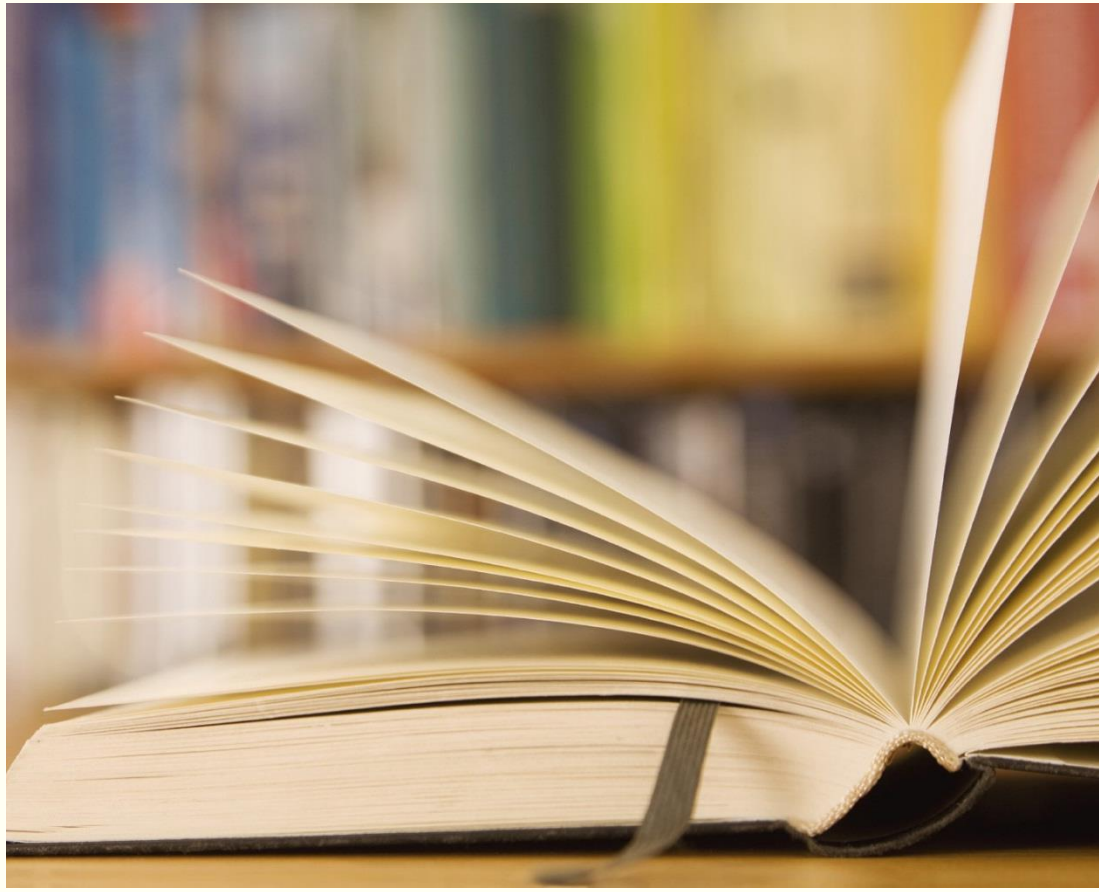
PERSONALIZED MEDICINE

Debra Wujcik, PhD, RN, FAAN
Director of Research
Carevive Systems, Inc™



Objectives

- Guide patients through the path of personalized medicine, including genetic testing and immunotherapies
- Identify the unique side effects that can affect the patient's experience with personalized cancer therapies in order to prepare proper interventions and management.

The Path to Personalized Medicine and Beyond

- 1990s – Molecularly targeted therapies terminology was used to discuss agents designed to work at the molecular level
  - Rituximab
  - Trastuzumab
- 2003 – Human genome sequenced
- Personalized medicine – treatment personalized to the individual characteristics of each patient
  - Tumor histology
  - Tumor genetics
  - Tumor proteomics
  - No longer one size fits all

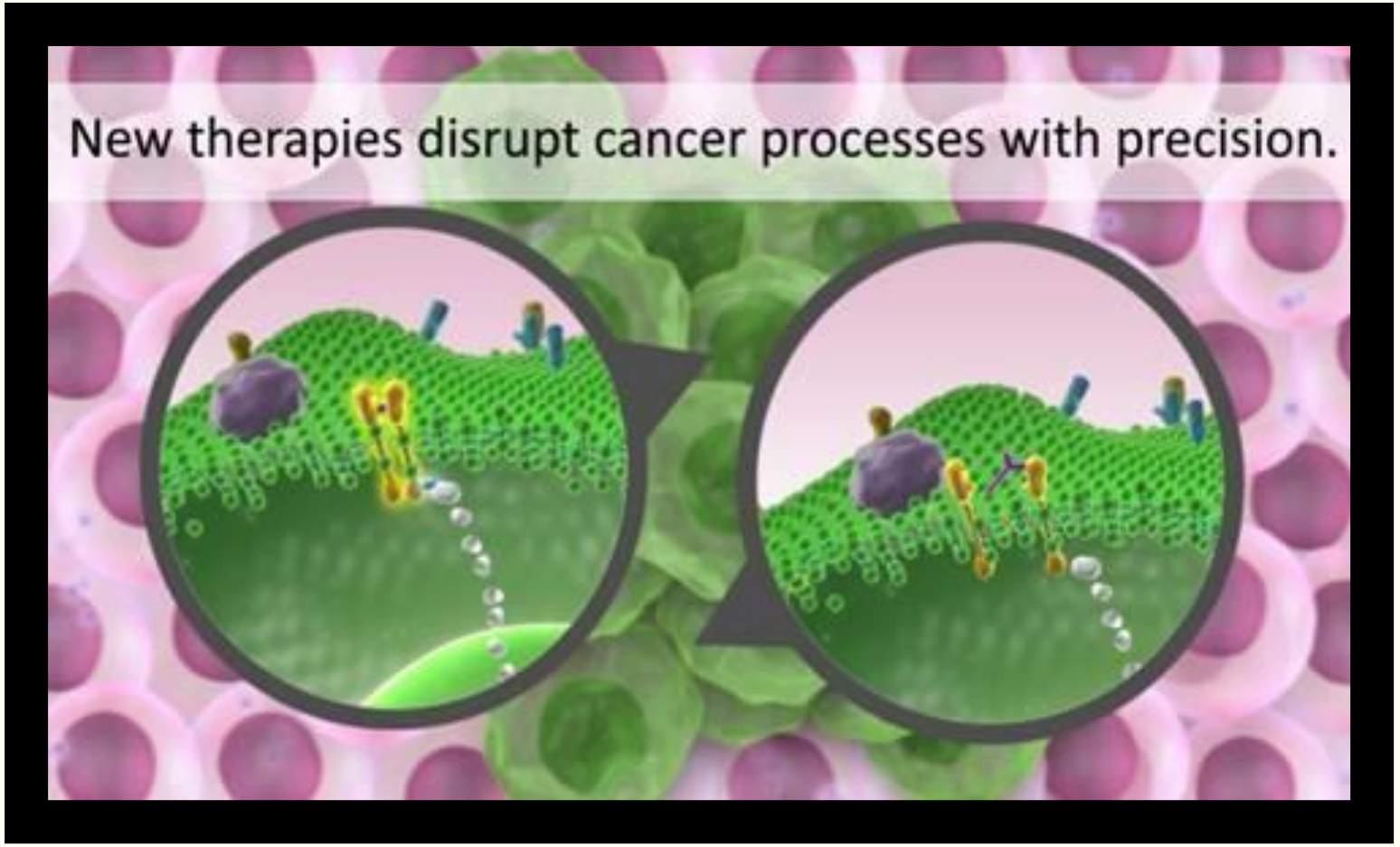
Precision Medicine

Identification of actionable mutations and agents that target the mutation pathway

Case Study 1

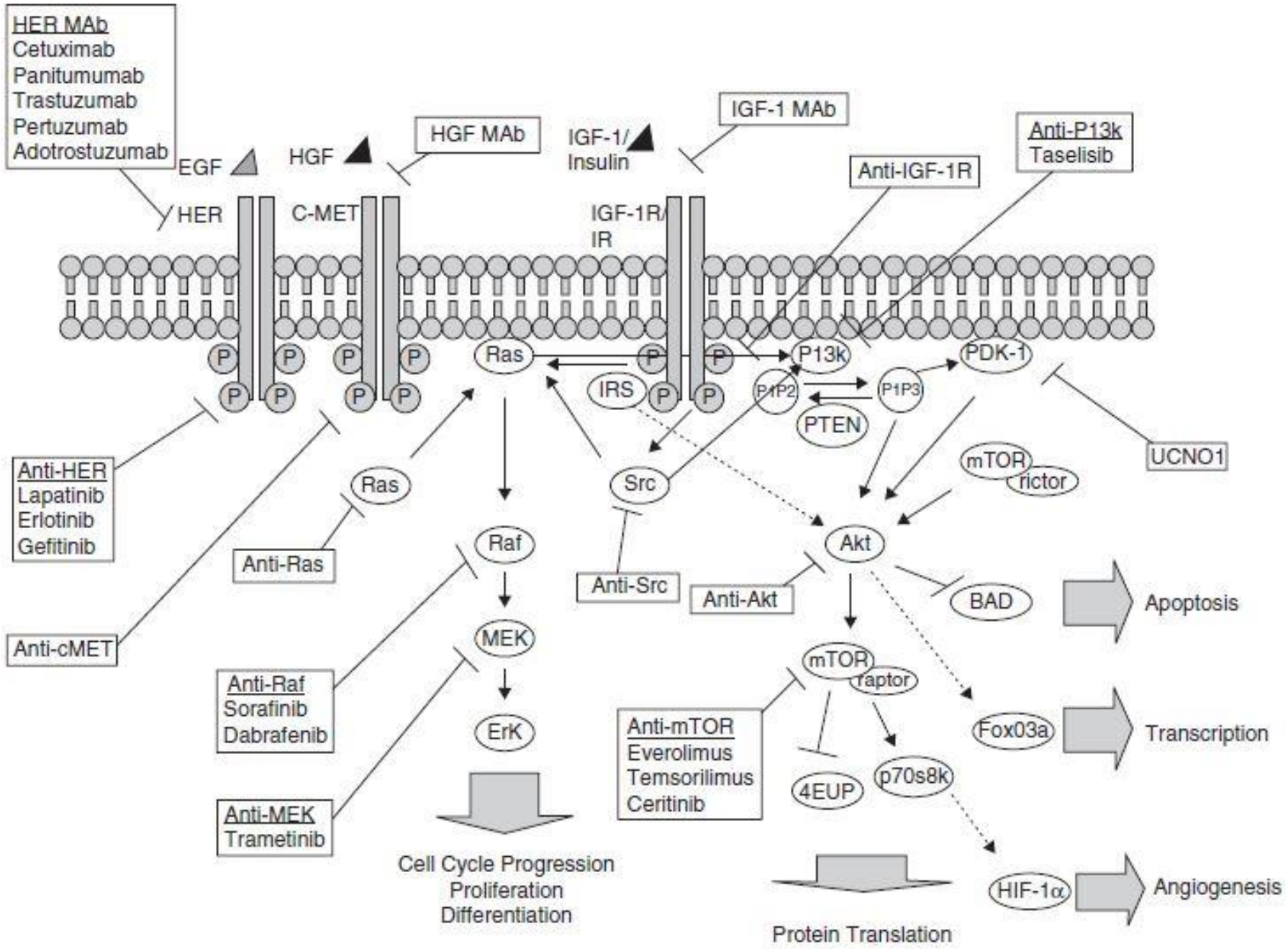
- 2002 Monthly education and support group for patients with lung cancer
  - Four patients recently diagnosed with Stage IV NSCLC
  - Each being treated with platinum doublet chemotherapy, either cisplatin or carboplatin with paclitxel.
  - Mary is able to provide information and education that is applicable to all in the group
  - All of the patients agree it is reassuring that they are getting the same treatment for the same disease
- 2017 Monthly education and support group
  - Four patients recently diagnosed with Stage IV NSCLC
  - Each patient is receiving a different treatment, some patients are receiving oral drugs and others receiving intravenous
  - Mary must explain that we have learned much in recent years about the differences within the diagnosis of NSCLC and now we have specific treatments for the different types of NSCLC

How are Targeted Therapies different than Cytotoxic Chemotherapy?



Different mechanisms of action, administration, and toxicity profiles

Http://www.cancer.gov/cancertopics/understandingcancer/targetedtherapies

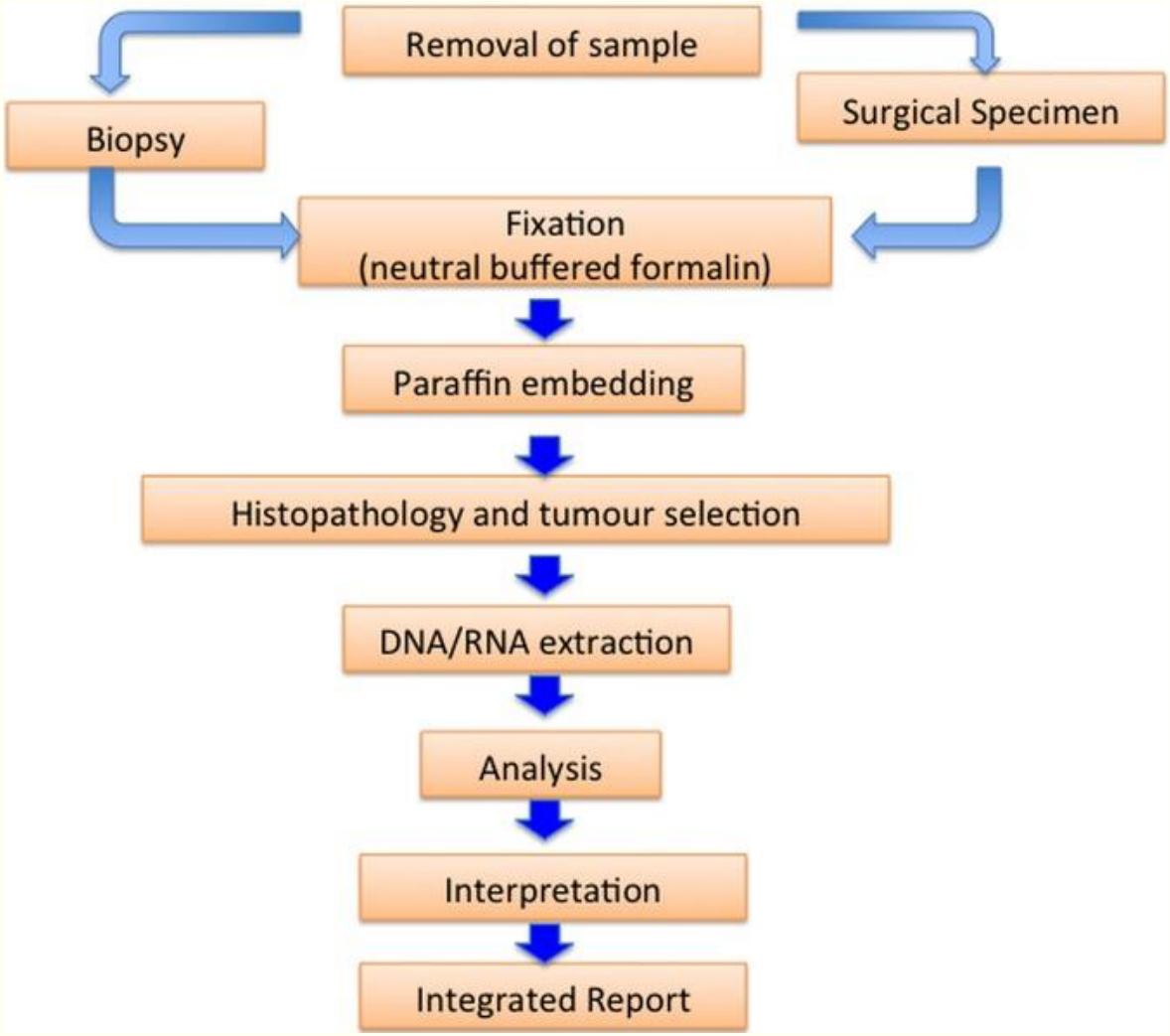

HER MAb
Cetuximab
Panitumumab
Trastuzumab
Pertuzumab
Adotrostuzumab
EGF
HGF
HGF MAb
IGF-1/
Insulin
IGF-1 MAb
Anti-P13k
Taselisib
Anti-IGF-1R
HER
C-MET
IGF-1R/
IR
P
Ras
P13k
PDK-1
IRS
P1P2
P1P3
PTEN
UCNO1
mTOR
rictor
Src
Anti-HER
Lapatinib
Erlotinib
Gefitinib
Ras
Anti-Ras
Raf
Akt
Anti-Src
Anti-Akt
BAD
Apoptosis
Anti-cMET
MEK
mTOR
raptor
Anti-Raf
Sorafinib
Dabrafenib
ErK
Anti-mTOR
Everolimus
Temsorilimus
Ceritinib
Fox03a
Transcription
4EUP
p70s8k
Anti-MEK
Trametinib
Cell Cycle Progression
Proliferation
Differentiation
Protein Translation
HIF-1α
Angiogenesis

Standard of Care

- Actionable mutations
  - Function and testing
  - Patient characteristics likely to be positive
  - Is the marker prognostic, predictive or both
- Molecular testing in standard for many cancers. NCCN guidelines for
  - Lung
  - Breast
  - Colorectal
  - Myeloma
  - Leukemia

Tissue Collection, Processing, and Analysis

- Where was tissue obtained?
  - Your institution
  - Community
- Is there enough tissue for diagnosis and molecular testing?
- When will results be available?
- Who gets (and communicates) results?



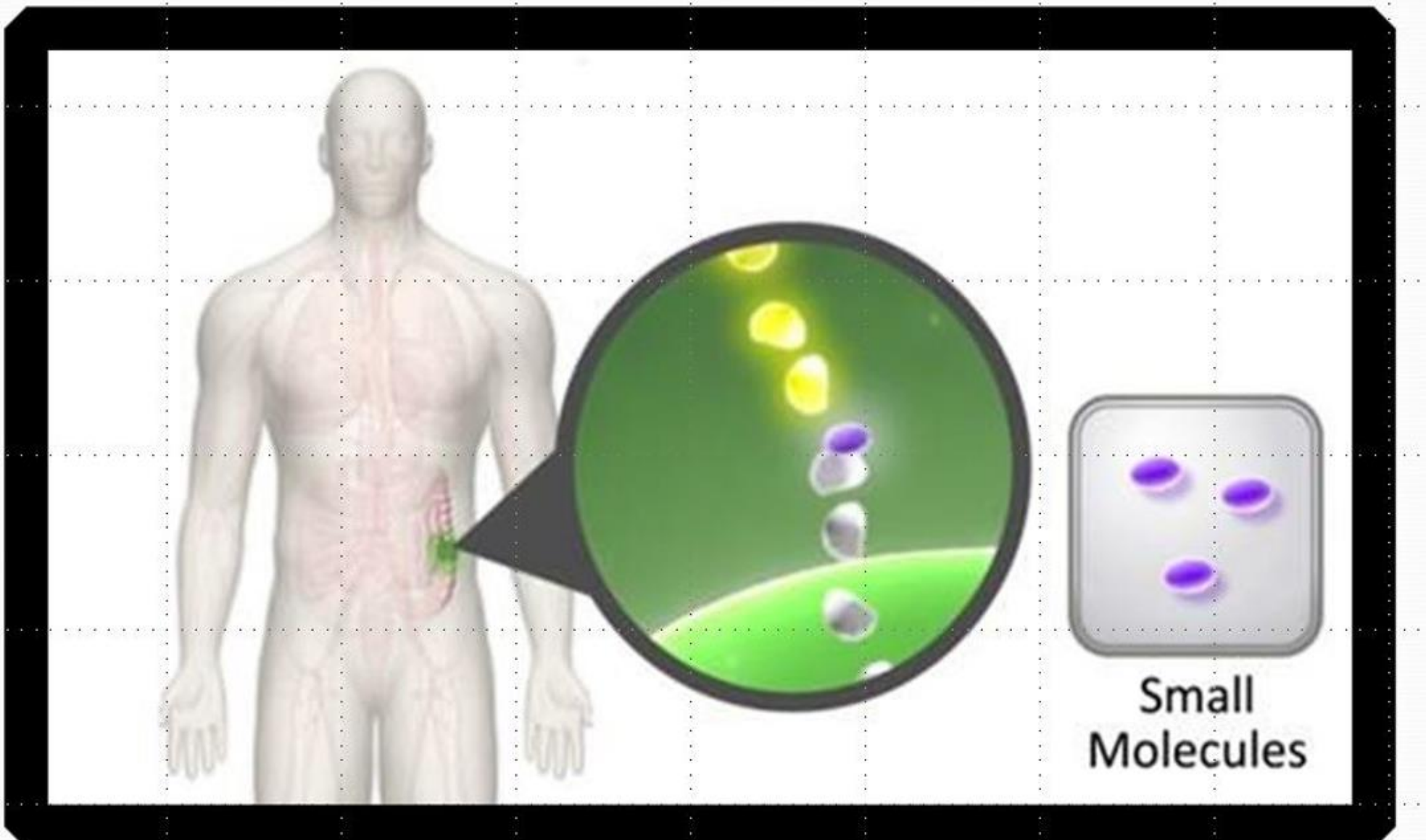
Actionable mutations

- Colon cancer
  - KRAS
- Breast
  - HER2
  - ER/RH
- NSCLC
  - EGFR
  - ALK (anaplastic lymphoma kinase)
- Malignant melanoma
  - BRAF

Types of Targeted Therapies

http://www.cancer.gov/cancertopics/understandingcancer/targetedtherapies

Drugs are designed to attach and interfere with specific pathways



Small Molecule Targeted Therapies: Oral Agents

Name Suffix	Target	Examples
nibs (tinibs)	Tyrosine kinase inhibitors targeting EGFR, VEGFR, and others	erlotinib, sunitinib, ponatinib, imatinib, dasatinib, ibrutinib
nibs (rafenibs, metanib)	Kinase inhibitors targeting RAF/RAS/MEK	sorafenib, dabrafenib, trametinib, vemurafenib
ibs (Paribs)	PARP inhibitors of mammalian polyadenosine 5'-diphosphoribose polymerase enzyme	olaparib, rucaparib
ibs (lisib)	PI3 kinase inhibitors (PI3K)	idelalisib
ibs (degibs)	Sonic hedgehog pathway inhibitors	sonidegib, vismodegib
ibs (ciclibs)	inhibitor of cyclin dependent kinase (CDK) 4 & 6	palbociclib

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ibs (lisib)	PI3 kinase inhibitors (PI3K)	idelalisib
ibs (degibs)	sonic hedgehog pathway inhibitors	sonidegib, vismodegib
ibs (ciclibs)	inhibitor of cyclin dependent kinase (CDK) 4 & 6	palbociclib

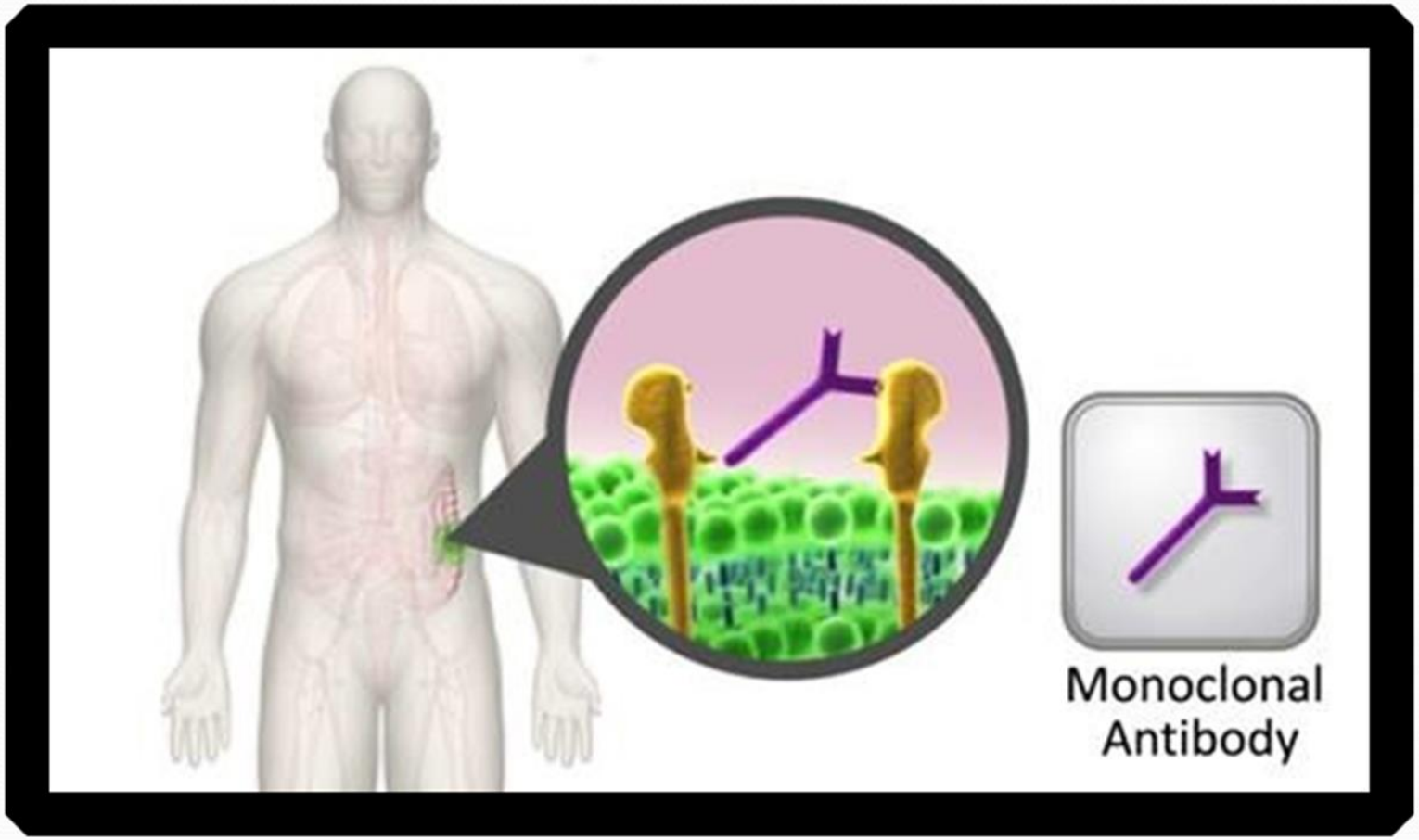
Care Issues

- Adherence
- Possible drug/food, drug/drug response
- Education regarding taking medication correctly
- Symptom management

Small Molecule Targeted Therapies: IV, Subq or oral

Name Suffix	Target	Examples
zomibs (IV, Subq, or oral)	Proteozome inhibitors	bortezomib, carfilzomib, ixazomib
inostat (IV or oral)	Histone deacetylase inhibitors (HDAC)	vorinostat, belinostat, panobinostat
toclax	BCL-2 inhibitors	venetoclax

Once potential targets are identified, then drugs are designed to best attack the target



http://www.cancer.gov/cancertopics/understandingcancer/targetedtherapies

Monoclonal Antibody Naming Conventions

- Prefix
- Infix
  - Target/Disease Class
  - Source
- Suffix
  - Monoclonal antibody = mab

What does the name mean?

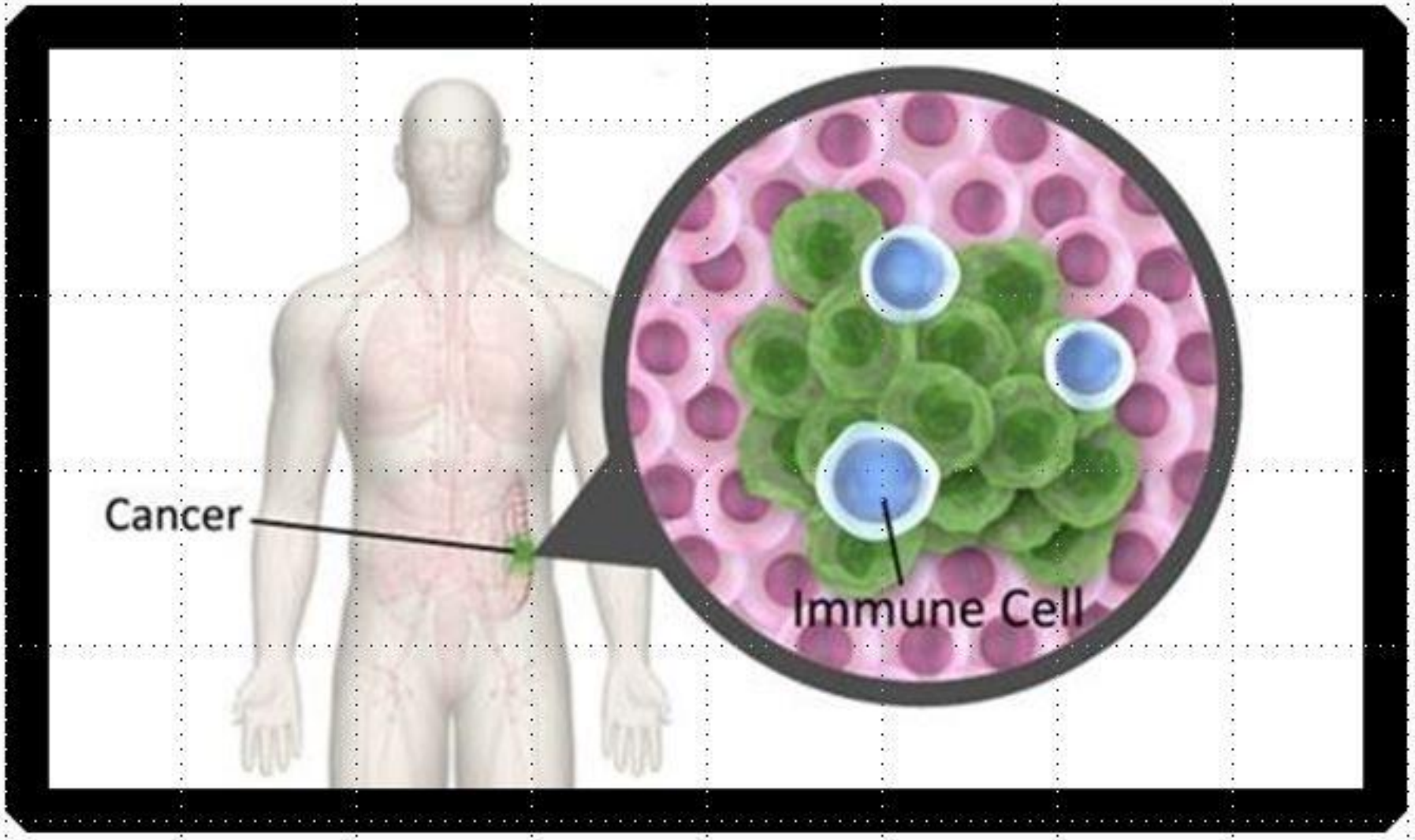
Target/Disease Class Infix

- Trastuzumab
  - Infix: tu/t = tumor
  - Example: -tuzumab/-tumab/-tomab
- Bevacizumab
  - Infix: ci/c = circulatory
  - Example: -cixumab/-cumab
- Ipilimumab
  - Infix: li/l = immunomodulator
  - Example: -liximab/-lumab/-lixizumab

Source Infix

- Tositumomab and iodine 131
  - mo = mouse
- Rituximab
  - xi = chimeric or cross between mouse and human
- Trastuzumab, bevacizumab
  - zu = humanized
- Panitumumab
  - u = fully human

Enhancing the Immune Response



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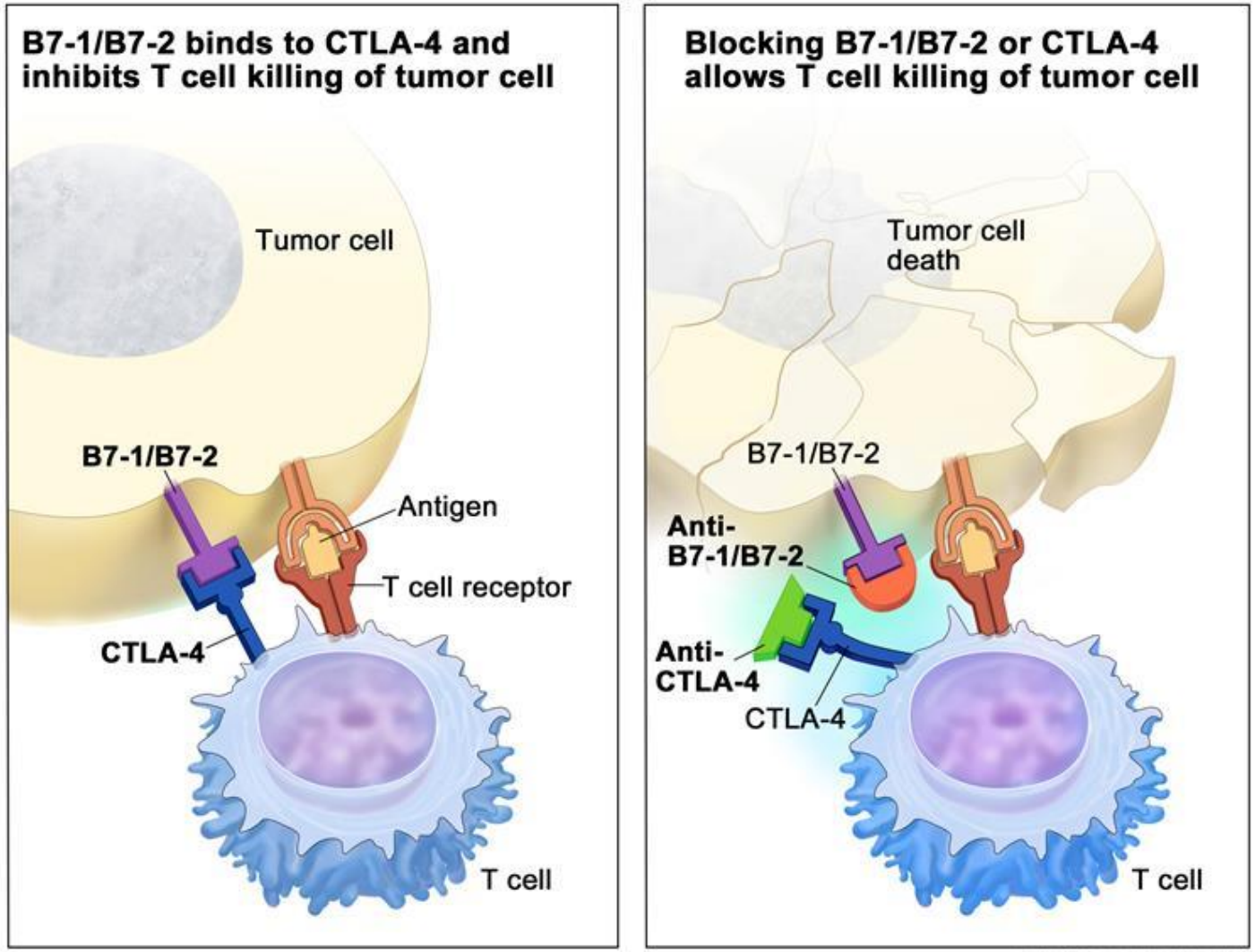
Checkpoint Inhibitors

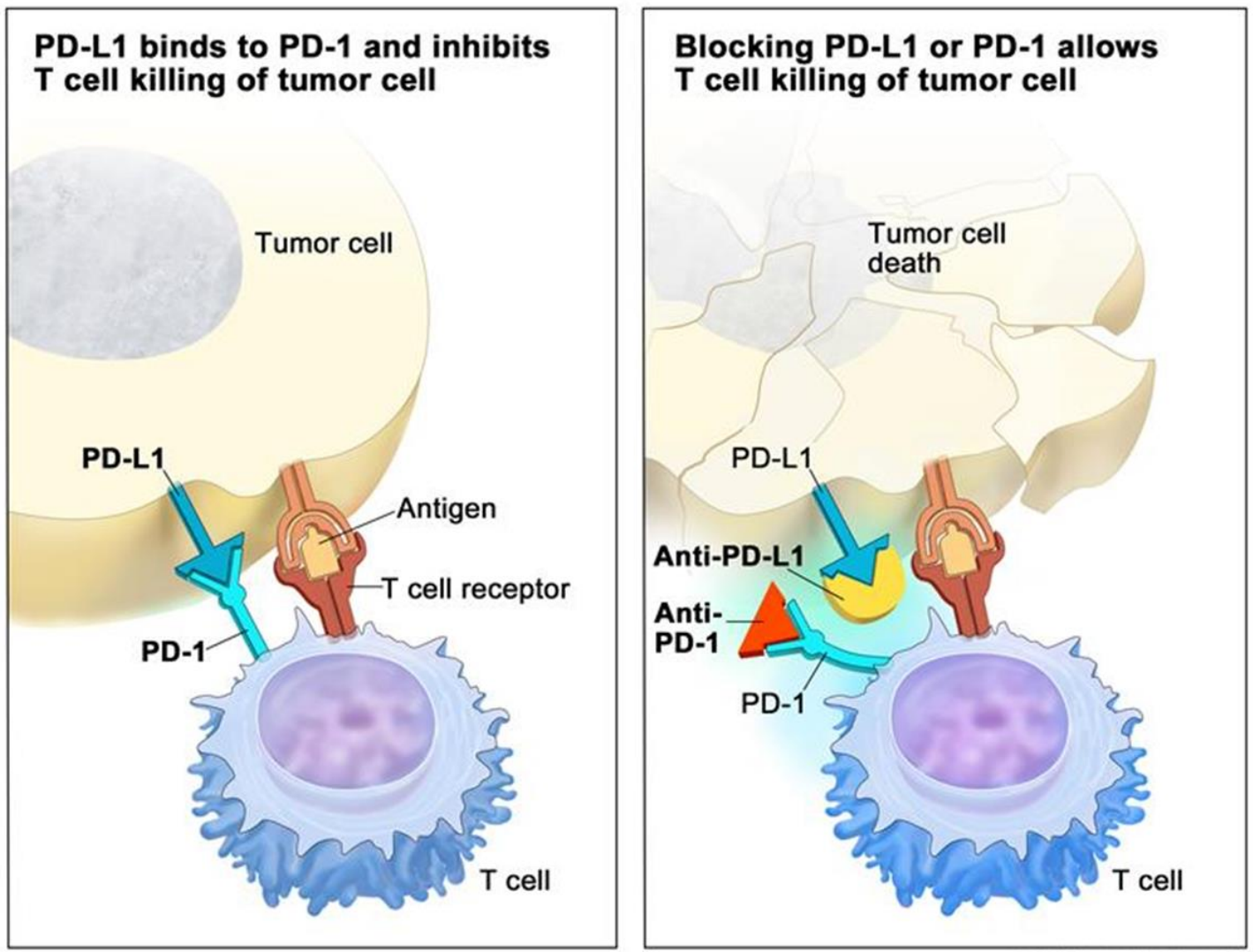
Targets receptors that promote t-cell proliferation to allow the immune system to recognize tumor antigens

- CTLA-4: cytotoxic T-lymphocyte-associated antigen-4
  - Ipilimumab (Yervoy)
- PD-1: programmed cell death protein
  - Nivolumab (Opdivo)
  - Pembrolizumab (Keytruda)
- PD-L1: programmed cell death protein ligand 1
  - Atezolizumab (Tecentriq)

Blocking CTLA-4



Blocking PD-1 and PD-L1

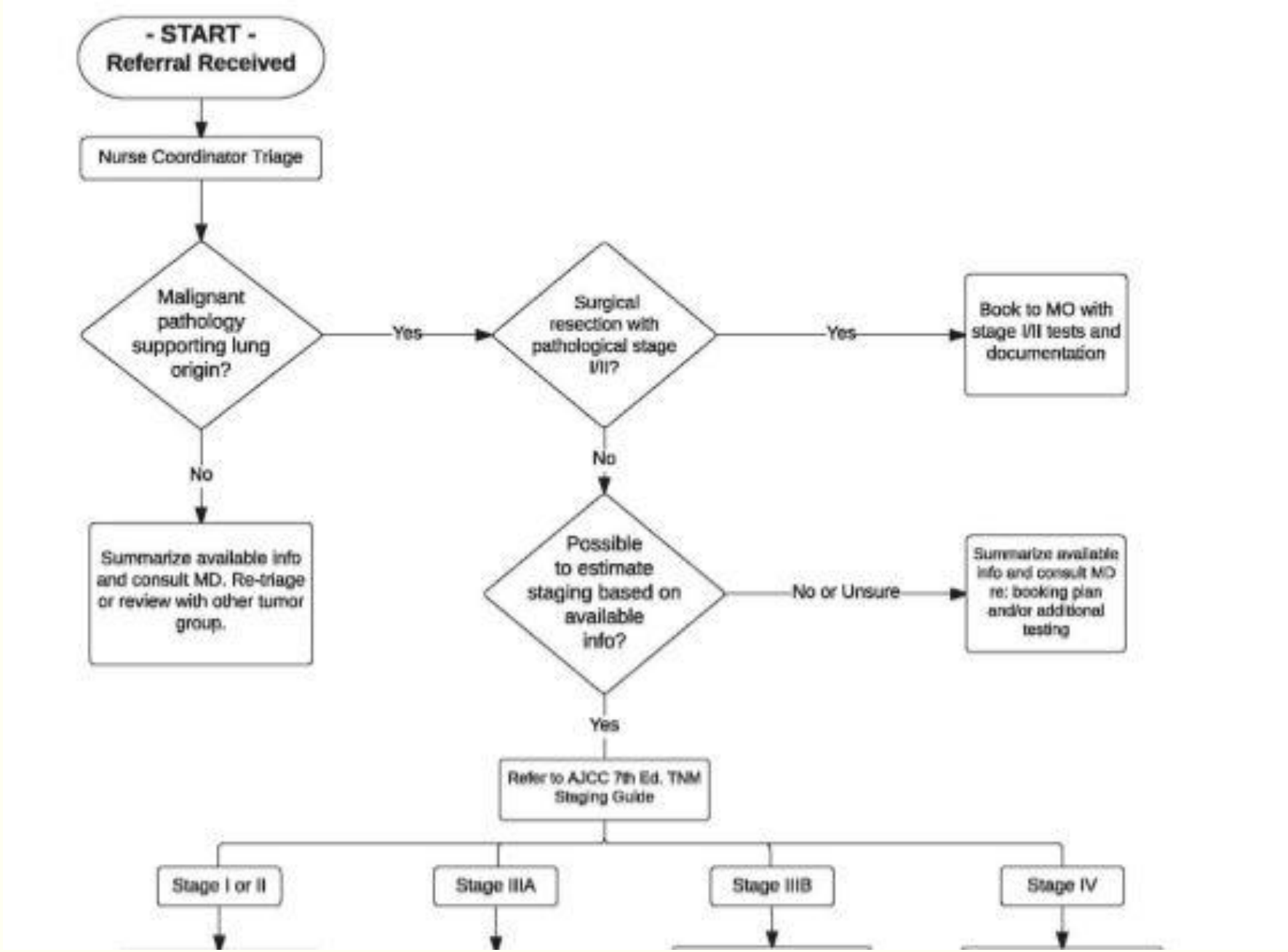


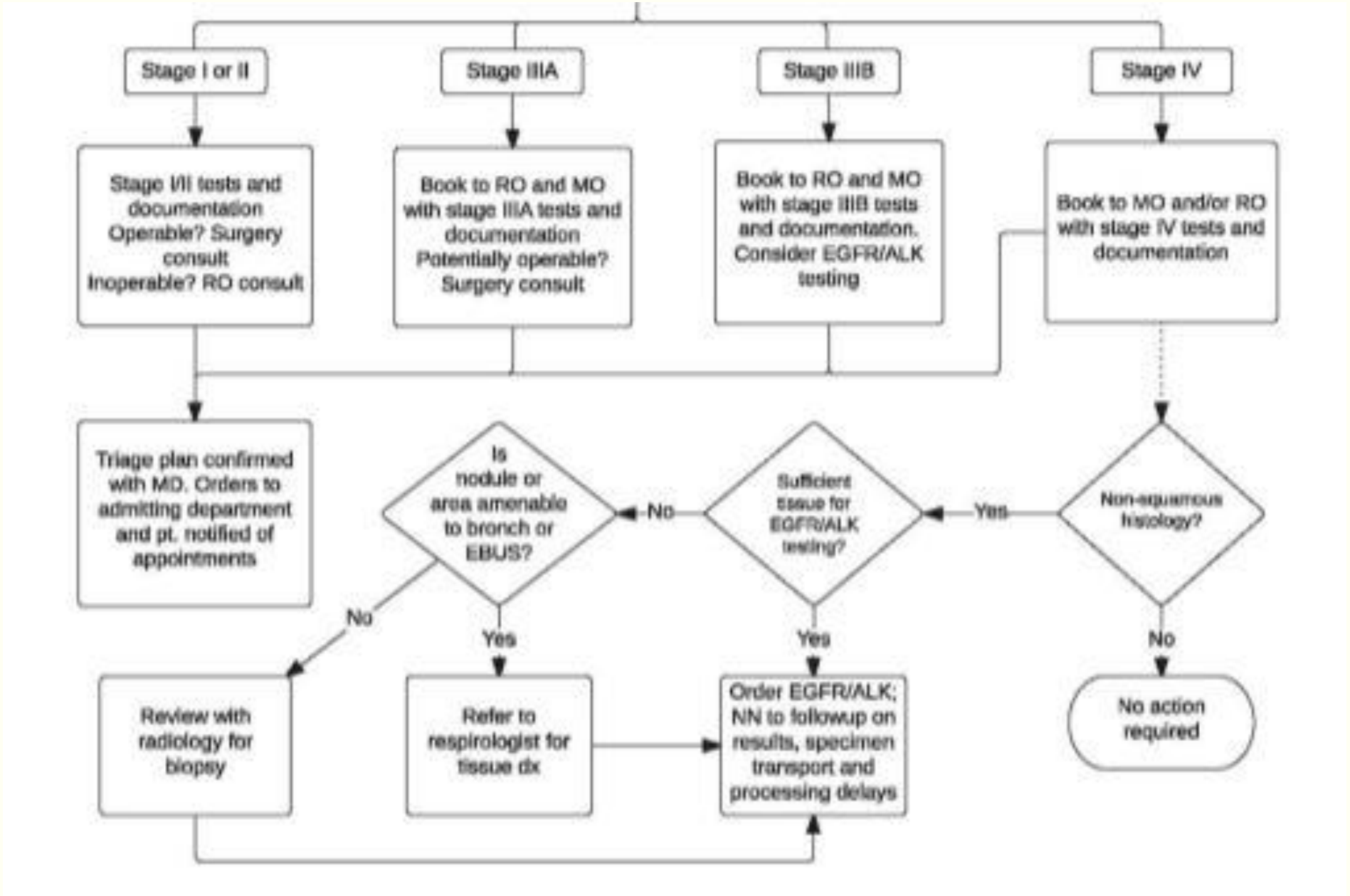
Potentially Serious/Life-threatening Immune Related Adverse Events (irAEs)

- GI (diarrhea > colitis)
- Pulmonary (pneumonitis/interstitial lung disease [ILD])
- Endocrine (thyroid, adrenal, pituitary)
- Liver (hepatitis)
- Kidney (nephritis)
- Eye (uveitis)
- Skin

Case Study 2

Zibrik K, Laskin J, Ho C. Integration of a nurse navigator into the triage process for patients with non-small-cell lung cancer: creating systematic improvements in patient care. *Curr Oncol*. 2016;23(3):280-283.


- START -
Referral Received
Nurse Coordinator Triage
Malignant pathology supporting lung origin?
Yes
No
Summarize available info and consult MD. Re-triage or review with other tumor group.
Surgical resection with pathological stage I/II?
Yes
Book to MO with stage I/II tests and documentation
No
Possible to estimate staging based on available info?
No or Unsure
Summarize available info and consult MO re: booking plan and/or additional testing
Yes
Refer to AJCC 7th Ed. TNM Staging Guide
Stage I or II
Stage IIIA
Stage IIIB
Stage IV


Stage I or II
Stage IIIA
Stage IIIB
Stage IV
Stage I/II tests and documentation
Operable? Surgery consult
Inoperable? RO consult
Book to RO and MO with stage IIIA tests and documentation
Potentially operable? Surgery consult
Book to RO and MO with stage IIIB tests and documentation. Consider EGFR/ALK testing
Book to MO and/or RO with stage IV tests and documentation
Triage plan confirmed with MD. Orders to admitting department and pt. notified of appointments
Is nodule or area amenable to bronch or EBUS?
No
Sufficient tissue for EGFR/ALK testing?
Yes
Non-squamous histology?
No
Yes
Yes
No
Review with radiology for biopsy
Refer to respirologist for tissue dx
Order EGFR/ALK; NN to followup on results, specimen transport and processing delays
No action required

References

- http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/naming-biologics/monoclonal-antibodies.page
- https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies
- http://www.cancer.gov/dictionary
- http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174. htm
- http://www.mycancergenome.org

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- Zibrik K, Laskin J, Ho C. Integration of a nurse navigator into the triage process for patients with non-small-cell lung cancer: creating systematic improvements in patient care. *Curr Oncol*. 2016;23(3):280-283.