Targeted Chemotherapy: Guiding patients to more personalized care

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Objectives

- Discuss the role targeted chemotherapy plays in the treatment of cancer patients
- Explore the decision making process used by practitioners to decide when to use targeted agents
- Outline several new targeted therapies that are currently being used in oncology practice

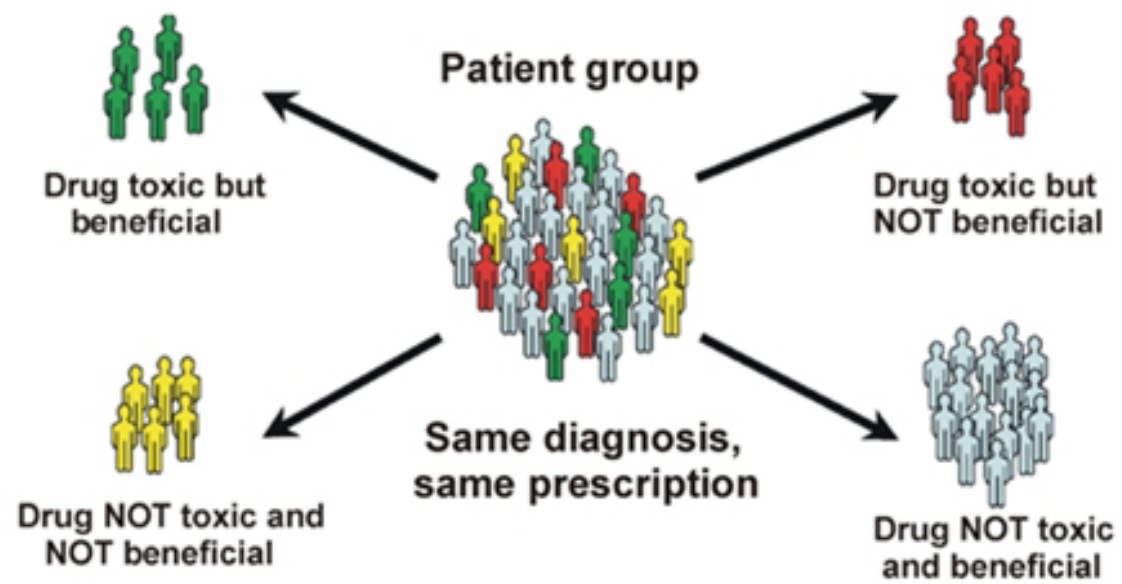
What is Targeted Therapy?

- Medications used to stop the growth, development or spread of cancer through the blockade of specific molecular targets around, on, or within the cancer cell
  - Most commonly include monoclonal antibodies (-mabs) and small molecule inhibitors (-nibs)
  - Often act only on a select number of cells
  - May be used alone or combined with traditional chemotherapy and/or radiation to enhance effects

National Cancer Institute. "Targeted Cancer Therapies". Available online at http://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/targeted-therapies-fact-sheet. Accessed 1 Sept 2015.

Why Targeted Therapy?

- Allows for more personalized care
  - Reduces traditional side effects
  - Increases chance patient will see response



http://sitemaker.umich.edu/hbhe669final/personalized_medicine

Risks of Targeted Therapy

- Not all patients are candidates
  - Tumor may not express target
  - Tumor may have mutated to develop resistance to target interaction
- Unexpected adverse effects
  - "Off-target toxicities" include rash, metabolic effects, cardiotoxicity, etc.
- Risk of poor adherence
- High cost

Gerber, DE. Targeted therapies: A new generation of cancer treatments. *American Family Physician*. 2008;77(3):311-319

Deciding to Use Targeted Therapy

- Art and Science
  - Observable facts
    - Symptoms
    - Diagnostic tests
  - Published data
    - Case reports
    - Clinical trials
  - Previous experience
    - Personal or collective

Eddy, DM. Successes and challenges of medical decision making. *Health Affairs* 1986;5(2):108-115

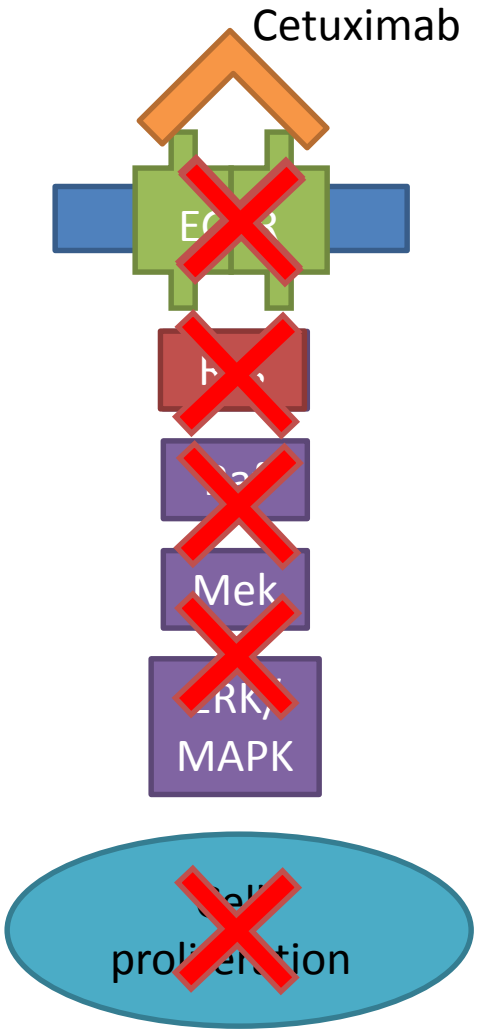
Woolever, DR. The art and science of clinical decision making. *American Family Physician*. 2008;15(5):31-36

Deciding to Use Targeted Therapy

- Tumor diagnosis
  - Often certain targets are only seen in certain types of tumors
  - Ex: BCR-ABL and CML or CD20+ and DLBCL
- Receptor testing
  - Certain mutations/receptor variations may only be present in some tumors of a particular type
  - Ex: HER2 in breast cancer or ALK in NSCLC

Deciding to Use Targeted Therapy

- Mutation testing
  - Mutations may affect the ability of a patient to respond to a targeted therapy, even if they possess the desired target.
  - Ex: Cetuximab and CRC



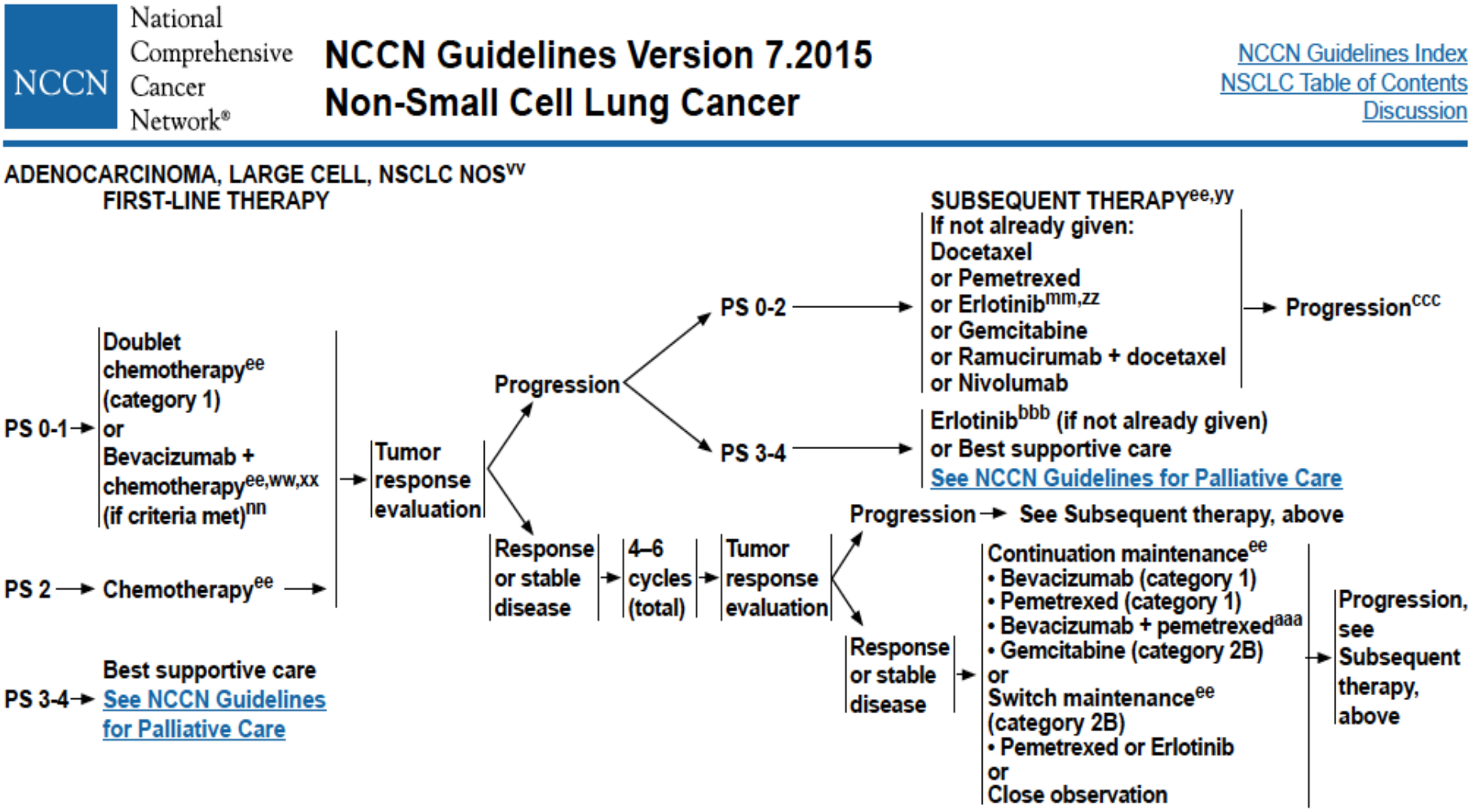
Deciding to Use Targeted Therapy

- Receptor testing and mutation testing
  - Single point tests specifically looking for a particular receptor or mutation
    - Often developed along with a drug
    - Ex: BRAF testing in melanoma
  - Gene panels may be run to assess patients for a large number of mutations or receptor targets at once
    - Provides a more complete picture of an individual tumor
    - Ex: FoundationOne testing

Deciding to Use Targeted Therapy

- Clinical Trials
  - Turns hypothetical efficacy from laboratory observations into proven treatments
  - Communicates information between providers
- Guidelines
  - Helps to organize and stratify data from clinical trials
  - May include consensus opinion regarding clinical data

The NCCN Guidelines



www.nccn.org

Specific Targeted Agents

Classes of Targeted Agents

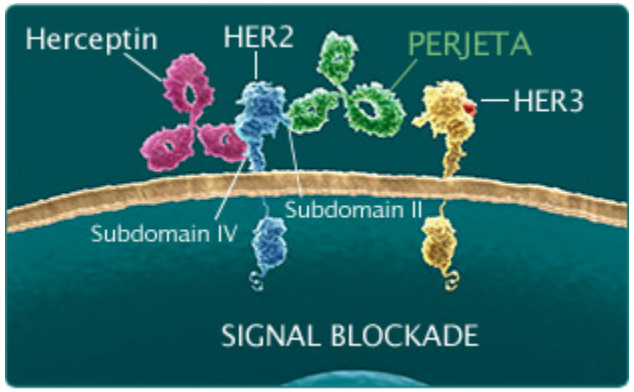
- 2 major classes
  - Monoclonal Antibodies
    - Uses antigen-antibody relationship to bind very specific receptors
    - Bind outside of the cell to either directly turn off the receptor or deliver a chemotherapeutic drug directly to a cancer cell (conjugate monoclonal antibody)
  - Small Molecule Inhibitors
    - Small molecules that are able to enter cells in order to exert their effects on receptors
    - Work at many points along a cell signal pathway

Specific Targeted Agents

- Ado-trastuzumab (Kadcyla®, Breast)
- Pertuzumab (Perjeta®)
- Ibrutinib (Imbruvica®)
- Ramucirumab (Cyramza®)
- Nivolumab (Opdivo®)

Pertuzumab (Perjeta®)

- Monoclonal antibody
- Targets HER2 that is overexpressed in some breast cancers
  - Similar to trastuzumab, it prevents further signaling from HER2, limiting cell growth
  - Binds to a different location of HER2 than trastuzumab
    - Provides more complete HER2 block



PERJETA® (pertuzumab for injection). Proposed Mechanism of Action. Available http://www.perjeta.com/hcp/moa. Genetech. 5/2015

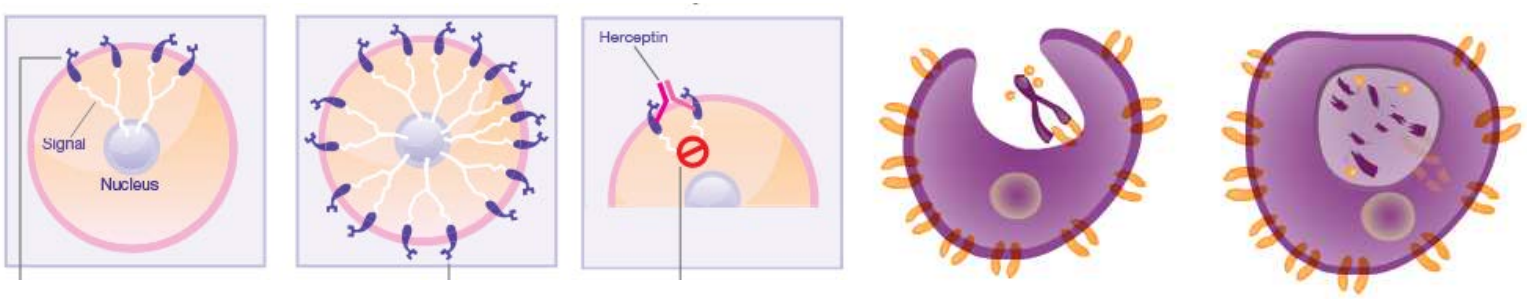
Pertuzumab (Perjeta®)

- Deciding to use pertuzumab
  - Observable facts
    - Breast cancer with HER2 overexpression
  - Published data
    - Patients studied included those with metastatic breast cancer
      - Increased PFS ~6 months and OS by ~16 months
      - Only studied with trastuzumab and docetaxel
    - Also studied in those with locally advanced, inflammatory or early stage tumors (>2cm or N+) who have NOT received HER2 therapy
      - Increased pCR by ~17%
      - Studied with FEC, TCH and docetaxel neoadjuvant
    - Increased risk of cardiotoxicity
  - Previous experience
    - Recommended by NCCN as first line for metastatic breast cancer
      - May consider second line
      - More information is needed regarding ideal sequencing
    - May use with trastuzumab after AC for early disease

PERJETA® (pertuzumab for injection). Proposed Mechanism of Action. Available http://www.perjeta.com/hcp/moa. Genetech. 5/2015
National Comprehensive Cancer Network. Invasive Breast Cancer. NCCN Guidelines Version 3.2015

Ado-trastuzumab (Kadcyla®)

- Monoclonal antibody drug conjugate
- Targets HER2 that is overexpressed in some breast cancers
  - Differs from trastuzumab (Herceptin®) through the conjugate chemotherapy drug emtansine which is bound to the antibody
  - Antibody is internalized by cell to deliver chemo to cause cell destruction



KADCYLA® (ado-trastuzumab emtansine) for injection. Genetech. 5/2015

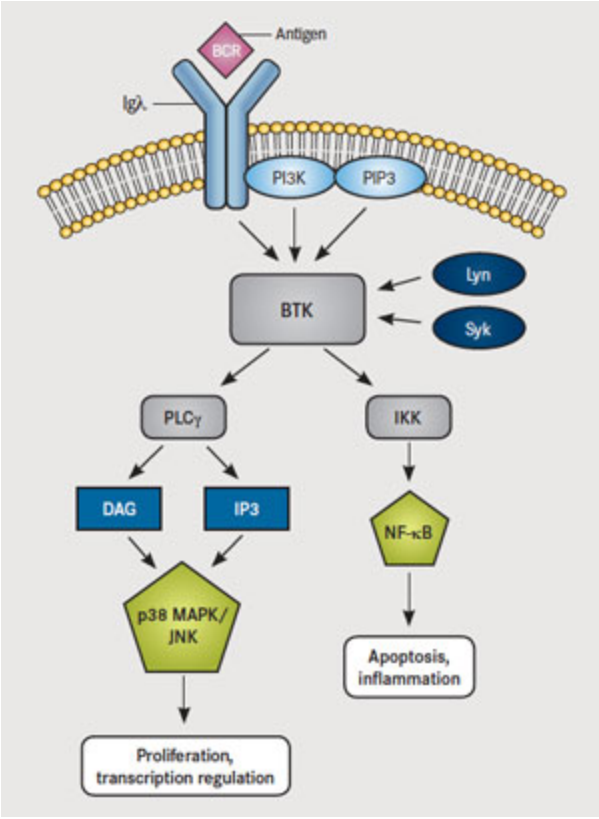
Ado-trastuzumab (Kadcyla®)

- Deciding to use ado-trastuzumab
  - Observable facts
    - Breast cancer with HER2 overexpression
  - Published data
    - Patients studied had metastatic or recurrent disease
      - Increased PFS by ~3 months and OS by ~5months
    - Found to cause cardiac and hepatotoxicity
  - Previous experience
    - Recommended by NCCN only after trastuzumab regimen
      - Preferred by NCCN for those with prior trastuzumab exposure
      - More information is needed regarding ideal sequencing
    - Recommended to stop therapy if no benefit or ECOG >3

KADCYLA® (ado-trastuzumab emtansine) for injection. Genetech. 5/2015
National Comprehensive Cancer Network. Invasive Breast Cancer. NCCN Guidelines Version 3.2015

Ibrutinib (Imbruvica®)

- Small molecule inhibitor
- Targets Bruton's tyrosine kinase (Btk)
  - Enters the cell and binds to Btk to stop downstream signaling
- Btk is crucial to B-cell development



IMBRUVICA® (ibrutinib) capsules for oral use..Pharmacyclics/Janssen Biotech. 1/2015

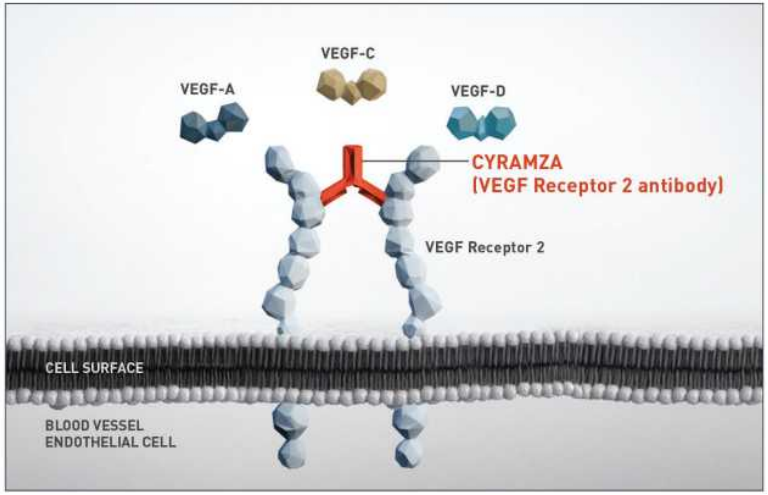
Ibrutinib (Imbruvica®)

- Deciding to use ibrutinib
  - Observable facts
    - Chronic lymphocytic leukemia
    - Mantle cell lymphoma
  - Published data
    - Mantle cell lymphoma patients had received at least 1 prior therapy
      - Found to have an overall response rate of 69%
    - CLL patients had received at least 1 prior therapy
      - Risk of progression was decreased by 78% and death was decreased by 57%
      - In those with high risk del 17p disease, the improved PFS was maintained
  - Previous experience
    - Well tolerated – recommended as category 1 for elderly/sick patients with CLL
    - First line agent for poor prognostic disease (17p deletion) CLL
    - Oral agent and expensive
    - Increased risk of bleeding
    - Increased drug interactions

IMBRUVICA® (ibrutinib) capsules for oral use..Pharmacyclics/Janssen Biotech. 1/2015

Ramucirumab (Cyramza®)

- Monoclonal antibody
- Targets vascular-endothelial growth factor (VEGF2)
  - Similar to bevacizumab, but targets the receptor not the ligand



CYRAMZA® (ramurcirumab) injection, for intravenous use. Eli Lilly. 4/2015

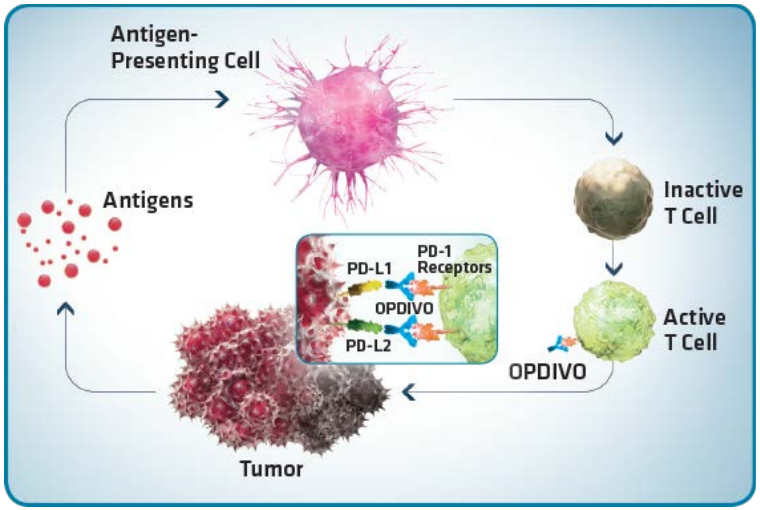
Ramucirumab (Cyramza®)

- Deciding to use ramucirumab
  - Observable facts
    - Metastatic non-small cell lung cancer (mNSCLC)
    - Metastatic colorectal cancer (mCRC)
    - Metastatic gastroesophageal (GE) junction or gastric tumors
  - Published data
    - mNSCLC
      - Studied in combination with docetaxel
      - Patients previously failed platinum based therapy; may have had bevacizumab
      - Improved OS and PFS by ~1.5 months
    - mCRC
      - Studied in combination with FOLFIRI
      - Patients previously failed therapy with 5FU, oxaliplatin and bevacizumab
      - Improved PFS by ~1.2 months and OS by ~1.5 months
    - Gastric/GE junction tumors
      - Studied as monotherapy or with paclitacel
      - Patients previously failed platinum or fluoropyrimidine regimen
      - Improved PFS by ~0.8-1.5 mo and OS by 1.5-2 months
  - Previous experience
    - Increased risk of bleeding and poor wound healing
    - Recommended as 2nd line agent in mCRC; bevacizumab is still preferred
    - Recommended as 2nd line agent in mNSCLC; no preference shown to other 2nd line agents

CYRAMZA® (ramurcirumab) injection, for intravenous use. Eli Lilly. 4/2015

Nivolumab (Opdivo®)

- Monoclonal antibody
- Targets programmed death-ligand (PD-L1) receptors
  - These are upregulated in both melanoma and non-small cell lung cancers limiting the normal T-cell monitoring process that inhibits cell overgrowth



OPDIVO® (nivolumab) injection, for intravenous use. Bristol Myers Squibb. 3/2015

Nivolumab (Opdivo®)

- Deciding to use nivolumab
  - Observable facts
    - Metastatic non-small cell lung cancer (mNSCLC)
    - Progressive melanoma
  - Published data
    - Melanoma
      - Patients had to have failed ipilimumab and BRAF inhibitor (if eligible)
      - Achieved overall response rate of 32%
    - mNSCLC
      - Patients had to have failed at least one prior platinum-based therapy
      - Improved OS by 3.2 months
  - Previous experience
    - Recommended 2nd line agent; no preference given compared to other 2nd line therapies

OPDIVO® (nivolumab) injection, for intravenous use. Bristol Myers Squibb. 3/2015

Summary

- Targeted therapies are becoming a mainstay within the treatment of cancer
- Allows clinicians to choose therapies that are more specific to tumor cells
  - Improves response while limits adverse effects
- The decision to use targeted therapy depends on the tumor type, presence of the target, mutation status as well as recommendations from literature
  - Risk/benefit of individual patient effects is always taken into account

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