Integrating New Therapies into the Treatment of Advanced Prostate Cancer
Learning Objectives

• Evaluate current and emerging clinical trial data for therapies for prostate cancer
• Integrate novel therapies into the treatment of patients with advanced prostate cancer based on patient and disease factors, as well as efficacy and safety evidence
• Implement strategies to monitor and manage adverse events (AEs) of novel treatments for prostate cancer
Prostate Cancer in 2020

- In 2020:
  - ~192,000 new cases
  - ~33,000 deaths
- Incidence and mortality rates have declined
- 10-year OS: 98%
- Risk factors
  - Advancing age
  - African ancestry
  - Family history
  - Genetic mutations


Advances in Treatment Approvals

<table>
<thead>
<tr>
<th>Year</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>Docetaxel (taxane)</td>
</tr>
<tr>
<td>2010</td>
<td>Cabazitaxel (novel taxane)</td>
</tr>
<tr>
<td>2011</td>
<td>Enzalutamide (2nd-generation hormone therapy) postdocetaxel</td>
</tr>
<tr>
<td>2012</td>
<td>Enzalutamide (2nd-generation hormone therapy) postdocetaxel</td>
</tr>
<tr>
<td>2013</td>
<td>Radium-223 (radiopharmaceutical)</td>
</tr>
<tr>
<td>2014</td>
<td>Abiraterone (2nd-generation hormone therapy) postdocetaxel</td>
</tr>
<tr>
<td>2018</td>
<td>Enzalutamide for nmCRPC</td>
</tr>
<tr>
<td>2019</td>
<td>Enzalutamide for mCSPC</td>
</tr>
<tr>
<td>2020</td>
<td>Olaparib and rucaparib (PARP inhibitors) for HRR-mutated mRPC</td>
</tr>
</tbody>
</table>

HRR = homologous recombination repair genes; mCRPC = metastatic castrate-resistant prostate cancer; mCSPC = metastatic castrate-sensitive prostate cancer; nmCRPC = nonmetastatic castrate-resistant prostate cancer; PARP = Poly (ADP-ribose) polymerase.

Typical Progression

Localized/locally advanced prostate cancer → Definitive therapy → Biochemical recurrence

- Criterion 1: Rising PSA despite castrate levels of testosterone
- Criterion 2: Identification of metastases

- mPC (de novo)
- mCSPC: Rising PSA despite castrate levels of testosterone; Identification of metastases
- mCRPC
- nmCRPC

ADT = androgen deprivation therapy; mPC = metastatic prostate cancer; PSA = prostate-specific antigen
Standard of Care for mHSPC: 4 Options Added to ADT

ASI = androgen signaling inhibitor; mHSPC = metastatic hormone-sensitive prostate cancer.
Meta-Analysis: Combination Therapy Better Than ADT Alone

<table>
<thead>
<tr>
<th>OS</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doc+ADT</td>
<td>0.72 (0.60-0.86)</td>
</tr>
<tr>
<td>Abi+ADT</td>
<td>0.64 (0.53-0.80)</td>
</tr>
<tr>
<td>Enza+ADT</td>
<td>0.64 (0.46-0.88)</td>
</tr>
<tr>
<td>Apa+ADT</td>
<td>0.63 (0.43-0.92)</td>
</tr>
<tr>
<td>Bis+ADT</td>
<td>0.86 (0.72-1.00)</td>
</tr>
<tr>
<td>Bis+Doc+ADT</td>
<td>0.79 (0.58-1.10)</td>
</tr>
<tr>
<td>Cel+ADT</td>
<td>0.94 (0.67-1.30)</td>
</tr>
<tr>
<td>Bis+Cel+ADT</td>
<td>0.78 (0.56-1.10)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Failure-Free Survival</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doc+ADT</td>
<td>0.63 (0.53-0.76)</td>
</tr>
<tr>
<td>Abi+ADT</td>
<td>0.37 (0.30-0.46)</td>
</tr>
<tr>
<td>Enza+ADT</td>
<td>0.36 (0.28-0.48)</td>
</tr>
<tr>
<td>Apa+ADT</td>
<td>0.49 (0.35-0.70)</td>
</tr>
<tr>
<td>Bis+ADT</td>
<td>0.86 (0.71-1.00)</td>
</tr>
<tr>
<td>Bis+Doc+ADT</td>
<td>0.60 (0.44-0.82)</td>
</tr>
<tr>
<td>Cel+ADT</td>
<td>0.86 (0.62-1.20)</td>
</tr>
<tr>
<td>Bis+Cel+ADT</td>
<td>0.77 (0.55-1.10)</td>
</tr>
</tbody>
</table>

Abi = abiraterone; Apa = apalutamide; Bis = bisphosphonate; Cel = celecoxib; CI = confidence interval; Doc = docetaxel; Enza = enzalutamide; HR = hazard ratio.

Decision-Making Factors in First Line Choices for mCSPC

Factors Influencing Treatment Choice

- Age
- Comorbidities, Particularly if Life-limiting
- Time Commitment
- Oral vs IV Preference
- Insurance Coverage
- Cost Reimbursement
- Treatment Aims
- Cancer/Comorbid Factors
- Disease Volume and Risk
- CHAARTED CRITERIA
- LATITUDE CRITERIA
- Social Characteristics
- Patient Factors
- Physical Characteristics
- FACTORS INFLUENCING TREATMENT CHOICE

Visceral Metastases AND/OR 4 Bone Lesions With ≥1 BeyondAxial Skeleton
≥3 Bone Metastases, Visceral Metastasis, Gleason ≥8
Performance Status
Presence of Symptoms
# Treatment Choice By Disease Stratification, Agent, and Patient Characteristics

<table>
<thead>
<tr>
<th>Disease Stratification</th>
<th>Docetaxel</th>
<th>Abiraterone</th>
<th>Enzalutamide</th>
<th>Apalutamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>• High/low volume*</td>
<td>• High/low volume</td>
<td>• High/low volume</td>
<td>• High/low volume ± prior docetaxel</td>
<td>• High/low volume ± prior docetaxel</td>
</tr>
</tbody>
</table>

**Agent-Related AEs**

- **Docetaxel**
  - Neutropenia
  - Febrile neutropenia
  - Infections with neutropenia
  - Peripheral neuropathy

- **Abiraterone**
  - Hypertension
  - Hepatotoxicity
  - Hyperglycemia
  - Hypokalemia

- **Enzalutamide**
  - Convulsions
  - Cognitive impairment
  - Hypertension
  - Fatigue
  - Loss of consciousness
  - Musculoskeletal events

- **Apalutamide**
  - Rash
  - Fall
  - Fracture
  - Hypothyroidism
  - Seizure

**Characteristics of Not Fit Patients**

- **Docetaxel**
  - Severe/active cardiac disease
  - Prior peripheral neuropathy
  - Fragile patients

- **Abiraterone**
  - Prednisone contraindication
  - Cardiac: NYHA ≥2, atrial fibrillation
  - Uncontrolled HTN
  - Hepatic, renal, or adrenal dysfunction

- **Enzalutamide**
  - History of seizure or any predisposing condition
  - Uncontrolled HTN

- **Apalutamide**
  - History of seizure or any predisposing condition
  - Uncontrolled HTN
  - Ischemic cardiac disease

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*Strongly recommended in high volume disease, moderate recommendation in low-volume disease.

HTN = hypertension; NYHA = New York Heart Association.

One of the following (all category 1 recommendations):

- Docetaxel
  - Patients with high-volume disease derive greater benefit
- Abiraterone acetate + steroid
- Apalutamide
- Enzalutamide
Castrate-Resistant Prostate Cancer

- Disease progression despite castrate-level testosterone (<50 ng/mL)
- Heterogeneous—can be symptomatic or asymptomatic, with or without metastases
- Affects 10% to 20% within 5 years of prostate cancer diagnosis
  - Before recent therapeutic advances, ≥50% of these patients would have died within 3 years
- Progressive decline in health-related QoL
- Metastasis-free survival (MFS) is a new and reasonable endpoint

QoL = quality of life.
Nonmetastatic CRPC

- CRPC with no clinical or radiologic evidence of metastases
- New imaging techniques (e.g., $^{18}$F-fluorocholine or PSMA-targeted PET)
  - May reveal metastases earlier
- Recommend PSA testing every 4 to 6 months
- Treatment recommended when PSADT $\leq$ 10 months
  - Memorial Sloan Kettering prostate cancer nomograms: PSADT
  - Sunnybrook PSA calculator tool

PET = positron emission tomography; PSMA = prostate-specific membrane antigen.
Case Study: Ben, 73 Years Old

- Mild COPD and hypertension
  - No family history of cancer
- Underwent radiotherapy for localized prostate cancer 5 years ago
- Experienced biochemical recurrence (increasing PSA)
- Not a surgical candidate because of previous radiotherapy
- Started on degarelix (ADT) 1 year ago
- He returns for a follow-up today
Case Study (cont’d): Ben’s Test Results

- PSA increased from 4 ng/mL to 14 ng/mL; PSADT = 9 months
  - Testosterone = 24 ng/dL
  - No evidence of metastases on CT or bone scan, no bone pain
  - No lymph node masses detected
- Now diagnosed with nmCRPC
SPARTAN, PROSPER, and ARAMIS: 2nd-Generation Hormone Therapy + ADT in nmCRPC

Safety Considerations With Newest Agents

<table>
<thead>
<tr>
<th>Apalutamide</th>
<th>Enzalutamide</th>
<th>Darolutamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Most common AEs (≥10%):</td>
<td>• Most common AEs (≥10%):</td>
<td>• Most common AEs (≥2%):</td>
</tr>
<tr>
<td>– Fatigue</td>
<td>– Asthenia/fatigue</td>
<td>– Fatigue</td>
</tr>
<tr>
<td>– Arthralgia</td>
<td>– Back pain</td>
<td>– Pain in extremity</td>
</tr>
<tr>
<td>– Rash</td>
<td>– Hot flushes</td>
<td>– Rash</td>
</tr>
<tr>
<td>– Decreased appetite</td>
<td>– Constipation</td>
<td></td>
</tr>
<tr>
<td>– Fall/fracture</td>
<td>– Arthralgia</td>
<td></td>
</tr>
<tr>
<td>– Decreased weight</td>
<td>– Decreased appetite</td>
<td></td>
</tr>
<tr>
<td>– Hypertension</td>
<td>– Diarrhea</td>
<td></td>
</tr>
<tr>
<td>– Hot flushes</td>
<td>– Hypertension</td>
<td></td>
</tr>
<tr>
<td>– Diarrhea</td>
<td>• Seizures, PRES,</td>
<td></td>
</tr>
<tr>
<td>• Cerebrovascular events,</td>
<td>hypersensitivity, ischemic</td>
<td></td>
</tr>
<tr>
<td>ischemic CVD, fractures,</td>
<td>CVD, falls and fractures,</td>
<td></td>
</tr>
<tr>
<td>falls, seizure, embryo-fetal</td>
<td>embryo-fetal toxicity</td>
<td></td>
</tr>
<tr>
<td>toxicity</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CVD = cardiovascular disease; PRES = posterior reversible encephalopathy syndrome.
2020 NCCN Guidelines for nmCRPC

Continue ADT to maintain castrate serum levels of testosterone (<50 ng/dL)

PSADT ≤10 months

• Apalutamide (category 1)
• Darolutamide (category 1)
• Enzalutamide (category 1), or
• Other secondary hormone therapy

PSADT >10 months

• Observation, or
• Other secondary hormone therapy

Case Conclusion

- Ben is taking darolutamide 600 mg twice daily and continuing ADT
- His bone health is being monitored closely
- PSA is now 2.9 ng/mL
- Will continue serial PSA monitoring
- Will undergo imaging only if new symptoms develop or PSA level increases
Metastatic Prostate Cancer

- 72% increase from 2004 to 2013, even as incidence of low-risk prostate cancer declined
- 5-year survival rate: ~30% vs nearly 100% for nonmetastatic disease
- 90% have bone metastases
- Treatment evolving rapidly
  - Novel therapies improve outcomes but increase treatment complexity
Case Study: Ted, 70 Years Old

- Ted has arterial hypertension and well-controlled diabetes
  - Family history: mother had breast cancer; uncle diagnosed with prostate cancer at age 48
- Diagnosed with *de novo* metastatic prostate cancer
  - PSA level of 38 ng/mL
- Metastases in multiple bone sites and lymph nodes; is considered low volume disease
Genetic Testing in Prostate Cancer

11.8% of men with mPC have germline DNA-repair gene mutations irrespective of family history.

ALL men with mPC should receive genetic testing. Testing should be considered in specific histologic/family history for localized disease or considered high risk of disease.

BRCA1 or BRCA2 and other DDR germline mutations associated with increased risk of prostate cancer.

Somatic mutations in DNA repair pathways in 19% of localized and 23% of mCRPC tumors.

## NCCN 2020 Recommendations for Biomarker and Germline Testing

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Molecular Analysis of Tumor</th>
<th>Germline Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>Not indicated</td>
<td>If family history positive or intraductal/cribriform histology</td>
</tr>
<tr>
<td>Low</td>
<td>Consider if life expectancy ≥10 years</td>
<td>If family history positive or intraductal/cribriform histology</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Consider if life expectancy ≥10 years</td>
<td>If family history positive or intraductal/cribriform histology</td>
</tr>
<tr>
<td>High</td>
<td>Consider if life expectancy ≥10 years</td>
<td>Recommended</td>
</tr>
<tr>
<td>Very High</td>
<td>Not routinely recommended</td>
<td>Recommended</td>
</tr>
<tr>
<td>Regional</td>
<td>Consider for homologous recombination gene mutation (HRRm)*, microsatellite instability (MSI) or mismatch repair deficiency (dMMR)</td>
<td>Recommended</td>
</tr>
<tr>
<td>Metastatic</td>
<td>Recommend for HRRm and consider for MSI or dMMR</td>
<td>Recommended</td>
</tr>
</tbody>
</table>

*Genes include: BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2.
NCCN 2020 Genetic Testing Recommendations

- Inquire about family and personal history at time of initial diagnosis
- Germline testing is recommended for patients with prostate cancer and any of the following:
  - High-risk, very high-risk, regional, or metastatic prostate cancer
  - Ashkenazi Jewish ancestry
  - Intraductal histology
  - Family history of high-risk germline mutations (e.g., BRCA1/2, Lynch mutation)
  - A positive family history of cancer:
    - Brother/father or multiple family members diagnosed at <60 years or who died from PC; OR
    - ≥3 cancers on same side of family, especially diagnoses at ≤50 years: bile duct, breast, colorectal, endometrial, gastric, kidney, melanoma, ovarian, pancreatic, prostate (but not clinically localized Grade Group 1), small bowel, or urothelial cancer
- A framework based on the Philadelphia Prostate Cancer Consensus Conference has recently been published

Suggested Genes:
- ATM
- BRCA1
- BRCA2
- CHEK2
- HOXB13
- MLH1
- MSH2
- MSH6
- PALB2
- PMS2

Role of Genetic and Molecular Biomarker Testing

- Germline genetic testing
  - Evaluate all patients with prostate cancer for family/personal history for risk of germline variants
  - If indicated, germline genetic testing and genetic counseling

- Somatic tumor testing recommended in metastatic prostate cancer
  - Somatic homologous recombination gene mutations (BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2)
  - MSI or dMMR
  - Multigene molecular testing assays
  - DNA repair gene mutations (eg, BRCA1/BRCA2) in 25% of patients with mCRPC

Case Study (cont’d): Ted’s Initial Treatment

- Molecular diagnostics revealed germline *BRCA2* mutation
- Started on ADT and enzalutamide 160 mg once daily
- His PSA level became undetectable but began to increase 6 months ago
- Presents with asymptomatic metastatic CRPC
  - Reports no pain
  - Imaging unchanged
Treatment Options: Immunotherapy

Sipuleucel-T

- OS benefit, even without PSA response
  - Patient education
- Most beneficial in less advanced disease → early use recommended
- AEs: chills, fatigue, pyrexia, nausea

Day 1
Leukapheresis

Days 2-3
Sipuleucel-T is manufactured

Days 3-4
Patient receives infusion

Apheresis Center
Central Processing
Clinician’s Office

COMPLETE COURSE OF THERAPY
Weeks 0, 2, 4

Phase 3 Trials in Chemotherapy-naïve mCRPC

**COU-302: Abiraterone + Prednisone**

- **Abiraterone + prednisone** vs. **Placebo + prednisone**
- **OS (months)**
  - HR, 0.81 (95% CI, 0.70-0.93)
  - *P* = .0033

- **PFS (months)**
  - HR, 0.53 (95% CI, 0.45-0.93)
  - *P* = .0033

**PREVAIL: Enzalutamide**

- **Enzalutamide** vs. **Placebo**
- Men with mild or no symptoms
- Primary endpoints: OS, rPFS
- No prior ketoconazole
- Men with liver metastases eligible in PREVAIL

**Men with mild or no symptoms**

- **OS (%)**
  - HR, 0.71 (95% CI, 0.60-0.84)
  - *P* < .001

- **PFS (%)**
  - HR, 0.19 (95% CI, 0.15-0.23)
  - *P* < .001

rPFS = radiographic progression-free survival.

COU-AA-301: Phase 3 Trial of Post-Chemo 2nd-line Abiraterone in mCRPC

- Abiraterone vs placebo: 1195 patients with mCRPC progressing after docetaxel
  - 2 prior chemo
    - OS: 14.0 months abiraterone vs 10.3 months placebo
  - 1 prior chemo
    - OS: 15.4 months abiraterone vs 11.5 months placebo
- Most common AEs, grade ≥3:
  - Fatigue (<9% vs 10%)
  - Anemia (7% vs 8%)
  - Back pain (<7% vs <10%)

HR, 0.65 (95% CI, 0.54-0.77) P <.001

Abiraterone acetate
Median survival: 14.8 months (95% CI, 14.1-15.4)

Placebo
Median survival: 10.9 months (95% CI, 10.2-12.0)

AFFIRM: Phase 3 Trial of Post-Chemo, 2nd-line Enzalutamide in mCRPC

Enzalutamide vs placebo for 1199 men with mCRPC after chemotherapy

Most common grade ≥3 AEs: fatigue (6% vs 7%), diarrhea (1% vs <1%), cardiac disorder (1% vs 2%)

Treatment Options for mCRPC: 2nd-Generation Hormone Therapy

- Both drugs are approved for use with or without prior docetaxel

<table>
<thead>
<tr>
<th>Abiraterone</th>
<th>Enzalutamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Inhibits CYP17, enzyme needed for androgen synthesis</td>
<td>• AR antagonist; binds competitively to ligand-binding domain of AR</td>
</tr>
<tr>
<td>• Administered with steroids</td>
<td>• Concomitant steroids not required</td>
</tr>
</tbody>
</table>

AR = androgen receptor; CYP = cytochrome.
## Abiraterone and Enzalutamide: Drug Characteristics and Toxicities

<table>
<thead>
<tr>
<th></th>
<th>Abiraterone</th>
<th>Enzalutamide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage</strong></td>
<td>1000 mg/day orally</td>
<td>160 mg/day orally</td>
</tr>
<tr>
<td><strong>Empty stomach required</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Prednisone required</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Drug interactions (CYP)</strong></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Hypokalemia</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Lowers seizure threshold</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Potential liver toxicity</strong></td>
<td>Yes</td>
<td>Less likely</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>Yes*</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>Yes</td>
<td>More likely</td>
</tr>
<tr>
<td><strong>Cardiac toxicity</strong></td>
<td>More likely</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Risk of hypertension is increased by required coadministration of prednisone.

Treatment Options: Radiopharmaceuticals — Radium-223

Unlike beta-emitting radioisotopes (eg, samarium-153), the alpha-emitting isotope radium-223 delivers less radiation to bone marrow → fewer effects of marrow suppression

ALSYMPCA: Symptomatic mCRPC with bone metastases

- Most common AEs: bone pain, nausea, anemia (no between-group differences)
- Phase 2 open-label studies: Radium-233 + enzalutamide or abiraterone decreased bone pain and increased QoL in patients with mCRPC and bone metastasis

Treatment Options: Chemotherapy

- Docetaxel (first-generation taxane)
  - Until 2010, only approved drug to improve OS for mCRPC
  - Appropriate for castrate-sensitive disease
- Cabazitaxel (next-generation taxane)
  - Improves OS in docetaxel-pretreated mCRPC
  - Improves QoL; reduces pain through 10 treatment cycles
  - Approved at lower dosage (20 mg/m²) in 2017 for patients with mCRPC previously treated with docetaxel

<table>
<thead>
<tr>
<th>AE Profile With Reduced-dose Cabazitaxel</th>
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<tbody>
<tr>
<td>Grade ≥3 AE</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Leukopenia</td>
</tr>
<tr>
<td>Neutropenia</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
</tbody>
</table>

CARD Trial: Randomized, Open-label Study of Cabazitaxel vs Abiraterone or Enzalutamide in mCRPC

N = 255 men with mCRPC that progressed ≤12 months on prior alternative 2nd-generation hormone therapy (before or after docetaxel)

### rPFS

- **rPFS, months (95% CI)**
  - Cabazitaxel: 8.0 (5.7-9.2)
  - ARSI: 3.7 (2.8-5.1)
- **HR for progression or death, 0.54 (95% CI, 0.40-0.73) \( P = .001 \)**

### OS

- **Median OS, months (95% CI)**
  - Cabazitaxel: 13.6 (11.5-17.5)
  - ARSI: 11.0 (9.2-12.9)
- **HR for death, 0.64 (95% CI, 0.46-0.89) \( P = .008 \)**

### Pain progression

- NE (NE-NE) vs Cabazitaxel: 8.5 (4.9-NE) \( P = 0.55 (0.32-0.97) \)

### Symptomatic skeletal events

- NE (20.0-NE) vs Cabazitaxel: 16.7 (10.8-NE) \( P = 0.59 (0.35-1.01) \)

**ARSI** = androgen receptor signaling inhibitor; **NE** = not evaluated.

Molecular Targeted Therapy

Pembrolizumab: PD-1 Inhibitor

- For the treatment of adult and pediatric patients with unresectable or metastatic MSI-H or dMMR solid tumors that have progressed following prior treatment or have no satisfactory alternative treatment options.

- For the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (≥10 mutation/megabase) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and have no satisfactory alternative treatment options.

PD-1 = programmed cell death protein 1.
Molecular Targeted Therapy

Olaparib: PARP inhibitor

- For the treatment of adults with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC who have progressed following treatment with enzalutamide or abiraterone
- Patients selected based on FDA-approved companion diagnostic

Rucaparib: PARP inhibitor

- For the treatment of adults with a deleterious BRCA mutation (germline or somatic)-associated mCRPC previously treated with AR-directed therapy and a taxane-based chemotherapy
- Patients selected based on FDA-approved companion diagnostic

PROfound: Randomized Open-label Trial of Olaparib vs Abiraterone or Enzalutamide

N = 378 men with mCRPC who progressed on abiraterone or enzalutamide and had alteration in one of 15 prespecified HRR genes

Median OS (95% CI) months
- Olaparib: 17.3 (15.5–18.6)
- Control: 14.0 (11.5–17.1)

OS

HR for death, 0.79 (95% CI 0.61–1.03)

PFS

Olaparib vs Control

Value at 6 mo

Value at 12 mo

Median: 5.8 vs 3.5 months (HR = 0.49; 95% CI 0.38–0.63)

No. of Deaths/No. of Patients

Olaparib: 160/256
Control: 86/131

No. at Risk

Olaparib
Control

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21

Months Since Randomization

Months Since Randomization

Percent of Patients Alive

Percent of Patients Alive

37
TRITON2: Rucaparib in mCRPC With DNA Damage Repair Mutations

- Confirmed PSA response 54.8% (95% CI, 38.1%; 64.1%)
- ORRs similar between BRCA1 and BRCA2; germline and somatic alterations

<table>
<thead>
<tr>
<th></th>
<th>ORR, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>43.5 (31.0; 56.7)</td>
</tr>
<tr>
<td>BRCA1</td>
<td>33.3 (7.5; 70.1)</td>
</tr>
<tr>
<td>BRCA2</td>
<td>45.3 (31.6; 59.6)</td>
</tr>
<tr>
<td>Germline</td>
<td>42.9 (21.8; 66.0)</td>
</tr>
<tr>
<td>Somatic</td>
<td>43.9 (28.5; 60.3)</td>
</tr>
</tbody>
</table>

rPFS in BRCA-altered mCRPC (n = 115)

- Median, Months: 9.0
- 95% CI: 8.3 to 13.5
- Range: 0.0-27.6+

## Toxicities with PARP Inhibitors

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Olaparib (n = 256)</th>
<th>Rucaparib (n = 115)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade ≥3 (%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>46</td>
<td>21</td>
</tr>
<tr>
<td>Nausea</td>
<td>41</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue or asthenia</td>
<td>41</td>
<td>3</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>ALT/AST increased</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Dizziness</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; AST = aspartate aminotransferase; NR = not reported.
## 2020 NCCN Guidelines for mCRPC: First- and Second-line

<table>
<thead>
<tr>
<th>First-line Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiraterone</td>
</tr>
<tr>
<td>Docetaxel</td>
</tr>
<tr>
<td>Enzalutamide</td>
</tr>
<tr>
<td>Sipuleucel-T</td>
</tr>
</tbody>
</table>

Useful in certain circumstances:
- Radium-223
- Mitoxantrone

Other recommended:
- Fine particle abiraterone
- Secondary hormone therapy

### Second-line Treatment

#### First-line Abiraterone/Enzalutamide

- Docetaxel
- Sipuleucel-T

Useful in certain circumstances:
- Olaparib
- Rucaparib
- Pembrolizumab
- Radium-223

Other recommended:
- Abiraterone
- Cabazitaxel
- Enzalutamide
- Fine particle abiraterone
- Secondary hormone therapy

#### First-line Docetaxel

- Abiraterone
- Cabazitaxel
- Enzalutamide

Useful in certain circumstances:
- Mitoxantrone
- Olaparib
- Rucaparib
- Pembrolizumab
- Radium-223

Other recommended:
- Consider docetaxel rechallenge
- Sipuleucel-T
- Fine particle abiraterone
- Secondary hormone therapy

### 2020 NCCN Guidelines for mCRPC: Subsequent Treatment

<table>
<thead>
<tr>
<th>Subsequent Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Abiraterone</td>
</tr>
<tr>
<td>• Docetaxel rechallenge</td>
</tr>
<tr>
<td>• Cabazitaxel</td>
</tr>
<tr>
<td>• Enzalutamide</td>
</tr>
<tr>
<td>Useful in certain circumstances:</td>
</tr>
<tr>
<td>• Olaparib</td>
</tr>
<tr>
<td>• Rucaparib</td>
</tr>
<tr>
<td>• Pembrolizumab</td>
</tr>
<tr>
<td>• Mitoxantrone</td>
</tr>
<tr>
<td>• Radium-223</td>
</tr>
<tr>
<td>Other recommended:</td>
</tr>
<tr>
<td>• Fine particle abiraterone</td>
</tr>
<tr>
<td>• Secondary hormone therapy</td>
</tr>
</tbody>
</table>

Patients may also require antiresorptive bone therapy: zoledronic acid or denosumab
Example of Therapy Sequencing for mCRPC

- Optimal sequencing not established (sample shown)
- Treatment pathway is unique for each patient
- Cross-resistance between abiraterone and enzalutamide
- Need to identify molecular subtypes for more rational sequencing

**First Line***
- Asymptomatic: Sipuleucel-T (chemonaïve)
- Symptomatic: Abiraterone or Enzalutamide

**Second Line***
- Abiraterone or Enzalutamide
- Docetaxel or Radium-223 (bone metastases) or PARP inhibitors†

**Third Line***
- Docetaxel or Cabazitaxel or PARP inhibitors†
- Cabazitaxel or Radium-223 (bone metastases) or PARP inhibitors†

*All treatment options should include ADT (surgical/medical orchiectomy); †In patients with BRCA-mutated mCRPC (rucaparib) or alterations in homologous recombination repair genes (olaparib).

Factors to Consider When Selecting Therapies

<table>
<thead>
<tr>
<th>Patient</th>
<th>Disease</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| • Preferences  
• Medical history, comorbidities, medications  
• Treatment and response history  
• Symptoms  
• Overall condition and performance status | • Metastatic?  
– To bone?  
– Visceral?  
• Disease volume  
– Low or high?  
• Risk level/aggressiveness | • Toxicity profile  
• Possible drug-drug interactions  
• Effects on pain, QoL  
• Practitioner experience and preference |

Lifestyle Modifications for Men with PC

• Improvements in diet:
  – ↓ saturated fat intake, dairy products
  – Limit alcohol (2 drinks/day)
  – ↑ fiber and lycopene-containing foods (tomatoes)

• Increased physical activity (150 min/week):
  – ↑ psychological well-being
  – ↓ depression
  – ↑ energy levels, improved fitness level

• Manage comorbid conditions: diabetes, hyperlipidemia, hypertension, cardiovascular

• Assess and treat: urinary, bowel, sexual dysfunction; anxiety; stress

<table>
<thead>
<tr>
<th>Risk Factors of Advanced or Lethal Prostate Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increased risk</strong></td>
</tr>
<tr>
<td>• Lipid levels</td>
</tr>
<tr>
<td>• Obesity</td>
</tr>
<tr>
<td>• Smoking</td>
</tr>
<tr>
<td>• Dairy, calcium</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Shared Decision-Making

- Patients and clinicians collaborate on treatment selection
- May enhance adherence to therapies → better treatment responses
- Discuss potential barriers: AEs, costs

- **S**eek patient’s participation
- **H**elp patients explore and compare treatment options
- **A**ssess patient’s values and preferences
- **R**each a decision with your patient
- **E**valuate your patient’s decision

Case Conclusion

- Ted receives olaparib 300 mg orally twice daily
- His blood glucose and CBC are monitored regularly
- After 3 months of treatment:
  - PSA has decreased to 6 ng/mL
  - He reports decreased pain but does notice fatigue; you recommend he try to increase his physical activity
  - Bone scans show stable lesions and no new lesions
  - Blood glucose managed by intensifying diabetes medications
  - CBC is stable
Bootcamp Takeaways

✓ For patients with mCSPC, consider adding docetaxel (± prednisone), abiraterone + steroid, apalutamide, or enzalutamide to ADT
✓ Consider early use of approved agents for nonmetastatic CRPC to improve MFS and OS
✓ Consider germline genetic testing and counseling for all patients with prostate cancer and somatic tumor testing in patients with metastatic prostate cancer
✓ Implement shared decision-making to optimize treatment outcomes

PCE Promotes Practice Change
New Options for Advanced Renal Cell Carcinoma: Targeted and Immunotherapies
Learning Objectives

• Assess available combination therapy based on the most recent clinical trial data
• Integrate targeted and immunotherapies into the treatment of patients with advanced renal cell carcinoma (RCC) as appropriate
• Apply recommended monitoring and management strategies for irAEs in patients treated with immunotherapies and TKIs for RCC
Overview of RCC

- More than 50% of patients with RCC have no symptoms
  - Diagnosis is through incidental imaging of the abdomen or chest ordered for unrelated symptoms
- Hematuria serves as a warning sign; necessitates further evaluation and imaging leading to a diagnosis and treatment plan
- Solid tumors are managed by size
  - 20% of tumors >3 cm discovered incidentally will be benign
  - Tumors ≥4 cm have metastatic potential
- Treatment options include active surveillance, ablation, nephron-sparing tumor excision, nephrectomy, and systemic treatment
- Predictors of a poor prognosis include poor functional status and metastasis
RCC Statistics

- 8th most common cancer – more common in men than women – representing 4.1% of all new cancers in the United States
- In 2020, there were ~73,750 new cases of kidney and renal pelvis cancer and ~14,830 deaths from this disease
Risk Factors for RCC

- Hereditary factors include familial syndromes, including:
  - von Hippel-Lindau syndrome
  - Hereditary type 1 papillary renal carcinoma
  - Familial renal oncocytoma
  - Birt-Hogg-Dube syndrome
- Few risk factors for RCC have been established
  - Nonhereditary risk factors that possibly contribute to RCC include:
    - Cigarette smoking (increases in a dose-dependent fashion)
    - Obesity, particularly in women (as weight increases, risk of RCC increases)
    - Older age (median age at diagnosis: 64 years)
Histology of RCC

- Clear-cell RCC is the most common variety: 70% to 90%
- Non-clear-cell RCC includes:
  - Papillary: 10% to 15%
  - Chromophobe: 3% to 5%
  - Collecting duct: 1% to 2%
  - Unclassified: 4% to 6%
- In one study of 254 patients with advanced RCC, 16.1% harbored pathogenic germline mutations
  - More than 20% of patients with non-clear-cell RCC had germline mutations
  - 9% had a mutation diagnostic of hereditary leiomyomatosis
- Sarcomatoid or rhabdoid features can be associated with any histology
  - Harbinger of a poor prognosis in the VEGF TKI era

TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor.
Patient Factors to Consider When Selecting Therapy

- Comorbidities, especially conditions that affect a patient’s immune status
- Symptoms of disease
- Sites of disease
- ECOG PS
- Histology
- Risk stratification
- Medication history, including use of steroids

ECOG PS = Eastern Cooperative Oncology Group performance status.
## Risk Stratification: Laboratory and Clinical

### IMDC Criteria Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Yes (1)/No (0)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>KPS</td>
<td>&lt;80%</td>
<td>1/0</td>
</tr>
<tr>
<td>Time from diagnosis</td>
<td>&lt;12 months</td>
<td>1/0</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>&lt;LLN</td>
<td>1/0</td>
</tr>
<tr>
<td>Neutrophil count</td>
<td>&gt;ULN</td>
<td>1/0</td>
</tr>
<tr>
<td>Platelet count</td>
<td>&gt;ULN</td>
<td>1/0</td>
</tr>
<tr>
<td>Corrected serum calcium</td>
<td>&gt;ULN</td>
<td>1/0</td>
</tr>
</tbody>
</table>

### Risk Group by Number of Risk Factors

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Number of Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1-2</td>
</tr>
<tr>
<td>Poor</td>
<td>3-6</td>
</tr>
</tbody>
</table>
Goals of Treatment

- Goal of therapy is different for each patient
  - May be curative vs improvement in length and/or quality of life, depending on staging
- For active sites of disease:
  - Medical treatments aim to shrink and destroy the cancer
  - Surgical treatment aims to remove the cancer
  - Ablative treatments (eg, radiation or thermal) aim to destroy local disease
- For patients with multiple disease sites, the mainstay treatment has been medical/systemic therapy
Changing Treatment Landscape for Metastatic RCC

- In the last 15 years, the landscape of treatment for clear-cell mRCC has changed immensely.

IFN = interferon; mRCC = metastatic renal cell carcinoma.
Immunotherapy Mechanism of Action

- T-cell activation is required for effective antitumor response
- PD-1 and CTLA-4 expressed on T cells act as “off” switches to down-regulate the immune response
- Tumor cells can masquerade as normal cells by expressing PD-L1
- Blockade of PD-1, PD-L1, and CTLA-4 ultimately allow up-regulation of immune responses targeting the tumor

CTLA-4 = cytotoxic T-lymphocyte antigen 4; MHC = major histocompatibility complex; PD-1 = programmed cell death protein; PD-L1 = programmed death-ligand 1; TCR = T-cell receptors.

Targeted Therapy Plus Immunotherapy in Advanced RCC

- Boosts the RCC armamentarium
- VEGF inhibitors infiltrate T cells into tumors and enhance antitumor immunity
- Adding PD-1 inhibitors may augment these effects
- Standard of care has shifted to immunotherapy-based combination regimens in the 1st-line setting

**Anticancer Immunity**

Case Study: Walter

- 73-year-old white man presents for evaluation of hematuria and urinary obstruction
- Medical history notable for diabetes and ongoing smoking
- CT scan showed a right renal mass: 13.3 x 12.3 x 10 cm
- Imaging revealed multiple lung nodules measuring up to 1.3 cm, consistent with metastatic disease
- Walter underwent biopsy of a lung nodule
  - Pathology revealed metastatic clear-cell RCC with no sarcomatoid features
- Walter has an intermediate PS with two IMDC risk factors: needing systemic therapy within a year of diagnosis and a KPS of 70%

KPS = Karnofsky performance status; PS = performance status.
### Guidelines for Recurrent or Advanced Clear-Cell RCC: First-line Therapy

<table>
<thead>
<tr>
<th>Risk Status</th>
<th>First-line Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preferred Regimens</strong></td>
<td></td>
</tr>
<tr>
<td>Favorable risk</td>
<td>• Axitinib + pembrolizumab</td>
</tr>
<tr>
<td></td>
<td>• Pazopanib</td>
</tr>
<tr>
<td></td>
<td>• Sunitinib</td>
</tr>
<tr>
<td>Poor/intermediate risk</td>
<td>• Ipilimumab + nivolumab <em>(category 1)</em></td>
</tr>
<tr>
<td></td>
<td>• Axitinib + pembrolizumab <em>(category 1)</em></td>
</tr>
<tr>
<td></td>
<td>• Cabozantinib</td>
</tr>
<tr>
<td><strong>Other Recommended Regimens</strong></td>
<td></td>
</tr>
<tr>
<td>Favorable risk</td>
<td>• Ipilimumab + nivolumab</td>
</tr>
<tr>
<td></td>
<td>• Axitinib + avelumab</td>
</tr>
<tr>
<td></td>
<td>• Cabozantinib <em>(category 2B)</em></td>
</tr>
<tr>
<td>Poor/intermediate risk</td>
<td>• Pazopanib</td>
</tr>
<tr>
<td></td>
<td>• Sunitinib</td>
</tr>
<tr>
<td></td>
<td>• Axitinib + avelumab</td>
</tr>
</tbody>
</table>

CheckMate 214: Nivolumab + Ipilimumab vs Sunitinib as First-line Treatment

- Combination of checkpoint inhibitors nivolumab + ipilimumab was studied in patients with intermediate- or poor-risk advanced RCC
  - Extended follow-up (minimum 42 months) showed superiority of nivolumab + ipilimumab vs sunitinib
    - OS: 47.0 vs 26.6 months
    - ORR: 42% vs 29% (CR: 12% vs 1%)
- An updated analysis (minimum 48 months) confirmed the improved efficacy of nivolumab + ipilimumab vs sunitinib
  - OS: 48.1 vs 26.6 months
  - ORR: 42% vs 27%

OS in Intermediate-/Poor-Risk Disease

CR = complete response; ORR = overall response rate; OS = overall survival.
KEYNOTE-426: Pembrolizumab + Axitinib in Treatment-naïve Advanced RCC (Updated Results)

- Pembrolizumab is an anti–PD-1 antibody that has shown antitumor activity
- Axitinib is a highly potent VEGFR-TKI approved in 2nd-line setting, with antitumor activity seen in 1st-line setting
- Combination pembrolizumab + axitinib demonstrated higher PFS, ORR, and OS vs sunitinib
  - OS in ITT population at 24 months: 74% vs 66%
  - PFS: 15.1 vs 11.1 months
  - ORR: 60.2% vs 40%

HR = hazard ratio; ITT = intent to treat; PFS = progression-free survival; VEGFR = vascular endothelial growth factor receptor.
• PD-L1 inhibitor avelumab was studied in combination with axitinib (VEGFR-TKI) vs sunitinib
• Patients stratified by ECOG PS and geographic region
• Improvements seen in patients with PD-L1–positive tumors
  – Median PFS: 13.8 vs 7.0 months ($P < 0.0001$)
  – ORR: 55.9% vs 27.2%
  – Median OS: HR 0.83 (95% CI, 0.596-1.151), 1-sided $P = 0.1301$
  – PFS benefit maintained in overall population as well, regardless of PD-L1 status

**JAVELIN Renal 101: Avelumab + Axitinib vs Sunitinib as First-line Treatment (Second Interim Analysis)**

CheckMate 9ER: Nivolumab + Cabozantinib vs Sunitinib as First-line Treatment

• Both cabozantinib (a TKI) and nivolumab (a checkpoint inhibitor) have demonstrated efficacy and a manageable safety profile as monotherapy in advanced RCC
  – Cabozantinib has immunomodulatory properties that may counteract tumor-induced immunosuppression, which provided a rationale for combining the two drugs

• Study results of cabozantinib + nivolumab vs sunitinib for the ITT population
  – Median PFS: 16.6 vs 8.3 months ($P < 0.0001$)
  – OS: HR 0.60 (98.89% CI: 0.40-0.89) ($P < 0.001$)
  – ORR: 55.7% vs 27.1% ($P < 0.0001$)
    • 8.0% vs 4.6% achieved CR
  – Median DOR: 20.2 vs 11.5 months

• The safety profile of cabozantinib + nivolumab was manageable and consistent with the known single-agent AE profiles of the individual drugs

• Nivolumab plus cabozantinib for advanced RCC is under priority review by the FDA with an expected decision by February 2021

DOR = duration of response; FDA = US Food and Drug Administration.
Case Study (cont’d): Walter

- Walter agrees to begin ipilimumab and nivolumab for his advanced RCC
- Both Walter and his family are educated on the treatment plan, mechanism of action, and potential adverse effects of immunotherapy
- He is instructed to call his oncology provider if he develops any new symptoms
Checkpoint inhibitors stimulate the immune environment and can cause irAEs.

irAEs differ from AEs with chemotherapy and targeted therapy:
- Many occur within 2 to 3 treatment cycles, but can occur any time—even after therapy is discontinued.
- Typically mild, but can be severe, irreversible, or life-threatening.

irAEs do not occur in all patients:
- Reasons are unknown.

irAEs Can Affect Any Organ System:
- Encephalitis
- Aseptic meningitis
- Hypophysitis
- Thyroiditis
- Hypothyroidism
- Hyperthyroidism
- Pneumonitis
- Hepatitis
- Autoimmune diabetes
- Pancreatitis
- Thrombocytopenia
- Anemia
- Vasculitis
- Neuropathy
- Uveitis
- Dry mouth
- Mucositis
- Myocarditis
- Colitis
- Enteritis
- Rash
- Vitiligo
- Arthralgia

### Most Common Treatment-related Select AEs (≥5%) Associated With Nivolumab + Ipilimumab Combination Treatment (n = 547)

<table>
<thead>
<tr>
<th>TRAE</th>
<th>Any Grade, %</th>
<th>Grade 3 or 4, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>29</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24</td>
<td>4</td>
</tr>
<tr>
<td>Rash</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>16</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>10</td>
<td>&lt;1</td>
</tr>
<tr>
<td>AST increased</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>7</td>
<td>&lt;1</td>
</tr>
<tr>
<td>ALT increased</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

Immunotherapy Patient Education

• Before starting treatment:
  ¬ Educate patients about mechanism of action and reasons for use of immune checkpoint inhibitors
  ¬ Record all medications, including over-the-counter medications and supplements
  ¬ Provide patients with a wallet card outlining the type of treatments they are receiving, potential AEs, and contact numbers for their care team
  ¬ Educate patients/caregivers about potential toxicity profiles, presenting symptoms, and timing of treatments
  ¬ Inform patients of educational resources

• Tell patients to notify the oncology healthcare team:
  ¬ If any new signs or symptoms develop
    • Monitor symptoms for at least 2 years after treatment has concluded
  ¬ If admitted to the hospital
  ¬ If any new medications are prescribed or prior to receiving any immunizations/vaccines

Case Study (cont’d): Walter

• Front-line treatment initiated
  – Ipilimumab 1 mg/kg IV every 3 weeks with nivolumab 3 mg/kg
• A follow-up call 2 days later revealed no adverse effects
• 3 months after beginning treatment with ipilimumab and nivolumab, Walter called the office with complaints of headaches, increasing fatigue, and sensitivity to cold
• Walter’s thyroid stimulating hormone (TSH) had increased from 3.4 mU/L at baseline to 13.0 mU/L and has remained elevated for several weeks, indicating grade 2 hypothyroidism
Immune-Related Hypothyroidism

- Nivolumab + ipilimumab is associated with the highest incidence of hypothyroidism; PD-1 inhibitor monotherapy has a lower incidence.
- Symptoms: related to hormonal changes (e.g., headaches, vision changes, rapid heartbeat, weight gain or loss, feeling cold, change in voice, frequent urination, etc).
- Management
  - Grade 1 (<10 mU/mL and asymptomatic): Continue therapy with close follow-up and monitoring of TSH and FT4.
  - Grade 2 (moderate symptoms; TSH persistently >10 mU/L): may hold therapy until symptoms resolve to baseline; consider endocrine consultation; prescribe thyroid hormone supplementation.
  - Grade 3-4 (severe symptoms, medically significant or life-threatening consequences): hold therapy until symptoms resolve to baseline with thyroid hormone supplementation; order endocrine consultation.

FT4 = free thyroxine.
# Guidelines for Managing irAEs

<table>
<thead>
<tr>
<th>Toxicity Grade</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Continue checkpoint inhibitors with close monitoring, with exception of some neurologic, hematologic, and cardiac toxicities</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Hold for most grade 2 toxicities and consider resuming when symptoms and/or laboratory values return to grade 1 or less. Corticosteroids (initial dose of 0.5 to 1 mg/kg/d of prednisone or equivalent) may be given</td>
</tr>
</tbody>
</table>
| Grade 3        | Hold checkpoint inhibitors for grade 3 irAEs and initiate high-dose corticosteroids (prednisone 1 to 2 mg/kg/d or methylprednisolone IV 1 to 2 mg/kg/d).  
  - Taper corticosteroids over course of at least 4 to 6 weeks.  
  - If symptoms do not improve with 48 to 72 hours of high-dose corticosteroid, infliximab may be offered for some toxicities |
| Grade 4        | Warrants permanent discontinuation of checkpoint inhibitors, with exception of endocrinopathies controlled by hormone replacement |

- When symptoms and/or lab values revert to grade 1 or less, rechallenging with checkpoint inhibitors may be offered.  
- Use caution when administering to patients with early-onset irAEs; dose adjustments are not recommended.
Case Conclusion: Walter

- Walter was put on levothyroxine and his TSH returned to normal
- Otherwise, he tolerated the combination of ipilimumab and nivolumab for four cycles with no other AEs except occasional diarrhea
- Imaging 3 months after start of treatment demonstrated regression of all lung nodules and shrinkage of the primary renal mass
- The plan is to continue nivolumab monotherapy maintenance treatment
Case Study: Liz

• 79-year-old Hispanic woman diagnosed with advanced clear-cell RCC and lung and liver metastases
• She was treated 1st-line with axitinib and pembrolizumab
• 8 days after initiation of cycle 3, the patient called with complaints of increasing fatigue, loss of appetite, difficulty with fluid intake, and five loose stools in the past 24 hours despite maximum dosing of loperamide
Managing Diarrhea Associated With Axitinib + Pembrolizumab

- Diarrhea is one of the most common side effects of both drugs
  - For most cases, supportive care and use of antidiarrheals can control this toxicity
  - For grade 3 or 4 diarrhea, reduce the axitinib dose or interrupt therapy until diarrhea improves to grade 1
- When diarrhea occurs when axitinib is given in combination with pembrolizumab and can be attributed to either drug, stop axitinib for a few days as initial step
  - Axitinib-induced toxicity should improve significantly with cessation of therapy due to its short half-life
  - Pembrolizumab-induced toxicity would not improve after stopping axitinib
- If diarrhea does not resolve with axitinib cessation and an irAE is suspected, follow the appropriate guidelines

Dealing with two different mechanisms of action with two sets of AE profiles is challenging.

Classic AEs of VEGF TKIs are fatigue, hypertension, diarrhea, oral pain, and hand-foot-skin reaction.

Classic AEs of immunotherapy involve organ inflammation.

Notable crossover AEs: fatigue, diarrhea, hypothyroidism, LFT elevations.

LFT = liver function test.
Case Study (cont’d): Liz

- After 3 months on axitinib and pembrolizumab, Liz’s first follow-up scan showed marked progression in her lung and local recurrence
- Her KPS was 60 and her risk score was 3 (poor)
The novel multitargeted TKIs cabozantinib and lenvatinib (combined with everolimus) have shown favorable data in advanced RCC:

- Cabozantinib is an inhibitor of multiple receptor tyrosine kinases, including VEGFR, MET, the TAM kinases, KIT, FLT3, TRKB, and TIE2
- Lenvatinib is an inhibitor of VEGFR1–3, FGFR1–4, PDGFRα, KIT, and RET

Inhibiting these signaling molecules contributes to the antitumor immunomodulatory effect of these drugs.

**Mechanism of Action of Multi-TKIs**

- Growth factor signals for the cell to divide
- Receptor
- Multi TKI blocks the signal
- TKI going into cell

### Guidelines for Recurrent or Advanced Clear-Cell RCC: Subsequent Lines

<table>
<thead>
<tr>
<th>Subsequent Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preferred Regimens</strong></td>
</tr>
<tr>
<td>• Cabozantinib <em>(category 1)</em></td>
</tr>
<tr>
<td>• Nivolumab <em>(category 1)</em></td>
</tr>
<tr>
<td>• Ipilimumab + nivolumab</td>
</tr>
<tr>
<td><strong>Other Recommended Regimens</strong></td>
</tr>
<tr>
<td>• Axitinib <em>(category 1)</em></td>
</tr>
<tr>
<td>• Lenvatinib + everolimus <em>(category 1)</em></td>
</tr>
<tr>
<td>• Axitinib + pembrolizumab</td>
</tr>
<tr>
<td>• Everolimus</td>
</tr>
<tr>
<td>• Pazopanib</td>
</tr>
<tr>
<td>• Sunitinib</td>
</tr>
<tr>
<td>• Axitinib + avelumab <em>(category 3)</em></td>
</tr>
</tbody>
</table>

Lenvatinib + Everolimus

- Multitargeted TKI lenvatinib was approved in 2016 as combination therapy with the mTOR inhibitor everolimus for 2nd-line treatment of advanced RCC
- Small, randomized phase 2 study with ~50 patients in each of 3 arms
- Median PFS vs everolimus monotherapy: 14.6 vs 5.5 months
- Median OS vs everolimus: 25.5 vs 15.4 months
- ORR: 43% lenvatinib + everolimus vs 27% lenvatinib and 6% everolimus

mTOR = mammalian target of rapamycin.
Cabozantinib

- Cabozantinib is a multitargeted TKI approved in 2017 for front-line use in previously untreated RCC in patients with intermediate/poor risk based on results from the phase 2 CABOSUN trial.
- The METEOR trial evaluated the efficacy of cabozantinib vs everolimus in patients with RCC who had progressed after VEGFR-targeted therapy.
  - Median PFS: 7.4 months vs 3.8 months ($P<0.001$)
  - ORR: 21% vs 5% ($P<0.001$)
  - In a long-term follow-up to the METEOR trial, median OS was 21.4 months with cabozantinib vs 16.5 months with everolimus ($P=0.0003$)
- Now approved for both 1st- and 2nd-line treatment of advanced RCC.
- Toxicity profile of cabozantinib similar to other VEGFR TKIs for the treatment of advanced RCC.
  - Most common grade 3 or 4 side effects were hypertension, diarrhea, and fatigue.

Case Study (cont’d): Liz

• After 3 months of treatment with combination lenvatinib + everolimus, Liz begins to experience extreme fatigue
Toxicity Profile of Lenvatinib + Everolimus

- Most common grade 1-2 TEAEs reported in lenvatinib + everolimus group
  - Diarrhea, decreased appetite, fatigue
- Most common TEAEs of grade ≥3 in lenvatinib + everolimus group
  - Constipation, diarrhea, fatigue
- For toxicities thought to be related to everolimus alone, such as stomatitis and noninfectious pneumonitis, the drug should be discontinued, interrupted, or used on alternate days, according to the label
- For toxicities considered to be related to both lenvatinib and everolimus, the lenvatinib dose should be reduced first

<table>
<thead>
<tr>
<th>TEAE</th>
<th>Lenvatinib + Everolimus, %</th>
<th>Lenvatinib, %</th>
<th>Everolimus, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>65</td>
<td>60</td>
<td>32</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>45</td>
<td>54</td>
<td>18</td>
</tr>
<tr>
<td>Fatigue</td>
<td>45</td>
<td>42</td>
<td>36</td>
</tr>
</tbody>
</table>
Case Conclusion: Liz

- Six months later, Liz complained of fatigue, abdominal discomfort, and weight loss; she subsequently developed back pain.
- CT scan of abdomen and chest showed new liver lesions and progression of previously identified lesions.
- MRI of the spine showed multiple metastatic lesions of the thoracic and lumbar vertebrae, with patient experiencing intermittent sciatica in her right buttocks and leg.
- She was switched to cabozantinib 60 mg and her symptoms subsided within 6 weeks.
- She was maintained on cabozantinib for approximately 13 months until the disease progressed.
- Liz is being considered for enrollment in a clinical trial.

MRI = magnetic resonance imaging.
Bootcamp Takeaways

✓ Be aware of patient factors that help determine the most appropriate therapy options
✓ Provide patients with resource materials, reminders, and other tools (eg, wallet cards) to reinforce details about toxicities related to combination therapy
✓ Consider rechallenge with checkpoint inhibitor therapy with caution in patients whose irAE symptoms and/or laboratory values revert to grade ≤1
✓ It is important to discern causative therapy, since management of AEs is dependent on differentiation

PCE Promotes Practice Change
Updates in Advanced Pancreatic Cancer: Integrating New Therapies Into Clinical Practice
Learning Objectives

• Summarize recent findings on the use of biomarkers in pancreatic cancer
• Identify the appropriate use of newer therapies for pancreatic cancer based on efficacy and safety data and patient factors
• Implement strategies to address treatment-related adverse events (TRAEs) and promote adherence among patients with pancreatic cancer
Pancreatic Cancer: Overview

- Estimated 57,600 new cases and 47,050 deaths in the US in 2020
  - Incidence and mortality rate are increasing
- Because it is typically diagnosed at later stages, >80% of pancreatic cancer is inoperable
- Median age at diagnosis: 70 years; median age at death: 72 years

![Stage at Diagnosis](image-url)
Staging of Pancreatic Cancer

<table>
<thead>
<tr>
<th>Clinical Staging</th>
<th>AJCC Pathologic Staging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resectable</td>
<td>Stage 0</td>
</tr>
<tr>
<td>Locally advanced, including</td>
<td>Stage IA</td>
</tr>
<tr>
<td>borderline and unresectable</td>
<td>Stage IB</td>
</tr>
<tr>
<td>Metastatic (unresectable)</td>
<td>Stage IIA</td>
</tr>
<tr>
<td></td>
<td>Stage IIB</td>
</tr>
<tr>
<td></td>
<td>Stage III</td>
</tr>
<tr>
<td></td>
<td>Stage IV</td>
</tr>
</tbody>
</table>

AJCC = American Joint Committee on Cancer; M = metastasis; N = [lymph] node; T = tumor; Tis = carcinoma in situ.

Pancreatic Ductal Adenocarcinoma (PDAC) Is the Most Common Type of Pancreatic Cancer

- Accounts for 90% of cases
- Has a poorer prognosis than pancreatic neuroendocrine tumor, which is rare

Pancreatic Cancer: Lowest Survival Rates of Any Major Cancer

- Overall 5-year relative survival: 10%
- PDAC accounts for 3.2% of new cancer cases, but causes 8% of all cancer deaths
- 3rd leading cause of US cancer deaths
  - Within the next decade, pancreatic cancer is expected to become the 2nd leading cause of US cancer-related deaths after lung cancer

Why Is the Prognosis for Patients With Pancreatic Cancer So Poor?

• Typically diagnosed at late stages
  – Symptoms are not apparent until cancer has grown or spread
• Lack of specific screening/diagnostic tools
  – Available tests may miss early-stage disease
• Limited treatment options
  – Inherently refractory to chemotherapy
  • Cascade of events—including accumulation of cancer-promoting mutations that permit checkpoint bypass and development of protective, collagenous difficult-to-penetrate stroma—encourage tumor to grow and thrive

## Pancreatic Cancer: Risk Factors

<table>
<thead>
<tr>
<th>Nonmodifiable Factors</th>
<th>Modifiable Factors</th>
<th>Possible Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&gt;45 years)</td>
<td>Tobacco use (2x the risk of nonsmokers)</td>
<td>Diet (eg, red and processed meats, saturated fats, excess sugar)</td>
</tr>
<tr>
<td>Male sex</td>
<td>Obesity</td>
<td>Physical inactivity</td>
</tr>
<tr>
<td>Black race</td>
<td>Type 2 diabetes</td>
<td>Type 1 diabetes</td>
</tr>
<tr>
<td>Family cancer history</td>
<td>Chronic pancreatitis (often associated with heavy alcohol and tobacco use)</td>
<td>Heavy alcohol use</td>
</tr>
<tr>
<td>Inherited genetic syndromes (eg, mutations in BRCA1/2, PALB2, p16/CDKN2A, PRSS1, MLH1, MSH2, STK11)</td>
<td>Workplace (eg, dry cleaning, metal work industries), chemical exposure</td>
<td>Hepatitis B or <em>Helicobacter pylori</em> infection</td>
</tr>
</tbody>
</table>

Signs and Symptoms of Pancreatic Cancer

- Jaundice and related symptoms (dark urine, light-colored or greasy stools, pruritus)
- GI symptoms (eg, anorexia, weight loss, early satiety, dyspepsia, nausea)
- Abdominal or back pain
- Gallbladder or liver enlargement
- Blood clots
- Panniculitis (less common)
- Depression (less common)

Pancreatic cancers can develop without symptoms until they are already advanced and metastatic.

Case Study: Alan

- 78-year-old man with stage IV pancreatic ductal adenocarcinoma (PDAC) metastatic to the lungs
- Medical history notable for type 2 diabetes, hypertension, atrial fibrillation
- No family history of breast or ovarian cancer
- KPS: 70%; ECOG PS: 1
Importance of Germline and Somatic Testing

- Germline (inherited gene) and somatic (tumor tissue) testing now guideline-recommended for all patients diagnosed with pancreatic cancer, regardless of family history
  - Study (N = 3030) identified high-risk gene mutations BRCA1, BRCA2, CDKN2A, TP53, MLH1, and ATM in 5.5% of patients with pancreatic cancer, including 7.9% with and 5.2% without family histories of pancreatic cancer
- Testing should include microsatellite instability (MSI) and DNA mismatch repair deficiency (dMMR), BRCA mutations, and NTRK gene fusions

ASCO = American Society of Clinical Oncology.
Biomarkers in Pancreatic Cancer

- **Diagnostic:** Currently no biomarker approved for early detection of pancreatic cancer
  - MIC-1 may prove useful in early detection of PDAC
  - Several microRNAs have potential utility in differentiating between precancerous and cancerous lesions (miR-21, miR-155, miR-196) and between early-stage PDAC and chronic pancreatitis (miR-223, miR-204)

- **Prognostic:** Favorable or unfavorable for survival, eg:
  - High levels of miR-21, miR-155, and miR-203, and low levels of miR-34a have been associated with decreased disease-free and overall survival (OS)

- **Predictive** of treatment response and/or disease recurrence, eg:
  - *BRCA1/2* mutations may predict response to platinum-based therapies and PARP inhibitors
  - MSI status may identify patients who will benefit from PD-1 blockade

MIC-1 = macrophage inhibitory cytokine 1; PARP = poly (ADP-ribose) polymerase; PD = programmed cell death.
Role of CA 19-9 in Pancreatic Cancer

- **Not for screening or early diagnosis**
  - Low specificity and sensitivity in asymptomatic patients
  - Degree of increase in PDAC may be useful in differential diagnosis
- **Prognostic:** High levels are independently associated with unfavorable survival odds
- **Predictive value:** Decline correlates with treatment response; elevation predicts recurrence

- **Example:** Analysis of MPACT trial results
  - CA 19-9 measured at baseline and week 8
  - Improved OS with any treatment with any CA 19-9 decline (80%) vs no decline: 11.1 months vs 8.0 months
  - In gemcitabine + nab-paclitaxel arm, median OS for those with decline in CA 19-9 vs those without at 8 week was 13.2 months vs 8.3 months

MPACT = Metastatic Pancreatic Adenocarcinoma Clinical Trial.
Case Study (cont’d)

Results of Alan’s testing show:

- CA 19-9: 191 U/mL
- Germline/somatic testing: microsatellite stable, no $BRCA/PALB2$ mutation or $NTRK$ fusion detected
Choice of Chemotherapy Regimen Is Based on Several Factors

- Biologic age is more relevant in treatment selection than chronologic age
- Consider number, type, and severity of comorbidities, especially for older patients
- PS also affects treatment selection
- Results of germline and somatic testing
# First-Line Therapy for Metastatic PDAC

<table>
<thead>
<tr>
<th>Options</th>
<th>Good PS</th>
<th>Poor PS</th>
</tr>
</thead>
</table>
| **Preferred** | One of the following:  
• FOLFIRINOX  
• Modified FOLFIRINOX  
• Gemcitabine with albumin-bound paclitaxel  
For *BRCA1*, *BRCA3*, or *PALB2* mutations only  
One of the following:  
• FOLFIRINOX  
• Modified FOLFIRINOX  
• Gemcitabine with cisplatin  
• Consider olaparib | One of the following:  
• Gemcitabine  
• Capecitabine  
• Continuous infusion 5-FU |
| **Other** | One of the following:  
• Gemcitabine with erlotinib  
• Gemcitabine  
• Gemcitabine with capecitabine  
• Fixed-dose-rate gemcitabine with docetaxel and capecitabine (GTX)  
• Oxaliplatin with 5-FU and leucovorin (OFF)  
• Capecitabine with oxaliplatin (CapeOx) | — |

First-Line nab-Paclitaxel + Gemcitabine: MPACT: Efficacy

Multicenter, open-label, randomized phase 3 study, N = 861

Median OS
- Gemcitabine + nab-paclitaxel: 8.5 months
- Gemcitabine: 6.7 months
HR: 0.72 (95% CI: 0.62-0.83; P < .001)

Median PFS
- Gemcitabine + nab-paclitaxel: 5.5 months
- Gemcitabine: 3.7 months
HR: 0.69 (95% CI: 0.58-0.82; P < .001)

PFS = progression-free survival; HR = hazard ratio; CI = confidence interval.
## First-Line *nab*-Paclitaxel + Gemcitabine: MPACT: Safety

<table>
<thead>
<tr>
<th>Adverse Event (AE)</th>
<th>Gemcitabine + <em>nab</em>-Paclitaxel (n = 421)</th>
<th>Gemcitabine (n = 402)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE leading to death, %</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Hematologic AEs grade ≥3, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Neutropenia</td>
<td>38</td>
<td>27</td>
</tr>
<tr>
<td>• Leukopenia</td>
<td>31</td>
<td>16</td>
</tr>
<tr>
<td>• Thrombocytopenia</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>• Anemia</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Receipt of growth factors, %</td>
<td>26</td>
<td>15</td>
</tr>
<tr>
<td>Febrile neutropenia, %</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Nonhematologic AEs grade ≥3 in ≥5% of patients, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Fatigue</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>• Peripheral neuropathy</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>• Diarrhea</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

**Modified Regimen* of Gemcitabine + nab-Paclitaxel for Patients With Metastatic Pancreatic Cancer**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Modified Gem + nab-P (n = 57)</th>
<th>MPACT (n = 431†)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months</td>
<td>5.4 (n = 57)</td>
<td>5.5 (n = 431)</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>10.0 (n = 57)</td>
<td>8.5 (n = 431)</td>
</tr>
<tr>
<td>Grade 3/4 hematologic toxicity, n/N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Anemia</td>
<td>8/57 (12)</td>
<td>53/405 (13)</td>
</tr>
<tr>
<td>• Neutropenia</td>
<td>11/57 (16)</td>
<td>153/405 (38)</td>
</tr>
<tr>
<td>• Thrombocytopenia</td>
<td>1/57 (1.5)</td>
<td>52/405 (13)</td>
</tr>
<tr>
<td>Growth factor support, n/N (%)</td>
<td>7/57 (10)</td>
<td>110/431 (26)</td>
</tr>
<tr>
<td>Grade 3/4 neurotoxicity, n/N (%)</td>
<td>1/57 (1.5)</td>
<td>70/421 (17)</td>
</tr>
<tr>
<td>Dose reduction, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• nab-Paclitaxel</td>
<td>20</td>
<td>41</td>
</tr>
<tr>
<td>• Gemcitabine</td>
<td>16</td>
<td>47</td>
</tr>
</tbody>
</table>

*Gemcitabine 1000 mg/m² + nab-paclitaxel 125 mg/m² IV piggyback over 30 min every 2 weeks; †Nab-paclitaxel + gemcitabine arm.
First-Line FOLFIRINOX vs Gemcitabine: PRODIGE 4/ACCORD 11—Efficacy

Multicenter, randomized phase 2/3 trial, N = 342

Median OS
- FOLFIRINOX: 11.1 months
- Gemcitabine: 6.8 months

HR: 0.57 (95% CI: 0.45-0.73; \( P < .001 \))

Median PFS
- FOLFIRINOX: 6.4 months
- Gemcitabine: 3.3 months

HR: 0.47 (95% CI: 0.37-0.59; \( P < .001 \))

Note: At 6 months, quality of life had decreased for 31% of patients in FOLFIRINOX group vs 66% in gemcitabine group

First-Line FOLFIRINOX vs Gemcitabine: PRODIGE 4/ACCORD 11—Safety

<table>
<thead>
<tr>
<th>Grade 3/4 AE</th>
<th>FOLFIRINOX (n = 171)</th>
<th>Gemcitabine (n = 171)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Neutropenia</td>
<td>45.7</td>
<td>21.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>• Febrile neutropenia</td>
<td>5.4</td>
<td>1.2</td>
<td>.03</td>
</tr>
<tr>
<td>• Thrombocytopenia</td>
<td>9.1</td>
<td>3.6</td>
<td>.04</td>
</tr>
<tr>
<td>Nonhematologic, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Fatigue</td>
<td>23.6</td>
<td>17.8</td>
<td>NS</td>
</tr>
<tr>
<td>• Vomiting</td>
<td>14.5</td>
<td>8.3</td>
<td>NS</td>
</tr>
<tr>
<td>• Diarrhea</td>
<td>12.7</td>
<td>1.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>• Sensory neuropathy</td>
<td>9.0</td>
<td>0.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>• Elevated ALT</td>
<td>7.3</td>
<td>20.8</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; NS = not significant.
Case Study: (cont’d)

• During treatment with gemcitabine + nab-paclitaxel, Alan’s CA 19-9 level decreased and a CT scan showed improvement in his tumor burden.

• After 6 cycles, however, disease progression was seen on CT scan; his KPS is 80% and ECOG 1.
Second-Line Therapy for Advanced PDAC

- Per ASCO and NCCN, second-line therapy should be reserved for patients with good PS
- Immuno- and targeted therapy are effective for patients with specific genetic mutations
  - Pembrolizumab, a PD-1 inhibitor, is approved for patients with unresectable or metastatic MSI-H or dMMR solid tumors that have progressed following prior treatment who have no satisfactory alternative treatment options
  - Larotrectinib and entrectinib are kinase inhibitors available for treatment of patients with pancreatic cancer who have NTRK gene fusion without a known acquired resistance mutation

MSI-H = microsatellite instability high.
Second-Line Therapy for Advanced PDAC (cont’d)

• nal-IRI + 5-FU/LV is approved for second-line treatment after gemcitabine-based therapy
  – It is preferred by ASCO and is the only NCCN Category 1 recommendation for second-line therapy after gemcitabine-based first-line treatment
• Gemcitabine + nab-paclitaxel may be appropriate as second-line treatment for patients whose first line was FOLFIRINOX
  – In one study, disease-control rate after a median of 4 cycles was 58%, median OS was 8.8 months, and median PFS was 5.1 months; neutropenia and neurotoxicity (12.5% each) were the most common AEs
NAPOLI-1: nal-IRI + 5-FU/LV vs 5-FU/LV After Progression on Gemcitabine-Based Therapy

Multicenter phase 3 trial: Final long-term survival analysis
nal-IRI + 5-FU/LV (n = 117) vs 5-FU/LV (n = 149)

- **OS (%):**
  - nal-IRI + 5-FU/LV: 6.24 (4.76–8.44)
  - 5-FU/LV: 4.24 (3.29–5.32)
  - HR: 0.75 (0.57–0.99)

- **6-month survival (%):**
  - nal-IRI + 5-FU/LV: 53
  - 5-FU/LV: 38

- **1-year survival (%):**
  - nal-IRI + 5-FU/LV: 26
  - 5-FU/LV: 16

- **PFS (%):**
  - nal-IRI + 5-FU/LV: 3.09 (2.69–4.17)
  - 5-FU/LV: 1.46 (1.41–1.84)
  - HR: 0.57 (0.43–0.76)

NAPOLI-1: Long-term Safety Outcomes

- TEAEs affecting treatment
  - Dose delay: 63.2% of nal-IRI + 5-FU/LV arm vs 32.1% of 5-FU/LV arm
  - Dose reduction: 34.2% vs 4.5%
  - Discontinuation: 12.8% vs 8.2%
- Note: Patients with UGT1A1 7/7 genotype should receive a starting dose of 50 vs 70 mg/m² to reduce risk of TEAEs

<table>
<thead>
<tr>
<th>Grade ≥3 TEAE, %</th>
<th>nal-IRI + 5-FU/LV (n = 117)</th>
<th>5-FU/LV (n = 134)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>80</td>
<td>56</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>32</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Anemia</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Asthenia</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

TEAE = treatment-emergent adverse event.
Case Conclusion

• Alan’s PDAC remained stable on his second-line treatment, but after 5 months it began to progress again
• You suggest that Alan participate in a clinical trial to optimize his chances of survival, and he agrees
• You embark together on a search for appropriate, available trials
Value of Clinical Trials in PDAC

- Some potentially effective treatments are available only in the setting of a clinical trial
  - Germline and somatic testing may have identified potential actionable mutations, fusions, mismatch repair, or deficiencies responding to treatment patients can access only in clinical trials
- Older patients are underrepresented in clinical trials
- NCCN and ASCO guidelines recommend offering information to all patients with pancreatic cancer about clinical trials of both active treatment and palliative care
- Relevant clinical trials should be discussed at every stage of treatment

### Novel and Investigational Agents

<table>
<thead>
<tr>
<th>Target</th>
<th>Population</th>
<th>Drug</th>
<th>Treatment Line</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Novel, FDA-Approved</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>NTRK</em> fusion</td>
<td>Metastatic solid tumors</td>
<td>Entrectinib, larotrectinib</td>
<td>Any</td>
</tr>
<tr>
<td><em>MSI-H or dMMR</em></td>
<td>Unresectable tumors</td>
<td>Pembrolizumab</td>
<td>Second+</td>
</tr>
<tr>
<td><strong>Investigational</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>BRAF V600E</em></td>
<td>Solid tumors</td>
<td>Encorafenib + binimetinib</td>
<td>Any</td>
</tr>
<tr>
<td><em>KRAS&lt;sup&gt;G12C&lt;/sup&gt;</em></td>
<td>PDAC, other solid tumors</td>
<td>AMG 510</td>
<td>Second+</td>
</tr>
<tr>
<td><em>KRAS&lt;sup&gt;G12C&lt;/sup&gt;</em></td>
<td>PDAC, other solid tumors</td>
<td>MRTX849</td>
<td>Second+</td>
</tr>
<tr>
<td>CD40</td>
<td>Metastatic PDAC</td>
<td>APX005M</td>
<td>First</td>
</tr>
<tr>
<td>DDR gene (<em>BRCA1/2, PALB2</em>)</td>
<td>Pancreatic cancer</td>
<td>Rucaparib</td>
<td>Maintenance</td>
</tr>
<tr>
<td><em>NRG1</em> fusion</td>
<td>Solid tumors</td>
<td>MCLA-128</td>
<td>Second+</td>
</tr>
</tbody>
</table>

DDR = DNA damage response; dMMR = mismatch repair deficient.
Case Study: Greg

- 56-year-old man with stage IV PDAC metastatic to the liver
- KPS: 100%
- Family history: sister with breast cancer, mother had ovarian cancer
- Patient germline testing: BRCA2 mutation
- Greg begins modified FOLFIRINOX chemotherapy, without 5-FU bolus
- After 6 cycles of modified FOLFIRINOX therapy, Greg develops grade 2 chemotherapy-induced neuropathy

KPS = Karnofsky Performance Status.
## Management of Key AEs: FOLFIRINOX

<table>
<thead>
<tr>
<th>AE</th>
<th>Key Management Considerations</th>
</tr>
</thead>
</table>
| Neuropathy                  | • Decrease dose of oxaliplatin  
• 5-FU ± irinotecan may be considered for maintenance therapy in the case of oxaliplatin-related progressive neuropathy                                                                                                                                                                                                                             |
| Neutropenia/febrile neutropenia | • Decrease dose of ≥1 component; eliminate 5-FU bolus  
• Consider addition of hematopoietic growth factor  
• Delay treatment until neutrophil count is ≥1.5 \( \times 10^9 \)/L; if not recovered after 2 weeks or third occurrence, discontinue treatment                                                                                                                                                                      |
| Thrombocytopenia            | • Reduce oxaliplatin dose and 5-FU bolus and dose until platelet count is ≥75 \( \times 10^9 \)/L; if not recovered after 2 weeks or third occurrence, discontinue treatment                                                                                                                                                                                                   |
| Diarrhea                    | • Decrease dose of ≥1 component  
• Treat with antidiarrheal  
• Discontinue FOLFIRINOX after third occurrence                                                                                                                                                                                                                                                                              |
| Infusion reactions          | • Slow infusion time, provide atropine and/or proton pump inhibitor  
• Desensitization protocols                                                                                                                                                                                                                                                                                                       |
Management of Key AEs: Gemcitabine + *nab*-Paclitaxel

<table>
<thead>
<tr>
<th>AE</th>
<th>Key Management Considerations</th>
</tr>
</thead>
</table>
| Peripheral neuropathy                                             | • Withhold therapy for grade 3/4  
• Resume *nab*-paclitaxel at next lower dose level when neuropathy improves to grade ≤1  
• No modification for gemcitabine                                  |
| Neutropenia/febrile neutropenia/thrombocytopenia                  | • Withhold until fever resolves and ANC is ≥1500; resume at next lower dose level                                                                           |
| Gastrointestinal toxicity                                          | • For grade 3/4: withhold until grade ≤1  
• Resume at next lower dose level                                    |
| Cutaneous toxicity                                                | • For grade 2/3: reduce to next lower dose level  
• Discontinue if toxicity persists                                   |

ANC = absolute neutrophil count.  
Abraxane [prescribing information]. Celgene; 2020.
Managing the TRAEs of Immunotherapy and Targeted Therapy

- The toxicities of targeted and immunotherapy are various and, therefore, especially difficult to recognize.
- Clinicians must emphasize the importance of reporting any unusual symptoms while patients are on either type of therapy.

**Targeted Therapy AEs**
- The type and severity of targeted therapy AEs depend mainly on the type of agent used and its target.
- Management is based on this information.

**Principles of irAE Management**

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Mild symptoms</th>
<th>Supportive measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3</td>
<td>Moderate symptoms</td>
<td>Delay Immunotherapy</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Severe symptoms</td>
<td>Discontinue/Delay Immunotherapy</td>
</tr>
</tbody>
</table>

Case Study (cont’d)

- Greg’s neuropathy has resolved
- He completes 12 cycles of modified FOLFIRINOX therapy
- A CT scan shows complete response
Maintenance Therapy After First-Line FOLFIRINOX

• Maintenance treatment can help maintain disease control but spare patients the ongoing effects of chemotherapy toxicities
• Although reduced-dose FOLFIRINOX (or a combination of fewer components) may be effective, the risks of attendant AEs are still high
• PARP inhibitors have been shown to be effective in cancers involving BRCA mutations, with much lower toxicity than with chemotherapy
  – Olaparib was approved in 2019 as maintenance therapy for adults with deleterious or suspected deleterious germline BRCA-mutated metastatic PDAC whose disease has not progressed on ≥16 weeks of platinum-based front-line therapy
  – Other PARP inhibitors are under study as maintenance therapy for advanced PDAC

POLO: Maintenance Olaparib After First-Line Chemotherapy in Metastatic Pancreatic Cancer: Efficacy

- International, randomized phase 3 trial
- N = 154 patients with metastatic pancreatic cancer and deleterious/suspected deleterious germline BRCA1/2 mutation, ≥16 weeks of platinum-based therapy without progression (4-8 weeks from last dose)

<table>
<thead>
<tr>
<th>Patients With Measurable Disease at Baseline</th>
<th>Olaparib (n = 78)</th>
<th>Placebo (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response, n (%)</td>
<td>18 (23.1)</td>
<td>6 (11.5)</td>
</tr>
<tr>
<td>Median time to response, months</td>
<td>5.4</td>
<td>3.6</td>
</tr>
<tr>
<td>Median duration of response, months</td>
<td>24.9</td>
<td>3.7</td>
</tr>
</tbody>
</table>

\[HR: 0.53 \ (95\% \ CI: 0.35-0.82; P = .004)\]

POLO: Safety and Quality of Life

- Median duration of treatment, olaparib vs placebo: 6.0 months (range: 0.8-45.3) vs 3.7 months (0.1-30.1)
- Patient-reported global HRQoL score: no clinically meaningful change from baseline in either arm

<table>
<thead>
<tr>
<th>AE, %</th>
<th>Olaparib (n = 91)</th>
<th>Placebo (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any</td>
<td>≥3</td>
</tr>
<tr>
<td>Fatigue/asthenia</td>
<td>60.4</td>
<td>5.5</td>
</tr>
<tr>
<td>Nausea</td>
<td>45.1</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>28.6</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>28.6</td>
<td>2.2</td>
</tr>
<tr>
<td>Anemia</td>
<td>27.5</td>
<td>11.0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>25.3</td>
<td>3.3</td>
</tr>
<tr>
<td>Constipation</td>
<td>23.1</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>19.8</td>
<td>1.1</td>
</tr>
<tr>
<td>Back pain</td>
<td>18.7</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>15.4</td>
<td>1.1</td>
</tr>
</tbody>
</table>

HRQoL = health-related quality of life.
Case Conclusion

- Greg’s PDAC is stable on maintenance olaparib
- He is experiencing fatigue, for which you encourage him to get rest, do some mild physical activity, and make sure to have adequate nutrition and hydration
- You continue monitoring his status, with the understanding that any change will trigger discussion of possible next steps
- You continue to research clinical trials that might benefit him
Disease-Related Symptoms: Fatigue

- Most common symptom affecting people with cancer
- Impacts several domains, eg, physical, emotional, cognitive, behavioral
- Results from interaction of disease, disease-related symptoms such as pain and sleep disorders, and treatment side effects
- Can be debilitating, yet is often undertreated
- Management
  - Identify and treat underlying cause if possible
  - Ensure adequate nutrition and hydration
  - Recommend regular physical exercise
  - Psychological interventions
  - Adequate rest/sleep

Disease-Related Symptoms: Pancreatic Exocrine Insufficiency

- Occurs in up to 60% of patients with unresectable pancreatic cancer and up to 94% of those undergoing pancreatic surgery
  - Frequently overlooked/underdiagnosed
- Symptoms: Bloating, steatorrhea, weight loss, flatulence, dyspepsia
- Major effects: loss of nutrients, malnutrition
- Management
  - Pancreatic enzyme replacement: may need higher dosages than for individuals with pancreatic exocrine insufficiency caused by other disorders
  - Consultation with nutritionist or dietitian, with possible dietary modification and/or supplementation

Management of Additional Disease-Related Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Key Management Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>• Analgesics if effective and tolerable</td>
</tr>
<tr>
<td></td>
<td>• Celiac plexus block</td>
</tr>
<tr>
<td></td>
<td>• Palliative radiation or chemoradiation</td>
</tr>
<tr>
<td>Biliary obstruction and jaundice</td>
<td>• Endoscopic biliary metal drain</td>
</tr>
<tr>
<td></td>
<td>• External biliary drain/percutaneous transhepatic cholangiogram</td>
</tr>
<tr>
<td>Gastric outlet obstruction</td>
<td>• Enteral stent</td>
</tr>
<tr>
<td></td>
<td>• Gastrojejunostomy (for patients with good PS)</td>
</tr>
</tbody>
</table>
### Management of Additional Disease-Related Symptoms (cont’d)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Key Management Considerations</th>
</tr>
</thead>
</table>
| Anorexia/early satiety/unexplained weight loss | • Referral to dietitian/nutrition services (culturally sensitive)  
• Appetite stimulants                                      |
| Venous thromboembolism                       | • Diagnosis may precede that of pancreatic cancer  
• Low-molecular-weight heparin (preferred over warfarin)                                |
| Depression                                   | • Pancreatic cancer believed to have one of the highest rates of concomitant depressive disorders  
• Monitor and screen for depression, anxiety; refer to psychology or psychiatry, social services  
• Consider antidepressant medication                                                  |
| Insomnia                                     | • Cognitive behavioral therapy  
• Sleep hygiene                                                                         |
• Dedicated palliative care, early in the disease course and concurrent with active treatment, is associated with improved outcomes among patients with advanced cancer
  – ↑ quality of life, ↑ survival, ↑ coping skills that decrease depressive symptoms
• Referral to interdisciplinary palliative care teams is optimal
• ASCO clinical practice guideline recommendation: Palliative care should be offered to all patients with pancreatic cancer, regardless of disease stage or prognosis
Bootcamp Takeaways

✓ Recommend germline and somatic testing for all patients diagnosed with pancreatic cancer
✓ Discuss clinical trials with patients at all stages of treatment and help them find and participate in them
✓ Emphasize to patients/caregivers the importance of reporting any unusual symptoms during treatment
✓ Offer patients palliative care throughout their disease course to help minimize disease-related symptoms and improve quality of life

PCE Promotes Practice Change
The Evolving Treatment Landscape for Advanced Gastric Cancer: New Data on Novel Treatment Options
Learning Objectives

- Summarize novel and emerging treatment options for advanced gastric cancer (GC)
- Identify recommended and emerging treatment strategies and sequences for GC
- Implement strategies to manage adverse events (AEs) associated with novel treatments for advanced GC and improve patient outcomes and quality of life
• Prevalence highest among people in/from East Asia, Eastern Europe, Central/South America
• 14th in prevalence among major cancers in the US
• Overall incidence decreasing due to improved risk factor management and prevention
• Associated mortality high due to late diagnosis; >80% of patients diagnosed with advanced disease
• 90% to 95% are adenocarcinoma
• Presentation changing in the US: rates of noncardia GC decreasing, except among patients <40 years
• Survival is improved with earlier diagnosis and treatment, as demonstrated in Japan

27,600 new diagnoses in 2020
11,000+ deaths in 2020
Case Study: Juan, 72 Years Old

- Immigrated from Guatemala 5 years ago to be with his family
- Presents with a complaint of persistent abdominal pain on left side
  - Feels bloated and full after a small portion of food, rarely finishes a meal
  - Unintended weight loss of >10 lbs over the past year

- Pertinent history:
  - Former smoker (quit 20 years ago)
  - Does not drink alcohol
  - Mononucleosis 15 years ago

- Physical exam and labs:
  - Blood pressure normal, no splenomegaly
  - Breath test positive for *H pylori*
  - WBC elevated
  - Glucose and other labs within normal ranges

WBC = white blood cell count.
Risk Factors for Gastric Cancer

- *H pylori* infection: most well-described risk for noncardia (distal) GC
- Other factors
  - Older age
  - Low socioeconomic status
  - Smoking
  - Alcohol consumption
  - Obesity
  - Pernicious anemia
- Infection with Epstein-Barr virus (EBV)
- GERD increases risk for proximal cancer
- Regional distribution
  - Most frequent in East Asia, Eastern Europe, Central/South America
- Familial predisposition
  - ~10% show familial aggregation
  - 1% to 3% have germline mutations

Between 3% and 5% of GC Is Associated With Inherited Predisposition Syndromes

<table>
<thead>
<tr>
<th>Disease</th>
<th>Clinical Features</th>
<th>Related Gene*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary diffuse GC</td>
<td>• Younger age at diagnosis</td>
<td>~50% truncating mutation in CDH1</td>
</tr>
<tr>
<td></td>
<td>• Increased risk of lobular breast cancer in women</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Lifetime risk for GC: 67% (men) and 83% (women)</td>
<td></td>
</tr>
<tr>
<td>Familial adenomatous polyposis</td>
<td>• More frequently seen in colorectal cancer</td>
<td>APC</td>
</tr>
<tr>
<td></td>
<td>• Lifetime risk for GC: 1% to 2%</td>
<td></td>
</tr>
<tr>
<td>Lynch syndrome</td>
<td>• Younger age at diagnosis</td>
<td>EPCAM, MLH1, MSH2, MSH6, PMS2</td>
</tr>
<tr>
<td></td>
<td>• Increases risk for colorectal and endometrial cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Lifetime risk for GC: 1% to 13%</td>
<td></td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>• Elevated risk for other cancer types</td>
<td>STK11</td>
</tr>
<tr>
<td></td>
<td>• Lifetime risk for GC: 29%</td>
<td></td>
</tr>
</tbody>
</table>

*All are autosomal dominant syndromes.
**Recommended Workup**

<table>
<thead>
<tr>
<th>Physical and Labs</th>
<th>Imaging and Biopsy</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and physical</td>
<td>Upper GI endoscopy and biopsy</td>
<td>Assess Siewert category</td>
</tr>
<tr>
<td>CBC and comprehensive chemistry profile</td>
<td>Chest/abdomen/pelvis CT</td>
<td>Nutritional assessment and counseling</td>
</tr>
<tr>
<td>If metastatic disease suspected or confirmed</td>
<td>Clinical staging with endoscopic ultrasound prior to treatment</td>
<td>Smoking cessation advice, counseling, support</td>
</tr>
<tr>
<td>• MSI by PCR or MMR by IHC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>•  <strong>HER2</strong> and PD-L1 testing</td>
<td>Biopsy of metastatic disease as clinically indicated</td>
<td>Screen for family history</td>
</tr>
</tbody>
</table>

CBC = complete blood count; IHC = immunohistochemistry; MMR = mismatch repair; PCR = polymerase chain reaction.
Pathology and report from biopsy should include:
- Invasion (if present)
- Histologic type: diffuse or intestinal
- Grade

Tumor location (distal, proximal)

Histologic and molecular classifications are complementary and factor into treatment decisions

### Histologic Classification of Gastric Adenocarcinoma

<table>
<thead>
<tr>
<th>WHO</th>
<th>Lauren</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma (95%)</td>
<td>Intestinal</td>
</tr>
<tr>
<td></td>
<td>• Related more often to modifiable risk factors</td>
</tr>
<tr>
<td>Signet ring cell adenocarcinoma</td>
<td>Diffuse</td>
</tr>
<tr>
<td></td>
<td>• Related more often to heritable genomic factors</td>
</tr>
<tr>
<td>Undifferentiated carcinoma</td>
<td>Mixed/unclassified</td>
</tr>
</tbody>
</table>

Lauren Classification

- **Adenocarcinoma (95%)**
  - Related more often to modifiable risk factors

- **Signet ring cell adenocarcinoma**
  - Related more often to heritable genomic factors

- **Undifferentiated carcinoma**
  - Mixed/unclassified

Case Study (cont’d)

• Endoscopy and biopsy confirm significant presence of distal GC
  – Adenocarcinoma
  – Lauren intestinal type—tumor cells exhibit adhesion, arranged in tubular or glandular formations, often associated with intestinal metaplasia
• Chest and abdominal CT reveal metastatic lesions in liver
• Unresectable stage 4 disease
Recommendations for Molecular Testing of Advanced GC

Molecular Features With Impact on Treatment Decisions

- HER2 amplification
- MSI/dMMR
- PD-L1 expression
- If using NGS:
  - NTRK fusion (rare)
  - TMB (later lines)

Recommended Testing

- All patients should be tested first for dMMR, HER2 amplification, PD-L1 expression
- IHC is “gold standard” and should be used if possible; must be used for PD-L1
- Other options: FISH (for HER2), NGS, “liquid biopsy” for mutations/amplifications

Note:

- TMB on NGS is an emerging biomarker for anti–PD-L1 therapies
- Not part of current NCCN guidance

FISH = fluorescence in situ hybridization; NCCN = National Comprehensive Cancer Network; NGS = next-generation sequencing; TMB = tumor mutational burden.
**The Cancer Genome Atlas Molecular Classification of Gastric Cancer**

**Epstein-Barr virus +**
- Most frequent in fundus body

**Chromosomal instability**
- Most frequent overall; predominant in cardia and EGJ

**EBV+**
- 8.81%
- $CDK_n24$ methylation
- $PIK3CA$ mutations
- PD-L1 overexpression
- EBV-CIMP
- Immune cell signaling

**MSI**
- 23.79%
- Gene hypermutation
- $MLH1$ silencing
- Mitotic pathways
- Gastric-CIMP
- TMB

**CIN**
- 45.84%
- Intestinal histology
- RTK-RAS activation
- $TP53$ mutation
- $HER2$ amplification
- $VEGFA$ amplification

**GS**
- 21.56%
- Diffuse subtype
- $CDH1/RHOA$ mutations
- $CLDN18-ARHGAP$ fusion
- Cell adhesion
- Worst prognosis

**Microsatellite instable**
- Most frequent in fundus body and antrum

**Genomically stable**
- Most frequent in antrum and pylorus

CIMP = CpG island methylator phenotype; EGJ = esophagogastric junction; VEGFA = vascular endothelial growth factor A.

Molecular Testing Aids Individualized Therapy

- Universal \textit{HER2}, dMMR/MSI, and PD-L1 testing using IHC is recommended in advanced GC
  - Alternative testing methods: FISH, NGS
- Different actionable targets predominate in different TCGA types
  - \textit{HER2} amplification: chromosomal instability (24%), but also found in EBV+ (12%), MSI (5%), GS (7%)
  - dMMR/MSI-H: MSI
  - PD-L1 overexpression: EBV+ (15%)
- However, these targets may be found in any molecular subtype, underscoring the need to test all patients
Case Study (cont’d)

- Juan’s molecular testing results
  - HER2 amplification: negative
  - dMMR/MSI-H: negative (eg, microsatellite stable)
  - PD-L1: CPS >10
Patients With Advanced or Metastatic GC

- HER2-positive
  - Platinum doublet + trastuzumab

- HER2-negative
  - Platinum doublet
  - 5-FU or capecitabine + platinum
  - Oxaliplatin preferred over cisplatin due to lower toxicity

- Aim to achieve best efficacy with lowest toxicity
- Reserve 3-drug regimens for medically fit, very symptomatic patients with high disease burden who are willing to accept more side effects
- Recommended use of immunotherapy changing rapidly with emerging data showing efficacy earlier in treatment sequence

5-FU = 5- fluorouracil.
Investigational: Phase 3 CheckMate-649  
Chemotherapy ± Nivolumab in Initial Therapy of mGC

- Patients: treatment-naïve mGC, regardless of PD-L1 expression
- HER2-positive excluded
- Dual primary endpoints in pts with PD-L1 CPS ≥5 (OS and PFS)
- Benefit in CPS <5 is uncertain
- Grade 3-4 AEs in PD-L1 CPS ≥5
  - 59% with nivolumab
  - 44% with chemotherapy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Nivolumab + Chemo</th>
<th>Chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1 CPS ≥5, n</td>
<td>473</td>
<td>482</td>
</tr>
<tr>
<td>Median OS (95% CI), months</td>
<td>14.4 (13.1-16.2)</td>
<td>11.1 (10-12.1)</td>
</tr>
<tr>
<td>HR (98.4% CI)</td>
<td>0.71 (0.59-0.86)</td>
<td><em>P &lt;0.0001</em></td>
</tr>
<tr>
<td>Median PFS (95% CI), months</td>
<td>7.7 (7.0-9.2)</td>
<td>6.1 (5.6-6.9)</td>
</tr>
<tr>
<td>HR (98% CI)</td>
<td>0.68 (0.56-0.81)</td>
<td><em>P &lt;0.0001</em></td>
</tr>
<tr>
<td>All randomized, n</td>
<td>789</td>
<td>792</td>
</tr>
<tr>
<td>HR (99.3% CI) for death</td>
<td>0.80 (0.68-0.94)</td>
<td><em>P = 0.0002</em></td>
</tr>
</tbody>
</table>

Chemo = oxaliplatin-based chemotherapy; HR = hazard ratio; mGC = metastatic gastric cancer; OS = overall survival; PFS = progression-free survival.
Investigational: Phase 2/3 ATTRACTION-4
Chemotherapy ± Nivolumab in Initial Therapy of mGC

- HER2-positive excluded
- Coprimary endpoints:
  - PFS, median follow-up: 11.6 months
  - OS, median follow-up: 26.6 months
- PFS was continuously longer with nivolumab
- Higher response rate ($P = 0.0088$) and longer DoR
- 25% of patients received subsequent nivolumab
- No difference in OS

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Nivolumab + Chemo*</th>
<th>Chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>362</td>
<td>362</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>10.5</td>
<td>8.3</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.68 (0.51 – 0.90)</td>
<td>$P = 0.0007$</td>
</tr>
<tr>
<td>1-year PFS, %</td>
<td>45.4</td>
<td>30.6</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>17.5</td>
<td>17.2</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.90 (0.75 – 1.08)</td>
<td>$P = 0.257$</td>
</tr>
<tr>
<td>ORR, %</td>
<td>57.5</td>
<td>47.8</td>
</tr>
<tr>
<td>Grade 3-4 SAE, %</td>
<td>57.9</td>
<td>49.2</td>
</tr>
</tbody>
</table>

*CapeOx (capecitabine + oxaliplatin) or SOX (S-1 + oxaliplatin).
DoR = duration of response; ORR = objective response rate (complete response [CR] + partial response [PR]); SAE = serious adverse events.
Investigational: Phase 3 KEYNOTE-062
Chemotherapy ± Pembrolizumab in Initial Therapy of mGC

Pembrolizumab “Noninferior” to Chemotherapy
Pembrolizumab did not add to Chemotherapy

- Unresectable locally advanced/mGC
- Cohorts (all, PD-L1 CPS ≥1)
  - Pembrolizumab
  - Platinum chemotherapy*
  - Chemotherapy + pembrolizumab
- Primary outcomes: noninferiority for OS and PFS by CPS ≥1 and ≥10
- Median follow-up: 29.4 months
- Grade ≥3 AE
  - Pembrolizumab: 17%
  - Combination: 73%
  - Chemotherapy: 69%

*Cisplatin + 5-FU or capecitabine.
Investigational: KEYNOTE-062 Survival in MSI-H Patients

Kaplan-Meier estimated OS in patients with MSI-H tumors in the PD-L1 CPS of 1 or greater population for pembrolizumab and pembrolizumab + chemotherapy vs chemotherapy. Analysis of OS in patients with MSI-H tumors was not adjusted for multiplicity.

Investigational: Phase 2 Pembrolizumab + Trastuzumab/Chemotherapy in Initial Therapy of HER2 + mGC

- 37 treatment-naïve patients with metastatic disease
- Platinum + fluoropyrimidine chemotherapy
- Primary endpoint: 6-month PFS
- ORR = 91%, including 17% CR
- DCR = 100%
- AEs
  - 4 d/c due to irAE
  - 2 (5%) grade 3 SAE
- Ongoing Phase 3 KEYNOTE-811 further exploring this combination (NCT03615326)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pembrolizumab + Trastuzumab + Chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>31</td>
</tr>
<tr>
<td>PD-L1 CPS ≥1, %</td>
<td>38</td>
</tr>
<tr>
<td>6-month PFS, %</td>
<td>70.0</td>
</tr>
<tr>
<td>Median PFS (95% CI), months</td>
<td>13.0 (8.6-NR)</td>
</tr>
<tr>
<td>12-month OS, %</td>
<td>80.0</td>
</tr>
<tr>
<td>Median OS (95% CI), months</td>
<td>27.3 (18.8-NR)</td>
</tr>
<tr>
<td>Grade ≥3 AE, %</td>
<td>57</td>
</tr>
</tbody>
</table>

DCR = disease control rate (ORR + stable disease [SD]); irAE = immune-related adverse event.
Case Study (cont’d)

- Juan received treatment with a fluoropyrimidine and oxaliplatin, followed by 5-FU maintenance therapy
- He progressed during maintenance and next received treatment with ramucirumab + paclitaxel
- After 2 months of treatment, his disease recurred
Second-Line and Subsequent Therapy: Preferred Regimens

- Choice depends on prior treatment and performance status
- Preferred second line: ramucirumab + paclitaxel
- If dMMR/MSI-H: use pembrolizumab
- Anti-PD-1 if PD-L1 positive
- Do not continue trastuzumab for HER2-positive patients who progress after initial trastuzumab/chemotherapy

Subsequent Therapy: Phase 3 KEYNOTE-061
Second-line Pembrolizumab vs Paclitaxel

- Patients progressed after initial platinum chemotherapy ± trastuzumab
  - All, PD-L1 CPS ≥1
  - Median follow-up for survival
    - All patients: 8.5 months
    - CPS subgroups: 2+ years
- Longer DoR with pembrolizumab
- Fewer grade ≥3 AE with pembrolizumab (14% vs 35%)
- Pembrolizumab was not superior to paclitaxel

<table>
<thead>
<tr>
<th>Outcome by CPS</th>
<th>Pembrolizumab vs Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OS, all patients: HR (95% CI)</strong></td>
<td>0.82 (0.66-1.03) ( P = 0.042 )</td>
</tr>
<tr>
<td>- CPS ≥1</td>
<td>0.81 (0.66-1.00) ( P = 0.03 )</td>
</tr>
<tr>
<td>- CPS ≥5</td>
<td>0.72 (0.53-0.99) ( P = 0.02 )</td>
</tr>
<tr>
<td>- CPS ≥10</td>
<td>0.69 (0.46-1.05) ( P = 0.04 )</td>
</tr>
<tr>
<td><strong>PFS, all patients: HR (95% CI)</strong></td>
<td>1.27 (1.03-1.57) ( P = \text{NS} )</td>
</tr>
<tr>
<td>- CPS ≥1</td>
<td>1.25 (1.02-1.54) ( P = \text{NS} )</td>
</tr>
<tr>
<td>- CPS ≥5</td>
<td>0.98 (0.71-1.34) ( P = \text{NS} )</td>
</tr>
<tr>
<td>- CPS ≥10</td>
<td>0.79 (0.51-1.21) ( P = \text{NS} )</td>
</tr>
</tbody>
</table>

Subsequent Therapy: Phase 3 ATTRACTION-2
Third-line Nivolumab vs Placebo

- Asian patients with advanced GC and progression after ≥2 prior lines
- ECOG PS 0/1 at baseline
- Post hoc study stratified by previous trastuzumab
  - OS and PFS benefit with nivolumab vs placebo regardless of previous trastuzumab
  - Similar rates of TRAE

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Nivolumab (n = 330)</th>
<th>Placebo (n = 163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow up, months</td>
<td>8.87</td>
<td>8.59</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>5.26</td>
<td>4.14</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.63 (0.51-0.78)</td>
<td>P &lt;0.001</td>
</tr>
<tr>
<td>12-month OS rate, %</td>
<td>26.2%</td>
<td>10.9%</td>
</tr>
<tr>
<td>Grade 3/4 AE</td>
<td>10%</td>
<td>4%</td>
</tr>
</tbody>
</table>

TRAE = treatment-related adverse event
Tumor Mutational Burden: Emerging Biomarker for ICI

- TMB is an independent biomarker for ICI response across several solid tumor types
  - PD-L1 expression does not always correlate with ICI response
  - Composite of TMB-H and high PD-L1 improves chance of good response
- TMB may be result of impaired DNA repair mechanisms or external factors that damage DNA
- Defined as the number of coding mutations per analyzed tumor genomic region
  - Can be performed on tissue or blood using available NGS platforms
- Standardized thresholds and quantification methods are needed to optimize use of TMB to guide treatment

ICI = immune checkpoint inhibitor; TMB-H = high tumor mutational burden.
Pembrolizumab in TMB-H: KEYNOTE 158

- Phase 2 basket study: solid tumors after progression on ≥1 standard therapy (N = 755)
  - ECOG PS: 0/1
  - TMB-H: ≥10 mut/Mb
- Tumor types: anal, biliary, cervical, endometrial, salivary gland, thyroid, mesothelioma, neuroendocrine tumor, small cell lung cancer, vulvar
- Pembrolizumab is approved in TMB-H based on response rate
- No colorectal, esophagogastric, or pancreatic cancers

<table>
<thead>
<tr>
<th>Outcome</th>
<th>TMB-H/MSI</th>
<th>TMB-low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>120</td>
<td>635</td>
</tr>
<tr>
<td>ORR</td>
<td>28.3%</td>
<td>6.5%</td>
</tr>
<tr>
<td>DoR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>PFS, months</td>
<td>2.1</td>
<td>2.1</td>
</tr>
<tr>
<td>12-month PFS</td>
<td>24.3%</td>
<td>14.0%</td>
</tr>
<tr>
<td>OS, months</td>
<td>11.1</td>
<td>13.3</td>
</tr>
<tr>
<td>12-month OS</td>
<td>48.0%</td>
<td>52.9%</td>
</tr>
</tbody>
</table>

ECOG PS = Eastern Cooperative Oncology Group Performance Status; NR = not reached.
Immunotherapy Improves Outcomes in Subsequent Therapy of mGC

- About 60% of gastric cancer is positive for PD-L1 over expression
- Current and emerging data suggest improved survival with pembrolizumab and nivolumab; other data show no survival benefit with avelumab
- NCCN now recommends pembrolizumab as a preferred:
  - 2nd-line therapy for dMMR/MSI-H advanced GC
  - 3rd-line therapy for PD-L1+ advanced GC
- Pembrolizumab is FDA approved
  - PD-L1+ advanced GC after ≥2 prior lines of therapy (HER2 irrelevant)
  - Any dMMR/MSI-H solid tumor after ≥1 prior line of therapy
  - Any TMB-H solid tumor after after ≥1 prior line of therapy

Case Study (cont’d)

- You prescribe Juan pembrolizumab and tell him that he can receive the treatment infusion either 200 mg every 3 weeks or 400 mg every 6 weeks.
- He would prefer less-frequent infusion center visits, and he begins treatment with 400 mg every 6 weeks.
- A few days after his second infusion, he calls you to report a new onset of diarrhea that he describes as “pretty bad.”
  - Further questioning reveals he is experiencing about 4 additional bowel movements than is usual.
- This meets criteria for grade 2 colitis.
Immune Checkpoint Inhibitor-Related Colitis

<table>
<thead>
<tr>
<th>Diagnosis and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopic biopsy is gold standard for diagnosis, but diagnosis often made on clinical symptoms</td>
</tr>
<tr>
<td>Exclude infectious causes (C difficile, other)</td>
</tr>
<tr>
<td>Exclude other GI irAE (eg, enterocolitis or gastritis)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depending on severity, consider withholding ICI until resolution; permanently d/c for grade ≥4</td>
</tr>
<tr>
<td>4 to 6 weeks of high-dose prednisone, taper after remission</td>
</tr>
<tr>
<td>30% to 40% may require biologic immunosuppression; infliximab or vedolizumab recommended</td>
</tr>
</tbody>
</table>

- Most frequently encountered irAE
- Estimated rate of GI irAEs with anti–PD-L1 therapy
  - Any grade: 20%
  - Severe: 2% to 5%
- Most common symptom: watery, non-bloody diarrhea
  - Grade 2/3 presents with cramping and urgency
  - Grade 3 may include incontinence
- CTLA-4 inhibitors (eg, ipilimumab) associated with higher rates of severe GI toxicity

## Frequent irAEs with ICIs

<table>
<thead>
<tr>
<th>GI Tract</th>
<th>Skin</th>
<th>Lungs</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Can occur anywhere in GI tract</td>
<td>• Presents as erythema multiforme minor or bullous dermatoses</td>
<td>• If pneumonitis suspected, chest x-ray and pulse oximetry needed</td>
</tr>
<tr>
<td>• Presentation similar to IBD, but rapid symptom development</td>
<td>• If mild, topical treatment and sun avoidance recommended</td>
<td>• Grade 1 may require withholding treatment if x-ray shows progression</td>
</tr>
</tbody>
</table>
| • Colitis: grade by stools above baseline  
  – Grade 2: 4 to 6  
  – Grade 3: 7+  
  – Grade 4: life-threatening | • If affecting quality of life, consider withholding and initiating steroid | |
| • Hold anti–PD-L1 therapy for grade 2-3 until resolution | | • Systemic prednisone for grade ≥2 |
| • Hepatotoxicity: 5% to 10%  
  – Assess LFTs regularly | • Potential for rare but serious SJS or TEN | |

Spectrum of Immune-Related Adverse Events

• Currently, no way to predict who will develop irAEs, which differ from AEs seen with other therapies

• Onset 2 to 3 months after starting therapy, but can occur up to 2 years after therapy completion

• Ask patients to contact oncology team if any symptoms develop, if they are admitted to hospital, or if they begin any new medications
  – Severe fatigue, headache, cough, dyspnea, chest pain, bloating, weight loss, severe muscle weakness/pain, bowel, vision, or mood changes

• If irAEs are suspected, conduct a complete workup, including lab tests, to rule out other causes

General Guide to Managing irAEs

<table>
<thead>
<tr>
<th>Severity</th>
<th>Recommended Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (mild)</td>
<td>• Symptomatic management                                                                                              • Continue therapy (some may require withhold or d/c; eg, neurologic, cardiac)</td>
</tr>
<tr>
<td></td>
<td>• Immunosuppression not needed</td>
</tr>
<tr>
<td>2 (mild to moderate)</td>
<td>• Symptomatic management                                                                                       • Consider withholding until resolution to grade ≤1</td>
</tr>
<tr>
<td></td>
<td>• Consider low-dose prednisone (0.5-1 mg/kg/d) if intolerable or persistent</td>
</tr>
<tr>
<td></td>
<td>• Involve consultants as needed</td>
</tr>
<tr>
<td>3 or 4 (severe)</td>
<td>• Grade 3: Withhold and initiate high-dose prednisone (1-2 mg/kg/d)</td>
</tr>
<tr>
<td></td>
<td>• Grade 4 (other than endocrine): Permanently discontinue therapy</td>
</tr>
<tr>
<td></td>
<td>• Refer/involve consultants</td>
</tr>
<tr>
<td></td>
<td>• At resolution, gradually taper off immunosuppression</td>
</tr>
</tbody>
</table>

- Dose adjustment is not recommended; instead, withhold treatment until resolution to grade ≤1
- Management of specific irAEs associated with each ICI should be reviewed in prescribing information

• Frequent sites of irAE are skin, GI tract, and lungs, but occur anywhere
• Assess for irAE at each cycle for the first 3 months, including laboratory tests
  – Thyroid tests every cycle for first 3 months, then every 2-3 cycles
• Early detection and proper management are key to successful outcomes: maintain high level of suspicion that reactions are treatment-related
• Maintain low threshold for systemic steroids if reaction is concerning
• Educate patients about toxicities and to contact oncology team if any symptoms develop, if they are admitted to hospital, or if they begin any new medications

Subsequent Therapy for Rare NRTK Fusion-Positive mGC: Tumor-Agnostic Entrectinib and Larotrectinib

**Entrectinib**
- Oral ROS1, ALK, and NTRK inhibitor
- Pooled data from phase 1 basket trials in NRTK+ metastatic GI cancers (n = 12/74)
- Primary outcome: ORR = 50.0% (all, PR)
- Median PFS: 7.1 (95% CI: 2.4-16) months
- Median OS: 16.0 (95% CI: 11.2-NE) months
- Grade ≥3 AEs: lung infections, fatigue, cognitive effects, dyspnea, syncope, pleural effusion, pulmonary embolism
- Warnings: Heart failure, CNS effects, fracture risk, hepatotoxicity, hyperuricemia, QT prolongation, vision disorders; embryo-fetal effects

**Larotrectinib**
- Selective oral TRK inhibitor
- Pooled analysis from phase 1/2 basket trials in NTRK+ metastatic solid tumors (N = 175)
- Primary outcome: ORR = 78% (19% CR)
- Median DoR: NE; 12-month DoR rate: 81%
- Median PFS: 36.8 (95% CI: 25.7-NE)
- Median OS not reached; 12-month OS rate: 90%
- Grade 3 AEs: anemia, neutrophil decrease, increase in liver enzymes and weight
- Warnings: Neurotoxicity, hepatotoxicity, embryo-fetal effects

CNS = central nervous system; NE = not estimable.
Investigational Agents for HER2 Amplification: Trastuzumab Deruxtecan (T-DXd) and Trastuzumab Emtansine (T-DM1)

T-DXd
- An antibody-drug conjugate combining trastuzumab and cytotoxic deruxtecan
- Open-label, phase 2 trial
  - Progression on ≥2 prior therapies
  - Previous trastuzumab allowed
- Side effects related to T-DXd
  - Interstitial lung disease in 12 patients, including 3 grade ≥3

T-DM1
- No OS benefit with T-DM1 vs taxane in phase 3 GATSBY

<table>
<thead>
<tr>
<th>Outcome</th>
<th>T-DXd</th>
<th>Chemotherapy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, %</td>
<td>51</td>
<td>14</td>
</tr>
<tr>
<td>OS, months</td>
<td>12.5</td>
<td>8.4</td>
</tr>
<tr>
<td>HR for death (95% CI)</td>
<td>0.59 (0.39-0.88)</td>
<td>P = 0.01</td>
</tr>
<tr>
<td>Grade ≥3 neutropenia</td>
<td>51%</td>
<td>24%</td>
</tr>
<tr>
<td>Grade ≥3 anemia</td>
<td>38%</td>
<td>23%</td>
</tr>
<tr>
<td>Grade ≥3 leukopenia</td>
<td>21%</td>
<td>11%</td>
</tr>
</tbody>
</table>

*Physician’s choice of standard chemotherapy regimens.
Molecular-Based Treatment Expands Options for Individualizing Therapy in Subsequent Lines

- **HER2 amplification**
  - Trastuzumab, if not used in initial therapy
  - Potential for trastuzumab deruxtecan
- **MSI-H/dMMR: pembrolizumab or nivolumab (if not used in prior therapy)**
- **PD-L1 expression: pembrolizumab or nivolumab (if not used in prior therapy)**
- **TMB-H after progression on other, non-ICI options: pembrolizumab**
- **NTRK fusion: entrectinib or larotrectinib after progression on other options**

**Third-Line and Beyond mGC: Trifluridine/Tipiracil**

**Description and Efficacy**
- Combination with tipiracil enhances trifluridine absorption
- Phase 3 TAGS study vs placebo found improved OS and PFS with trifluridine/tipiracil in mGC after ≥2 prior therapies
- Subgroup analysis found benefit across most subgroups, including gastrectomy patients
- Treatment stabilizes cancer growth and prolongs maintenance of baseline ECOG vs placebo
- Appropriate for previously treated patients with ECOG PS 0/1

**Toxicity Management**
- Grade ≥3 neutropenia (38%) and anemia (18%)
- Grade ≥3 GI events: ≤3%
- Monitor for hematologic events, especially patients with history of neutropenia/anemia
  - Weekly or biweekly cycles 1 and 2; then monthly
  - If hematologic event occurs, hold treatment until ANC/platelet recovery
  - Reintroduce at lower (5 mg/m²) dose
- Educate patients: keep antidiarrheals on hand; maintain fluid intake; when to call office for AE

• Identify patients at risk for nonadherence and develop a triage strategy
• Toxicity management is key to ensuring timely delivery of the planned dose
  – Educate patients, caregivers, and all support staff about possible treatment toxicities and preventive strategies
  – Reassure patients that toxicities will decrease over time
• Provide tools and strategies to lessen confusion about dosing schedules
  – Calendar or electronic reminders
• Make use of digital tools such as patient portals
  – Emphasize when to call the office rather than email or text
✓ Test all patients with advanced GC for HER2 amplification, dMMR/MSI, and PD-L1 before starting therapy
✓ Consider the role and benefit of immunotherapy in MSI-H or PD-L1+ advanced or metastatic disease
✓ Be alert to the type and potential for irAEs in patients receiving immunotherapy and educate patients on symptoms
✓ Molecular profiling can help individualize treatment in subsequent lines; some therapies warrant consideration earlier in sequence as evidence of benefit evolves
✓ Educate patients and their caregivers about the importance of adherence to oral therapies in optimizing treatment outcomes

PCE Promotes Practice Change
Applying Recent Advances in Metastatic Colorectal Cancer to Improving Patient Care
Learning Objectives

• Summarize key mutations and biomarkers that can impact metastatic colorectal cancer (mCRC) progression and management
• Identify novel and emerging therapies and strategies to optimize treatment of patients with mCRC
• Implement strategies to recognize and manage toxicities of novel therapies for mCRC
Epidemiology

- 4th most frequently diagnosed cancer and 2nd leading cause of cancer death in the US
  - 2-year survival for mCRC has improved from 21% to 31% since the mid-1990s
- Overall incidence and mortality have decreased, but among patients aged <50 years:
  - Incidence increased 2.2% annually 2012-2016
  - Mortality increased 1.3% annually 2004-2017
- Incidence rates for colon/rectal cancers expected to increase markedly for patients aged 20 to 34 years by 2030
- USPSTF updated screening recommendation to start screening patients for CRC at age 45

53,200 deaths from mCRC expected in 2020

Number of New Cases and Deaths per 100,000 (2000-2017)

USPSTF = United States Preventive Services Task Force.
Case Study: Stephen

- 62-year-old insurance executive presents with persistent constipation and abdominal cramps/pain; his primary care clinician ruled out IBS and IBD
- Assessment reveals:
  - Right-sided primary tumor in colon
  - Metastatic lesions in lungs and liver
- Not a candidate for surgery
- Biopsy of primary and liver metastases shows adenocarcinoma
- Molecular testing shows:
  - Negative for: KRAS mutation, HER2 amplification, and NTRK fusion
  - Positive for: BRAF V600E mutation
  - MSI-H/dMMR

IBD = inflammatory bowel disease; IBS = irritable bowel syndrome.
Recommendations for Molecular Testing of mCRC

**Molecular Features**

- **RAS** mutations
- **MSI/dMMR**
- **Others**
  - **BRAF V600E**
  - **NTRK** fusions
  - **HER2** amplification
- Routine **EGFR** testing **not** recommended

**Recommended Testing**

- Use NGS certified for suspected mutation (e.g., **MSI/dMMR**, **TMB**, **RAS**)
- IHC or FISH for **HER2** amplification if not done with NGS
- PCR for other mutations if not done with NGS

**Note:**

- TMB using NGS is an emerging biomarker for PD-1/PD-L1 therapies
- Not part of current NCCN Guidelines

---

**EGFR** = epidermal growth factor receptor; **FISH** = fluorescence in situ hybridization; **IHC** = immunohistochemistry; **NCCN** = National Comprehensive Cancer Network; **NGS** = next-generation sequencing; **PCR** = polymerase chain reaction; **TMB** = tumor mutational burden.

**HER2 amplification**: rates higher in tumors with wild-type *RAS* or *BRAF*

*RAS* mutations predict lack of response to EGFR therapy

*NTRK* fusions very rare, but may be present in 30% of MSI-H patients

---

**Frequency of Mutations in mCRC**

- **HER2 amplification**: rates higher in tumors with wild-type *RAS* or *BRAF*
- *RAS* mutations predict lack of response to EGFR therapy
- *NTRK* fusions very rare, but may be present in 30% of MSI-H patients

---

Clinical Characteristics That Affect Prognosis

- Stage at diagnosis
- Performance status, as patients with inoperable disease will require lifetime treatment
- Right-sidedness associated with poor prognosis
- Risk factors (history, IBD, T2DM, smoking, alcohol, obesity)
- Prognostic molecular features

T2DM = type 2 diabetes.
Individualizing Therapy: Primary Tumor Sidedness

- Prognostic factor independent of molecular features and tumor burden; further study needed to identify mechanisms for sidedness as prognostic factor
- Left-sided tumors significantly associated with improved OS, regardless of biologic treatment
- Unless MSI-H, right-sided tumors are associated with poor prognosis
  - More likely to have *KRAS* or *BRAF* mutations and to be MSI-H
  - Optimal treatment yet to be defined
  - Patients fared worse with anti-EGFR therapy in combination with chemotherapy
  - Sidedness of most importance in treatment-naïve stage IV patients

OS = overall survival.
Universal MSI/dMMR testing is recommended in newly diagnosed colorectal cancer
  – Use PCR or validated NGS panel for MSI level
  – Use IHC for dMMR: a positive result should indicate loss of MMR gene expression
• All patients with mCRC should have tumor tissue tested for RAS (KRAS and NRAS) and BRAF mutations individually or as part of an NGS panel
  – Positive result contraindicates EGFR therapy
• Others
  – HER2 amplification using NGS, IHC, or FISH
  – NTRK fusion: rare, test only those with wild-type RAS, wild-type BRAF
  – Consider TMB assessment if using validated NGS

MMR = mismatch repair; MSI = microsatellite instability.
**Considerations for Treatment Choice**

<table>
<thead>
<tr>
<th>Clinical Status</th>
<th>Molecular Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior treatment (if any)</td>
<td><strong>RAS</strong></td>
</tr>
<tr>
<td>Comorbidities</td>
<td><strong>TMB</strong></td>
</tr>
<tr>
<td>Performance status</td>
<td><strong>BRAF</strong></td>
</tr>
<tr>
<td>Age</td>
<td><strong>NTRK</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor Characteristics</th>
<th><strong>MSI-H</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor burden</td>
<td><strong>HER2</strong></td>
</tr>
<tr>
<td>Resectability</td>
<td></td>
</tr>
<tr>
<td>Location/sidedness</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient-Centered</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of life</td>
<td></td>
</tr>
<tr>
<td>Treatment toxicities</td>
<td></td>
</tr>
<tr>
<td>Adherence</td>
<td></td>
</tr>
<tr>
<td>Psychosocial factors</td>
<td></td>
</tr>
</tbody>
</table>

Preferred Initial Therapy of mCRC: Patients Appropriate for Intensive Therapy

Patients appropriate for intensive therapy: good tolerance for therapy where a high tumor response rate is potentially beneficial

<table>
<thead>
<tr>
<th>Most Patients</th>
<th>Patients With Wild-type RAS/BRAF*</th>
<th>MSI-H/dMMR Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy ± bevacizumab</td>
<td>Chemotherapy ± EGFR therapy (left-sided primary only) or bevacizumab**</td>
<td>Immunotherapy</td>
</tr>
<tr>
<td>• FOLFOX</td>
<td>• Cetuximab</td>
<td>• Pembrolizumab</td>
</tr>
<tr>
<td>• FOLFIRI</td>
<td>• Panitumumab</td>
<td></td>
</tr>
</tbody>
</table>

For patients not appropriate for intensive therapy
- Capecitabine or 5-FU/leucovorin (± bevacizumab**)
- Wild-type RAS/BRAF: Single-agent cetuximab or panitumumab
- HER2+, WT RAS/BRAF: Trastuzumab** + pertuzumab
- MSI-H/dMMR: Pembrolizumab, nivolumab, or nivolumab ± ipilimumab

*In colon cancer, for left-sided tumors only; **FDA-approved biosimilar may be substituted.
FOLFIRI = leucovorin calcium [folinic acid] + 5-fluorouracil + irinotecan; FOLFOX = leucovorin calcium [folinic acid] + 5-fluorouracil + oxaliplatin.
Individualizing Therapy in mCRC: MSI-H/dMMR

• Associated with high mutational burden
  – MMR system identifies and removes DNA errors
  – dMMR causes unrepaired, repetitive DNA sequences ("microsatellite" regions)
• MSI-H/dMMR phenotype predictive of response to ICI independent of PD-1/PD-L1
• Clinical relevance
  – Genetic assessment of Lynch syndrome in younger adults
  – Predictive of chemotherapy resistance
  – Treat MSI-H/dMMR patients with pembrolizumab or nivolumab
• Universal testing recommended; recent survey found ~70% compliance with recommendation among US physicians treating patients with CRC

ICI = immune checkpoint inhibitor.
Initial Therapy of MSI-H/dMMR mCRC: Pembrolizumab Improved PFS vs Standard of Care

- Phase 3 KEYNOTE-177
- Random assignment
  - Pembrolizumab (n = 153)
  - Recommended platinum-based chemotherapy* (n = 154)
- Primary outcome: PFS
- Median follow-up: 28 months
- Fewer grade ≥3 adverse events (AEs) with pembrolizumab (22% vs 66%)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pembrolizumab</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months</td>
<td>16.5</td>
<td>8.2</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.60 (0.45-0.80)</td>
<td>P = 0.0002</td>
</tr>
<tr>
<td>12-month PFS, %</td>
<td>55.3</td>
<td>37.3</td>
</tr>
<tr>
<td>24-month PFS, %</td>
<td>48.3</td>
<td>18.6</td>
</tr>
</tbody>
</table>

*FOLFIRI ± bevacizumab or cetuximab; PFS = progression-free survival.
Initial Therapy of MSI-H/dMMR mCRC: Nivolumab + Low-Dose Ipilimumab

- Phase 2 CheckMate-142 study (ongoing)
  - Previously established efficacy in subsequent therapy, 12-month PFS = 71%
  - Updated analysis of patients not previously treated for metastatic disease (N = 45)
  - Primary outcome: ORR
- Nivolumab 3 mg + ipilimumab 1 mg
- Responses seen across subgroups of age, BRAF/KRAS mutation status

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Nivolumab + Ipilimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up</td>
<td>19.9 months</td>
</tr>
<tr>
<td>ORR (95% CI)</td>
<td>60% (44-74)</td>
</tr>
<tr>
<td>DCR</td>
<td>84%</td>
</tr>
<tr>
<td>Grade 3-4 AE</td>
<td>16%</td>
</tr>
</tbody>
</table>

ORR = objective response rate (complete response [CR] + partial response [PR]); DCR = disease control rate.
Tumor Mutational Burden: Emerging Biomarker for ICI

- TMB is independent biomarker for ICI response across several solid tumor types
  - PD-L1 expression does not always correlate with ICI response
  - Composite of TMB-H and high PD-L1 improves chance of good response
- TMB may be result of impaired DNA repair mechanisms or external factors that damage DNA
- Defined as the number of coding mutations per analyzed tumor genomic region
  - Can be performed on tissue or blood using available NGS platforms
- Standardized thresholds and quantification methods are needed to optimize use of TMB to guide treatment

Immunotherapy in mCRC

- Recommended for treatment-naïve and previously treated patients with MSI-H/dMMR molecular profile
- FDA indications
  - Pembrolizumab (PD-1 inhibitor)
    - Initial therapy for patients with MSI-H/dMMR unresectable mCRC
    - Subsequent therapy for patients with high TMB
  - Nivolumab (PD-1 inhibitor)
    - Subsequent therapy for patients with MSI-H/dMMR mCRC
      - Monotherapy or in combination with ipilimumab (CTLA4 inhibitor)
- Role for PD-L1 inhibitors (atezolizumab, avelumab, durvalumab) uncertain

Immunotherapy With Pembrolizumab Improves Survival vs Chemotherapy in MSI-H/dMMR mCRC

- MSI-H/dMMR is associated with chemotherapy-refractory disease in mCRC
- KEYNOTE-177 demonstrated that initial therapy with pembrolizumab vs recommended chemotherapy improves PFS and is associated with lower rate of grade ≥3 AEs
- NCCN now recommends pembrolizumab for initial therapy of MSI-H/dMMR disease in patients appropriate for intensive therapy
  - Pembrolizumab, nivolumab, or nivolumab + ipilimumab also are recommended initial therapy for patients not appropriate for intensive therapy and as subsequent therapy in MSI-H/dMMR or PD-L1
You prescribe Stephen pembrolizumab and tell him that he can receive the treatment infusion either 200 mg every 3 weeks or 400 mg every 6 weeks.

You both think less-frequent visits to the infusion center will be helpful during the ongoing pandemic, and he begins treatment with 400 mg every 6 weeks.

About 10 days after his second infusion, he calls you to report a bumpy rash on his abdomen.

You have him come into the office and determine that the rash is of moderate severity (grade 2).
Spectrum of Immune-Related Adverse Events

- Currently, no way to predict who will develop an irAE, which differs from AEs seen with other therapies
- Onset 2 to 3 months after starting therapy, but can occur for up to 2 years after therapy completion
- Ask patients to contact oncology team if any symptoms develop, if they are admitted to hospital, or if they begin any new medications
  - Severe fatigue, headache, cough, dyspnea, chest pain, bloating, weight loss, severe muscle weakness/pain, bowel, vision, or mood changes
- If irAEs are suspected, conduct a complete work up, including lab tests, to rule out other causes

Frequent irAEs with ICIs

<table>
<thead>
<tr>
<th>GI Tract</th>
<th>Skin</th>
<th>Lungs</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Can occur anywhere in GI tract</td>
<td>• Presents as erythema multiforme minor or bullous dermatoses</td>
<td>• If pneumonitis is suspected, chest x-ray and pulse oximetry needed</td>
</tr>
<tr>
<td>• Clinical presentation similar to IBD, but rapid symptom development</td>
<td>• If mild, topical treatment and sun avoidance recommended • If affecting quality of life, consider withholding and initiating steroid</td>
<td>• Grade 1 may require withholding treatment if x-ray shows progression</td>
</tr>
<tr>
<td>• 5% to 10% may develop hepatotoxicity; assess LFTs regularly</td>
<td>• Potential for rare but serious SJS or TEN</td>
<td>• Systemic prednisone for grade ≥2</td>
</tr>
</tbody>
</table>

SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis.
## General Guide to Managing irAEs

<table>
<thead>
<tr>
<th>Severity</th>
<th>Recommended Management</th>
</tr>
</thead>
</table>
| 1 (mild) | • Symptomatic management  
           • Continue therapy (some may require withhold or d/c; eg, neurologic, cardiac)  
           • Immunosuppression not needed |
| 2 (mild to moderate) | • Symptomatic management  
                         • Consider withholding until resolve to grade ≤1  
                         • Consider low-dose prednisone (0.5-1 mg/kd/d) if intolerable or persistent  
                         • Involve consultants as needed |
| 3 or 4 (severe) | • Grade 3: Withhold and initiate high-dose prednisone (1-2 mg/kd/d)  
                       • Grade 4 (other than endocrine): Permanently discontinue therapy  
                       • Refer/involve consultants  
                       • At resolution, gradually taper off immunosuppression |

- Dose adjustment is not recommended; instead, withhold treatment until resolution to grade ≤1
- Management of specific irAEs associated with each ICI should be reviewed in prescribing information

## irAEs: Warnings and Precautions

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Warnings and Precautions for Immune-Mediated AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>Pneumonitis, colitis, hepatitis, adrenal insufficiency, hypophysitis, thyroid disorders, type 1 diabetes, nephritis, skin reactions (including SJS or TEN)</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Pneumonitis, colitis, hepatitis, adrenal insufficiency, hypophysitis, thyroid disorders, type 1 diabetes, nephritis/renal dysfunction, skin reactions, encephalitis</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>Severe and fatal immune reactions (hepatitis, colitis, skin reactions, endocrinopathies, etc)</td>
</tr>
</tbody>
</table>
Immunotherapy Is Associated With Unique Adverse Reactions Requiring Special Management

- Frequent irAE sites are skin, GI tract, and lungs
- Assess for irAE at each cycle for the first 3 months, including laboratory tests
- Thyroid tests every cycle for first 3 months, then every 2 to 3 cycles
- Early detection and proper management are key to successful outcomes: maintain high level of suspicion that reactions are treatment-related
- Maintain low threshold for systemic steroids if reaction is concerning
- Educate patients about toxicities and to contact oncology team if any symptoms develop, if they are admitted to hospital, or if they begin any new medications

Case Study (cont’d)

• Stephen’s rash responds to prednisone and he continues without treatment interruption
• He has had a good response to pembrolizumab, and has completed 15 cycles of treatment
• At his recent follow-up visit, imaging revealed disease progression and new metastases
Systemic therapy in mCRC shown to:
- Increase median survival in patients who did not respond to first-line treatment, especially with targeted agents + chemotherapy
- Improve median survival with increased lines of therapy

Nevertheless, patients with mCRC do not always receive later lines of therapy

## Preferred Subsequent Therapy Based on Molecular Profile

<table>
<thead>
<tr>
<th>RAS/BRAF WT</th>
<th>RAS WT/BRAF V600E</th>
<th>MSI-H/dMMR</th>
<th>HER2+</th>
<th>NTRK fusion</th>
</tr>
</thead>
</table>
| • EGFR-naïve patients only  
  • Chemotherapy + anti-EGFR | • Encorafenib + cetuximab  
  • Encorafenib + panitumumab | • ICI-naïve patients only  
  • Nivolumab ± ipilimumab  
  • Pembrolizumab | • Trastuzumab ± pertuzumab  
  • Trastuzumab ± lapatinib | • Entrectinib  
  • Larotrectinib |

- Patients without actionable mutations or MSI-H/dMMR should receive standard chemotherapy ± bevacizumab (preferred) or other VEGF inhibitor (ziv-aflibercept, ramucirumab)
- Type of chemotherapy dependent on previous regimen; retreatment after progression on a regimen is not recommended
- Patients who have progressed through all standard lines of therapy may receive regorafenib or trifluridine + tipiracil

VEGF = vascular endothelial growth factor.
**BRAF** V600E-Mutated mCRC: Phase 3 BEACON Study

- Patients who progressed after ≥1 prior therapy, random assignment:
  - Triplet therapy: encorafenib + binimetinib + cetuximab
  - Doublet: encorafenib + cetuximab
  - Irinotecan-based chemotherapy + cetuximab
- Either regimen significantly improved OS and ORR vs chemotherapy
- Grade ≥3 AE: 66% on triplet, 57% on doublet, 64% on chemotherapy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Triplet</th>
<th>Doublet</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months</td>
<td>9.3</td>
<td>9.3</td>
<td>5.9</td>
</tr>
<tr>
<td>HR (95% CI) vs Chemotherapy</td>
<td>0.60 (0.47-0.75)</td>
<td>0.61 (0.48-0.77)</td>
<td>—</td>
</tr>
</tbody>
</table>

HR = hazard ratio.
Investigational: Initial Therapy With Encorafenib Triplet

- Phase 2, single-arm ANCHOR study
- No prior systemic therapy for metastatic disease
- Intervention: encorafenib + binimetinib + cetuximab
- Primary endpoint: confirmed ORR
- Grade ≥3 AE: 68%
  - Diarrhea: 15%
  - Acute kidney injury: 12%
  - Anemia: 12%

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Encorafenib Triplet (N = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>50% (33.8-66.2)</td>
</tr>
<tr>
<td>PFS (95% CI)</td>
<td>4.9 months (4.4-8.1)</td>
</tr>
</tbody>
</table>

## Subsequent Therapy for \( \text{HER2} \) Amplification: Dual \( \text{HER2} \) Inhibition

<table>
<thead>
<tr>
<th>Trastuzumab + Pertuzumab</th>
<th>Trastuzumab + Oral Lapatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing phase 2a MyPathway study (N = 57)</strong></td>
<td><strong>Phase 2 HERACLES-A study (N = 32) in previously treated mCRC</strong></td>
</tr>
<tr>
<td><strong>Median 4 prior therapies for mCRC; median follow-up 10.6 months at time of report</strong></td>
<td><strong>At 82 months’ follow-up</strong></td>
</tr>
<tr>
<td><strong>Primary outcome: ORR = 32% (1 CR, 17 PR)</strong></td>
<td></td>
</tr>
</tbody>
</table>
  – ORR = 28%; 1 CR ongoing at 7 years |
| **CBR = 25%** |  
  – Median PFS = 4.7 (3.7-6.1) months |
| **Estimated median PFS = 2.9 (1.4-5.3) months** |  
  – Median OS = 10.0 (7.9-15.8) months |
| **Estimated median OS = 11.5 (7.7-NE) months** |  
  – CNS progression in 19% |
| **Grade ≥3 AE: 37%** | **No unexpected toxicities** |

CBR = clinical benefit rate (objective response or stable disease >4 months); CNS = central nervous system; NE = not estimable.
Investigational: Subsequent Therapy with Dual HER2 Targeting Using Oral Tucatinib

**Trastuzumab + Tucatinib**

- Ongoing phase 2 MOUNTAINEER study
- Patients with RAS wild-type, HER2+ mCRC (N = 22) and prior treatment with chemotherapy + anti-VEGF
- Primary outcome: ORR = 55%
- CBR = 64%
- Estimated median PFS = 6.2 (3.5-NE) months
- Estimated median OS = 17.3 (12.3-NE) months
- Grade ≥3 AE: 9% (4% grade 3 diarrhea)
### Investigational: mCRC With HER2 Amplification: ADCs

<table>
<thead>
<tr>
<th>Trastuzumab Deruxtecan*</th>
<th>T-DM1 + Pertuzumab*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combines trastuzumab and cytotoxic deruxtecan</td>
<td>Dual HER2 strategy with pertuzumab and T-DM1, (trastuzumab + cytotoxic emtansine)</td>
</tr>
<tr>
<td>DESTINY-CRC01 trial in previously treated HER2+ mCRC (N = 53 IHC confirmed HER2+)</td>
<td>Established efficacy in HER2+ breast cancer</td>
</tr>
<tr>
<td>Prior HER2 therapy allowed</td>
<td>Single-arm phase 2 HERACLES-B (N = 31)</td>
</tr>
<tr>
<td>Primary outcome:</td>
<td></td>
</tr>
<tr>
<td>– ORR = 45.3% (all HER2+)</td>
<td>– ORR = 9.7%</td>
</tr>
<tr>
<td>– ORR = 43.8% (previous HER2+ therapy)</td>
<td>– Did not achieve primary endpoint (≥30%)</td>
</tr>
<tr>
<td>DCR = 83.3%</td>
<td>DCR = 77.4%</td>
</tr>
<tr>
<td>Median PFS = 6.9 months</td>
<td>Median PFS = 4.1 months</td>
</tr>
<tr>
<td>Grade ≥3 AE: 61.5%; ≥10% neutropenia, anemia</td>
<td>Grade 3 AE: thrombocytopenia in 2 patients</td>
</tr>
</tbody>
</table>

---

Subsequent Therapy for *NRTK* Fusion: Tumor-Agnostic Entrectinib and Larotrectinib

<table>
<thead>
<tr>
<th><strong>Entrectinib</strong></th>
<th><strong>Larotrectinib</strong></th>
</tr>
</thead>
</table>
| • Oral *ROS1, ALK*, and *NTRK* inhibitor  
• Phase 1 basket trial in previously treated solid tumor metastatic disease  
  (N = 54; n = 4 with *NTRK* fusion-positive mCRC)  
• Primary outcome: ORR = 57% all patients;  
  25% in mCRC  
• Grade ≥3 AE: lung infections, fatigue, cognitive effects, dyspnea, syncope, pleural effusion, pulmonary embolism  
• Warnings: heart failure, CNS effects, fracture risk, hepatotoxicity, hyperuricemia, QT prolongation, vision disorders, embryo-fetal effects | • Selective oral *NTRK* inhibitor  
• Phase 1 basket trial in previously treated solid tumor metastatic disease  
  (N = 55; n = 4 with *NTRK* fusion-positive mCRC)  
• Primary outcome: ORR = 75% (all patients)  
• 1-year duration of response = 71%;  
  1-year PFS = 55%  
• Grade 3 AE: anemia, neutrophil decrease, increase in liver enzymes and weight  
• Warnings: neurotoxicity, hepatotoxicity, embryo-fetal effects |

Molecular-Based Treatment Expands Options for Individualizing Therapy

- **RAS/BRAF WT:** chemotherapy ± bevacizumab or EGFR inhibitor
- **MSI-H/dMMR:** pembrolizumab or nivolumab ± ipilimumab
- **HER2 amplification:** dual anti-HER2 therapy with trastuzumab
- **BRAF V600E:** BRAF inhibitor plus cetuximab or panitumumab
- **TMB-H after progression on other, non-ICI options:** pembrolizumab
- **NTRK fusion:** entrectinib or larotrectinib after progression on other options

Case Conclusion

- You start Stephen on encorafenib 300 mg orally once daily, and cetuximab infusion administered as a 400 mg/m$^2$ initial dose, followed by 250 mg/m$^2$ subsequent weekly dose.
- You counsel Stephen and his caregiver to alert the oncology team if symptoms of possible AEs develop.
## Description and Efficacy

- Blocks activity of kinases involved in angiogenesis, oncogenesis, tumor microenvironment
- Phase 3 CORRECT (N = 760): Improved survival vs placebo in heavily pretreated mCRC
  - OS (95% CI): 0.77 (0.64-0.94) \( P = 0.005 \)
    - 12-month OS rate: 24.3% vs 24.0%
  - PFS (95% CI): 0.49 (0.42-0.58) \( P < 0.0001 \)
  - Significant improvement in PFS regardless of baseline KRAS status

## Toxicity Management

- AEs tend to occur early and diminish over time
- Grade \( \geq 3 \) AE: 54% (HFSR, diarrhea, hypertension)
- Dose escalation strategy, based on results of ReDOS study, reduces grade \( \geq 3 \) AE
  - Start treatment at 80 mg/d and increase weekly by 40 mg to recommended 160 mg/d

### Minimizing HFSR

- Before starting, check condition of hands and feet; keep nails short; remove calluses
- During therapy, avoid pressure points, rubbing, pinching, friction on skin

HFSR = hand-foot skin reaction.
**Third-Line and Beyond for mCRC: Trifluridine/Tipiracil**

<table>
<thead>
<tr>
<th>Description and Efficacy</th>
<th>Toxicity Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Synergistic effect of 2 cytotoxic agents may have antitumor activity in 5-FU-resistant cancer cells</td>
<td>• Grade ≥3 neutropenia (38%) and anemia (18%)</td>
</tr>
<tr>
<td>• Phase 3 RECOURSE (N = 800): Improved survival vs placebo in refractory mCRC</td>
<td>• Grade ≥3 GI events: ≤3%</td>
</tr>
<tr>
<td>• OS (95% CI): 0.68 (0.58-0.81) ( P &lt;0.001 )</td>
<td>• Monitor for hematologic events, especially patients with history of neutropenia/anemia</td>
</tr>
<tr>
<td>– 12-month OS rate: 27% vs 18%</td>
<td>– Weekly or biweekly cycles 1 and 2; then monthly</td>
</tr>
<tr>
<td>• PFS (95% CI): 0.48 (0.41-0.57) ( P &lt;0.001 )</td>
<td>– If hematologic event occurs, hold treatment until ANC/platelet recovery</td>
</tr>
<tr>
<td>• Significant improvement in OS and PFS regardless of baseline KRAS status</td>
<td>– Reintroduce at lower (5 mg/m(^2)) dose</td>
</tr>
</tbody>
</table>

Both regorafenib and trifluridine/tipiracil significantly improve OS and PFS in patients who have progressed after all standard therapies.

No biomarkers identified to predict which patients will benefit from these agents; patients who progress on one can receive the other if clinically indicated.

Side effects vary between these interventions: consider patient factors, including ECOG PS, when choosing therapy.

ECOG PS = Eastern Cooperative Oncology Group Performance Status.
Identify patients at risk for nonadherence and develop a triage strategy
• Toxicity management is key to ensuring timely delivery of the planned dose
  – Educate patients, caregivers, and all support staff about possible treatment toxicities and preventive strategies
  – Reassure patients on regorafenib that toxicities will decrease over time
• Provide tools and strategies to lessen confusion about dosing schedules
  – Calendar or electronic reminders
• Make use of digital tools such as patient portals
  – Emphasize when to call the office rather than email or text
Test all patients with mCRC for RAS and BRAF mutations and MSI/dMMR; if using NGS, include HER2 amplification and NTRK fusion

Consider tumor characteristics, prior treatments, responses, and the patient's current status and goals when selecting therapy for mCRC

Pembrolizumab should be considered as initial therapy for MSI-H/dMMR metastatic disease

Be alert to the type and potential for irAEs in patients receiving immunotherapy and educate patients about symptoms

Use molecular profiling to guide treatment discussions and individualize therapy; some therapies warrant consideration in initial setting as evidence of benefit evolves

Choose later-line treatments based on patient factors and side effect profiles of therapy

Educate patients and their caregivers about the importance of adherence to oral therapies in optimizing treatment outcomes

PCE Promotes Practice Change