Pharmacology/Pharmacogenetics
Oncology Updates 2017
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Columbus Chapter of Oncology Nursing Society (CCONS)
28th Annual Spring Conference Kaleidoscope of Oncology Care
Columbus, Ohio
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Objectives
• Review new oncology drugs approved in 2016
  – class/MOA, dosing/administration, monitoring, adverse effects, place in therapy
• Review new 2016 indications of already approved oncology drugs
• Review the personalized medicine through precision medicine

Audience question 1
New Drug Approvals Past 5 Years

![Graph showing new drug approvals from 2012 to 2016, with bar heights indicating the number of approvals each year.]


New FDA approvals in 2016
- Venetoclax
- Atezolizumab
- Olaratumab
- Rucaparib

New FDA indications in 2016
- Ofatumumab
- Eribulin
- Palbociclib
- Obinutuzumab
- Everolimus
- Crizotinib
- Lenvatinib
- Nivolumab
- Pembrolizumab
- Erlotinib
- Daratumumab
Venetoclax (Venclexta®)

- Indication: treatment of patients with chronic lymphocytic leukemia (CLL)
  - with 17p deletion
  - at least 1 prior line of therapy
  - accelerated approval based on ORR

- MOA: BCL-2 Inhibitor

https://www.venclextahcp.com/moa.html accessed online February 22, 2017

<table>
<thead>
<tr>
<th>Trial Design</th>
<th>Efficacy</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily venetoclax with stepwise dose escalation over 4-5 weeks</td>
<td>ORR = 79.4% (95% CI 70.5–86.6)</td>
<td>40% grades 3-4 neutropenia</td>
</tr>
<tr>
<td></td>
<td>CR* = 8%</td>
<td>5% Febrile neutropenia</td>
</tr>
<tr>
<td></td>
<td>Nodular PR + 3%</td>
<td>5% grade 3 TLS</td>
</tr>
<tr>
<td></td>
<td>PR = 69%</td>
<td>19% grades 3-5 infections</td>
</tr>
</tbody>
</table>

*CR* +/- incomplete recovery of blood counts

Trial Design  Efficacy  Safety
Daily venetoclax with stepwise dose escalation over 5 weeks  phase 2, two-arm, multicenter study  - Arm A post ibrutinib (n=43)  - Arm B postidelalisib (n=21)  interim analysis  ORR*  - Arm A = 70%  - Arm B = 48%  PFS/OS not yet reached (both arms)  12-month PFS = 72%  12-month OS = 90%  *by independent review  31% grades 3-4 neutropenia  9% Febrile neutropenia  3% grade 3 TLS

Venetoclax (Venclexta®)

- Take once daily with food and water  – Avoid grapefruit (juice), Seville oranges and starfruit
- Available in 10 mg, 50 mg and 100 mg tabs  – Starter pack for weeks 1-4
- Tumor Lysis Syndrome (TLS)  – Hydration, anti-hyperuricemics and lab monitoring  – Risk assessment for outpatient vs inpatient initiation

Venetoclax (Venclexta®)

Venetoclax (Venclexta®)

- Drug interactions – metabolized by CYP3A4/5
  - Strong 3A4 inhibitors
    - Contraindicated during ramp-up
    - Dose reduce by ≥ 75% at steady-state
  - Moderate 3A4 inhibitors and P-gp Inhibitors
    - Dose reduce by ≥ 50% at steady-state
  - Avoid 3A4 Inducers
  - P-gp substrates with narrow TI
    - Avoid or take 6+ hours later
    - Monitor warfarin closely
  - Avoid live vaccines (safety and efficacy)
  - Pregnancy, lactation and male infertility risks

<table>
<thead>
<tr>
<th>Strong CYP3A4 inhibitors</th>
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<th>Moderate CYP3A4 inducers</th>
<th>P-gp inhibitors</th>
<th>P-gp substrates (narrow TI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole, voriconazole, itraconazole, telaprevir, nafcinol, posaconazole, voriconazole</td>
<td>Erlotinib, nelfinavir, tipranavir, indinavir, saquinavir, sultiam, efavirenz, telaprevir, nafcinol, posaconazole, voriconazole</td>
<td>Erythromycin, clarithromycin, ciprofloxacin, dexamethasone, drotaverine, verapamil, sultiam, efavirenz, telaprevir, nafcinol, posaconazole, voriconazole</td>
<td>( \text{St. John’s wort} )</td>
<td>Amiodarone, cyclosporine, cyclosporine, diltiazem, diltiazem, diltiazem, diltiazem, diltiazem, diltiazem</td>
<td>( \text{St. John’s wort} )</td>
</tr>
</tbody>
</table>
Atezolizumab (Tecentriq®)

- **Indications**
  - LA or metastatic urothelial carcinoma
    - PD during/following platinum chemo
    - PD within 12 months of (neo)adj platinum chemo
    - Accelerated approval based on ORR and DOR
  - Metastatic NSCLC
    - PD during/following platinum chemo
      - And EGFR/ALK directed therapy if appropriate
  - MOA: mAB to PD-L1

Accessed online February 22, 2017

Accessed online February 22, 2017
## Atezolizumab (Tecentriq®)

**Trial Design**
- Phase 2, single-arm, multicenter study (n=310)
  - Urothelial carcinoma
  - LA or metastatic
  - Prior platinum-based chemotherapy

**Efficacy**
- ORR* = 15%
  - 95% CI 11–19%
- ORR = 19%
  - 95% CI 15–24%
- 84% of responders continued to respond at 11.7 months
- Increased PD-L1 levels associated with increased RR

**Safety**
- 16% grades 3–4 AEs overall
  - Fatigue 2%
  - All others ≤ 1%
- 69% all grades AEs
  - Fatigue 30%
  - Nausea 14%
  - Decreased appetite 12%
  - Pruritis 10%
  - <10% fever, diarrhea, rash, arthralgia

*ORR* by independent review

<table>
<thead>
<tr>
<th>Atezolizumab (A)</th>
<th>Docetaxel (D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1200 mg IV every 3 weeks (n=425)</td>
<td>75 mg/m² IV every 3 weeks (n=425)</td>
</tr>
</tbody>
</table>

**Primary endpoint**
- OS (both ITT and PD-L1+)
- PFS (both ITT and PD-L1+)

**ITT = intent to treat**

### Atezolizumab (Tecentriq®)

- IV infusion every 3 weeks
  - Fixed dose = 1200 mg
  - First dose infused over 60 minutes; if tolerated subsequent infusions can be over 30 minutes
  - Compound in 250 ml - 0.9% sodium chloride only
  - No filter or low-protein binding (0.2–0.22 micron) in-line filter
  - Do not y-site with other infusions

_Tecentriq® [package insert]. South San Francisco, CA: Genentech; 2016._
Atezolizumab (Tecentriq®)

Withhold criteria
- Grade 2 pneumonitis
- Grade 2 AST, ALT or total bilirubin
- Grade 2-3 diarrhea/colitis
- Symptomatic endocrinopathies
  - Hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism, hyperglycemia grade 3-4
- Grade 2 ocular inflammatory toxicity
- Grade 2-3 pancreatitis
  - Or grade 3-4 amylase/lipase increases
- Grade 3-4 infection
- Grade 3 rash
- Grade 2 infusion-related reaction

May resume when AEs ≤ grade 1

Discontinue criteria
- Grade 3-4 pneumonitis
- Grade 3-4 AST, ALT, total bilirubin
- Grade 4 diarrhea/colitis
- Grade 4 hypophysitis
- Myasthenic syndrome/myasthenia gravis, Guillain-Barré, meningoencephalitis
- Grade 3-4 ocular inflammatory toxicity
- Grade 4 or any grade recurrent pancreatitis
- Grade 3-4 infusion-related reaction
- Grade 4 rash


Atezolizumab (Tecentriq®)

- Immune-mediated AEs treatment
  - Hold or discontinue based on severity
  - High dose steroids
    - Prednisone 1-2 mg/kg PO daily
    - Methylprednisolone 1-2 mg/kg IV daily
    - When grade 0-1, slowly taper over 4+ weeks
    - If grade 0-1 and stable on ≤10 mg prednisone/day within 12 weeks, may resume
  - Replace hormone deficiencies as necessary
    - Hydrocortisone
    - Levothyroxine
    - Insulin

Olaratumab (Lartruvo®)

- Indication: treatment of adult patients with soft tissue sarcoma (STS) in combination with doxorubicin
  - Other subtypes treatable with anthracycline-containing regimen
  - Not candidate for curative surgery or radiation
  - Accelerated approval

- MOA: Platelet-derived growth factor alpha (PDGFR-α) blocking antibody
Olaratumab (Lartruvo®)

<table>
<thead>
<tr>
<th>Trial Design</th>
<th>Efficacy</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaratumab 15 mg/kg IV on days 1, 8 with doxorubicin 75 mg/m² IV on day 1 of 21-day cycle</td>
<td>Versus Doxorubicin 75 mg/m² IV on day 1 of 21-day cycle</td>
<td>For up to 8 cycles</td>
</tr>
<tr>
<td>Combo (C) arm (n=50)</td>
<td>Dosed (D) arm (n=50)</td>
<td>Olaratumab after C8</td>
</tr>
<tr>
<td>Soft tissue sarcoma</td>
<td>No prior anthracycline</td>
<td>No prior PDGFR tx</td>
</tr>
</tbody>
</table>

- C– PFS = 6.6 mo [95% CI 4.1-8.3]  
  - D– PFS = 4.1 mo [95% CI 2.8-5.4]  
  - HR = 0.67, p= 0.0615  
  - 95% CI 0.44-1.02  
  - C– OS = 26.5 mo [95% CI 20.9-31.7]  
  - D– OS = 14.7 mo [95% CI 9.2-17.1]  
  - HR = 0.46, p= 0.0003  
  - 95% CI 0.30-0.71  
  - C– ORR = 18.2%  
  - D– ORR = 11.9%  
  - p= 0.3421  
  - ± set at significance level of 0.2  
  - Tx-related AEs, any (gr 3-4)  
  - C– 67%  
  - D– 55%  
  - FN  
  - C– 13%  
  - D– 14%  
  - Neutropenia (gr 3-4)  
  - C– 43%  
  - D– 33%  
  - Cardiac dysfunction  
  - C– 10%  
  - D– 6%  

Olaratumab (Lartruvo®)

- 15 mg/kg IV infusion days 1 and 8 of a 21-day cycle
  - With doxorubicin 75 mg/m² IV day 1 (cycles 1-8)
  - Premedication required for first dose
    - Diphenhydramine IV 25-50 mg
    - Dexamethasone IV 10-20 mg
  - 60 minute infusion
  - Compound in 250 ml - 0.9% sodium chloride only
  - Do not y-site with other infusions


Olaratumab (Lartruvo®)

- Infusion-related reaction (IRR)
  - Common
    - flushing, SOB, bronchospasm, fever/chills
  - Severe
    - hypotension, anaphylactic shock, cardiac arrest
  - All grades = 14%
  - Grades 3-5 = 2.3% (1 fatality)
  - 97% occur in cycles 1-2
  - Grades 1-2: Stop, if resolved resume at 50% rate
  - Grades 3-4: Stop, support – permanently D/C


Olaratumab (Lartruvo®)

- Dose modifications for FN or grade 4 ANC > 1 week
  - Reduce to 12 mg/kg (permanent) once ANC ≥ 1000
- No dose adjustments for liver or renal function
- No known drug interactions
- Potential pregnancy, lactation and male infertility risks

Rucaparib (Rubraca®)

- **Indication:** Ovarian cancer
  - Deleterious BRCA mutation
  - ≥ 2 prior treatments
  - accelerated approval based on ORR and DOR

- **MOA:** poly (ADP-ribose) polymerase (PARP) inhibitor
  - PARP-1, PARP-2, PARP-3

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PARP Mechanisms and Inhibition

- Single-stranded breaks in DNA require repair
- PARP inhibitors block this repair through the BER pathway
- There are alternate pathways that can overcome this
- BRCA1 and BRCA2 mutated cells have mutations in these other pathways which make them susceptible to PARP inhibition

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Rucaparib (Rubraca®)

- Two open-label, single arm studies (n=106)
  - BRCA-mutant ovarian cancer ≥ 2 lines of tx
- ORR and DOR by investigator and independently

<table>
<thead>
<tr>
<th>Measure</th>
<th>Investigator-assessed (N=106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective Response Rate (%)</td>
<td>58% (44, 74)</td>
</tr>
<tr>
<td>Complete Response (%)</td>
<td>0%</td>
</tr>
<tr>
<td>Partial Response (%)</td>
<td>47%</td>
</tr>
<tr>
<td>Median DOR in months (95% CI)</td>
<td>9.2 (5.8, 12.0)</td>
</tr>
</tbody>
</table>

Rucaparib (Rubraca®)

- **Dose:** 600 mg PO BID ~12 hours apart
  - With or without food
  - Skip missed doses
  - Do not replace vomited doses

- **Supplied:** 300 mg tabs, 200 mg tabs


Rucaparib (Rubraca®)

- Metabolized hepatically
  - CYP2D6 (primarily), CYP1A2, CYP3A4
  - No significant drug interactions known/expected

- No dose recommendations for hepatic/renal impairment
  - T. bilirubin > 1.5 x ULN
  - CrCl < 30 ml/min


Rucaparib (Rubraca®)

Table 2: Adverse Reactions Experienced by Patients with Prostate Cancer Treated with Rubraca 40 and 60 mg Once Daily

Rucaparib (Rubraca®)

- Monitor
  - CBC at initiation and at least monthly
  - Intolerable AEs
- Warnings
  - MDS/AML risk (0.5%, n=2)
  - Fetal harm risk based on animal studies
### New indications 2016

<table>
<thead>
<tr>
<th>Medication</th>
<th>New FDA-approved indication</th>
<th>Prior indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ofatumuzab (Arzerra®)</td>
<td>CLL - recurrent or progressive disease with or without prior lines of therapy</td>
<td>CLL refractory to fludarabine and alemtuzumab; first line when fludarabine therapy is inappropriate</td>
</tr>
</tbody>
</table>
| Daratumumab (DARZALEX®) | Multiple myeloma in combination with: Bortezomib or dexamethasone OR Lenalidomide and dexamethasone  
> ≥ 1 prior line of therapy | Multiple myeloma mono tx  
> ≥ 3 prior lines of therapy  
> Refractory to proteosome inhibitor or immunomodulatory agent |
| Obinutuzumab (GAZYVA®) | Follicular lymphoma in combination with bendamustine, followed by monotherapy  
> Relapsed/refractory to prior rituxan tx | CLL  
> In combination with chlorambucil  
> Initial therapy |
| Crizotinib (XALKORI®) | Metastatic NSCLC  
> ROS-1 positive | Metastatic NSCLC  
> ALK positive |
| Erlotinib (TARCEVA®) | Metastatic NSCLC  
> EGFR exon 19 deletions or exon 21  
> L858R substitution mutations  
> Maintenance or ≥1 line prior tx | This is same tumor genetics already required with first-line indication. Prior second-line indication did not require. |
| Eribulin (HAIWEN®) | Metastatic or unresectable liposarcoma  
> Post anthracycline-containing therapy | Metastatic breast cancer  
> ≥2 lines of therapy prior [anthracycline and taxane] |
| Palbociclib (IBRANCE®) | Metastatic/advanced breast cancer  
> HR+, HER2-, ≥1 line of prior endocrine therapy  
> In combination with fulvestrant | Metastatic/advanced breast cancer with letrozole  
> HR+, HER2-  
> Initial therapy |
| Everolimus (AFINITOR®) | Neuroendocrine tumors (NET)  
> GI/Lung  
> unresectable, LA or metastatic  
> well-differentiated, non-functional | Advanced HR+, HER- Breast Ca  
> Advanced Pancreatic NET  
> Advanced Renal Cell Ca  
> SEGA  
> TSC-Renal Angiomyolipoma |
| Lenvatinib (Lenvima®) | Advanced Renal Cell Carcinoma  
> Prior anti-angiogenic therapy  
> In combination with everolimus | Thyroid cancer  
> locally recurrent or metastatic  
> Radioactive iodine-refractory and progressive |
| Cabozantinib (CABOMETYX®) | Advanced Renal Cell Carcinoma  
> Prior anti-angiogenic therapy | *Medullary thyroid cancer, progressive and metastatic (COMETRIQ®)* |

*Cabozantinib is the active medication in both CABOMETYX® and COMETRIQ®. They are different formulations that should not be used interchangeably. CABOMETYX® comes in 20 mg, 40 mg and 60 mg tablets. COMETRIQ® comes in 20 mg and 80 mg capsules.*
Nivolumab Updates

<table>
<thead>
<tr>
<th>Indication</th>
<th>Place in therapy</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>Metastatic or unresectable</td>
<td>800 mg V600 wild-type or mutant -Single agent or in combination with ipilimumab 10 mg/kg IV Q3 weeks + Ipilimumab x 4 doses, then 240 mg IV Q2 weeks</td>
</tr>
<tr>
<td>NSCLC, metastatic</td>
<td>Post platinum-based therapy (and EGFR/Aux tx as indicated)</td>
<td>240 mg IV Q2 weeks</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>Advanced</td>
<td>240 mg IV Q2 weeks</td>
</tr>
<tr>
<td>Classical Hodgkin's lymphoma</td>
<td>Relapsed or progressed after autologous HSCT and post-transplant brentuximab vedotin</td>
<td>3 mg/kg IV Q2 weeks</td>
</tr>
<tr>
<td>Head and Neck</td>
<td>Squamous cell carcinoma</td>
<td>Post platinum-based therapy</td>
</tr>
<tr>
<td></td>
<td>Recurrent or metastatic</td>
<td>240 mg IV Q2 weeks</td>
</tr>
</tbody>
</table>

Pembrolizumab Updates

<table>
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<tr>
<th>Indication</th>
<th>Place in therapy</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>Metastatic or unresectable</td>
<td>No restrictions 2 mg/kg IV Q3 weeks</td>
</tr>
<tr>
<td>NSCLC, metastatic</td>
<td>First-line if express PD-L1 ≥ 50%* -No EGFR or Aux tx available Second-line post platinum tx -If express PD-L1 ≥ 1%* -Post EGFR/Aux-directed therapy as appropriate</td>
<td>200 mg IV Q3 weeks (up to 24 months)</td>
</tr>
<tr>
<td>Head and Neck</td>
<td>Squamous cell carcinoma</td>
<td>Post platinum-based therapy</td>
</tr>
<tr>
<td></td>
<td>Recurrent or metastatic</td>
<td>200 mg IV Q3 weeks (up to 24 months)</td>
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</table>

*PD-L1 expression based on Tumor Proportion Score (TPS). PD-L1 is an immune-related biomarker

PD-1/PD-L1 Immunotherapy Dosing

- Fixed vs Weight-based Dosing
  - Nivolumab – Both
    - Melanoma, NSCLC, RCC – fixed
      - population PK analyses and dose/exposure-response analyses demonstrate comparable PK exposure, safety, and efficacy 1
      - ≤6% difference in overall exposure 1
  - Pembrolizumab – Both
    - NSCLC and SCC of Head and Neck - fixed
    - Atezolizumab – Fixed dose

1. [https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm520871.htm](https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm520871.htm) accessed online March 6, 2017.
Audience question 3

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Precision Medicine

- **Precision Medicine**
  - "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person." - NIH

- **Precision Medicine Initiative® (PMI)**
  - A research effort focusing on bringing precision medicine to many aspects of healthcare
    - 2016 Federal Budget = $216 million
    - NIH, NCI, FDA
  - Short-term goals
    - Expanding precision medicine in the area of cancer research
  - Long-term goals
    - Bring precision medicine to all areas of health and healthcare on a large scale


[Image of NCI Precision Medicine infographic]

HER2/neu Targeted Treatment

- Cancers overexpressing HER2/neu have rapid cell division and growth.
- This is targetable with anti-HER2/neu therapy
  - Breast Cancer ~15-20% of patients
    - Trastuzumab, ado-Trastuzumab emtansine, Pertuzumab, Lapatinib, Neratinib
  - Gastroesophageal Cancers ~20%
    - Trastuzumab
  - Colon Cancer ~2-3% (Still investigational)
    - No approved treatments – early data with trastuzumab and lapatinib combination


HER2/neu Targeted Treatment

![HER2/neu Targeted Treatment Diagram](image)

**Normal Cell**
- HER-2 Oncoprotein
  - HER-2 Overexpression is quantified by FISH (Tissue test)
  - HER-2 membrane bound protein is measured by IHC (Tissue test)

**Cancer Cell**
- Extracellular Domain (ECD) of HER-2 protein is released into blood and can be measured by ELISA (Blood test)


**Figure. Mechanisms of Action of HER2-Directed Agents for Breast Cancer**

![HER2-Directed Agents for Breast Cancer Diagram](image)

EGFR Inhibitors

- Epidermal Growth Factor Receptor
  - Can be overexpressed in tumors
  - Extracellular, transmembrane
  - Activation can induce activation of intracellular tyrosine kinase pathway (Ras-Raf-MEK-ERK)
  - Cellular proliferation

- Inhibitors for metastatic colorectal cancer (mCRC)
  - Only for Ras wild-type mCRC, require extended Ras testing
    - KRAS, exons 2,3,4
    - NRAS, exons 2,3,4
  - Cetuximab
  - Panitumumab

**EGFR SIGNALING PATHWAY:**

Panitumumab & Cetuximab block action here

Ras signaling pathway

**Precision Medicine for NSCLC**

- Molecular testing at staging
  - Nonsquamous histology (+/- squamous)
    - EGFR (exon 19 deletion or exon 21 L858R substitution)
    - T790M testing after progression on EGFR targeted therapy
    - ALK rearrangement
    - ROS1
  - Nonsquamous and squamous histology
    - PD-L1
Precision Medicine for NSCLC

**EGFR positive**
- Erlotinib
- Afatinib
- Gefitinib

**ALK positive**
- Crizotinib

**ROS1 positive**
- Crizotinib

**T790M positive**
- Osimertinib

**T790M negative**

**PD-L1 positive, ≥50%**
- Pembrolizumab

**PD-L1 positive, ≤50%**
- Pembrolizumab

**PD-L1 <50%**
- Ceritinib
- Alectinib

**Platinum-based doublet**

**If no prior immunotherapy:**
- Nivolumab
- Atezolizumab
- Pembrolizumab

**Adapted from NCCN guidelines: Non-small cell lung cancer. Version 4.2017.**

Thank you

Questions?