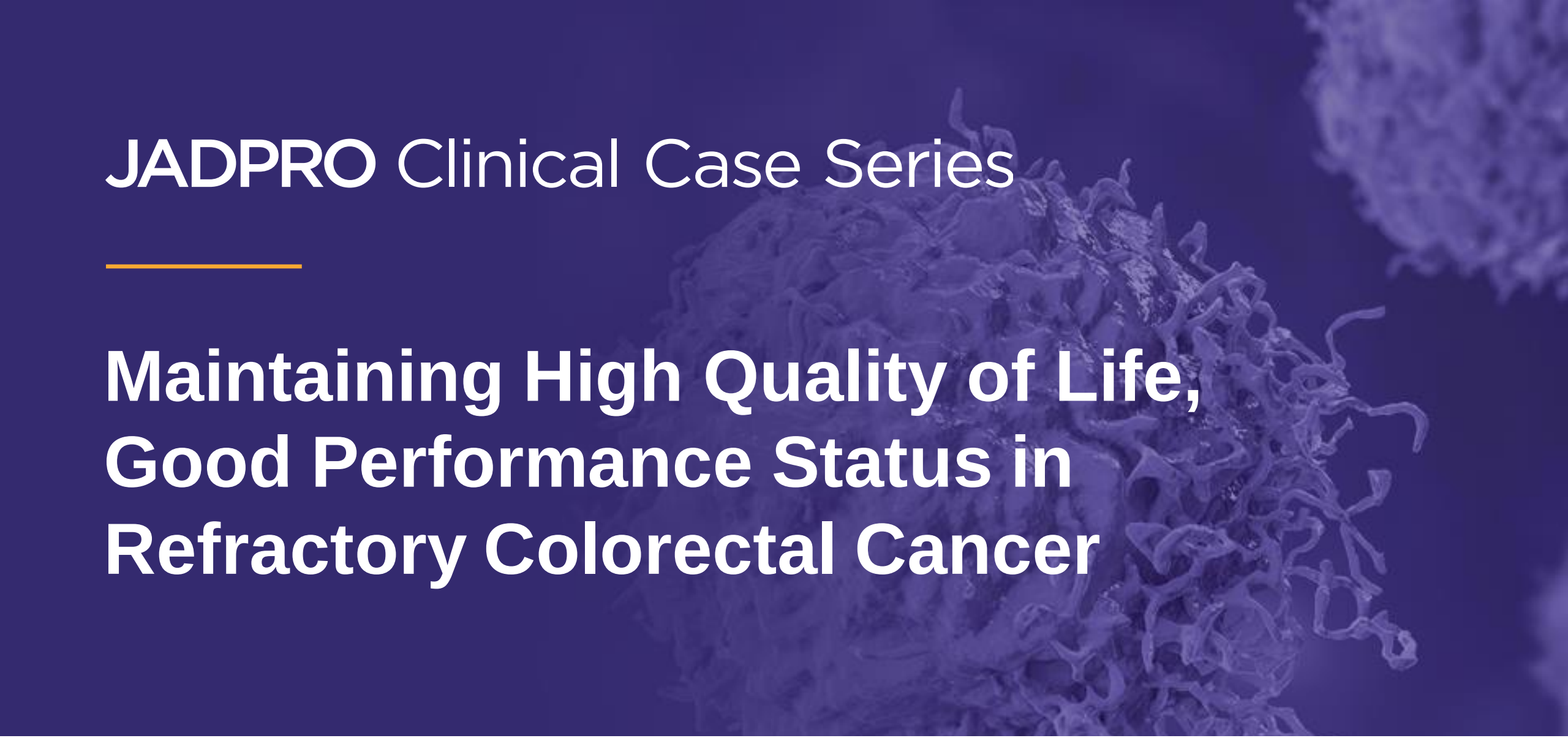
JADPRO Clinical Case Series

Maintaining High Quality of Life, Good Performance Status in Refractory Colorectal Cancer



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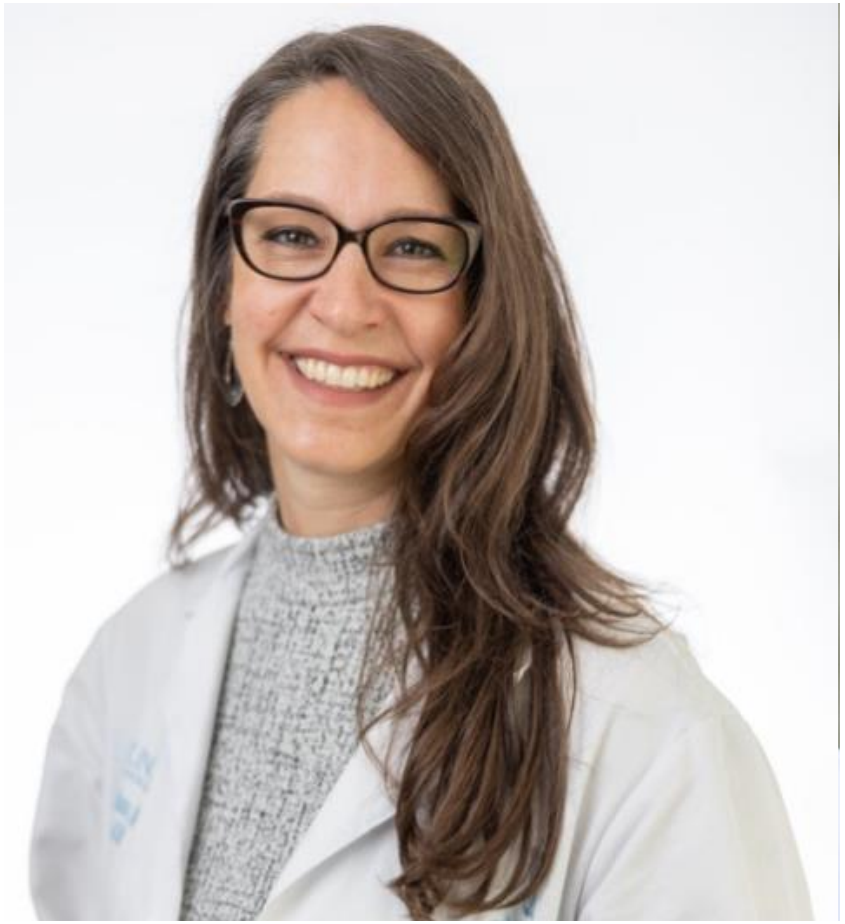

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Program Agenda

- Introduction: Colorectal cancer
- Overview of refractory colorectal cancer
- Principles of treatment
- SUNSHINE trial
- Clinical management and implications of treatment

Introduction: Colorectal Cancer

- Third most common cancer diagnosed in men and women in the United States
- Second leading cause of cancer-related deaths
- Median age of onset is 66 (65-74 years)
- Increasing incidence in younger adults
- 5-year survival significantly lower for advanced stages (16%)
- Decline in mortality

American Cancer Society. https://www.cancer.org/cancer/types/colon-rectal-cancer/about/key-statistics.html. Colorectal Cancer Alliance. https://www.ccalliance.org/colorectal-cancer-information/facts-and-statistics. NCI SEER Program. https://seer.cancer.gov/statfacts/html/colorect.html.

Introduction: Refractory Colorectal Cancer

- Resistance to standard therapy
- Challenges: Genetic mutations, tumor heterogeneity, resistance mechanisms
- Limited life expectancy

Case 1: Understanding Dosing

49-year-old man

Initial Presentation

- Abdominal pain, nausea, and vomiting

Initial workup

- Hemoglobin 7.6 g/dL
- CT abdominal/pelvis: Right-sided bladder mass with extension into distal ileum, concern for small bowel obstruction

Diagnostic laparoscopy with diverting ileostomy
Findings: Carcinomatosis

Moderately differentiated adenocarcinoma
Diagnosis: Primary colorectal cancer

Treatment: FOLFOXIRI (folinic acid, fluorouracil, oxaliplatin, and irinotecan)

Principles of Treatment

Clinical Parameters

- Burden of metastatic disease
- Potential for curative resection
- Age
- Performance status
- Comorbidities

Tumor/Molecular Parameters

- Extended RAS/RAF testing
- MSI status
- Sidedness of tumor (right vs left)
- Next-generation sequencing data

MSI, microsatellite instability

Case 1: Understanding Dosing (cont.)

49-year-old man

Treated with FOLFOXIRI to maximum response → OR

Right hemicolectomy, partial cystectomy
Findings: NO carcinomatosis

Diagnosis: Adenocarcinoma of cecum (ypT4bN2a)
MSS, KRAS mutant

Progressed through
first- and second-line therapy
Determined to have **refractory disease**

OR, operating room; MSS, microsatellite stable.

Polling Question: Case 1

In your practice, which of the following is the treatment of choice for patients with refractory metastatic colorectal cancer?

A. Combination trifluridine and tipiracil alone **21%**

B. Combination trifluridine and tipiracil with bevacizumab **57%**

C. Regorafenib **0%**

D. Rechallenge/recycle FOLFOX/FOLFIRI/FOLFOXIRI **14%**

E. Clinical trial **17%**

Principles of Treatment

First Line

- FOLFOX + targeted therapy

OR

- FOLFIRI + targeted therapy

Second Line

- FOLFIRI + targeted therapy

OR

- FOLFOX + targeted therapy

Third Line

- Trifluridine and tipiracil +/- bevacizumab

OR

- Regorafenib

OR

- Best supportive care

FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX, folinic acid, fluorouracil, and oxaliplatin.

NCCN Guidelines Colon Cancer, v3.2023. chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

Trifluridine and Tipiracil

- Combination therapy of two agents (can be given with or without bevacizumab)
- Administered orally
  - 35 mg/m^2 every 12 hours (1 hour after eating) on Days 1-5 and 8-12, every 28 days (max dose of 80 mg BID)
  - **Alternate dosing:** 35 mg/m^2 every 12 hours on Days 1–5, Days 15-19, every 28 days
- Initially approved as monotherapy
  - RECOURSE phase 3 trial

Case 1: Understanding Dosing

Patient Instructions for Combination Trifluridine and Tipiracil

BSA 2.0 = **70 mg** 2 times a day

- 15 mg: Take 2 tablets (30 mg total) by mouth 2 times a day with meals on Days 1-5 and Days 8-12 of each 28-day cycle.
- 20 mg: Take 2 tablets (40 mg total) by mouth 2 times a day with meals on Days 1-5 and Days 8-12 of each 28-day cycle.
- Take within 1 hour after completion of morning and evening meals.

BSA, body surface area.

Overview of SUNLIGHT Trial

- Phase 3 trial
- Efficacy and safety of trifluridine/tipiracil + bevacizumab vs trifluridine/tipiracil alone
- Primary end point: Overall survival (time from randomization to death from any cause)
- Secondary end points: Progression-free survival, objective response, disease control, quality of life, safety

Results of SUNLIGHT Trial

Trifluridine/tipiracil + Bevacizumab

Trifluridine/tipiracil Alone

Trifluridine/tipiracil + Bevacizumab		Trifluridine/tipiracil Alone
10.8 mo	**Primary endpoint** Overall survival	7.5 mo
5.6 mo	**Secondary endpoints** • Progression-free survival	2.4 mo
6.1%	• Objective response	1.2%
9.3 mo	• Median time to worsening ECOG status	6.3 mo

Results of SUNLIGHT Trial (cont.)

- Adverse events: 98% in each group
- Most commonly reported: Neutropenia, nausea, anemia
- Dose reductions: 16.3% in the trifluridine/tipiracil + bevacizumab group and 12.2% in the trifluridine/tipiracil alone group
- Dose delays 69.5% and 53.3%, respectively

Case 2: Maintain Performance Status

62-year-old man

Initial Presentation

- Cecal mass identified on colonoscopy screening
- Stage IIIB cecal adenocarcinoma (pT4aN1bM0)
- Adjuvant FOLFOX

Radiographic recurrence with new liver metastases

Pathology: Recurrent cecal adenocarcinoma
MSS, KRAS wild type

Progressed through first- and second-line therapy + HIPEC
Determined to have **refractory disease**

HIPEC, hyperthermic intraperitoneal chemotherapy

Case 2: Maintain Performance Status (cont.)

62-year-old man

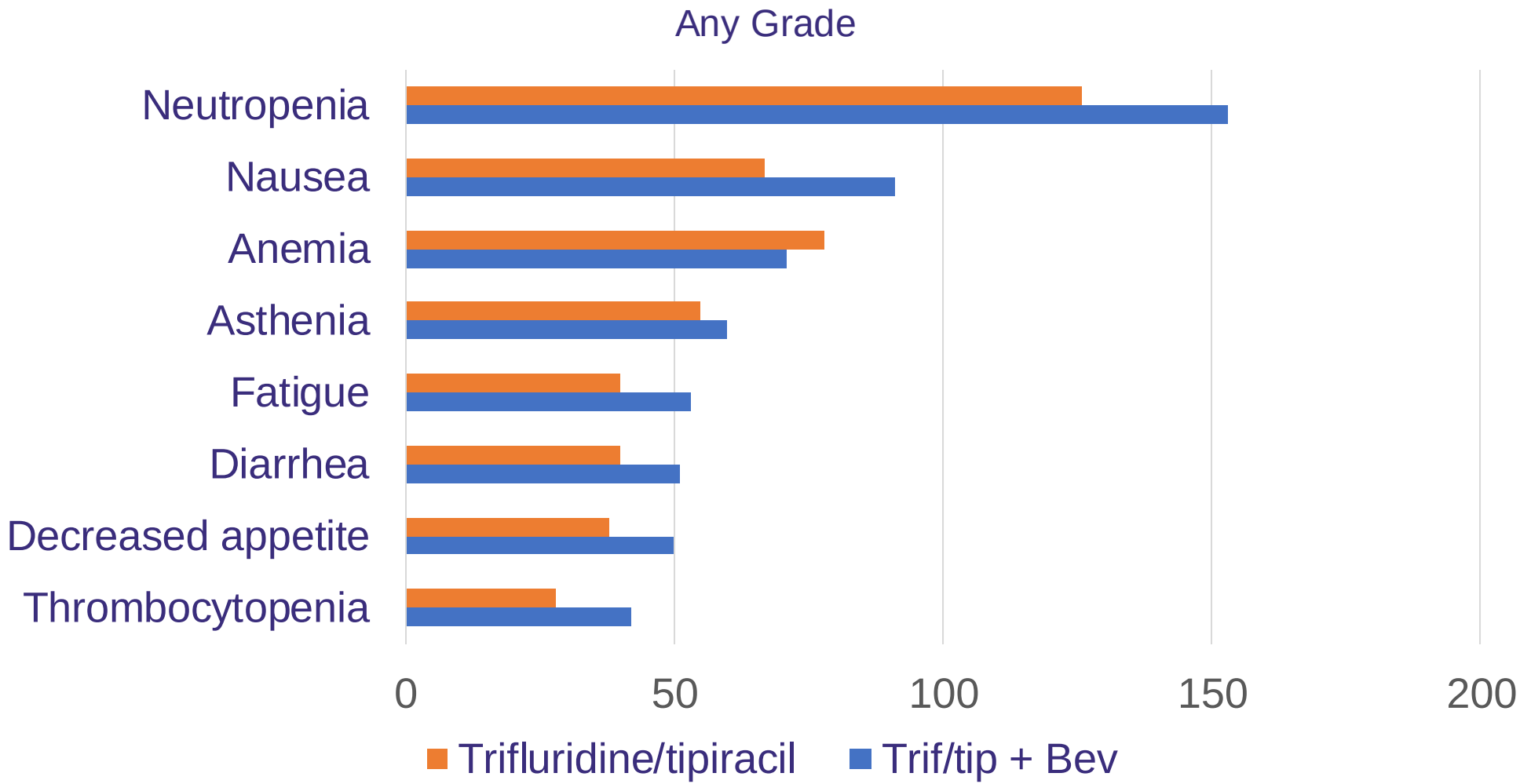
Recurrent, metastatic cecal adenocarcinoma
MSS, KRAS wild type

BSA 1.6 m^2
Treatment: Trifluridine/tipiracil 60 mg BID
Days 1-5, 8-12 every 28 days
+ bevacizumab

8 months of therapy, mild disease progression (< 20% RECIST)
ECOG 0

Maintain trifluridine/tipiracil + bevacizumab

SUNLIGHT: Adverse Events



Trifluridine/Tipiracil Monitoring Parameters

- CBC with differential prior to and on Day 15
- Treatment parameters
  - ANC ≥ 1,500/mm^3
  - Platelets ≥ 75,000/mm^3
  - Any grade 3 or 4 non-hematologic adverse reaction resolved or grade 0 or 1
- Dose reduction (by 5 mg/m^2/dose)
  - Febrile neutropenia
  - More than 1 week delay start of next cycle

ANC, absolute neutrophil count

Polling Question: Case 2

In your practice, how do you help your patients with oral medication adherence? (Check all that apply.)

A. Provide a medication schedule calendar **31%**

B. Schedule phone visits to assess adherence **22%**

C. Refer to a clinical pharmacist practitioner **6%**

D. Arrange for a nurse or nurse navigator to follow up with the patient by phone **16%**

E. Engage with the patient's caregiver **25%**

Bevacizumab

Common

- Cardiovascular: Hypertension, nosebleeds
  - Should not be initiated in patients with uncontrolled hypertension
- Genitourinary: Proteinuria
- Skin: Wound dehiscence
  - Do not use for at least 28 days before or after surgery

Rare

- Cardiovascular: Hemorrhage, thrombosis
- Gastrointestinal: GI perforation

Hypertension Management

1	2	3	4	5
Pre-hypertension (systolic BP 120-139 mm Hg or diastolic BP 80-89 mm Hg)	Stage 1 hypertension (systolic BP 140-159 mm Hg or diastolic BP 90-99 mm Hg); medical intervention indicated; recurrent or persistent (≥ 24 hours); symptomatic increase by > 20 mm Hg (diastolic) or to > 140/90 mm Hg if previously WNL; monotherapy indicated	Stage 2 hypertension (systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated	Death

Medication Management

- Angiotensin-converting enzyme (ACE) inhibitor
- Angiotensin receptor blocker (ARB)
- Calcium channel blocker

CTCAE, Common Terminology Criteria for Adverse Events

www.evs.nci.hih.gov

Proteinuria Management

- Measurement of urine protein is convenient and reliable
- Urine protein ≥ 2: Further evaluate with 24-hour urine collection
- Suspend therapy for proteinuria ≥ 2 g/24 hours; may resume when it is < 2 g/24 hours
- Clinical significance: Renal damage and cardiovascular risk
- Preventive measures
  - Optimal control of hypertension
  - Use of ACE inhibitors

Case 3: Quality of Life

53-year-old woman

Initial Presentation

- Iron deficiency anemia
- Stage IV ascending colon adenocarcinoma
- FOLFOXIRI + bevacizumab

Metastatic disease to liver and peritoneum

MSS, KRAS mutant

Progressed through first- and second-line therapy, declined HIPEC
Determined to have **refractory disease**

Case 3: Quality of Life (cont.)

53-year-old woman

Stage IV ascending colon adenocarcinoma

MSS, KRAS mutant

BSA 2.0 m^2

Treatment: Trifluridine/tipiracil 70 mg BID
Days 1-5, 8-12 every 28 days
+ Bevacizumab

- Cycle 1: Grade 2 neutropenia
- Cycle 2: Grade 4 neutropenia, grade 2 thrombocytopenia, grade 3 anemia

Trifluridine/tipiracil 50 mg BID
Days 1-5 every 14 days
+ bevacizumab

Satake H, et al., 2020

Polling Question: Case 3

In your practice, which of the following is the most significant driving factor for therapeutic selection for a patient like the one in this case?

A. Cost **10%**

B. Quality of life **80%**

C. Extension of overall survival **10%**

D. Other **0%**

Clinical Pearls

- The SUNLIGHT trial provides assurance that trifluridine/tipiracil + bevacizumab provides clinically meaningful benefit for refractory colorectal cancer, regardless of RAS status.
- Safety and tolerability of trifluridine/tipiracil + bevacizumab is manageable.
- Engagement of a multimodality approach can improve adherence given a complex dosing and treatment schedule.

Q & A

Please type your questions for Tammy Triglianos
into the **question box**.

Thank You