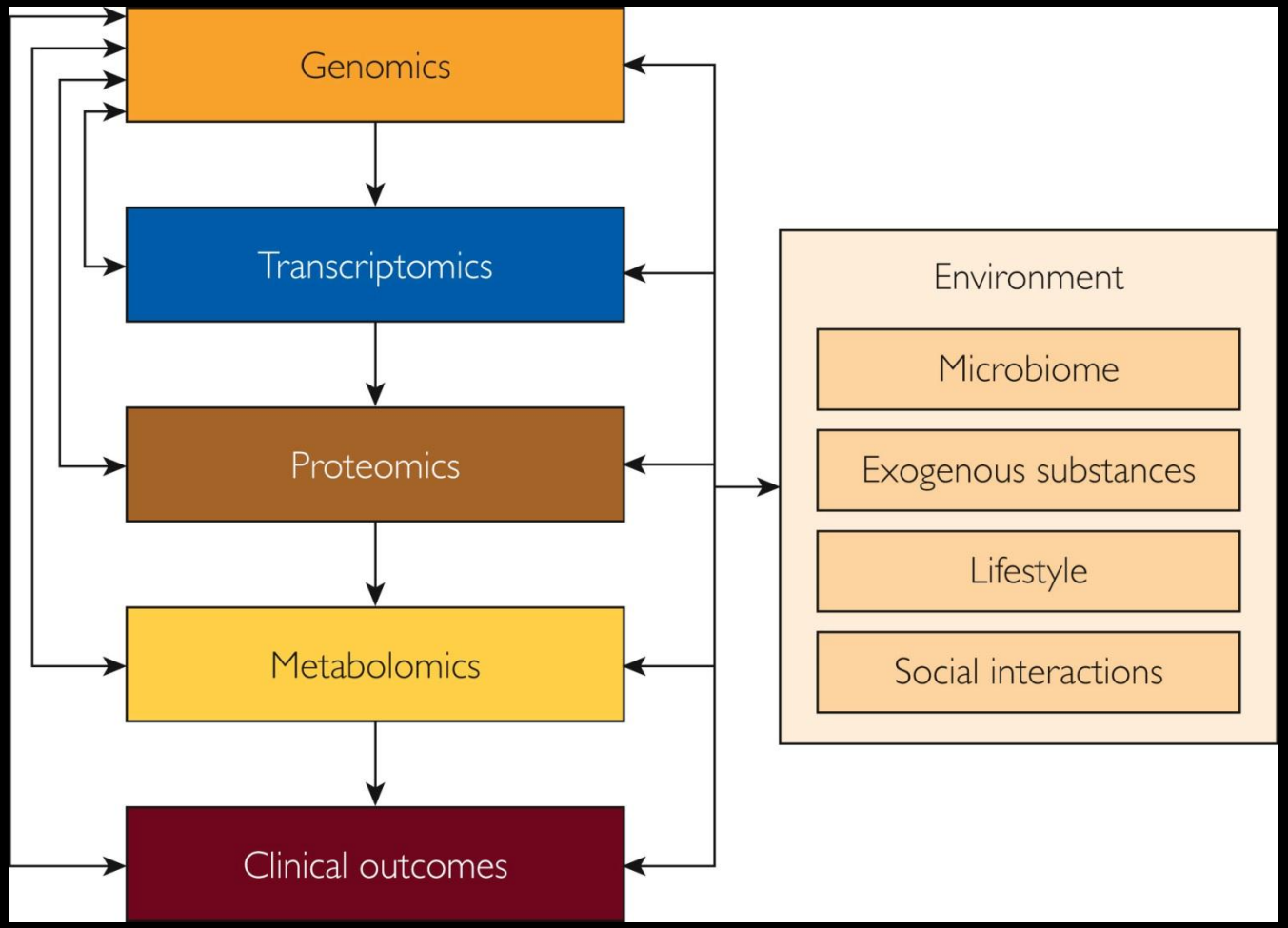
- Lung cancer
- What is Precision Medicine?
- PM in Lung CA
- Immunotherapy / Immuno-oncology
- Immune Related Adverse Events (irAEs)
- **Remaining Issues**

Remaining Issues

- Value
- Sequencing
- Pathology operational issues
- Combinations – PM, IO, chemo
- Biomarker testing
  - Timing – initial dx, surgery, mets?
  - # of tests, validation vs research
  - Tissue (+?amount) vs liquid biopsy
  - Cost & value

Pharmacogenomics: Precision Medicine and Drug Response

Weinshilboum & Wang



Mayo Clinic Proceedings 2017 92, 1711-1722DOI: (10.1016/j.mayocp.2017.09.001)

Take Home

- Lung cancer Tx is evolving to PM and IO directed
- Optimal implementation & value is evolving
- PM – high response rates, but resistance
- IO – lower response rates, but longer benefit
- New AE and irAEs to consider
- Future research on combinations needed

Q & A

Q: What are current precision medicine targets in lung cancer?

A: EGFR, ALK, ROS1, PDL1, BRAF, HER2, RET, MET, and others emerging

Q: What is the abscopal effect?

A: The out of [radiation] field effect – ie localized radiation treatment of a cancer mass causes shrinking of cancers outside the localized area

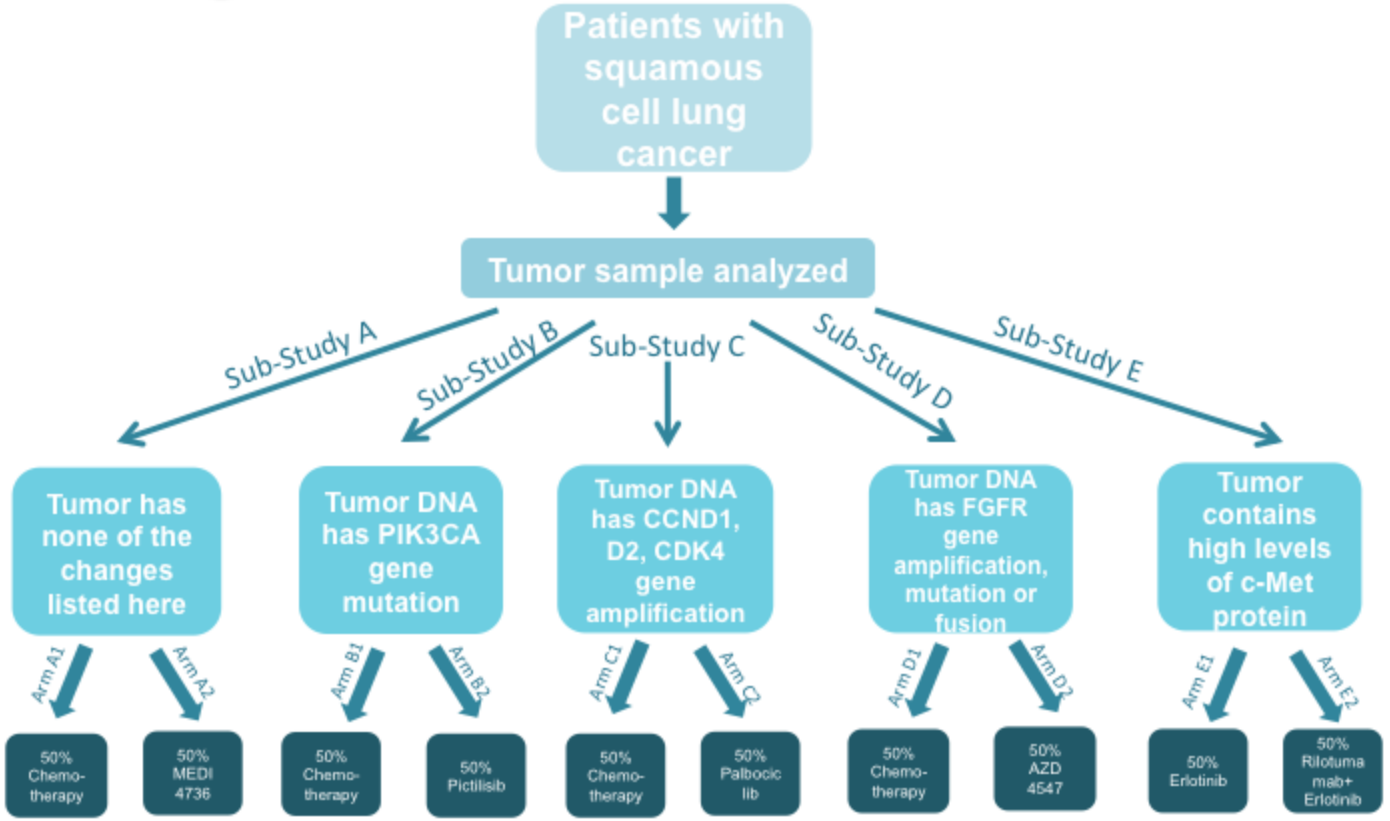
Q: What are the kinetics of immune-related adverse events (irAEs)?

A: Skin -> GI (colitis) -> hypophysitis/hypothyroidism -> liver

Q: What is the treatment of irAEs?

A: Steroids first. Then other immunosuppressants.

Lung-MAP Sub-Studies for Treatment

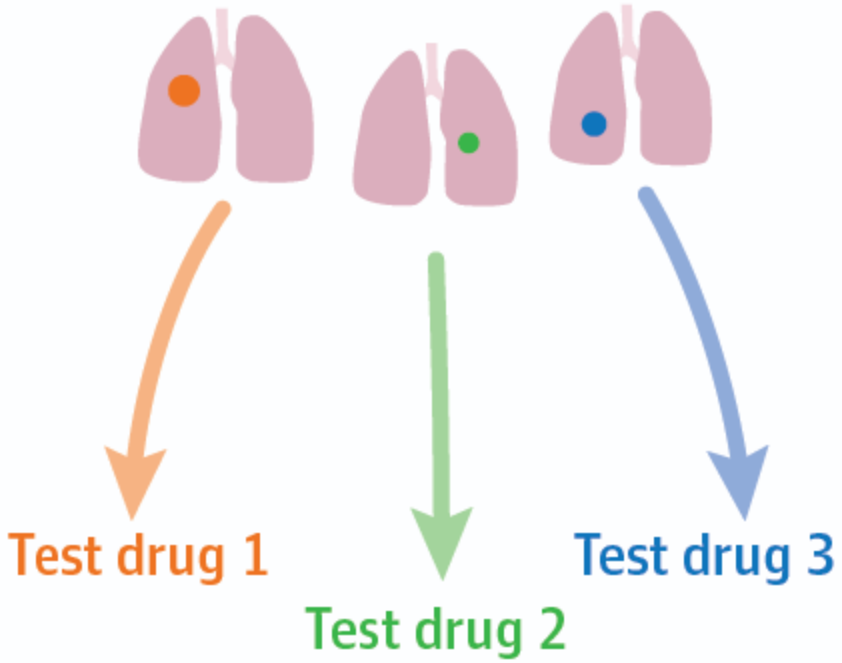


Novel precision medicine trial designs

Umbrella trial

1 type of cancer

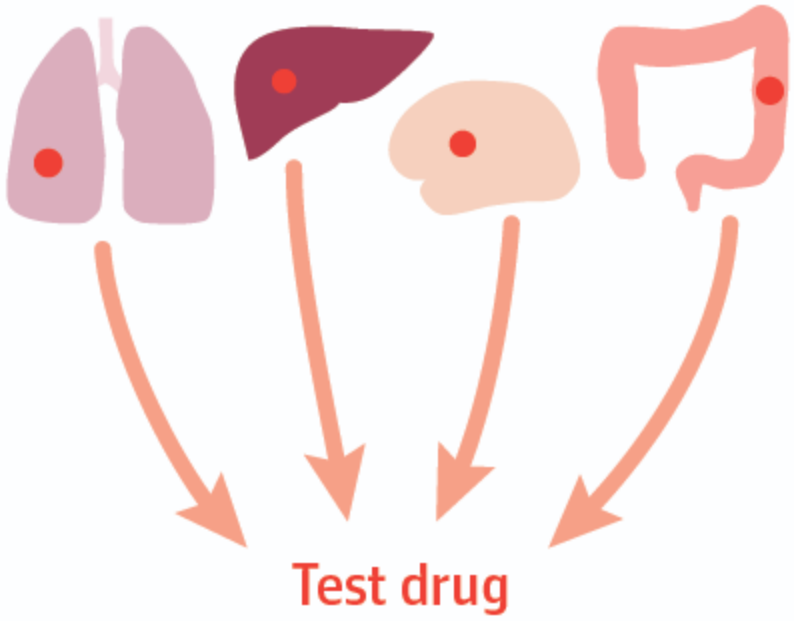
Different genetic mutations (●●●)



Basket trial

Multiple types of cancer

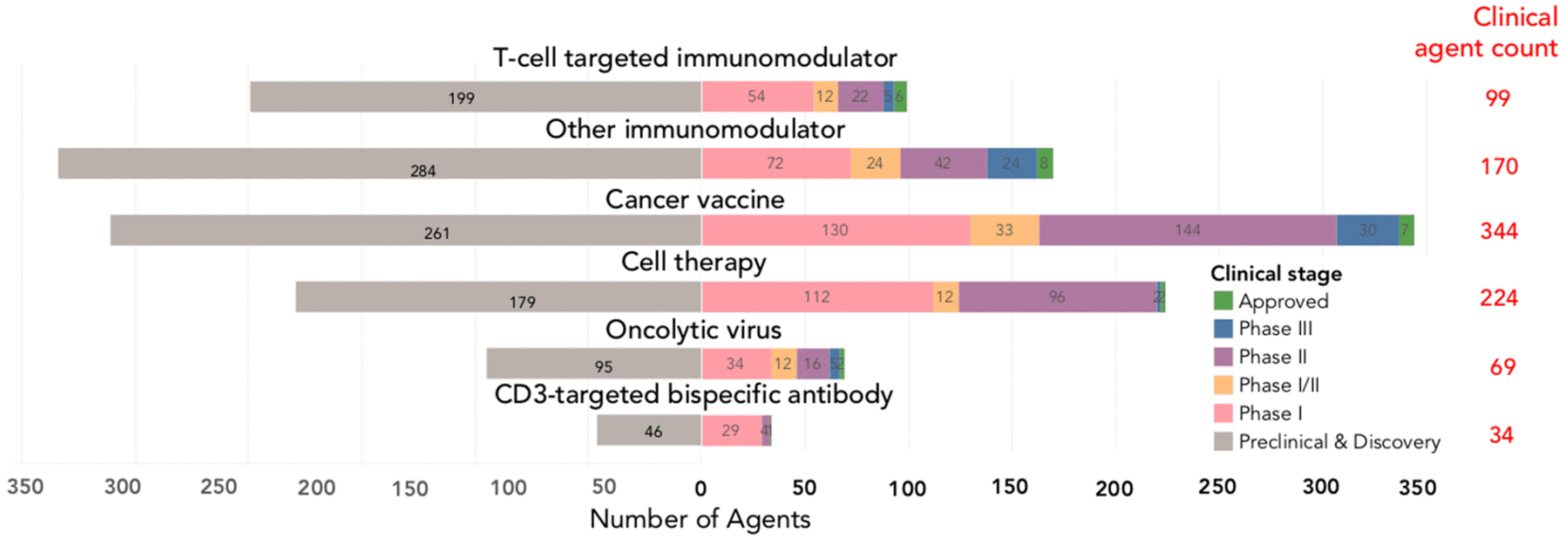
1 common genetic mutation (●)



There are 2,004 cancer immunotherapies crowding into the pipeline. Now what? [12/7/17] @JohnCendpts @endpts http://ow.ly/FbVU30h5w3I

2,004 IO AGENTS IN DEVELOPMENT

940 AGENTS ARE IN CLINICAL STAGES, AND 1,064 IN PRECLINICAL



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

CANCER RESEARCH INSTITUTE The Anna-Maria Kellen Clinical Accelerator

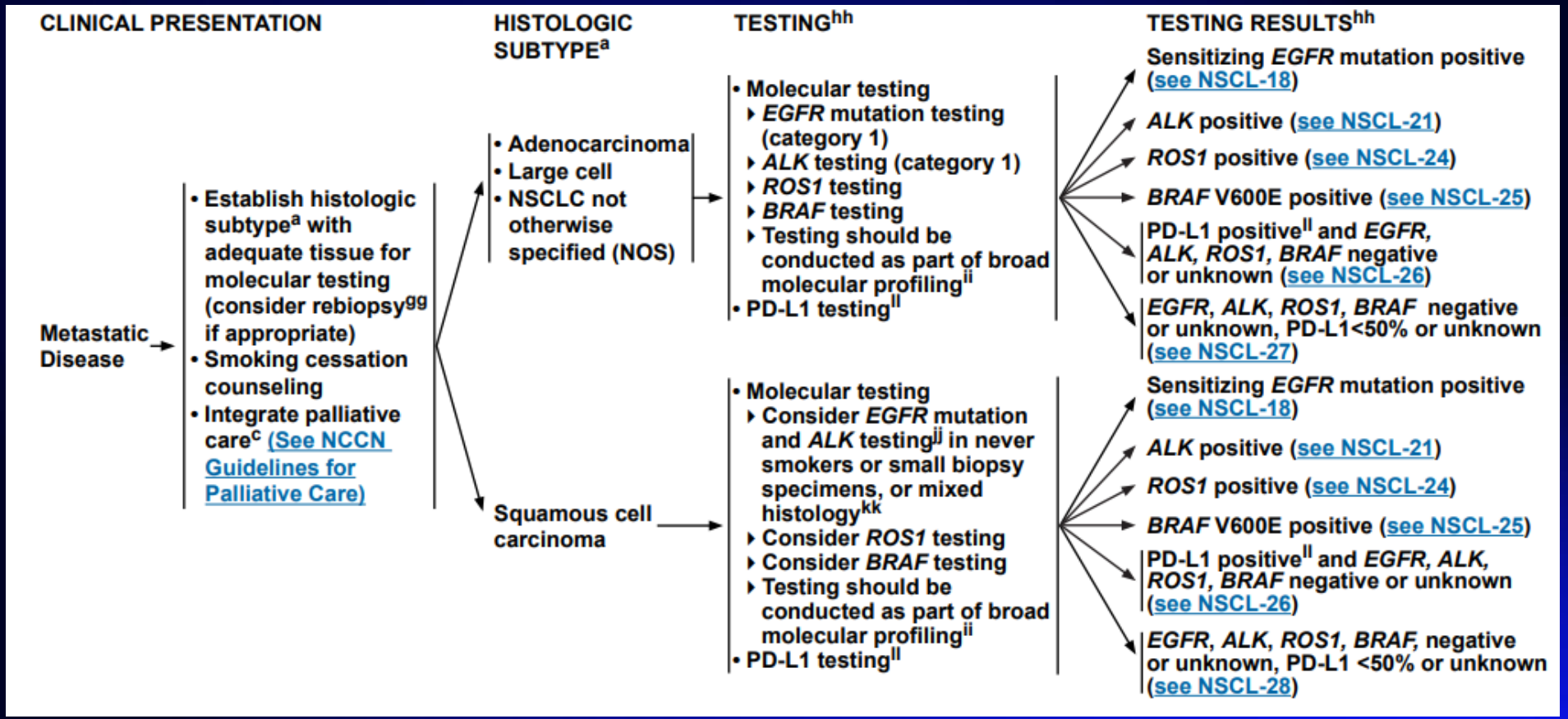
irAEs (3)

Toxicities of Immunotherapy for the Practitioner [2015] - Weber et al. #JCOResearch http://ow.ly/PeEZy #ImmunoOnc

Immunotherapy Ushers in New Era of Toxicity Management [10/6/16] @ClinOncNews **http://ow.ly/NLuR305qk0Y #ImmunoOnc #SuppOnc**

Pearls for Managing Immune-Related Toxicities [10/10/16] by Caroline Helwick @ASCOPost **http://ow.ly/njXX305qjSm #ImmunoOnc #SuppOnc**

- **Oncogenic Driver Mutations & Environ Factors: Japan Mol Epi Lung Cancer Study [5/9/16] Kawaguchi et al. @JCO_ASCO http://ow.ly/tYvU300fJU6**
- **Other driver alterations**
  - *DDR2*


CLINICAL PRESENTATION
HISTOLOGIC SUBTYPE[a]
TESTING[hh]
TESTING RESULTS[hh]
Metastatic Disease
• Establish histologic subtype[a] with adequate tissue for molecular testing (consider rebiopsy[gg] if appropriate)
• Smoking cessation counseling
• Integrate palliative care[c] (See NCCN Guidelines for Palliative Care)
• Adenocarcinoma
• Large cell
• NSCLC not otherwise specified (NOS)
• Molecular testing
▸ EGFR mutation testing (category 1)
▸ ALK testing (category 1)
▸ ROS1 testing
▸ BRAF testing
▸ Testing should be conducted as part of broad molecular profiling[ii]
• PD-L1 testing[ll]
Sensitizing EGFR mutation positive (see NSCL-18)
ALK positive (see NSCL-21)
ROS1 positive (see NSCL-24)
BRAF V600E positive (see NSCL-25)
PD-L1 positive[ll] and EGFR, ALK, ROS1, BRAF negative or unknown (see NSCL-26)
EGFR, ALK, ROS1, BRAF negative or unknown, PD-L1<50% or unknown (see NSCL-27)
Squamous cell carcinoma
• Molecular testing
▸ Consider EGFR mutation and ALK testing[ij] in never smokers or small biopsy specimens, or mixed histology[kk]
▸ Consider ROS1 testing
▸ Consider BRAF testing
▸ Testing should be conducted as part of broad molecular profiling[ii]
• PD-L1 testing[ll]
Sensitizing EGFR mutation positive (see NSCL-18)
ALK positive (see NSCL-21)
ROS1 positive (see NSCL-24)
BRAF V600E positive (see NSCL-25)
PD-L1 positive[ll] and EGFR, ALK, ROS1, BRAF negative or unknown (see NSCL-26)
EGFR, ALK, ROS1, BRAF, negative or unknown, PD-L1 <50% or unknown (see NSCL-28)