Advanced NSCLC*

Oncogene driver

- **EGFR:** Osimertinib**, erlotinib, afatinib, gefitinib, erlotinib + ramucirumab
- **ALK:** Alectinib**, brigatinib, lorlatinib, crizotinib, ceritinib
- **ROS1:** Entrectinib**, crizotinib, ceritinib
- **RET:** Selpercatinib**, pralsetinib**, cabozantinib
- **BRAF V600E:** Dabrafenib / trametinib**
- **MET Exon 14:** Capmatinib, tepotinib, crizotinib
- **NTRK:** Larotrectinib, entrectinib
- **EGFR Exon 20†:** Larotrectinib, entrectinib
  KRAS G12C†: Sotorasib

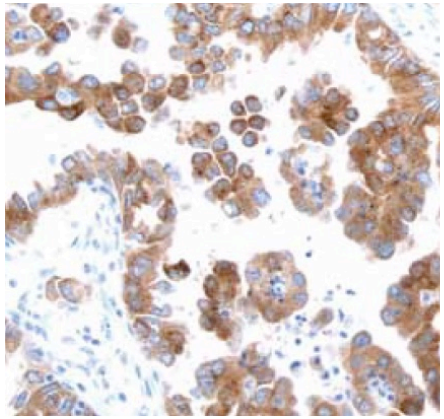
No driver mutation

Adenocarcinoma	Squamous
PDL1 ≥ 1% - Pembrolizumab - Carboplatin + pemetrexed + pembrolizumab - Carboplatin + paclitaxel + bevacizumab + atezolizumab - Carboplatin + abraxane + atezolizumab - Nivolumab + ipilimumab - Nivolumab + ipilimumab + platinum + pemetrexed **PDL1 ≥ 50% (including above)** - Atezolizumab - Cemiplimab	**PDL1 ≥ 1%** - Pembrolizumab - Carboplatin + paclitaxel + pembrolizumab - Carboplatin + paclitaxel + bevacizumab + atezolizumab - Carboplatin + abraxane + pembrolizumab - Nivolumab + ipilimumab - Nivolumab + ipilimumab + platinum + paclitaxel **PDL1 ≥ 50% (including above)** - Atezolizumab - Cemiplimab

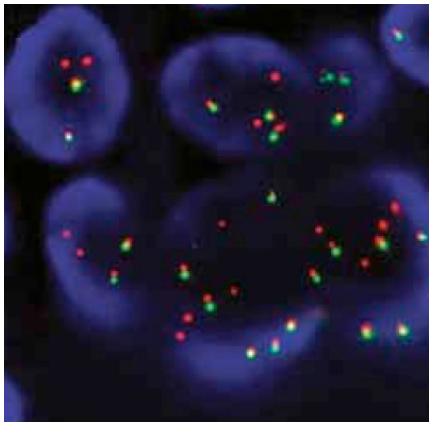
*Locally advanced (not amenable to chemoXRT) or metastatic
**Indicates preferred options
†Second line setting only

Testing methodologies

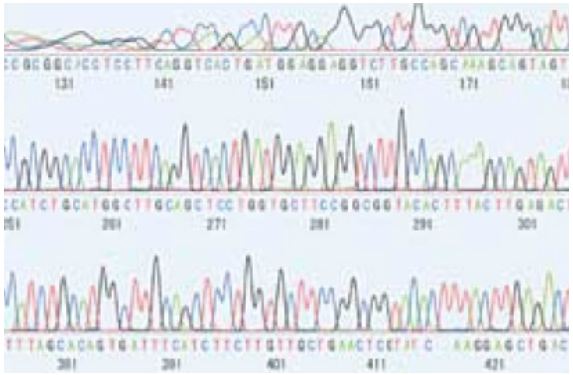
Immunohistochemistry



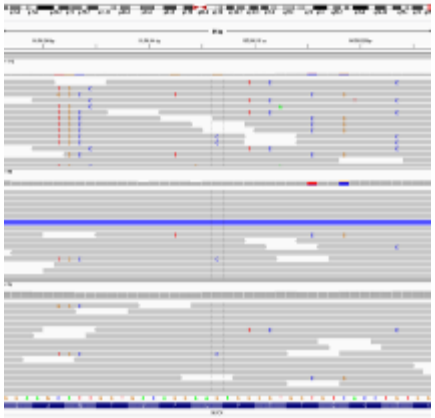
FISH



RT-PCR



Next Generation Seq



Current actionable oncogenes

- **IHC** – ALK, ROS1, MET, HER2, PD-L1
- **FISH** – ALK, ROS1, RET, NTRK, MET amp, HER2 amp, *NRG1**
- **RT-PCR** – EGFR, KRAS, BRAF, HER2 Exon 20, *FGFR3*, PIK3CA**
- **NGS** – All of the above
  - *RNA-NGS may be better for MET Ex14, gene fusions*
  - ***FISH may be better for gene amplification than NGS***

***Represent emerging oncogene targets*

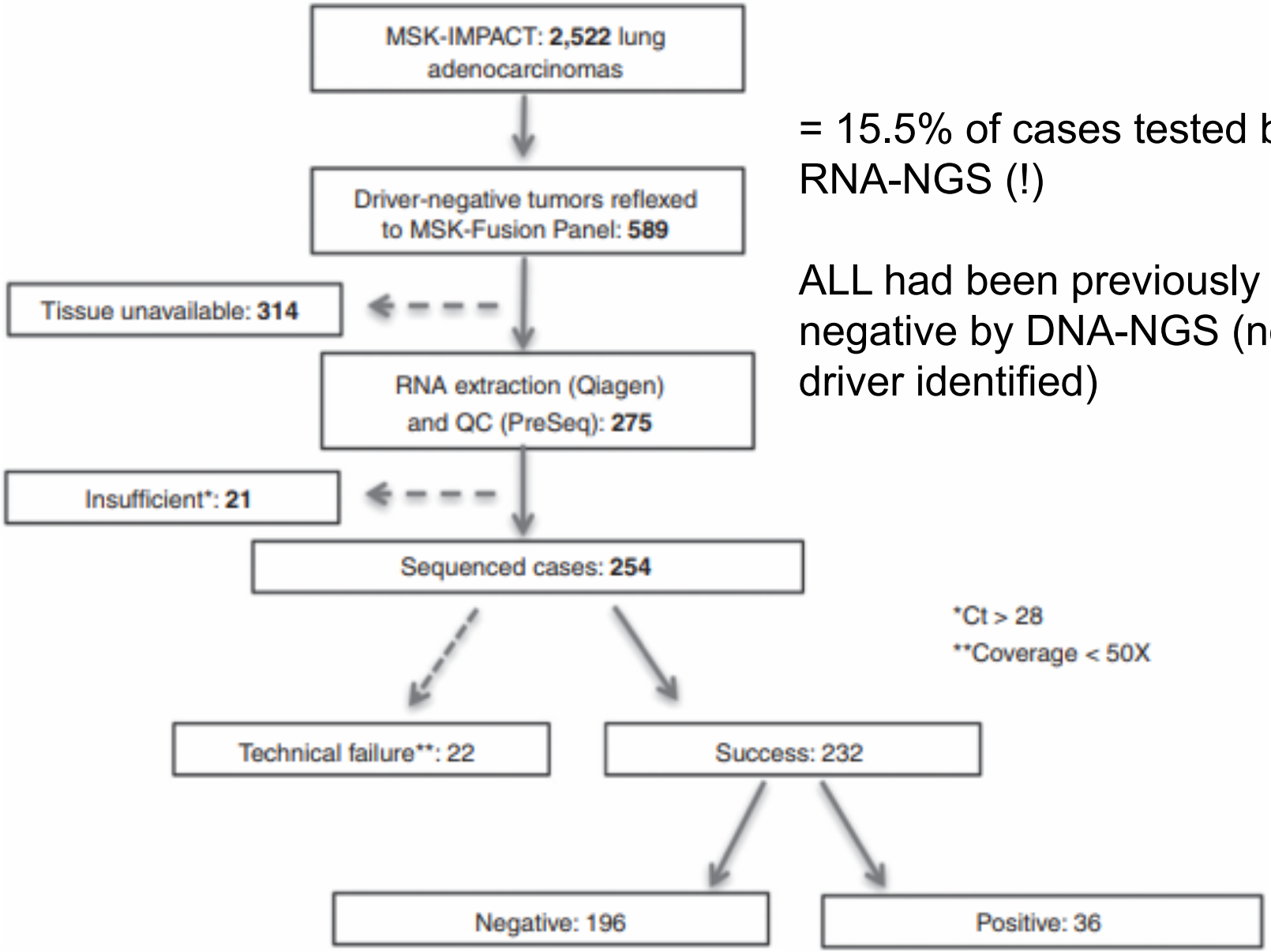
IHC – practical applications

- Used as target in antibody drug conjugate trials[1]

ADC	Target	NCT
DS-8201a	HER2	NCT02564900
ABBV-399	MET	NCT03311477
DS-1062a	TROP2	NCT03401385
ASG-22CE	Nectin-4	NCT02091999
PF-06647020	PTK7	NCT02222922
HuMax-AXL-ADC	AXL	NCT02988817

Different types of NGS

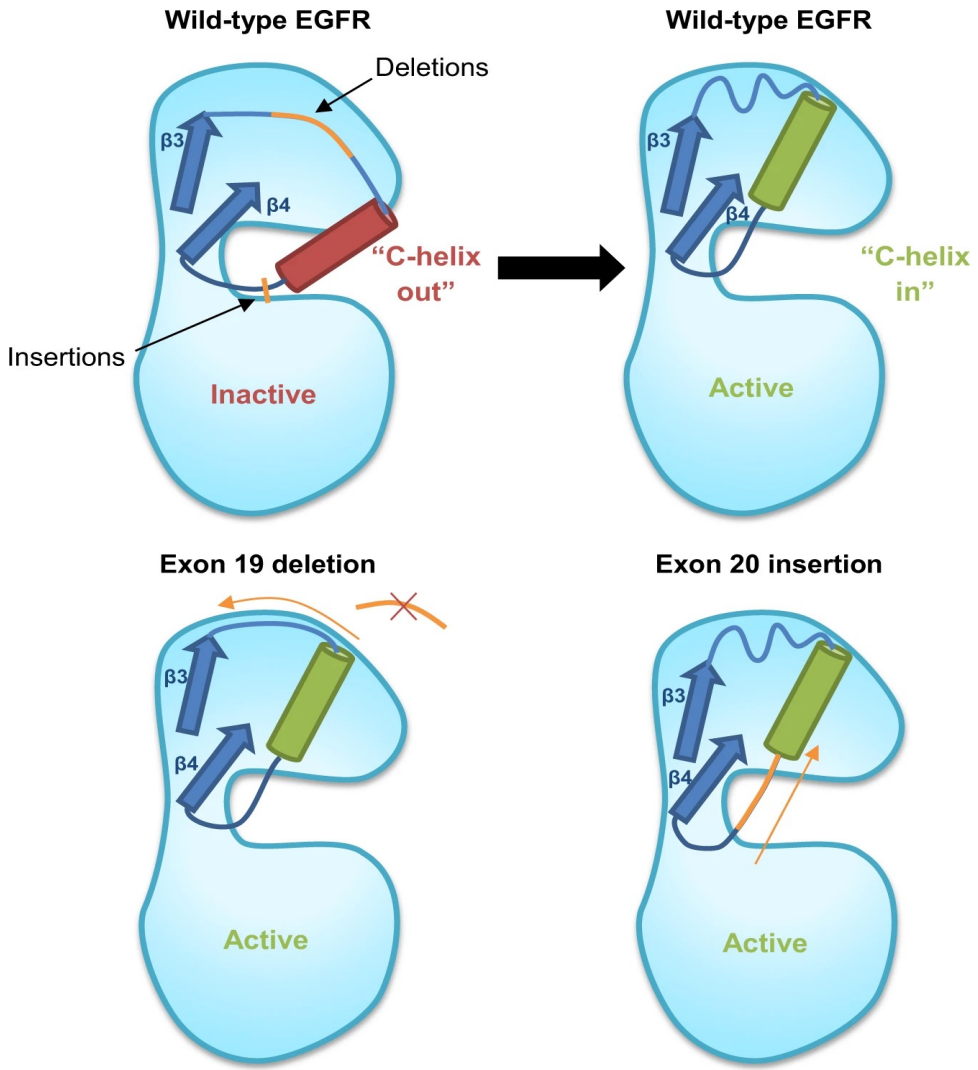
	DNA-NGS (capture)	RNA-NGS (amplicon)	RNA-NGS (capture)
Major strength(s)	• Fusion targets already included in many NGS assays • Does not require a second/separate assay	• Already included in some commercially available assays (e.g. Oncomine)	• Best performance for challenging fusions
Major weakness(es)	• Significant false negative for challenging fusions *(e.g. ROS1-GOPC)*	• Like qRT-PCR, will only detect fusions where there is a primer for the fusion partner	• Performance relies on RNA quality



= 15.5% of cases tested by RNA-NGS (!)

ALL had been previously negative by DNA-NGS (no driver identified)

EGFR mutations



Knowing that your patient is EGFR positive is **not** enough! You need to know which mutations are sensitizing to TKIs

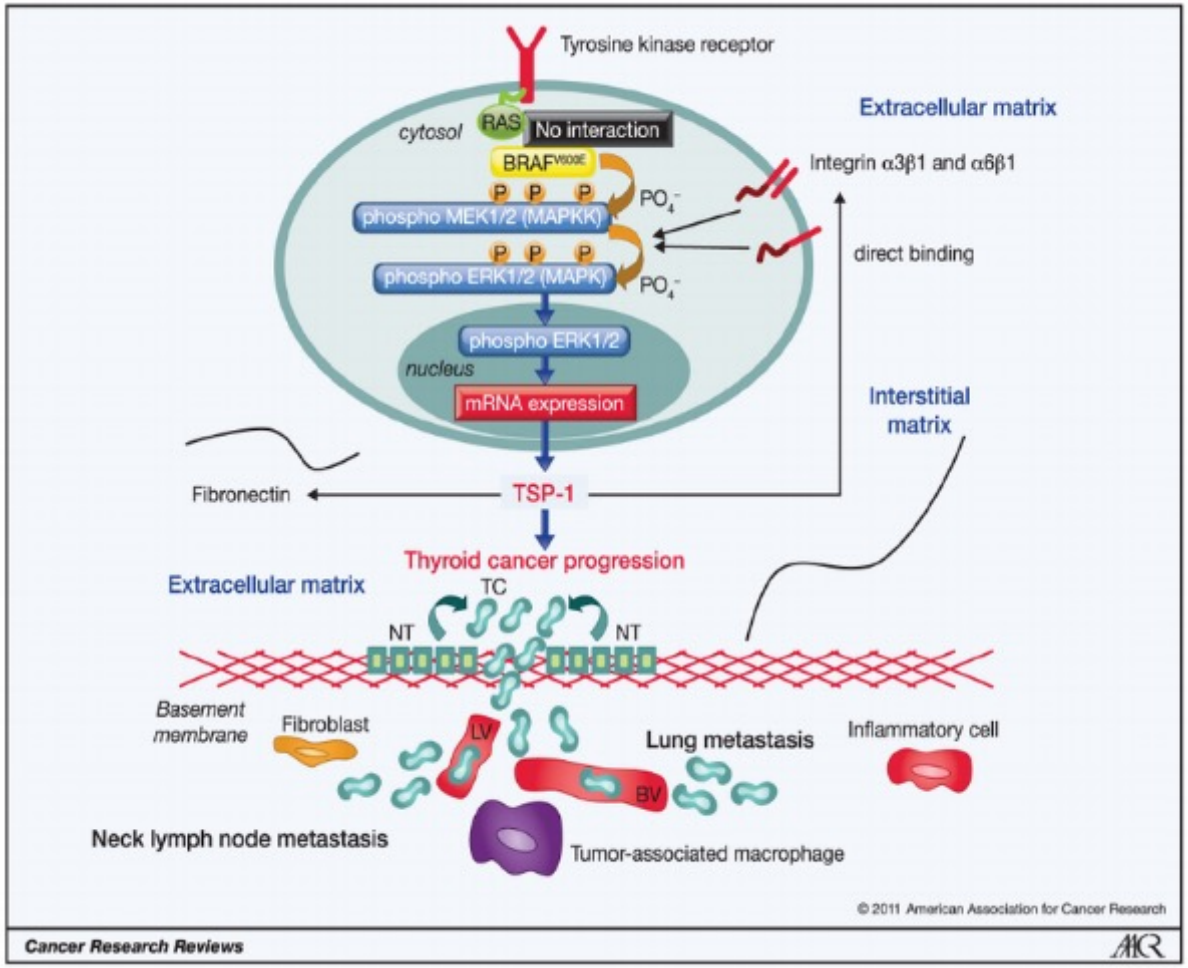
- *Drug-sensitive*: Exon 19 del, L858R
- *Less drug-sensitive*: G719, L861Q
- *Insensitive*: Exon 20 insertions (except FQEA)

For EGFR Exon 20 insertions

- Clinical trial (preferred)
- Amivantamab
- Afatinib > osimertinib > erlotinib

Vyse & Huang *Nature* 2019

BRAF mutations

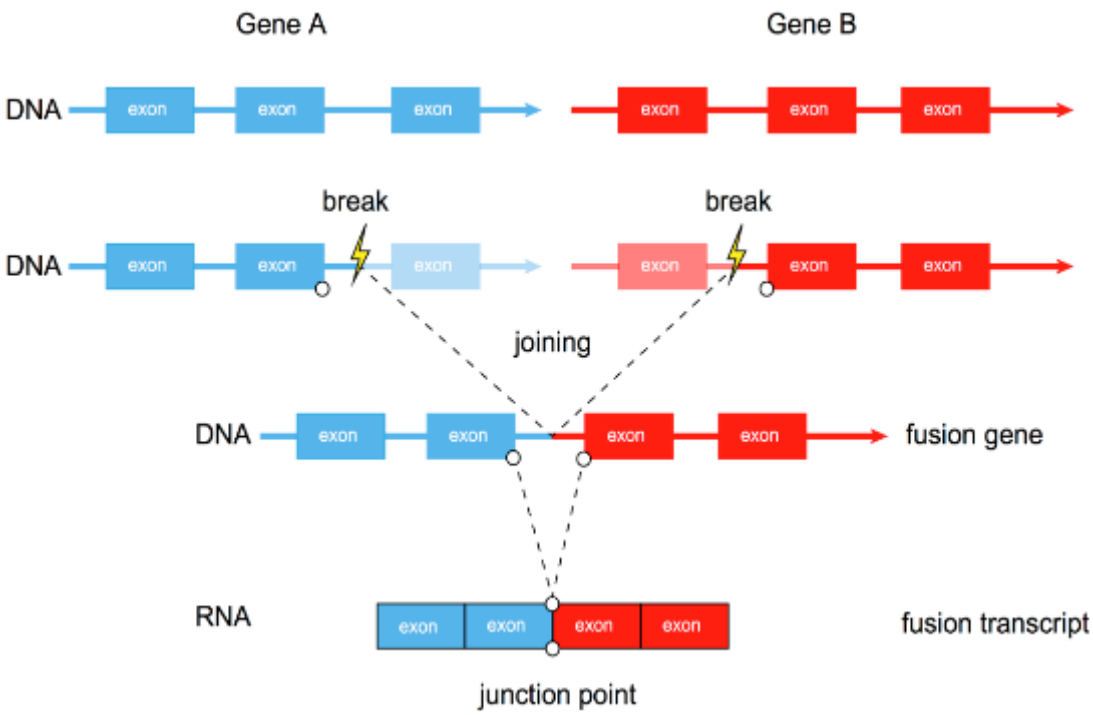


BRAF V600E/K/D/R mutations will respond to BRAF + MEK TKIs

Do **not** use these for other BRAF mutations (eg, G465A) - many do not have the same mechanism for activating signaling

Gene fusions (*ALK, ROS1, RET, NTRK, NRG1)*

Gene Fusion – a hybrid gene formed erroneous rejoining and replication of DNA. Leads to fused RNA transcript and abnormal (or chimeric) fusion protein.



Key points

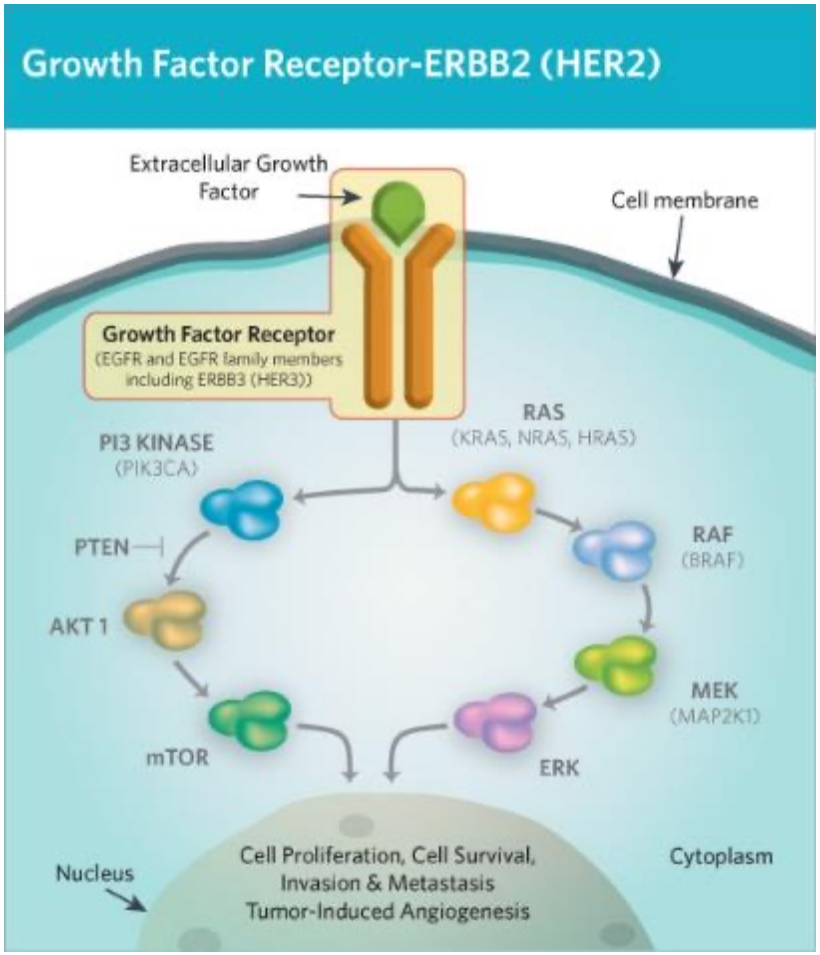
- *In general*, fusions (not mutations) are expected to be sensitizing in NSCLC
- RNA-based NGS potentially better at detecting fusions with novel partners

EML4-ALK → alectinib, brigatinib, lorlatinib
CD74-ROS1 → entrectinib, crizotinib
KIF5B-RET → selpercatinib, pralsetinib
NTRK2-ETV6 → larotrectinib, entrectinib
*CD74-NRG1** → *clinical trials*

**NRG1* fusions unique in that chimeric protein functions as ligand

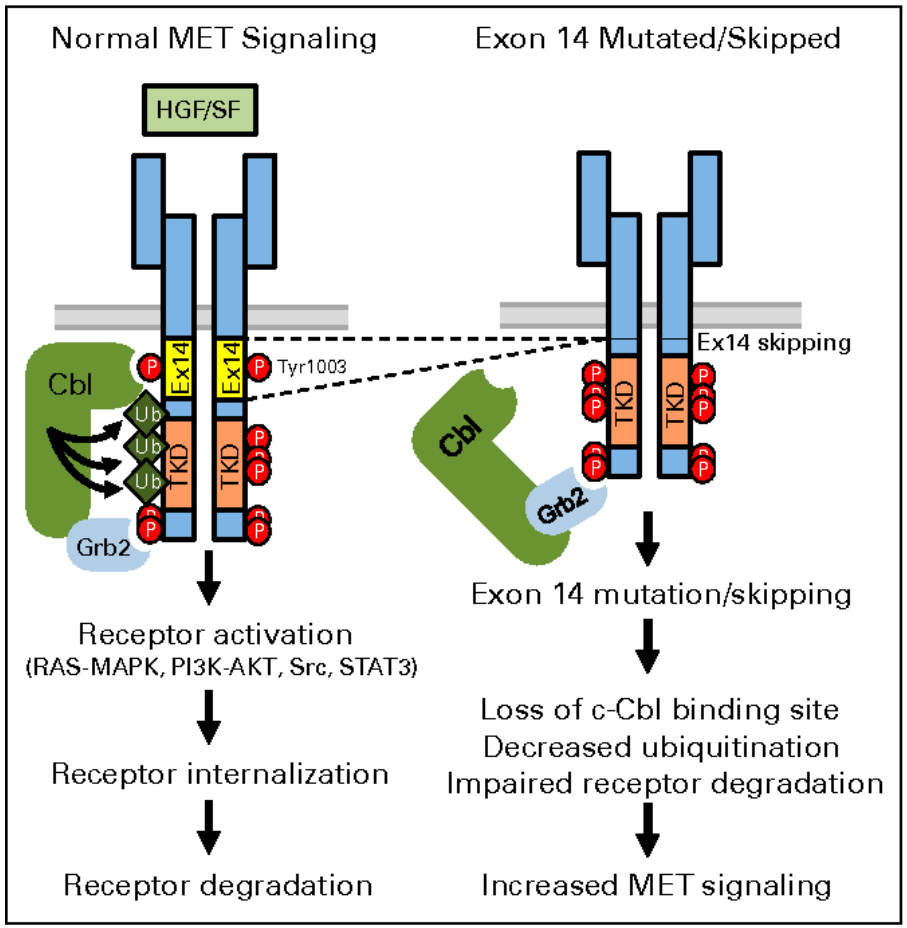
HER2 (ERBB2) alterations

- Current options
  - ❑ Clinical trial (preferred)
  - ❑ HER2 ADCs: Trastuzumab deruxtecan
  - ❑ HER2 mABs: TDM1, trastuzumab +/- pertuzumab
  - ❑ TKIs: Afatinib, lapatinib, neratinib
- Most data regarding efficacy relates to HER2 exon 20 insertions. HER2 gene amplification less well defined
  - ❑ Definitional problem: copy number vs ratio
  - ❑ What is optimal threshold?
  - ❑ Are TKI based approaches more effective than monoclonal antibodies?



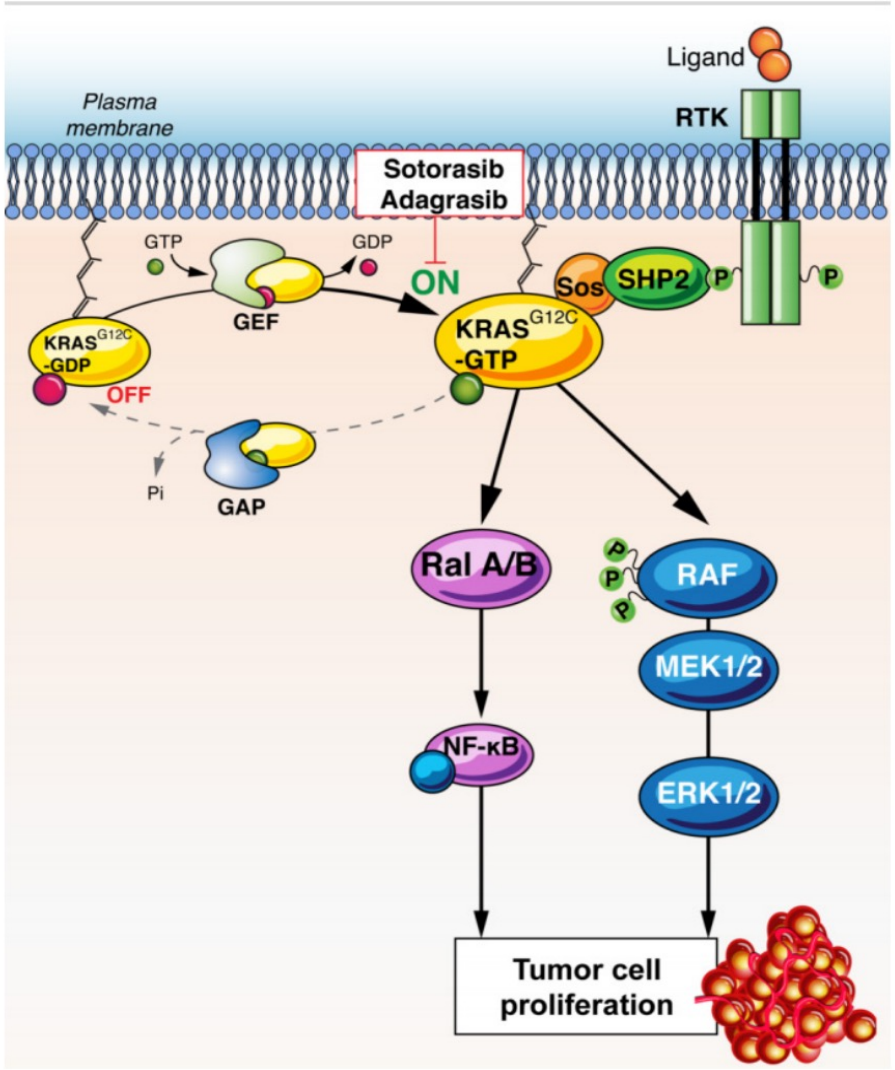
MET alterations

- Current options (outside of a clinical trial)
  - ❑ Capmatinib, tepotinib, and crizotinib (off-label)
- Greatest efficacy seen with MET Exon 14 mutations
  - ❑ RNA NGS will likely improve detection of these skip mutations
  - ❑ Not all MET Exon 14 are functional - need better assays
  - ❑ Overlap with MET amplification

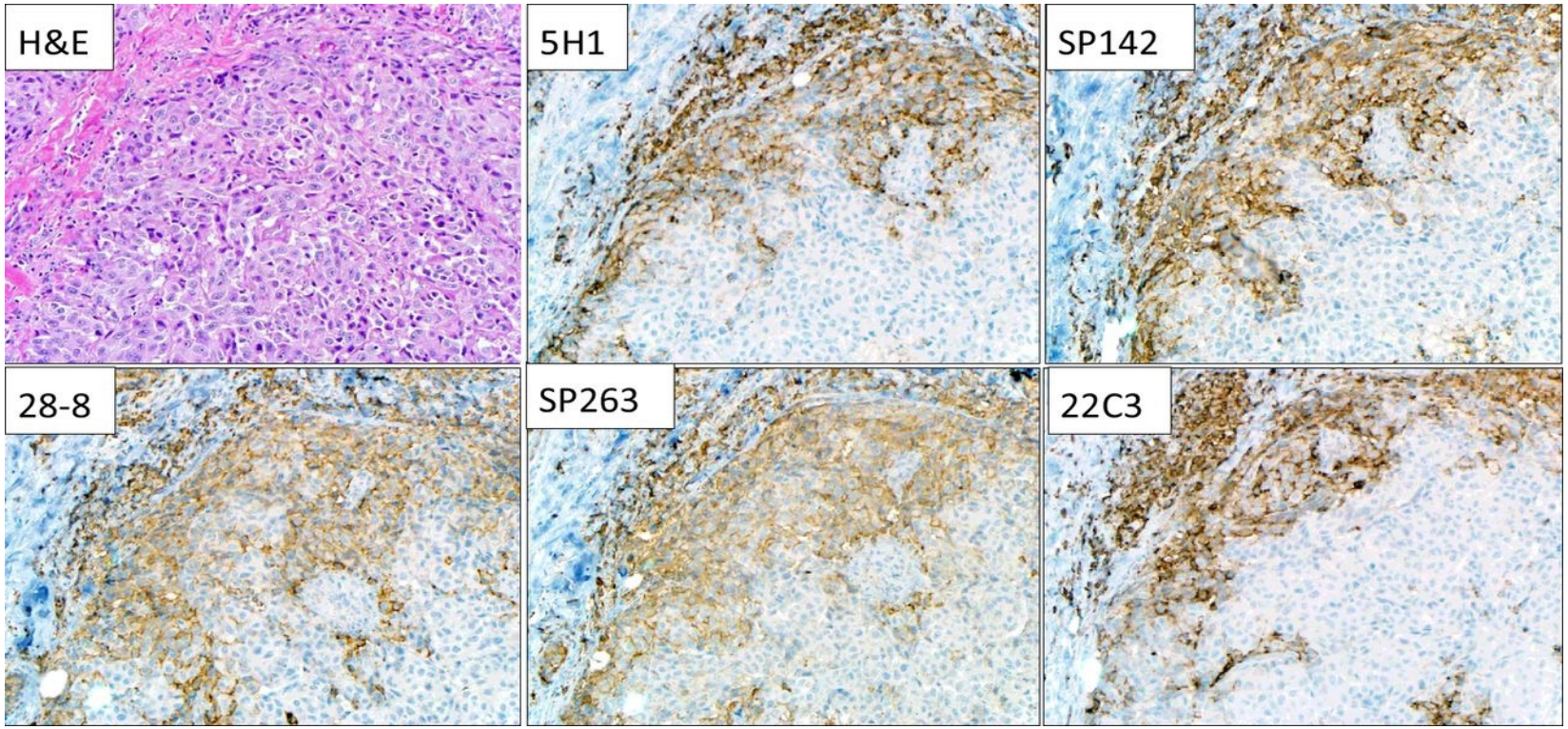


KRAS alterations

- KRAS proto-oncogenes → Ras-Raf-Mek-Erk pathway
  - GTP-bound = active
  - GDP-bound = inactive
- Missense mutations in codon 12, 13 and 61 hinder GTP hydrolysis → activation
- Sotorasib (and adagrasib)
  - Irreversibly bind mutant cysteine
  - Disrupt switch I/II and lock KRAS into a GDP bound state
  - Inhibits Raf signaling
- Response rates not as high as other oncogene drivers (e.g. *ALK, ROS1, RET*)



PD-L1 in lung cancer



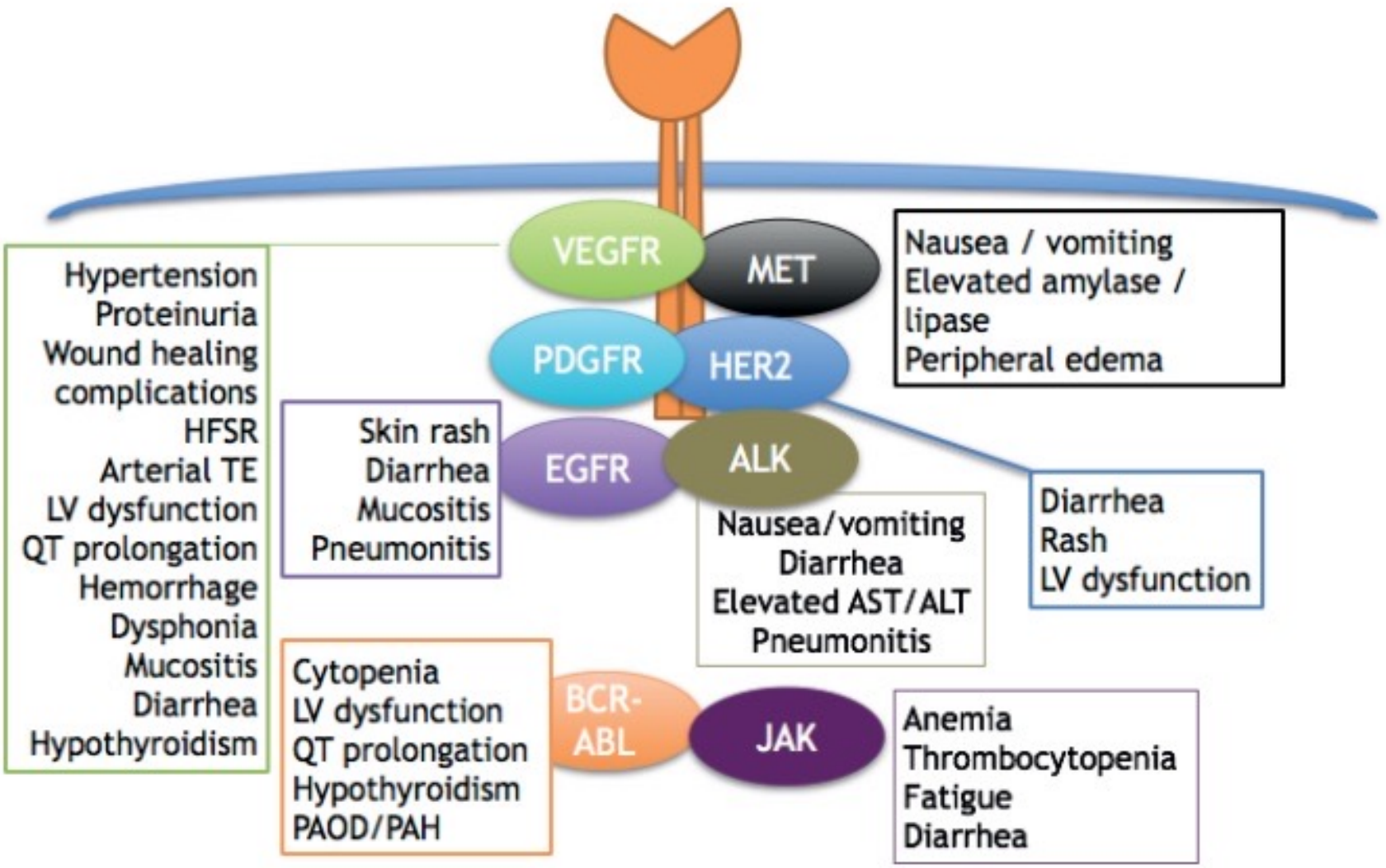
Remember that PD-L1 is a *qualitative* score and reported as a *continuous* variable

PD-L1 - important considerations

- **PD-L1 is a reported as a range**. Trials will use different cut-offs, but this may be arbitrary
  - KEYNOTE-024: PD-L1 ≥ 50%
  - PACIFIC: PD-L1 ≥ 25%*
- Recognize that different companies have different companion PD-L1 IHC assays (e.g. DAKO 22C3, Ventana SP263, etc)
- Many trials will try to collapse PD-L1 (continuous variable) into a categorical variable
  - KEYNOTE-189: Subset analysis

*PDL1 score not used as inclusion criteria for PACIFIC

OVERVIEW OF TOXICITIES ASSOCIATED WITH DIFFERENT TKI TARGETS



Chronic AEs of ALK inhibitors

Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
Vision issues Hepatotoxicity Edema Nausea Diarrhea	Diarrhea Anemia Nausea Hepatotoxicity Hyperglycemia	Anemia Edema Hepatotoxicity* Myalgia Photosensitivity rash	Diarrhea Elevated CK Cough** Hypertension Hepatotoxicity* Elevated amylase / lipase	Elevated lipids Hepatotoxicity Nausea Anemia Edema Low PO4 Neurotoxicity†

*All of these cases were in lower frequency than seen with crizotinib
**Brigatinib has rare incidence of early-onset pulmonary events. In most cases, this is reversible, but needs to be monitored
†Unique side effect not seen in another ALK TKIs

Chronic AEs of NTRK inhibitors

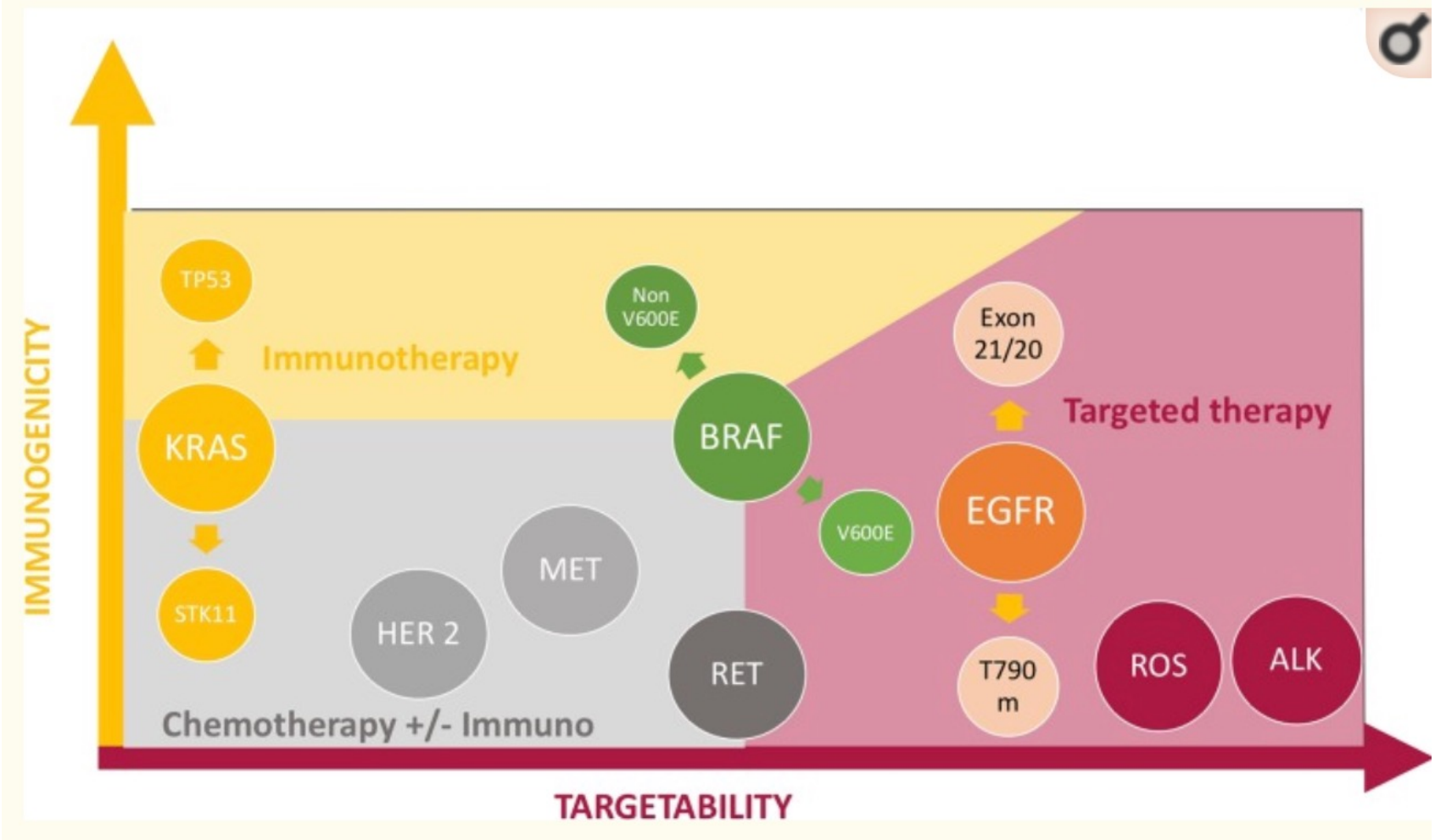
Entrectinib

- Fatigue
- Taste changes
- Paresthesia
- Nausea
- Arthralgia
- Dizziness

Larotrectinib

- Hepatotoxicity
- Dizziness
- Fatigue
- Nausea
- Constipation

A word on waiting for molecular testing



Mhanna *Curr Treat Options Oncol* 2019

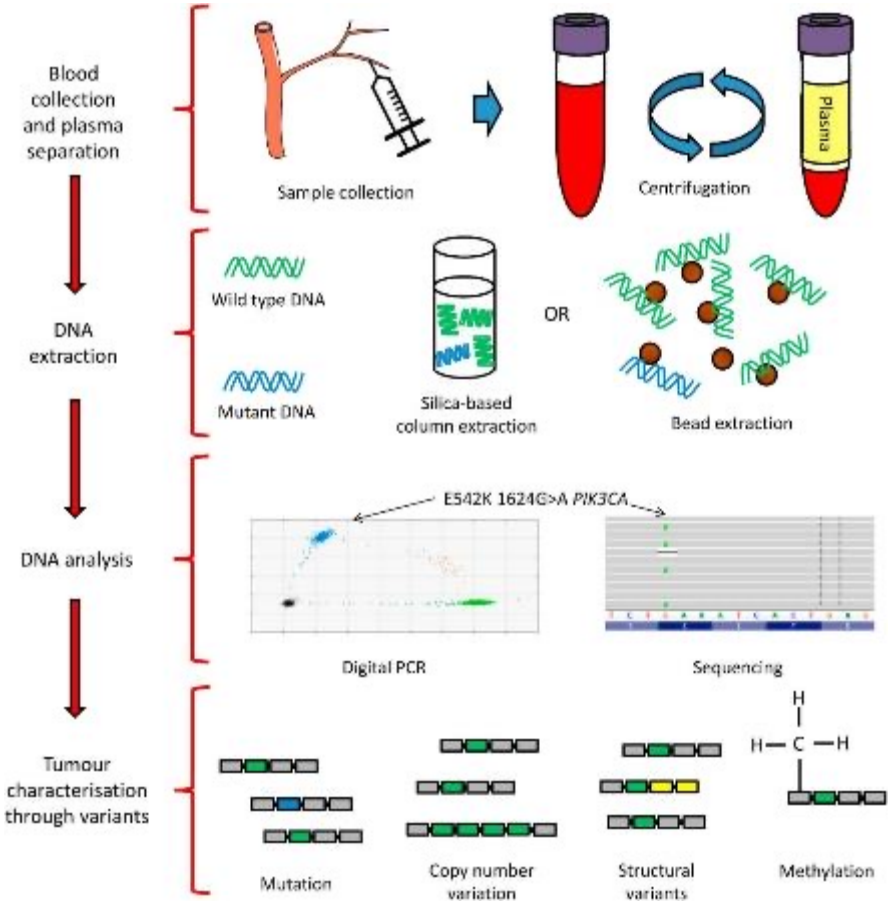
Higher iRAE with sequential immunotherapy and targeted therapy

- Remember that checkpoint inhibitors have long half lives!
- Multiple studies have shown marked increase in immune toxicity when TKI is given after checkpoint inhibitor therapy[1-3]
- At bare minimum, wait for EGFR, ALK, and ROS1 before starting chemo-immunotherapy

[1]Schoenfeld *Annal Oncol* 2019; [2]Oshima *JAMA Onc* 2019; [3] Lin *JTO* 2019

What about blood-based testing?

- Tumors shed DNA into the bloodstream (mostly related to tumor cell death)
- Small units of DNA are protected through binding to histones (these can be extracted and analyzed)



Caveats on circulating tumor DNA

- Highly specific, but less sensitive
  - *Absence of **known** driver is **not** informative*
  - *Tissue is gold standard*
- DNA-based assays (RNA degrades too quickly)
- Careful on over-interpreting VAF. Yield is proportional to blood flow to relevant organ sites
  - *Decreased yield for lung and pleural disease*
  - *Decreased yield for isolated brain metastases*

SUMMARY

- Understand importance of biomarker testing in lung cancer
- Understand common testing methodologies and their limitations
- Understand biology of common oncogenes
- Recognize real-world use of biomarker testing in lung cancer