Are you familiar with the new cancer drugs that the FDA has approved within the last year? Get introduced to these novel treatments while learning valuable tips to help you quickly grasp drug classifications. You’ll discuss multidisciplinary trends in drug development, newly approved molecular and radiotherapeutic agents, and future directions for cancer therapies.

Target Audience: All Levels

Level of Content: Advanced

Speaker:
Rowena N. Schwartz, PharmD
Vice President, Clinical Content and Pharmacy Services
McKesson Specialty Health
The Woodlands, TX

Full Disclosure:
Nothing to Disclose

Objectives:
At the end of this session, participants will be able to:
1. Describe the evolution of new strategies for drug therapy in cancer care.
2. Discuss new targets for cancer drug therapy.
3. Outline the current and potential applications of some of the new agents that have come onto the market in the last few years.
Drug Update in Oncology: The Evolution of Pharmacotherapy in Cancer Care

Rowena N. Schwartz, PharmD, BCOP
McKesson Specialty Health

Objectives

- Describe the evolution of new strategies for drug therapy in cancer care.
- Discuss new targets for cancer drug therapy.
- Outline the current and potential applications of some of the new agents that have come onto the market in the last few years.

Evolution of Cancer Drug Development

Financial Disclosure

Rowena N. Schwartz, Pharm.D., BCOP is employed by McKesson Specialty Health

Phase of Anticancer Drug Development

- Preclinical testing
- Phase 0 clinical trials
- Phase 1 clinical trials
- Phase 2 clinical trials
- Phase 3 clinical trials
- Phase 4 clinical trials

Anticancer Drug Development: Phase 0 Clinical Trials

- Strategy for accelerating the development of next generation of anticancer treatment → subtherapeutic doses of an agent are administered to a small number of participants
  - Pharmacokinetics
  - Pharmacodynamics
- Conducted prior to conventional toxicity-defined dose escalation studies
Anticancer Drug Development: **Phase 0**

**EXAMPLE:**
- Study that examined the mechanism of action of a novel oral poly (ADP-ribose) polymerase inhibitor ABT-888
- Primary goals of study:
  - Determine the non-toxic dose ranges at which ABT-888 inhibits PARP in tumor tissue and PBMC
  - To examine the time course of PARP inhibition
- Secondary goals:
  - Define safety of single dose of ABT-888 (not MTD)
- Ten patients were enrolled and treated at three dose levels


---

Anticancer Drug Development: **Phase I**

**Objectives of Phase I Studies for New Therapeutics:**
- Determination of maximum tolerated dose
- Determination of adverse effects
- Determination of proper schedule
- Pharmacology
- Bioavailability
- Effect on biologic target
- Observation for activity

**Phase I: Dose Escalation Strategy**
- Phase I trial in which cixutumumab was combined with temsirolimus in patients with advanced cancer.
- The study used a standard 3+3 design and patient were enrolled across 4 dose cohorts.
- Dose scheme (N=42)

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Cixutumumab Dose</th>
<th>Temsirolimus Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3mg/kg</td>
<td>25 mg</td>
</tr>
<tr>
<td>2</td>
<td>5mg/kg</td>
<td>25 mg</td>
</tr>
<tr>
<td>3</td>
<td>6mg/kg</td>
<td>25 mg</td>
</tr>
<tr>
<td>4</td>
<td>6mg/kg</td>
<td>37.5 mg</td>
</tr>
</tbody>
</table>


---

Anticancer Clinical Development: **Phase II**

**Objectives:**
- **Activity of drug(s)**
- Effect on biologic target
- Dose-response relationships
- Increased characterization of toxicity

---

Phase I: Common Endpoints

**Single Agent:**
- Toxicity
- Biomarkers
- Novel imaging endpoints
- Pharmacokinetics

**Combination:**
- Scheduling and sequence
- Toxicology
- Pharmacokinetics
Anticancer Clinical Development: **Phase II**

Primary Endpoints of Phase II Studies:
- Objective tumor response
- Survival
- Patient reported outcomes (QOL)
- Biomarker endpoints

Anticancer Clinical Development: **Phase III**

Objectives:
- Therapeutic effectiveness/benefit
- Risk/benefit
- Goal to compare new drug or combination to standard of care treatment

Anticancer Clinical Development: **Phase IV**

Objectives:
- Continued development to optimize use in marketed indication
- Explore activity and demonstrate benefit in other cancer indications
- Monitor for rare and long-term toxic effects

Accelerated Approval of Oncology Products

- Accelerated approval (AA) was initiated by the US FDA to shorten development time of drugs for serious medical conditions.
  - AA applications are often designed on basis of interim analyses of Phase III trials
  - Sponsors must confirm efficacy in post approval studies.

- History:
  - Dec 1992 – July 2010 the FDA granted AA to 35 products (47 new indications)
  - Clinical benefit was confirmed in post approval trials for 26 (55%) of new indications.
  - Confirmatory trials were not completed for 14 (30%) of new indications.

Endpoints for Treatment Studies in Oncology

- Tumor response
  - Measurement is determined by cancer
  - Solid tumors – RECIST
  - CLL – International Workshop on CLL criteria
- Survival
  - Progression free survival (PFS)
  - Disease free survival (DFS)
  - Overall survival (OS)
- Patient reported outcomes
  - Quality of life (QOL)
- Biomarkers
Surrogate End Points

- Definition:
  - laboratory measurement or physical sign used as a substitute for a clinically meaningful end point that measures how a patient feels, functions or survives.
- Examples of surrogate endpoints:
  - Bone mineral density
  - PSA
- Benefit → faster answers about new treatment
- Risk → answers may not reflect meaningful end point

CTCAE v 4: Severity of AE

Toxicities – grade 1:
- Mild
- Asymptomatic or mild symptoms
- Clinical or diagnostic observations
- Interventions not indicated

Example: abdominal distention
Grade 1: asymptomatic, clinical or diagnostic observations only; intervention not indicated

CTCAE v 4: Severity of AE

Toxicities – grade 2:
- moderate
- minimal, local or noninvasive intervention indicated
- limiting age-appropriate instrumental activities of daily living (ADL)

Example: abdominal distention
Grade 2: symptomatic; limiting instrumental ADL (e.g. preparing meals, shopping for groceries or clothes, using telephone, managing money)

CTCAE v 4: Severity of AE

Toxicities – grade 3:
- severe or medically significant but not immediately life-threatening
- hospitalization of prolongation of hospitalization indicated
- disabling
- limiting self care ADL

Example: abdominal distention
Grade 3: severe discomfort; limiting self care ADL (e.g. bathing, dressing, self feeding, toileting, taking medications)

CTCAE v 4: Severity of AE

Toxicities – grade 4:
- Life-threatening consequences
- Urgent intervention indicated

Example: abdominal distention
Grade 4: no description listed*

* Not all grades are appropriate for all AEs

Common Terminology Criteria for Adverse Events (CTCAE version 4.0)

- Published May 2009, version 4.03 June 2010
- Organization by system organ class
- Adverse events (AEs) are listed and accompanied by descriptions of severity
- CTCAE terms
  - AE is any unfavorable and unintended sign, symptoms or disease temporarily associated with the use of a medical treatment or procedure that may or may not be considered related to the treatment.

REPORTING OF ADVERSE EVENTS

- Not all grades of toxicity are appropriate for all AEs
- Results of clinical trials often include summary of adverse effects seen during the trial.
  - Any grade
  - Grade 3 and 4
- Strategies to prevent and/or manage may be discussed in the methods and/or results.
- Laboratory abnormalities

NON-INFERIORITY TRIALS: RATIONALE

- Treatment is not to be more effective than another treatment, but may be “better” for another reason.
- Conclusions are based on non-inferiority thresholds specified by authors.

IPILUMAB(Yervoy™): PHASE III

- Patients (n=502) with previously untreated metastatic melanoma randomized:
  - ipilimumab + dacarbazine
  - dacarbazine + placebo (n=502)
- ipilimumab 10 mg/kg q 3 weeks for 4 doses
- Maintenance dose of ipilimumab every 3 months

<table>
<thead>
<tr>
<th>Survival</th>
<th>ipilimumab + DTIC</th>
<th>DTIC</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (months)</td>
<td>11.2</td>
<td>9.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1 yr OS (%)</td>
<td>47.2</td>
<td>36.3</td>
<td>NA</td>
</tr>
<tr>
<td>2 yr OS (%)</td>
<td>28.5</td>
<td>17.9</td>
<td>NA</td>
</tr>
<tr>
<td>3 yr OS (%)</td>
<td>20.8</td>
<td>12.2</td>
<td>NA</td>
</tr>
</tbody>
</table>


IMMUNE RELATED RESPONSE CRITERIA (IRRC)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Change in Baseline in Total Tumor Burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>irCR</td>
<td>Decrease by 100% [complete resolution]</td>
</tr>
<tr>
<td>irPR</td>
<td>Decrease by ≥ 50%</td>
</tr>
<tr>
<td>irPD</td>
<td>Increase by ≥ 25%</td>
</tr>
<tr>
<td>irSD</td>
<td>Any response not inclusive of above criteria</td>
</tr>
</tbody>
</table>


EVOLUTION OF CANCER DRUG DEVELOPMENT: IMMUNOTHERAPY

- Durability of responses were seen in phase III trials
- Retrospective evaluation of individuals (n = 177) treated on early clinical trials
  - Patients that achieved CR may have long lasting response
  - Patients who had a PR may achieve long term disease control
  - Response to ipilimumab can be delayed
  - Initial progression of disease - disease response

*Immune-related response criteria (IRRC)
  - New lesions are included in the determination of overall tumor burden but do not automatically indicate progressive disease
  - Evidence of disease progression requires confirmation with radiographic assessment at least 4 weeks later

Ipilimumab: Adverse Events

- The potent ability of CTLA-4 blockade activates the immune system:
  - Tissue specific inflammation
    - Skin dermatitis
    - Gastrointestinal tract enterocolitis
    - Liver hepatitis
    - Endocrine system hypophysitis, thyroiditis
  - Immune-related adverse events (irAE)
    - Usually transient and reversible
    - Patient education for early recognition
    - Interventions depend on severity and side effect
      - Interrupt dose
      - Immunosuppression (e.g. steroids)


Ipilimumab irAE

- Manifestation:
  - Gastrointestinal tract → 6-7 wk
    - Colitis
  - Liver → 6-7 wk
    - Hepatitis
  - Skin → 2-3 wk
    - Erythematous maculopapular rash
  - Endocrine → 9 wk
    - Hypophysitis

Ipilimumab: irAE

Hypophysitis
- Uncommon complication of treatment
- Hypophysitis with clinically significant adrenal insufficiency → adrenal crisis
- Symptoms
  - Behavioral changes
  - Fatigue
  - Headaches
  - Visual changes: blurring, diplopia
  - Myalgia
  - Anorexia
- When hypophysitis with pituitary dysfunction is suspected:
  - TSH, free T4, adrenocorticotrophic stimulating hormone, Cortisol,
  - Females: LH, FSH
  - Males: testosterone


Incorporating Immunotherapy into Care of the Individual with Cancer

- What should be the focus of education for ipilimumab-related hypophysitis in survivorship planning?

Johnson DB, et al. AACR 2015 (published Online First 2/3/15)

Incorporating Immunotherapy into Care of the Individual with Cancer

- What should be the focus of education for ipilimumab-related hypophysitis when the used in combination therapy?

Rini B. Semin Oncol 2014:S30-S40.
Looking at Targets for Drug Therapy

- Approximately 80 percent of investigational agents for cancer in the pipeline are potentially first-in-class treatments!

Ramucirumab (Cyramza®)

**Mechanism:**
- Human vascular endothelial growth factor receptor 2 (VEGF 2) antagonist
  - Prevents ligand binding and receptor-mediated pathway activation in endothelial cells (prevents angiogenesis)

**Indication:**
- April 2014:
  - As a single agent for treatment of advanced gastric or GEJ adenocarcinoma, with disease progression on or after prior fluoropyrimidine or platinum-containing chemotherapy
- November 2014:
  - In combination with paclitaxel, for treatment of advanced gastric or GEJ adenocarcinoma, with disease progression on or after prior fluoropyrimidine or platinum-containing chemotherapy
- December 2014:
  - In combination with docetaxel, for treatment of metastatic NSCLC with disease progression on or after platinum-based chemotherapy. Patients with EFR or ALK genomic tumors aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving ramucirumab

**Ramucirumab + Paclitaxel: Gastric Cancer RAINBOW Trial**

- **Methods:**
  - Multinational, randomized, double-blind, placebo-controlled Phase 3 trial
  - Inclusion:
    - Advanced gastric or gastroesophageal adenocarcinoma and disease progression on or within 4 months after 1st line chemotherapy (fluoropyrimidine + platinum +/- anthracycline)
    - Randomized 1:1
      - Ramucirumab 8 mg/kg IV P1,15 + paclitaxel 80 mg/m2 IV P1,8,15 Q28D (n=665)
      - Placebo + paclitaxel 80 mg/m2 IV P1,8,15 Q28D (n=665)
  - **Endpoints:**
    - Primary: overall survival
    - Secondary: progression free survival, objective tumor response, disease control, patient-reported outcomes

**Results**

<table>
<thead>
<tr>
<th>RAM + PTX</th>
<th>PBO + PTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS</td>
<td>9.6 mos</td>
</tr>
<tr>
<td>Median PFS</td>
<td>4.4 mos</td>
</tr>
<tr>
<td>Median TTP</td>
<td>5.5 mos</td>
</tr>
<tr>
<td>ORR</td>
<td>26%</td>
</tr>
</tbody>
</table>

*Median duration of treatment: 18 wks vs 12 wks

Ramucirumab + Docetaxel: Non-Small Cell Lung Cancer REVEL

- Methods:
  - Multicenter, randomized, double-blind, placebo-controlled Phase 3 trial
- Inclusion:
  - Stage IV NSCLC that progressed during or after platinum-based chemo +/- bevacizumab or maintenance therapy
  - Recurrent disease post adjuvant/neoadjuvant therapy or chemorT for locally advanced disease if progression occurred up to 6 months after completion of initial tx, or if progression 6 months after initial tx and during or after one subsequent platinum-based regimen
- Randomized 1:1
  - Ramucirumab 10 mg/kg IV at D1 + docetaxel 75 mg/m² IV at D1 Q3W (n=628)
  - Placebo + docetaxel 75 mg/m² IV at D1 Q3W (n=625)
- Endpoints:
  - Primary: overall survival
  - Secondary: progression free survival, overall response rate, toxicity, patient-reported outcomes/QOL


Results:

- Median duration of treatment: 15 wks vs 12 wks

Ramucirumab + Docetaxel: Lung Cancer REVEL

<table>
<thead>
<tr>
<th></th>
<th>RAM + DOCE (n=628)</th>
<th>PBO + DOCE (n=625)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS</td>
<td>10.5 mos</td>
<td>9.1 mos</td>
</tr>
<tr>
<td>OS subset analyses (study not powered for subset analyses)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-squamous</td>
<td>11.1 mos</td>
<td>9.7 mos</td>
</tr>
<tr>
<td>Squamous</td>
<td>9.5 mos</td>
<td>8.2 mos</td>
</tr>
<tr>
<td>Responders to 1st LOT</td>
<td>11.2 mos</td>
<td>10.3 mos</td>
</tr>
<tr>
<td>Median PFS</td>
<td>4.5 mos</td>
<td>3 mos</td>
</tr>
<tr>
<td>OSM</td>
<td>25%</td>
<td>14%</td>
</tr>
<tr>
<td>PFSM</td>
<td>5</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>


TARGET: MAPK PATHWAY (MITOGEN ACTIVATED PROTEIN KINASE)

Melanoma: MAPK Signaling Pathway

- BRAF inhibition:
  - Vemurafenib
  - Dabrafenib
- MEK inhibition:
  - Trametinib


Melanoma: MAPK Signaling Pathway

- BRAF inhibition:
  - Vemurafenib (Zelboraf®)
    - Potent competitive inhibitor of mutant BRAF
    - Phase I trial demonstrated responses rates of 81%
    - Phase II (BRIM-2): RR 53%, SD 29%, median PFS 6.7 mo
    - Phase III (BRIM-3): stopped early secondary to OS benefit of vemurafenib over dacarbazine
  - Dabrafenib
- MEK inhibition:
  - Trametinib

Vemurafenib (Zelboraf®): Adverse Effects

- Arthralgias
- Rash
- Photosensitivity
- Fatigue
- Cutaneous squamous cell carcinoma
- Keratoacanthoma
- Nausea
- Diarrhea
- Fever
- Dose interruption and modification were required in > 35% patients.

Melanoma: MAPK Signaling Pathway

**BRAF inhibition:**
- Vemurafenib
- Dabrafenib (Tafinlar®)

**MEK inhibition:**
- Trametinib


Dabrafenib: Phase III

Methods:
- Open-label phase III trial Dec 2010-Sept 2011
- Patients with previously untreated stage IV or unresectable stage III BRAF V600E mutated melanoma
- Randomized (3:1):
  - Dabrafenib 150 mg po twice daily
  - Dacarbazine 1000 mg/m2 IV q 3 weeks
- Primary endpoint:
  - Investigator assessed PFS


Dabrafenib: Phase III

- Patients (n=250) with untreated stage IV or unresectable stage III melanoma with BRAF V600E

<table>
<thead>
<tr>
<th>Response</th>
<th>Dabrafenib (n=187)</th>
<th>Dacarbazine (n=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (median)</td>
<td>5.1 mo</td>
<td>2.7 mo</td>
</tr>
<tr>
<td>CR</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>PR</td>
<td>47%</td>
<td>5%</td>
</tr>
<tr>
<td>SD</td>
<td>42%</td>
<td>48%</td>
</tr>
<tr>
<td>PD</td>
<td>5%</td>
<td>37%</td>
</tr>
<tr>
<td>ORR</td>
<td>50%</td>
<td>6%</td>
</tr>
</tbody>
</table>


Melanoma: MAPK Signaling Pathway

**BRAF inhibition:**
- Vemurafenib
- Dabrafenib

**MEK inhibition:**
- Trametinib (Mekinist™)


Trametinib: Phase III

Methods:
- Open label study
- Randomly assigned patients (n=322) with metastatic melanoma with V600E or V600K BRAF mutations in 2:1 ratio:
  - Trametinib (trametinib 2 mg po daily)
  - Chemotherapy (dacarbazine 1000 mg/m2 IV q 3 weeks or paclitaxel 175 mg/m2 IV q 3 weeks)
- Patients in the chemotherapy group who had progressive disease were permitted to cross over to the trametinib arm.
- Endpoints:
  - Primary endpoint: PFS
  - Secondary endpoint: OS

Trametinib

Open label study randomly assigned patients (n=322) with metastatic melanoma with V600E or V600K BRAF mutations

<table>
<thead>
<tr>
<th>Type of Response</th>
<th>Trametinib (n=214)</th>
<th>Chemotherapy (n=108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>PR</td>
<td>20%</td>
<td>8%</td>
</tr>
<tr>
<td>SD</td>
<td>56%</td>
<td>31%</td>
</tr>
</tbody>
</table>

PFS 4.8 mo 1.5 mo <0.001
OS (6 mo) 81% 67% =0.01


Trametinib Chemotherapy P value
PFS 4.8 mo 1.5 mo <0.001
OS (6 mo) 81% 67% =0.01

Type of Response Trametinib (n=214) Chemotherapy (n=108)
CR 2% 0%
PR 20% 8%
SD 56% 31%


Combined Targeted Therapies

- 50% of patients treated with BRAF or MEK inhibitors relapse within 6 months
- Resistance to therapy with BRAF kinase inhibitors → reactivation of MAPK pathway
- Strategy to delay resistance to BRAF inhibition: dabrafenib + trametinib

Dabrafenib + Trametinib: Phase I/II

Method:
- Open-label study
- Patients with metastatic melanoma and BRAF V600 mutations
- Treatment to determine p’kinetics + safety (n=85):
  - Dabrafenib 75 or 150 mg po twice daily AND
  - Trametinib 1, 1.5 or 2 mg po daily
- Treatment to assess combination (n=162):
  - Dabrafenib (150 mg) + trametinib (1 or 2 mg)
  - Dabrafenib monotherapy
- Endpoints:
  - Primary: incidence of cutaneous squamous-cell carcinoma, survival free of melanoma progression and response
  - PFS with combination RR


Results:
- Dose-limiting toxic effects were infrequently observed in patients receiving combination therapy
- Pyrexia more common in the combination group:
  - Combination 71%
  - Dabrafenib monotherapy 26%
- Cutaneous squamous cell carcinoma
  - Combination 7%
  - Dabrafenib monotherapy 19%


Dabrafenib + Trametinib: Phase I/II


Trametinib (Mekinist™): Toxocities

- Skin toxicities: Rash, dermatitis acniform, dry skin
- Diarrhea and abdominal pain
- Peripheral edema
- Cardiac
- Ocular
- Secondary skin neoplasms were not observed.


The Rationale for Multikinase Inhibitors: Thyroid Cancer

- TKI have been shown to improve response rates and progression-free survival in differentiated thyroid cancer (DTC)
- Variety of TKI that target signaling by vascular endothelial growth factor (VEGF) and VEGF-receptors have demonstrated activity in thyroid cancer:
  - Sorafenib → RET, VEGFR, FLT3, c-KIT, BRAF
  - Sunitinib → VEGFR, PDGFR, c-KIT, FLT3, and RET
  - Axitinib → VEGFR
  - Pazopanib → VEGFR, FGFR, PDGFR, IL2 receptor T-cell kinase, and others
  - Lenvatinib → VEGFR, FGFR, c-KIT, PDGFR

Lenvatinib (Lenvima™)

- MOA:
  - Multitarget kinase inhibitor
- Indication:
  - Treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer
- Warnings/Precautions:
  - Hypertension
  - Cardiac failure
  - Arterial thromboembolic events
  - Hepatotoxicity
  - Proteinuria

**Lenvatinib**

Methods:
- Phase III, randomized, double-blind, multicenter study
- Patients with progressive thyroid cancer refractory to 131 I
- Randomized (2:1) lenvatinib 24 mg po daily vs. placebo
  - Placebo → lenvatinib at disease progression

Endpoints:
- Primary endpoints: PFS
- Secondary endpoints: RR, OS, safety

Results:
- Increase PFS: Lenvatinib 18.3 mo vs. placebo 3.6 mo
- Increase RR: Lenvatinib 64.8% vs. placebo 1.5%
- Side effects included HTN (68%), diarrhea (59%), fatigue (59%), decreased appetite (50%), decrease weight (46%) and nausea (41%)
- d/c of drug secondary to side effects in 14% patients
- 6 deaths thought to be due to drug-related effects


**Targeting: PI3K δ**

- Role of Phosphatidylinositol 3-kinases:
  - PI3Ks regulate cellular function → production PI3,4,5 triphosphates → activate downstream serine-threonine kinase Akt → cellular growth, proliferation and survival
- Rationale as target for B-cell lymphoproliferative disorders:
  - Dysregulation of PI3K/Akt pathway seen in some malignancies
  - Expression of p110 isoform mainly seen in lymphoid cells
- Potential applications of this approach:
  - CLL
  - Follicular B-cell lymphoma
  - SLL

**New Targets in Cancer Care**

**Idelalisib + Rituximab in relapsed CLL**

- MOA: potent oral selective small-molecule inhibitor of PI3K δ
- Methods: multicenter, randomized, double-blind, placebo-controlled phase 3 study
- Inclusion:
  - CLls that had progressed within 24 months after last treatment and were not able to receive cytotoxic agents
  - Severe neutropenia or thrombocytopenia
  - CrCl <60 mL/min
  - Cumulative illness rating scale ≥6 for coexisting illnesses not related to CLL
  - Previous treatment must have included a CD20 antibody-based regimen OR at least 2 previous cytotoxic regimens
- Endpoints:
  - Primary: progression free survival
  - Secondary: overall response rate, overall survival, lymph node response

Idelalisib + Rituximab in relapsed CLL:

- Study enrollment: May 2012 – August 2013
- Treatment:
  - Rituximab IV 375 mg/m2 → 500 mg/m2 q 2 wk × 4 doses, then q 4 wks × 3 doses for a total of 8 infusions
  - Idelalisib 150 mg po BID or placebo BID
- Patients in the idelalisib group that had disease progression could receive increase dose of drug to 300 mg BID
- Idelalisib + rituximab treatment group: 110 treated
- Placebo + rituximab treatment group: 107 treated
  - 2 patients withdrew because of adverse effects
  - 1 patient had not received study treatment before data cutoff

Idelalisib + Rituximab in relapsed CLL:

- Lymphocytosis seen with single agent idelalisib in trials not seen when rituximab added
  - Blunts and shortens duration of lymphocytosis

### Table: Grade 3/4 Adverse Events

<table>
<thead>
<tr>
<th>Grade 3/4 Adverse Events</th>
<th>IDEL+ RTX</th>
<th>PBO + RTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>56%</td>
<td>48%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>14%</td>
<td>22%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>10%</td>
<td>16%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Idelalisib + Rituximab in relapsed CLL:

- Demographics: median age: 71, Rai stage 3 or 4, unmutated (no 17p deletion TP53 mutation)

<table>
<thead>
<tr>
<th></th>
<th>IDEL+ RTX</th>
<th>PBO + RTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of PFS</td>
<td>93%</td>
<td>46%</td>
</tr>
<tr>
<td>Median PFS</td>
<td>NR</td>
<td>5.5 mo</td>
</tr>
<tr>
<td>Median OS at 12 mo</td>
<td>92%</td>
<td>80%</td>
</tr>
<tr>
<td>Median ORR</td>
<td>81%</td>
<td>13%</td>
</tr>
<tr>
<td>Lymph node response</td>
<td>93%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Bruton’s Tyrosine Kinase

- Kinase inhibitor

BTK as a target:
- BTK is a non-receptor tyrosine kinase member of the Tec kinase family
- BTK is important in B-cell development

Therapeutic potential of **BTK inhibition**:
- BTK inhibition in CLL: inhibits binding, reduces cell migration, proliferation, and survival, disrupts integrin-mediated adhesion, DNA synthesis and cellular response to tissue chemokines
- BTK inhibition in MCL: induces apoptosis, decrease levels of anti-apoptotic proteins and ultimately MCL growth and cellular migration

Ibrutinib (Imbruvica®)

Current Indications:
- Mantle Cell Lymphoma
  - Patients with mantle cell lymphoma who have received at least one other therapy
  - Accelerated approval was granted based on ORR
- Chronic Lymphocytic Leukemia
  - Patients with CLL who have received at least one prior therapy
- Chronic Lymphocytic Leukemia with 17p deletion
- Waldenstrom’s Macroglobulinemia
### Ibrutinib (Imbruvica®)

Adverse Effects:
- In phase I-II trials most AEs were grade 1 or 2
- Most common toxicities:
  - Diarrhea (50%)
  - Fatigue (32-41%)
  - Nausea (18-31%)
  - Cough (31%)
  - Peripheral edema (21-28%)
  - Dypnea (27%)
  - Arthralgia (27%)
  - Rash (27%)
  - Pyrexia (27%)
  - Constipation (18-35%)
  - Upper respiratory tract infection (23-33%)
  - Vomiting (16-21%)
  - Decreased appetite (21%)
  - Muscle spasm (20%)

### Cyclin-Dependent Kinases

- Cell cycle transition and cell division are coordinated by cyclin-dependent kinases (CDK)
  - CDK1 regulates transition from G2 to M
  - CDK 2, -4, and -6 regulate transition from G1 to S

### Targeting Cyclin-Dependent Kinases

CDK as a target:
- Cyclin-dependent kinases (CDK) are critical regulatory enzymes that drive all cell cycle transitions.
- Integration of multiple signaling pathways through control of select CDK activation.
- Crucial role in orderly and controlled progression through cell cycle
- Deregulation of select CDK dependent pathways associated with some malignancies.

The therapeutic potential of CDK inhibitors:
- First generation: relatively non-specific “panCDK inhibitors”
- Second generation: target inhibition of select CDK
  - Single agent approach
  - Combination approach

### Palbociclib (Ibrance®)

- Reversible, oral, highly selective inhibitor of CDK 4/6
- Prevents cell-cycle progression from G1 to S
- Reduction of cellular proliferation of ER+ breast cancer cell lines by blocking progression of the cell from G1→S phase of cell cycle
- Inhibits proliferation in cultured and xenografted leukemia, myeloma, breast, colon and lung cancer cells

### Palbociclib

- Current indications:
  - Palbociclib is indicated in combination with letrozole for treatment of postmenopausal women with ER+, HER2- advanced breast cancer as initial endocrine-based therapy for metastatic disease (Accelerated approval – PFS)

### Phase I of Palbociclib

- Rb-positive solid tumors and non-Hodgkin’s lymphoma
- Two different treatment schedules
  - 3/1 Schedule: 4-week treatment cycle; daily for 21 days followed by 7 days off treatment
    - 41 patients enrolled, MTD 125 mg daily
  - 2/1 Schedule: 3-week treatment cycle; daily for 14 days followed by 7 days off treatment
    - 33 patients enrolled, MTD 200 mg daily
- Neutropenia was the only dose-limiting toxicity in both schedules

---

Palbociclib in Breast Cancer Cohort

- Dose reductions in 19 patients, the majority at the start of cycle 2
- Grade 3-4 toxicity included neutropenia (51%), anemia (5%) and thrombocytopenia (22%)
- No biomarker identified a sensitive tumor population

Palbociclib + Letrozole: Breast Cancer (PALOMA-1/TRIO-18)

- Methods:
  - International, phase 2, multicenter, open-label randomized study
- Inclusion:
  - Postmenopausal women with ER+, HER2-, advanced breast cancer
  - Cohorts (2) accrued sequentially:
    - ER status, HER2 status
    - Required amplification of cyclin D1, loss of p16, or both
- Randomized 1:1
  - Palbociclib 125 mg PO daily x3 wk (1 wk off) + letrozole 2.5 mg PO daily (n=84)
  - Letrozole 2.5 mg PO daily (n=81)
- Study endpoints:
  - Primary endpoints: PFS
  - Secondary endpoints: OR (RECIST), clinical benefit, duration response, OS, safety, biomarker analysis.

Unplanned interim analysis (when 2x patients progressing on control group)

- Median follow up: 29.6 mos

<table>
<thead>
<tr>
<th></th>
<th>PAL+ LET</th>
<th>LET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>20.2 mos</td>
<td>10.2 mos</td>
</tr>
<tr>
<td>Objective response</td>
<td>36%</td>
<td>27%</td>
</tr>
<tr>
<td>Median duration of response</td>
<td>20.3 mos</td>
<td>11.1 mos</td>
</tr>
<tr>
<td>Overall survival</td>
<td>37.5 mos</td>
<td>33.3 mos</td>
</tr>
</tbody>
</table>

- HR 0.488, one-sided p=0.0004

Future Directions of CDK4 inhibitors

- Synergy of CDK4 targeting with inhibitors of RAS-RAF-MEK
- Other CDK4 inhibitors in development
- Combination trials with CDK4 inhibitors

Optimizing Strategy via a Target: PARP

PARP Inhibitors

Olaparib (Lynparza) the first of a new class of drug to treat ovarian cancer. (R. Padzur, MD)
Poly-(ADP-ribose) polymerases (PARP)

- PARP is a family of enzymes found in plants and animals
- Play a key role in cellular damage response pathways
  - inflammation
  - trigger cell death in response to ischemia
  - DNA damage repair
- PARP-1 is the most common of the enzymes
  - found in the nucleus of the cell
  - acts as a sensor
  - recruits repair proteins
  - improves access to repair proteins
- PARP-2 has both unique and common functions as compared to PARP-1

Poly-(ADP-ribose) polymerases (PARP)

- Inactive until bound to a DNA strand break
- Key role in DNA repair mechanisms
  - detecting DNA strand breaks
  - initiating repair of DNA
- DNA strand break → PARP-1 binds → synthesizes polymers
  - PARP-1 is released from DNA
  - polymers are degraded

Potential Clinical Applications of PARP Inhibition

- Combine with chemotherapy to block the repair of damage caused by the chemotherapy agents
- Combine with other DNA damaging therapy to block the damage (e.g. radiation therapy)
- Synthetic lethality

PARP Inhibitors: Combination Treatment

Preclinical studies:
- Synergy with chemotherapy and PARP inhibitions
  - synergy is dependent on chemotherapy
  - synergy is dependent on PARP inhibitor

Examples of chemotherapy:
- topoisomerase inhibitors: topotecan, irinotecan
- alkylation agents: temozolomide, cyclophosphamide
- DNA damaging agents: platinins
- anthracyclines: doxorubicin

Potential Applications of PARP Inhibitors

Single Agent Activities:
- cells with loss of repair pathways are hypersensitive to blockade of single strand break repair with PARP inhibitor
- preclinical rationale for use of single agent PARP inhibitors in individuals with BRCA-associated breast and ovarian cancer
- PARP inhibitors may have activity in other cancers with deficiencies in DNA repair mechanisms

BRCA1/BRCA2 Proteins

- BRCA1 and BRCA2 proteins
  - tumor-suppressor proteins responsible for:
    - cell division control
    - surveillance of DNA errors
    - repair mechanisms
    - apoptosis
  - important to DNA integrity and maintenance of genomic stability
  - 5 – 10% of breast cancer results from inherited mutations in the genes responsible for these proteins
- cells mutant in BRCA1 and BRCA2 have deficiency in the repair of DNA
- BRCA – deficient cells are sensitive to inhibition of PARP
PARP – Inhibitors: Olaparib

- **Phase I**
  - 60 patients (20 with mutations in BRCA1 or BRCA2)
  - Diagnosis: breast, ovarian, colorectal, melanoma, sarcoma, prostate
  - Dose range (10 mg to 600 mg po BID)
  - MTD 400 mg bid
  - Toxicities:
    - mood alterations
    - fatigue
    - thrombocytopenia
  - Response:
    - Objective tumor response: 9 pts
    - Clinical benefit: 17 patients
    - Only mutation carriers experienced durable antitumor activity


- **Phase II**
  - women with BRCA-deficient advanced breast cancer who had progressed through prior treatments (n=54)
  - single arm, two sequential patient cohort design
    - First cohort: (n=27)
      - Treatment: continuous olaparib 400 mg po bid
      - objective response (ORR): 41%
      - median progression free survival (PFS): 5.7 months
    - Second cohort (n=27)
      - Treatment: olaparib 100 mg po BID
      - ORR: 22%
      - median PFS: 3.8 months


PARP – Inhibitors: Olaparib

- **Ovarian Cancer**
  - Monotherapy (400 mg po BID)
    - median PFS compared to placebo (Phase II)
  - ICEBERG trials - BRCA 1/2
  - Combination therapy
    - chemotherapy


Olaparib (Lynparza™)

- **Indication:**
  - Monotherapy in patients with deleterious or suspected deleterious germline BRCA mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy (Accelerated approval based on objective response and duration of response)

- **Warnings:**
  - Myelodysplastic syndrome / AML
  - Pneumonitis

The Evolving Definition of Immunotherapy

- Cytokines
- Therapeutic cancer vaccines
- Adoptive T-cell therapy
- Immune checkpoint inhibitors
- Co-stimulatory receptors

Disis, ML. Semin Oncol 2014:53-515.

TARGET: IMMUNE RESPONSE
( OPTIMIZING THE IMMUNE SYSTEM)
The Evolving Definition of Immunotherapy

Classification of Anticancer Immunotherapies:
- Passive immunotherapy
  - Tumor-targeting monoclonal antibodies
  - Adoptive cell transfer
  - Oncolytic viruses
- Active immunotherapy
  - DC-based immunotherapies
  - Peptide- and DNA-based anticancer vaccines
  - Immunostimulatory cytokines
  - Immunomodulatory monoclonal antibodies
  - Inhibitors of immunosuppressive metabolism
  - Pattern recognition receptors (PRRs) agonists
  - Immunogenic cell death inducers
- Others


Immune Checkpoint Blockade

- Activation of T cells to enhance antitumor response:
  - Antigen-specific signal mediated by the T-cell receptor (TCR)
  - Co-stimulatory signal mediated by stimulatory and inhibitory receptor and ligand pairs (immune checkpoints)
- Checkpoints:
  - Cytotoxic T lymphocyte antigen-4 (CTLA-4)
    - Operational during early activation of T cells
  - PD-1/PD-L1 (PD-programmed death)
    - Operational during the effector phase of T-cell activation

PD-1 Receptor

- Programmed death-1 (PD-1) receptor is up-regulated on activated T-cells and engages two ligands → PD-L1 and PD-L2
- PD-L1 (B7-H1)
  - Expression seen on a variety of solid tumors
  - Expression is upregulated by cytokines (e.g. gamma interferon)
  - Expressed in 40% of metastatic melanoma
  - Can suppress immunity by binding to CD80
- PD-L2 (B7-DC)
  - Higher binding affinity than PD-L1 for PD-1
  - Expressed on dendritic cell, macrophages and some tumors (although the expression in melanoma is not well characterized)


Pembrolizumab (Keytruda)

- Humanized monoclonal immunoglobulin G4 kappa antibody against PD-1
- First anti-PD-1 therapy to receive regulatory approval in the US
  - January 2013: Pembrolizumab was granted breakthrough designation based on preliminary evidence of clinical activity in patients with unresectable or metastatic melanoma previously untreated with or refractory to ipilimumab
  - Sept 4th, 2014: FDA granted accelerated approval to pembrolizumab for the treatment of patients with:
    - unresectable or metastatic melanoma AND
    - disease progression following ipilimumab AND
    - a BRAF inhibitor (if BRAF V600 mutation positive)

Pembrolizumab

- Approval based on KEYNOTE-001 study
  - Open label phase Ib multicohort trial.
  - Cohort of 173 pts with advanced melanoma refractory to ipilimumab
    - Pembrolizumab 2 mg/kg IV q 3 weeks
    - Pembrolizumab 10 mg/kg IV q 3 weeks

Keytruda package insert 2015.

Pembrolizumab: Phase I

- Method:
  - Open-label, international, multicenter expansion cohort of a phase I trial
  - Patients with advanced melanoma whose disease progressed after at least 2 ipilimumab doses randomized
    - Pembrolizumab 2 mg/kg IV q 3 weeks
    - Pembrolizumab 10 mg/kg IV q 3 weeks
  - Treatment continued:
    - Disease progression
    - Intolerable toxicity
    - Consent withdrawal
  - Endpoints:
    - ORR assessed with RECIST

**Pembrolizumab: Phase I Antitumor Activity**

<table>
<thead>
<tr>
<th>Response</th>
<th>Pembrolizumab 2 mg/kg</th>
<th>Pembrolizumab 10 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>26%</td>
<td>26%</td>
</tr>
<tr>
<td>Disease control rate</td>
<td>51%</td>
<td>50%</td>
</tr>
<tr>
<td>PFS (median)</td>
<td>22 weeks</td>
<td>14 weeks</td>
</tr>
<tr>
<td>PFS (24 weeks)</td>
<td>43%</td>
<td>37%</td>
</tr>
</tbody>
</table>


**Pembrolizumab: Phase I Adverse Events**

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Pembrolizumab 2 mg/kg (n=89)</th>
<th>Pembrolizumab 10 mg/kg (n=84)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>82%</td>
<td>82%</td>
<td>82%</td>
</tr>
<tr>
<td>All grade 3 or 4</td>
<td>15%</td>
<td>8%</td>
<td>12%</td>
</tr>
<tr>
<td>Serious</td>
<td>8%</td>
<td>1%</td>
<td>5%</td>
</tr>
<tr>
<td>Immune-related Grade 3 or 4</td>
<td>1%</td>
<td>2%</td>
<td>6%</td>
</tr>
</tbody>
</table>


**Pembrolizumab: Phase I Drug-Related Adverse Events (grade 3 or 4)**

- Fatigue
- Increase amylase
- Anemia
- Autoimmune hepatitis
- Confusion
- Diarrhea
- Dyspnea
- Pruritus
- Encephalopathy
- Hypophysitis
- Hypoxia
- Muscular weakness
- Musculoskeletal pain
- Pancreatitis
- Peripheral motor neuropathy
- Pneumonitis
- Rash
- Rash maculopapular


**Pembrolizumab**

- Recommended dose:
  - Pembrolizumab 2 mg/kg IV over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.

- Dose Modifications:
  - Grade 2 pneumonitis
  - Grade 2 or 3 colitis
  - Symptomatic hypophysitis
  - Grade 2 nephritis
  - Grade 3 hypothyroidism
  - Increase LFT

Keytruda package insert. 9.2014

**Pembrolizumab**

- Immune-Mediated Toxicities:
  - Pneumonitis
  - Colitis
  - Hepatitis
  - Hypophysitis
  - Nephritis
  - Hyperthyroidism / hypothyroidism


**Nivolumab (Opdivo®)**

- Mechanism:
  - Programmed death receptor-1 (PD-1) blocking antibody

- Indication
  - Treatment of unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor
  - Received accelerated approval by the FDA based on response rate and durability of response

- NSCLC
Nivolumab: Melanoma CheckMate-037

- Phase III, multicenter, open-label trial in 370 patients
- Randomization (2:1)
  - Nivolumab 3 mg/kg IV every 2 weeks
  - Investigator’s choice chemotherapy
    - Dacarbazine 1000 mg/m² every 3 weeks
    - Carboplatin AUC 6 + Paclitaxel 175 mg/m² every 3 weeks
- Co-primary endpoints: overall response rate and overall survival

Nivolumab: Melanoma CheckMate-037

- Interim analysis of 120 patients receiving nivolumab
  - Overall response rate = 32%
  - 13 patients have responses of ≥ 6 months
  - Responses observed in patients with and without BRAF V600 mutations
- Most commonly reported adverse event with nivolumab is rash (21%)
  - Most frequent grade 3/4 adverse events (2% - <5%) of patients
    - Hypo- or hyperthyroidism
    - Patients should be monitored and nivolumab withheld for moderate reactions and discontinued for severe or life-threatening reactions

Nivolumab: Melanoma CheckMate-066

- Phase III trial in 418 previously untreated patients with metastatic melanoma without a BRAF mutation
- Randomization (1:1)
  - Nivolumab 3 mg/kg IV every 2 weeks
  - Dacarbazine 1000 mg/m² every 3 weeks
- Primary endpoint: overall survival

Nivolumab: Melanoma CheckMate-066

- Increase OS
  - Nivolumab: 72.9% at 1 yr
  - Dacarbazine: 42.1% at 1 year
- Improved median PFS
  - Nivolumab: 5.1 month
  - Dacarbazine: 2.2 month
- Note: Survival benefit was observed across prespecified subgroups
- Improved objective response rate
  - Nivolumab: 40%
  - Dacarbazine: 13.9%
- Adverse effects:
  - Fatigue
  - Rash
  - Pruritus
  - Nausea

Efficacy and Safety: Phase II Data

<table>
<thead>
<tr>
<th>Adverse Events in &gt; 10% of Patients</th>
<th>All Grade</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue, %</td>
<td>11.8</td>
<td>1.0</td>
</tr>
<tr>
<td>Rash, %</td>
<td>23.4</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus, %</td>
<td>13.1</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea, %</td>
<td>17.8</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Nivolumab: Warnings and Precautions

- Immune mediated adverse events may require corticosteroids depending upon severity
  - Pneumonitis
  - Colitis potentially leading to bowel perforation
  - Hepatitis
  - Nephritis
  - Hypo- or hyperthyroidism

- Patients should be monitored and nivolumab withheld for moderate reactions and discontinued for severe or life-threatening reactions
Immunotherapy in Combination

- Multiple immunotherapy
  - combination
  - sequenced
- Immunotherapy + “targeted” therapy
- Immunotherapy + chemotherapy
- Immunotherapy + radiation therapy

Rini B. Semin Oncol 2014:S30-S40.

Considerations for Cost of Care

- Cost of immunotherapy
  - Single agent
  - Combination
  - Place in therapy
- Cost associated with management of immunotherapy complications
  - Prevention
  - Management