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MARCH 2026

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AVAHO

The Association of VA Hematology/Oncology (AVAHO), a nonprofit organization, provides a forum for interaction among VA hematology/oncology staff to enhance professional careers and improve patient care. AVAHO provides opportunities for networking, strengthening educational activities, and improving research capabilities among VA hematology/oncology professionals. Membership is extended to individuals interested in the organizational goals.

AUDITED BY ALLIANCE FOR AUDITED MEDIA

AMM Association of Medical Media

1L aRCC

CABOMETYX® (cabozantinib) tablets + OPDIVO® (nivolumab)

#1 PRESCRIBED TKI+IO COMBINATION IN 1L aRCC

Based on IQVIA BrandImpact data as of September 2025. Subject to change without notice.[1]

EFFICACY IN BALANCE

CABOMETYX + OPDIVO brings together efficacy, safety, and tolerability data for your 1L aRCC patients[2]

A BALANCE OF DATA*

A 1L aRCC treatment that offers a balance of data:

superior OS, safety and tolerability, and patient-reported quality of life[2-4] *

*Superior OS vs sunitinib in patients with previously untreated aRCC. Primary analysis OS results: 40% reduction in risk of death with CABOMETYX + OPDIVO vs sunitinib (HR=0.60; 98.89% CI: 0.40-0.89; *P*=0.001); median OS was not reached in either arm. The primary endpoint was PFS, and secondary endpoints included OS, ORR, and safety. Quality of life was evaluated as an exploratory endpoint using the FKSI-19 scale, and the clinical significance is unknown.[2,3]

Explore the balance of data

1L=first-line; aRCC=advanced renal cell carcinoma; CI=confidence interval; FKSI-19=Functional Assessment of Cancer Therapy-Kidney Symptom Index 19; HR=hazard ratio; IO=immunotherapy; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; TKI=tyrosine kinase inhibitor.

INDICATION

CABOMETYX® (cabozantinib), in combination with nivolumab, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

Hemorrhage: CABOMETYX can cause severe and fatal hemorrhages. The incidence of Grade 3-5 hemorrhagic events was 5% in CABOMETYX patients in RCC, HCC, and DTC studies. Discontinue CABOMETYX for Grade 3-4 hemorrhage and before surgery. Do not administer to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

Perforations and Fistulas: Fistulas, including fatal cases, and gastrointestinal (GI) perforations, including fatal cases, each occurred in 1% of CABOMETYX patients. Monitor for signs and symptoms, and discontinue CABOMETYX in patients with Grade 4 fistulas or GI perforation.

Thromboembolic Events: CABOMETYX can cause arterial or venous thromboembolic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism in 2% of CABOMETYX patients. Fatal thrombotic events have occurred. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events.

Hypertension and Hypertensive Crisis: CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension was reported in 37% (16% Grade 3 and <1% Grade 4) of CABOMETYX patients. In CABINET (n=195), hypertension occurred in 65% (26% Grade 3) of CABOMETYX patients. Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled; when controlled, resume at a reduced dose. Permanently discontinue CABOMETYX for severe hypertension that cannot be controlled with antihypertensive therapy or for hypertensive crisis.

Cardiac Failure: CABOMETYX can cause severe and fatal cardiac failure. Cardiac failure occurred in 0.5% of patients treated with CABOMETYX as a single agent, including fatal cardiac failure in 0.1% of patients. Consider baseline and periodic evaluations of left ventricular ejection fraction. Monitor for signs and symptoms of cardiovascular events. Withhold and resume at a reduced dose upon recovery or permanently discontinue depending on the severity.

Please see additional Important Safety Information and Brief Summary of the Prescribing Information for CABOMETYX on the following pages.

Superior PFS and ORR results in the primary analysis[2]

Primary analysis results in the ITT population
Median follow-up time of 18.1 months; range: 10.6-30.6 months[3]

Primary endpoint, assessed by BICR
P **Double median PFS[2]**
16.6 months with CABOMETYX + OPDIVO
(95% CI: 12.5-24.9, n=323)

vs

8.3 months with sunitinib (95% CI: 7.0-9.7, n=328)
HR=0.51 (95% CI: 0.41-0.64; *P*<0.0001)

Secondary endpoint, assessed by BICR
P **Double ORR[2]**
55.7% with CABOMETYX + OPDIVO
(95% CI: 50.1-61.2; n=323)
CR: 8% (n=26/323); PR: 48% (n=154/323)

vs

27.1% with sunitinib (95% CI: 22.4-32.3; n=328);
CR: 4.6% (n=15/328); PR: 23% (n=74/328) (*P*<0.0001)

5-year minimum follow-up analysis
Median follow-up time of 67.6 months; range: 60.2-80.2 months[5]

Primary endpoint, assessed by BICR
5Y **Median PFS[5]**
16.4 months with CABOMETYX + OPDIVO
(95% CI: 12.5-19.3; n=323)

vs

8.3 months with sunitinib (95% CI: 7.0-9.7; n=328)
HR=0.58 (95% CI: 0.49-0.70)

Secondary endpoint, assessed by BICR
5Y **ORR[5]**
55.7% with CABOMETYX + OPDIVO
(95% CI: 50.1-61.2; n=323)
CR: 13.9% (n=45/323); PR: 41.8% (n=135/323)

vs

27.4% with sunitinib (95% CI: 22.7-32.6; n=328);
CR: 4.6% (n=15/328); PR: 22.9% (n=75/328)

No formal statistical testing was conducted at the time of the updated analysis.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) PREFERRED OPTION[6]

Cabozantinib (CABOMETYX) + nivolumab (OPDIVO) was the first TKI + IO regimen with an NCCN recommendation in both clear-cell and non–clear-cell aRCC

NCCN CATEGORY 1, PREFERRED OPTION IN CLEAR-CELL RCC

- **Category 1**, preferred option across all risk groups in 1L clear-cell RCC
- NCCN Category 1: Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate

NCCN PREFERRED OPTION IN NON–CLEAR-CELL RCC

- **Category 2A**, preferred option in non–clear-cell RCC
- NCCN Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate

NCCN makes no representations or warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

ITT=intent to treat.

IMPORTANT SAFETY INFORMATION (cont'd)
WARNINGS AND PRECAUTIONS

Diarrhea: CABOMETYX can cause diarrhea and it occurred in 62% (10% Grade 3) of treated patients. Monitor and manage patients using antidiarrheals as indicated. Withhold CABOMETYX until improvement to ≤ Grade 1; resume at a reduced dose.

Palmar-Plantar Erythrodysesthesia (PPE): CABOMETYX can cause PPE and it occurred in 45% of treated patients (13% Grade 3). Withhold CABOMETYX until PPE resolves or decreases to Grade 1 and resume at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

Hepatotoxicity: CABOMETYX in combination with nivolumab in RCC can cause hepatic toxicity with higher frequencies of Grades 3 and 4 ALT and AST elevations compared to CABOMETYX alone. With the combination of CABOMETYX and nivolumab, Grades 3 and 4 increased ALT or AST were seen in 11% of patients. Monitor liver enzymes before initiation of treatment and periodically. Consider more frequent monitoring as compared to when the drugs are administered as single agents. Consider withholding CABOMETYX and/or nivolumab, initiating corticosteroid therapy, and/or permanently discontinuing the combination for severe or life-threatening hepatotoxicity.

Adrenal Insufficiency: CABOMETYX in combination with nivolumab can cause primary or secondary adrenal insufficiency. Adrenal insufficiency occurred in 4.7% (15/320) of patients with RCC who received CABOMETYX with nivolumab, including Grade 3 (2.2%), and Grade 2 (1.9%) adverse reactions. Withhold CABOMETYX and/or nivolumab and resume CABOMETYX at a reduced dose depending on severity.

Proteinuria: Proteinuria was observed in 8% of CABOMETYX patients. Monitor urine protein regularly during CABOMETYX treatment. For Grade 2 or 3 proteinuria, withhold CABOMETYX until improvement to ≤ Grade 1 proteinuria; resume CABOMETYX at a reduced dose. Discontinue CABOMETYX in patients who develop nephrotic syndrome.

Osteonecrosis of the Jaw (ONJ): CABOMETYX can cause ONJ and it occurred in <1% of treated patients. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to scheduled dental surgery or invasive dental procedures. Withhold CABOMETYX for development of ONJ until complete resolution; resume at a reduced dose.

Please see additional Important Safety Information throughout and Brief Summary of the Prescribing Information for CABOMETYX on the following pages.

Superior OS outcomes in the primary analysis[2]

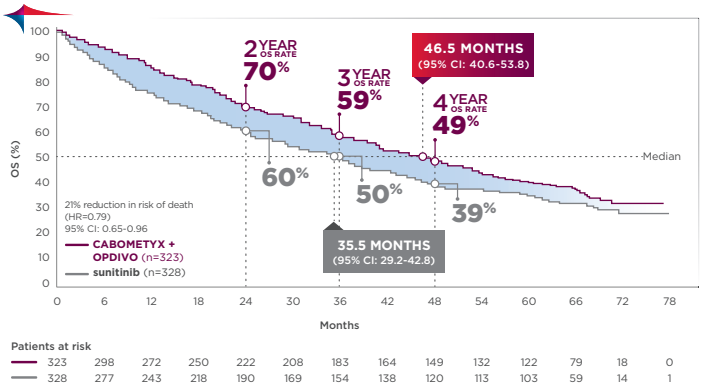
CABOMETYX® (cabozantinib) tablets + OPDIVO® (nivolumab)

Primary analysis in the ITT population
Median follow-up time of 18.1 months; range: 10.6-30.6 months[3]

Secondary endpoint
P Superior median OS[2]
Median OS was not reached with either CABOMETYX + OPDIVO or sunitinib

HR=0.60 (98.89% CI: 0.40-0.89, *P*=0.001)

5Y 5-year minimum follow-up analysis[5,7]
Median follow-up time of 67.6 months; range: 60.2-80.2 months



No formal statistical testing was conducted at the time of the updated analysis.

CheckMate-9ER was a randomized (1:1), open-label, Phase 3 trial of CABOMETYX + OPDIVO vs sunitinib in 651 patients with previously untreated aRCC with a clear-cell component. The trial evaluated CABOMETYX 40 mg (starting dose) PO once daily in combination with OPDIVO. The primary endpoint was PFS, and secondary endpoints included OS, ORR, and safety. Quality of life was evaluated as an exploratory endpoint; the clinical significance is unknown.[2,3,8,9]

- **Pre-planned final analysis of OS** (median follow-up: 32.9 months; range: 25.4-45.4 months): Median OS was 37.7 months for CABOMETYX + OPDIVO (95% CI: 35.5-NR; n=323) compared with 34.3 months for sunitinib (95% CI: 29.0-NR; n=328); HR=0.70 (95% CI: 0.55-0.90)[2,10]

BICR=blinded independent central review; CR=complete response; NR=not reached; PO=by mouth; PR=partial response.

IMPORTANT SAFETY INFORMATION (cont'd)
WARNINGS AND PRECAUTIONS

Impaired Wound Healing: CABOMETYX can cause impaired wound healing. Withhold CABOMETYX for at least 3 weeks prior to elective surgery. Do not administer for at least 2 weeks after major surgery and until adequate wound healing. The safety of resumption of CABOMETYX after resolution of wound healing complications has not been established.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): CABOMETYX can cause RPLS. Perform evaluation for RPLS and diagnose by characteristic finding on MRI any patient presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

Thyroid Dysfunction: CABOMETYX can cause thyroid dysfunction, primarily hypothyroidism, and it occurred in 19% of treated patients (0.4% Grade 3). Assess for signs of thyroid dysfunction prior to the initiation of CABOMETYX and monitor for signs and symptoms during treatment.

Hypocalcemia: CABOMETYX can cause hypocalcemia, with the highest incidence in DTC patients. Based on the safety population, hypocalcemia occurred in 13% of CABOMETYX patients (2% Grade 3 and 1% Grade 4).

Monitor blood calcium levels and replace calcium as necessary during treatment. Withhold and resume CABOMETYX at a reduced dose upon recovery or permanently discontinue CABOMETYX depending on severity.

Embryo-Fetal Toxicity: CABOMETYX can cause fetal harm. Advise pregnant women of the potential risk to a fetus and advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the last dose.

ADVERSE REACTIONS

The most common (≥20%) adverse reactions are:

CABOMETYX in combination with nivolumab: diarrhea, fatigue, hepatotoxicity, PPE, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abdominal pain, cough, and upper respiratory tract infection.

DRUG INTERACTIONS

Strong CYP3A4 Inhibitors: If coadministration with strong CYP3A4 inhibitors cannot be avoided, reduce the CABOMETYX dosage. Avoid grapefruit or grapefruit juice.

Strong or Moderate CYP3A4 Inducers: If coadministration with strong or moderate CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage. Avoid St. John's wort.

USE IN SPECIFIC POPULATIONS

Lactation: Advise women not to breastfeed during CABOMETYX treatment and for 4 months after the final dose.

Hepatic Impairment: In patients with moderate hepatic impairment, reduce the CABOMETYX dosage. Avoid CABOMETYX in patients with severe hepatic impairment.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.

For additional safety information, please see Brief Summary of the Prescribing Information for CABOMETYX on the following pages.

References: 1. Data on file. IQVIA National Prescription Audit. September 2025. Exelixis, Inc. **2.** CABOMETYX® (cabozantinib) Prescribing Information. Exelixis, Inc. **3.** Choueiri TK, Powles T, Burotto M, et al; CheckMate 9ER Investigators. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med*. 2021;384(9):829-841. **4.** Choueiri TK, Powles T, Burotto M, et al; CheckMate 9ER Investigators. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma [supplementary appendix]. *N Engl J Med*. 2021;384(9):829-841. **5.** Motzer RJ, Escudier B, Burotto M, et al. Final analysis of nivolumab plus cabozantinib for advanced renal cell carcinoma from the randomized phase III CheckMate 9ER trial. *Ann Oncol*. Published online September 23, 2025. doi:10.1016/j.annonc.2025.09.006. **6.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Kidney Cancer V.1.2026. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed July 24, 2025. To view the most recent and complete version of the guideline, go online to NCCN.org. **7.** Data on file. Exelixis, Inc. **8.** Choueiri TK, Powles T, Burotto M, et al; CheckMate 9ER Investigators. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma [protocol]. *N Engl J Med*. 2021;384(9):829-841. **9.** Powles T, Choueiri TK, Burotto M, et al. Final overall survival analysis and organ-specific target lesion assessments with 2-year follow-up in CheckMate 9ER: nivolumab plus cabozantinib versus sunitinib for patients with advanced renal cell carcinoma. Poster presented at the American Society of Clinical Oncology Genitourinary Cancers Symposium; February 17-19, 2022. **10.** Motzer RJ, Powles T, Burotto M, et al. Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma (CheckMate 9ER): long-term follow-up results from an open-label, randomized, phase 3 trial. *Lancet Oncol*. 2022;23(7):888-898.

DISCOVER MORE AT CABOMETYXhcp.com

EXELIXIS®

CABOMETYX® (cabozantinib) TABLETS

BRIEF SUMMARY OF PRESCRIBING INFORMATION.

PLEASE SEE THE CABOMETYX PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.
INITIAL U.S. APPROVAL: 2012

1 INDICATIONS AND USAGE

1.1 Renal Cell Carcinoma

CABOMETYX is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

CABOMETYX, in combination with nivolumab, is indicated for the first-line treatment of patients with advanced RCC.

1.2 Hepatocellular Carcinoma

CABOMETYX is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

1.3 Differentiated Thyroid Cancer

CABOMETYX is indicated for the treatment of adult and pediatric patients 12 years of age and older with locally advanced or metastatic differentiated thyroid cancer (DTC) that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine-refractory or ineligible.

1.4 Neuroendocrine Tumors

CABOMETYX is indicated for the treatment of adult and pediatric patients 12 years of age and older with previously treated, unresectable, locally advanced or metastatic, well-differentiated pancreatic neuroendocrine tumors (pNET).

CABOMETYX is indicated for the treatment of adult and pediatric patients 12 years of age and older with previously treated, unresectable, locally advanced or metastatic, well-differentiated extra-pancreatic neuroendocrine tumors (epNET).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage

CABOMETYX can cause severe and fatal hemorrhages. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX-treated patients in RCC, HCC, and DTC studies.

Withhold CABOMETYX for 3 weeks prior to scheduled surgery, including dental surgery to reduce the risk of hemorrhage. Permanently discontinue CABOMETYX for Grade 3 or 4 hemorrhage and prior to surgery as recommended.

5.2 Perforations and Fistulas

CABOMETYX can cause gastrointestinal (GI) perforations and fistulas.

Fistulas, including fatal cases, occurred in 1% of CABOMETYX-treated patients. GI perforations, including fatal cases, occurred in 1% of CABOMETYX-treated patients.

Monitor patients for signs and symptoms of fistulas and perforations, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a Grade 4 fistula or a GI perforation.

5.3 Thromboembolic Events

CABOMETYX can cause arterial or venous thromboembolic events.

Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism occurred in 2% of CABOMETYX-treated patients. Fatal thromboembolic events occurred in CABOMETYX-treated patients.

Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events that require medical intervention.

5.4 Hypertension and Hypertensive Crisis

CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension was reported in 37% (16% Grade 3 and <1% Grade 4) of CABOMETYX-treated patients. In CABINET (n=195), hypertension was reported in 65% (26% Grade 3) of CABOMETYX-treated patients.

Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume CABOMETYX at a reduced dose. Permanently discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

5.5 Cardiac Failure

CABOMETYX can cause severe and fatal cardiac failure. Cardiac failure occurred in 0.5% of patients treated with CABOMETYX as a single agent, including fatal cardiac failure in 0.1% of patients. Median time to onset of cardiac failure was 73 days (range: 44 days to 159 days).

Consider baseline and periodic evaluations of left ventricular ejection fraction. Monitor for signs and symptoms of cardiovascular events. Withhold and resume at a reduced dose upon recovery or permanently discontinue CABOMETYX depending on the severity.

5.6 Diarrhea

CABOMETYX can cause diarrhea. Diarrhea occurred in 62% of patients treated with CABOMETYX. Grade 3 diarrhea occurred in 10% of patients treated with CABOMETYX.

Monitor and manage patients using antidiarrheals as indicated. Withhold CABOMETYX until improvement to ≤Grade 1, resume CABOMETYX at a reduced dose.

5.7 Palmar-Plantar Erythrodysesthesia

CABOMETYX can cause palmar-plantar erythrodysesthesia (PPE). PPE occurred in 45% of patients treated with CABOMETYX. Grade 3 PPE occurred in 13% of patients treated with CABOMETYX.

Withhold CABOMETYX until improvement to Grade 1 and resume CABOMETYX at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

5.8 Hepatotoxicity

CABOMETYX in combination with nivolumab can cause hepatic toxicity with higher frequencies of Grades 3 and 4 ALT and AST elevations compared to CABOMETYX alone.

Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes as compared to when the drugs are administered as single agents. For elevated liver enzymes, interrupt CABOMETYX and nivolumab and consider administering corticosteroids.

With the combination of CABOMETYX and nivolumab, Grades 3 and 4 increased ALT or AST were seen in 11% of patients. ALT or AST >3 times ULN (Grade ≥2) was reported in 83 patients, of whom 23 (28%) received systemic corticosteroids; ALT or AST resolved to Grades 0-1 in 74 (89%). Among the 44 patients with Grade ≥2 increased ALT or AST who were rechallenged with either CABOMETYX (n=9) or nivolumab (n=11) as a single agent or with both (n=24), recurrence of Grade ≥2 increased ALT or AST was observed in 2 patients receiving CABOMETYX, 2 patients receiving nivolumab, and 7 patients receiving both CABOMETYX and nivolumab.

Withhold and then resume CABOMETYX at a reduced dose based on severity.

5.9 Adrenal Insufficiency

CABOMETYX in combination with nivolumab can cause primary or secondary adrenal insufficiency.

Adrenal insufficiency occurred in 4.7% (15/320) of patients treated with the combination of CABOMETYX and nivolumab including Grade 3 (2.2%), and Grade 2 (1.9%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of CABOMETYX and nivolumab in 0.9% and withholding of CABOMETYX and nivolumab in 2.8% of patients with RCC.

Approximately 80% (12/15) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 27% (n=4) of the 15 patients. Of the 9 patients in whom CABOMETYX with nivolumab was withheld for adrenal insufficiency, 6 reinstated treatment after symptom improvement; of these, all (n=6) received hormone replacement therapy and 2 had recurrence of adrenal insufficiency.

For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold CABOMETYX and/or nivolumab and resume CABOMETYX at a reduced dose depending on severity.

5.10 Proteinuria

CABOMETYX can cause proteinuria.

Proteinuria was observed in 8% of patients receiving CABOMETYX.

Monitor urine protein regularly during CABOMETYX treatment. For Grade 2 or 3 proteinuria, withhold CABOMETYX until improvement to ≤Grade 1 proteinuria, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX in patients who develop nephrotic syndrome.

5.11 Osteonecrosis of the Jaw

CABOMETYX can cause osteonecrosis of the jaw (ONJ).

ONJ occurred in <1% of patients treated with CABOMETYX.

ONJ can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration or erosion, persistent jaw pain or slow healing of the mouth or jaw after dental surgery. Perform an oral examination prior to initiation of CABOMETYX and periodically during CABOMETYX. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold CABOMETYX for development of ONJ until complete resolution, resume at a reduced dose.

5.12 Impaired Wound Healing

CABOMETYX can cause impaired wound healing. Withhold CABOMETYX for at least 3 weeks prior to elective surgery. Do not administer CABOMETYX for at least 2 weeks after major surgery and until adequate wound healing. The safety of resumption of CABOMETYX after resolution of wound healing complications has not been established.

5.13 Reversible Posterior Leukoencephalopathy Syndrome

CABOMETYX can cause reversible Posterior Leukoencephalopathy Syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI. Perform an evaluation for RPLS in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

5.14 Thyroid Dysfunction

CABOMETYX can cause thyroid dysfunction, primarily hypothyroidism. Thyroid dysfunction occurred in 19% of patients treated with CABOMETYX, including Grade 3 in 0.4% of patients.

Assess patients for signs of thyroid dysfunction prior to the initiation of CABOMETYX and monitor for signs and symptoms of thyroid dysfunction during CABOMETYX treatment. Thyroid function testing and management of dysfunction should be performed as clinically indicated.

5.15 Hypocalcemia

CABOMETYX can cause hypocalcemia. Hypocalcemia occurred in 13% of patients treated with CABOMETYX, including Grade 3 in 2% and Grade 4 in 1% of patients. Laboratory abnormality data were not collected in CABOSUN and CABINET.

In COSMIC-311 (n=125), hypocalcemia occurred in 36% of patients treated with CABOMETYX, including Grade 3 in 6% and Grade 4 in 3% of patients.

Monitor blood calcium levels and replace calcium as necessary during treatment. Withhold and resume at reduced dose upon recovery or permanently discontinue CABOMETYX depending on severity.

5.16 Embryo-Fetal Toxicity

Based on data from animal studies and its mechanism of action, CABOMETYX can cause fetal harm when administered to a pregnant woman. Cabozantinib administration to pregnant animals during organogenesis resulted in embryolethality at exposures below those occurring clinically at the recommended dose, and in increased incidences of skeletal variations in rats and visceral variations and malformations in rabbits.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the last dose.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed elsewhere in the labeling: Hemorrhage, Perforations and Fistulas, Thromboembolic Events, Hypertension and Hypertensive Crisis, Cardiac Failure, Diarrhea, Palmar-plantar Erythrodysesthesia, Hepatotoxicity, Adrenal Insufficiency, Proteinuria, Osteonecrosis of the Jaw, Impaired Wound Healing, Reversible Posterior Leukoencephalopathy Syndrome, Thyroid Dysfunction, and Hypocalcemia.

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described in the WARNINGS AND PRECAUTIONS section and below reflect exposure to CABOMETYX as a single agent at 60 mg orally once daily until disease progression or unacceptable toxicity in 409 patients with RCC enrolled in a randomized, active-controlled trial (CABOSUN, METEOR), 467 patients with HCC enrolled in a randomized, placebo-controlled trial (CELESTIAL), 125 patients with DTC enrolled in a randomized, placebo-controlled trial (COSMIC-311), 195 patients with pNET or epNET enrolled in a randomized, placebo-controlled trial (CABINET), and at 40 mg CABOMETYX in combination with nivolumab 240 mg/m^2 every 2 weeks, in 320 patients with RCC enrolled in a randomized, active-controlled trial (CHECKMATE-9ER).

Renal Cell Carcinoma

METEOR

The safety of CABOMETYX was evaluated in METEOR, a randomized, open-label trial in which 331 patients with advanced renal cell carcinoma received CABOMETYX 60 mg once daily and 322 patients received everolimus 10 mg once daily until disease progression or unacceptable toxicity. Patients on both arms who had disease progression could continue treatment at the discretion of the investigator. The median duration of treatment was 7.6 months (range 0.3 – 20.5) for patients receiving CABOMETYX and 4.4 months (range 0.21 – 18.9) for patients receiving everolimus.

Adverse reactions which occurred in ≥25% of CABOMETYX-treated patients, in order of decreasing frequency, were: diarrhea, fatigue, nausea, decreased appetite, palmar-plantar erythrodysesthesia (PPE), hypertension, vomiting, weight decreased, and constipation. Grade 3-4 adverse reactions and laboratory abnormalities which occurred in ≥5% of patients were hypertension, diarrhea, fatigue, PPE, hyponatremia, hypophosphatemia, hypomagnesemia, lymphopenia, anemia, hypokalemia, and increased GGT.

The dose was reduced in 60% of patients receiving CABOMETYX and in 24% of patients receiving everolimus. Twenty percent (20%) of patients received CABOMETYX 20 mg once daily as their lowest dose. The most frequent adverse reactions leading to dose reduction in patients treated with CABOMETYX were: diarrhea, PPE, fatigue, and hypertension. Adverse reactions leading to dose interruption occurred in 70% patients receiving CABOMETYX and in 59% patients receiving everolimus. Adverse reactions led to study treatment discontinuation in 10% of patients receiving CABOMETYX and in 10% of patients receiving everolimus. The most frequent adverse reactions leading to permanent discontinuation in patients treated with CABOMETYX were decreased appetite (2%) and fatigue (1%).

Table 1. Adverse Reactions Occurring in ≥10% Patients Who Received CABOMETYX in METEOR

Adverse Reaction	CABOMETYX (n=331)[1]		Everolimus (n=322)	
	All Grades[2]	Grade 3-4	All Grades[2]	Grade 3-4
	Percentage (%) of Patients			
Gastrointestinal				
Diarrhea	74	11	28	2
Nausea	50	4	28	<1
Vomiting	32	2	14	<1
Stomatitis	22	2	24	2
Constipation	25	<1	19	<1
Abdominal pain[3]	23	4	13	2
Dyspepsia	12	<1	5	0
General				
Fatigue	56	9	47	7
Mucosal inflammation	19	<1	23	3
Asthenia	19	4	16	2
Metabolism and Nutrition				
Decreased appetite	46	3	34	<1
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia	42	8	6	<1
Rash[4]	23	<1	43	<1
Dry skin	11	0	10	0
Vascular				
Hypertension[5]	39	16	8	3
Investigations				
Weight decreased	31	2	12	0
Nervous System				
Dysgeusia	24	0	9	0
Headache	11	<1	12	<1
Dizziness	11	0	7	0
Endocrine				
Hypothyroidism	21	0	<1	<1
Respiratory, Thoracic, and Mediastinal				
Dysphonia	20	<1	4	0
Dyspnea	19	3	29	4
Cough	18	<1	33	<1
Blood and Lymphatic				
Anemia	17	5	38	16
Musculoskeletal and Connective Tissue				
Pain in extremity	14	1	8	<1
Muscle spasms	13	0	5	0
Arthralgia	11	<1	14	1
Renal and Urinary				
Proteinuria	12	2	9	<1

[1] One subject randomized to everolimus received cabozantinib.
[2] National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0
[3] Includes the following terms: abdominal pain, abdominal pain upper, and abdominal pain lower
[4] Includes the following terms: rash, rash erythematous, rash follicular, rash macular, rash papular, rash pustular, rash vesicular, genital rash, intermittent leg rash, rash on scrotum and penis, rash maculo-papular, rash pruritic, contact dermatitis, dermatitis acneiform
[5] Includes the following terms: hypertension, blood pressure increased, hypertensive crisis, blood pressure fluctuation

Other clinically relevant adverse reactions (all grades) that were reported in <10% of patients treated with CABOMETYX included: wound complications (2%), cardiac failure (<1%), convulsion (<1%), pancreatitis (<1%), osteonecrosis of the jaw (<1%), and hepatitis cholestatic (<1%).

Table 2. Laboratory Abnormalities Occurring in ≥25% Patients Who Received CABOMETYX in METEOR

Laboratory Abnormality	CABOMETYX (n=331)		Everolimus (n=322)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
	Percentage (%) of Patients			
Chemistry				
Increased AST	74	3	40	<1
Increased ALT	68	3	32	<1
Increased creatinine	58	<1	71	0
Increased triglycerides	53	4	73	13
Hypophosphatemia	48	8	36	5
Hyperglycemia	37	2	59	8
Hypoalbuminemia	36	2	28	<1
Increased ALP	35	2	29	1
Hypomagnesemia	31	7	4	<1
Hyponatremia	30	8	26	6
Increased GGT	27	5	43	9
Hematology				
Leukopenia	35	<1	31	<1
Neutropenia	31	2	17	<1
Anemia[1]	31	4	71	17
Lymphopenia	25	7	39	12
Thrombocytopenia	25	<1	27	<1

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase.
NCI CTCAE, Version 4.0
[1] Based on laboratory abnormalities

CABOSUN

The safety of CABOMETYX was evaluated in CABOSUN, a randomized, open-label trial in patients with advanced renal cell carcinoma, in which 78 patients received CABOMETYX 60 mg once daily and 72 patients received sunitinib 50 mg once daily (4 weeks on treatment followed by 2 weeks off), until disease progression or unacceptable toxicity. The median duration of treatment was 6.5 months (range 0.2 – 28.7) for patients receiving CABOMETYX and 3.1 months (range 0.2 – 25.5) for patients receiving sunitinib.

Within 30 days of treatment, there were 4 deaths in patients treated with CABOMETYX and 6 deaths in patients treated with sunitinib. Of the 4 patients treated with CABOMETYX, 2 patients died due to gastrointestinal perforation, 1 patient had acute renal failure, and 1 patient died due to clinical deterioration. All Grade 3-4 adverse reactions were collected in the entire safety population. The most frequent Grade 3-4 adverse reactions (≥5%) in patients treated with CABOMETYX were hypertension, diarrhea, hyponatremia, hypophosphatemia, PPE, fatigue, increased ALT, decreased appetite, stomatitis, pain, hypotension, and syncope.

The median average daily dose was 50.3 mg for CABOMETYX and 44.7 mg for sunitinib (excluding scheduled sunitinib non-dosing days). The dose was reduced in 46% of patients receiving CABOMETYX and in 35% of patients receiving sunitinib. The dose was held in 73% of patients receiving CABOMETYX and in 71% of patients receiving sunitinib. Based on patient disposition, 21% of patients receiving CABOMETYX and 22% of patients receiving sunitinib discontinued due to an adverse reaction.

Table 3. Grade 3-4 Adverse Reactions Occurring in ≥1% Patients Who Received CABOMETYX in CABOSUN

Adverse Reaction	CABOMETYX (n = 78)	Sunitinib (n = 72)
	Grade 3-4[1]	Grade 3-4[1]
	Percentage (%) of Patients	
Patients with any Grade 3-4 Adverse Reaction	68	65
Gastrointestinal		
Diarrhea	10	11
Stomatitis	5	6
Nausea	3	4
Vomiting	1	3
Constipation	1	0
General		
Fatigue	6	17
Pain	5	0
Metabolism and Nutrition		
Hyponatremia[2]	9	8
Hypophosphatemia[2]	9	7
Decreased appetite	5	1
Dehydration	4	1
Hypocalcemia[2]	3	0
Hypomagnesemia[2]	3	0
Hyperkalemia[2]	1	3
Skin and Subcutaneous Tissue		
Palmar-plantar erythrodysesthesia	8	4
Skin ulcer	3	0
Vascular		
Hypertension[3]	28	21
Hypotension	5	1
Angiopathy	1	1
Investigations		
Increased ALT[2]	5	0
Weight decreased	4	0
Increased AST[2]	3	3
Increased blood creatinine[2]	3	3
Lymphopenia[2]	1	6
Thrombocytopenia[2]	1	11
Nervous System		
Syncope	5	0
Respiratory, Thoracic, and Mediastinal		
Dyspnea	1	6
Dysphonia	1	0
Blood and Lymphatic		
Anemia	1	3
Psychiatric		
Depression	4	0
Confusional state	1	1
Infections		
Lung infection	4	0
Musculoskeletal and Connective Tissue		
Back pain	4	0
Bone pain	3	1
Pain in extremity	3	0
Arthralgia	1	0
Renal and Urinary		
Renal failure acute	4	1
Proteinuria	3	1

ALT, alanine aminotransferase; AST, aspartate aminotransferase
[1] NCI CTCAE Version 4.0
[2] Laboratory abnormalities are reported as adverse reactions and not based on shifts in laboratory values
[3] Includes the following term: hypertension

CHECKMATE-9ER

The safety of CABOMETYX with nivolumab was evaluated in CHECKMATE-9ER, a randomized, open-label study in patients with previously untreated advanced RCC. Patients received CABOMETYX 40 mg orally once daily with nivolumab 240 mg over 30 minutes every 2 weeks (n=320) or sunitinib 50 mg daily, administered orally for 4 weeks on treatment followed by 2 weeks off (n=320). CABOMETYX could be interrupted or reduced to 20 mg daily or 20 mg every other day. The median duration of treatment was 14 months (range: 0.2 to 27 months) in CABOMETYX and nivolumab-treated patients. In this trial, 82% of patients in the CABOMETYX and nivolumab arm were exposed to treatment for >6 months and 60% of patients were exposed to treatment for >1 year.

Serious adverse reactions occurred in 48% of patients receiving CABOMETYX and nivolumab. The most frequent (≥2%) serious adverse reactions were diarrhea, pneumonia, pneumonitis, pulmonary embolism, urinary tract infection, and hyponatremia. Fatal intestinal perforations occurred in 3 (0.9%) patients.

Adverse reactions leading to discontinuation of either CABOMETYX or nivolumab occurred in 20% of patients: 8% CABOMETYX only, 7% nivolumab only, and 6% both drugs due to the same adverse reaction at the same time. Adverse reactions leading to dose interruption or reduction of either CABOMETYX or nivolumab occurred in 83% of patients: 46% CABOMETYX only, 3% nivolumab only, and 21% both drugs due to the same adverse reaction at the same time, and 6% both drugs sequentially.

The most common adverse reactions reported in ≥20% of patients treated with CABOMETYX and nivolumab were diarrhea, fatigue, hepatotoxicity, PPE, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abdominal pain, cough, and upper respiratory tract infection.

Table 4. Adverse Reactions in >15% of Patients Receiving CABOMETYX and Nivolumab - CHECKMATE-9ER

Adverse Reaction	CABOMETYX and Nivolumab (n=320)		Sunitinib (n=320)	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
	Percentage (%) of Patients			
Gastrointestinal				
Diarrhea	64	7	47	4.4
Nausea	27	0.6	31	0.3
Abdominal pain[a]	22	1.9	15	0.3
Vomiting	17	1.9	21	0.3
Dyspepsia[b]	15	0	22	0.3
General				
Fatigue[c]	51	8	50	8
Hepatobiliary				
Hepatotoxicity[d]	44	11	26	5
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia	40	8	41	8
Stomatitis[e]	37	3.4	46	4.4
Rash[f]	36	3.1	14	0
Pruritus	19	0.3	4.4	0
Vascular				
Hypertension[g]	36	13	39	14
Endocrine				
Hypothyroidism[h]	34	0.3	30	0.3
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[i]	33	3.8	29	3.1
Arthralgia	18	0.3	9	0.3
Metabolism and Nutrition				
Decreased appetite	28	1.9	20	1.3
Nervous System Disorders				
Dysgeusia	24	0	22	0
Headache	16	0	12	0.6
Respiratory, Thoracic and Mediastinal				
Cough[j]	20	0.3	17	0
Dysphonia	17	0.3	3.4	0
Infections and Infestations				
Upper respiratory tract infection[k]	20	0.3	8	0.3

Toxicity was graded per NCI CTCAE v4.

[a] Includes abdominal discomfort, abdominal pain lower, abdominal pain upper.

[b] Includes gastroesophageal reflux disease.

[c] Includes asthenia.

[d] Includes hepatotoxicity, ALT increased, AST increased, blood alkaline phosphatase increased, gamma-glutamyl transferase increased, autoimmune hepatitis, blood bilirubin increased, drug induced liver injury, hepatic enzyme increased, hepatitis, hyperbilirubinemia, liver function test increased, liver function test abnormal, transaminases increased, hepatic failure.

[e] Includes mucosal inflammation, aphthous ulcer, mouth ulceration.

[f] Includes dermatitis, dermatitis acneiform, dermatitis bullous, exfoliative rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic.

[g] Includes blood pressure increased, blood pressure systolic increased.

[h] Includes primary hypothyroidism.

[i] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, spinal pain.

[j] Includes productive cough.

[k] Includes nasopharyngitis, pharyngitis, rhinitis.

Table 5. Laboratory Values Worsening from Baseline[a] Occurring in >20% of Patients Receiving CABOMETYX and Nivolumab - CHECKMATE-9ER

Laboratory Abnormality	CABOMETYX and Nivolumab		Sunitinib	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
	Percentage (%) of Patients			
Chemistry				
Increased ALT	79	9.8	39	3.5
Increased AST	77	7.9	57	2.6
Hypophosphatemia	69	28	48	10
Hypocalcemia	54	1.9	24	0.6
Hypomagnesemia	47	1.3	25	0.3
Hyperglycemia	44	3.5	44	1.7
Hyponatremia	43	11	36	12
Increased lipase	41	14	38	13
Increased amylase	41	10	28	6
Increased alkaline phosphatase	41	2.8	37	1.6
Increased creatinine	39	1.3	42	0.6
Hyperkalemia	35	4.7	27	1
Hypoglycemia	26	0.8	14	0.4
Hematology				
Lymphopenia	42	6.6	45	10
Thrombocytopenia	41	0.3	70	9.7
Anemia	37	2.5	61	4.8
Leukopenia	37	0.3	66	5.1
Neutropenia	35	3.2	67	12

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: CABOMETYX and nivolumab group (range: 170 to 317 patients) and sunitinib group (range: 173 to 311 patients).

Hepatocellular Carcinoma

The safety of CABOMETYX was evaluated in CELESTIAL, a randomized, double-blind, placebo-controlled trial in which 704 patients with advanced hepatocellular carcinoma were randomized to receive CABOMETYX 60 mg orally once daily (n=467) or placebo (n=237) until disease progression or unacceptable toxicity. The median duration of treatment was 3.8 months (range 0.1 – 37.3) for patients receiving CABOMETYX and 2.0 months (range 0.0 – 27.2) for patients receiving placebo. The population exposed to CABOMETYX was 81% male, 56% White, and had a median age of 64 years.

Adverse reactions occurring in ≥25% of CABOMETYX- treated patients, in order of decreasing frequency were: diarrhea, decreased appetite, PPE, fatigue, nausea, hypertension, and vomiting. Grade 3-4 adverse reactions which occurred in ≥5% of patients were PPE, hypertension, fatigue, diarrhea, asthenia, and decreased appetite. There were 6 adverse reactions leading to death in patients receiving CABOMETYX (hepatic failure, hepatorenal syndrome, esophagobronchial fistula, portal vein thrombosis, pulmonary embolism, upper gastrointestinal hemorrhage).

The median average daily dose was 35.8 mg for CABOMETYX. The dose was reduced in 62% of patients receiving CABOMETYX; 33% of patients required a reduction to 20 mg daily. The most frequent adverse reactions or laboratory abnormalities leading to dose reduction of CABOMETYX were: PPE, diarrhea, fatigue, hypertension, and increased AST. Adverse reactions leading to dose interruption occurred in 84% patients receiving CABOMETYX. Adverse reactions leading to permanent discontinuation of CABOMETYX occurred in 16% of patients. The most frequent adverse reactions leading to permanent discontinuation of CABOMETYX were PPE (2%), fatigue (2%), decreased appetite (1%), diarrhea (1%), and nausea (1%).

Table 6. Adverse Reactions Occurring in ≥5% of CABOMETYX-Treated Patients in CELESTIAL[1]

Adverse Reaction	CABOMETYX (n = 467)		Placebo (n = 237)	
	All Grades[2]	Grade 3-4	All Grades[2]	Grade 3-4
	Percentage (%) of Patients			
Gastrointestinal				
Diarrhea	54	10	19	2
Nausea	31	2	18	2
Vomiting	26	<1	12	3
Stomatitis	13	2	2	0
Dyspepsia	10	0	3	0
General				
Fatigue	45	10	30	4
Asthenia	22	7	8	2
Mucosal inflammation	14	2	2	<1
Metabolism and Nutrition				
Decreased appetite	48	6	18	<1
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia	46	17	5	0
Rash[3]	21	2	9	<1
Vascular				
Hypertension[4]	30	16	6	2
Investigations				
Weight decreased	17	1	6	0
Nervous System				
Dysgeusia	12	0	2	0
Endocrine				
Hypothyroidism	8	<1	<1	0
Respiratory, Thoracic, and Mediastinal				
Dysphonia	19	1	2	0
Dyspnea	12	3	10	<1
Musculoskeletal and Connective Tissue				
Pain in extremity	9	<1	4	1
Muscle spasms	8	<1	2	0

[1] Includes terms with a between-arm difference of ≥5% (all grades) or ≥2% (Grade 3-4)

[2] NCI CTCAE Version 4.0

[3] Includes the following terms: rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, dermatitis, dermatitis acneiform, dermatitis contact, dermatitis diaper, dermatitis exfoliative, dermatitis infected

[4] Includes the following terms: hypertension, blood pressure diastolic increased, blood pressure increased

Table 7: Laboratory Abnormalities Occurring in ≥5% of CABOMETYX-Treated Patients in CELESTIAL[1]

Laboratory Abnormality	CABOMETYX (N=467)		Placebo (N=237)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
	Percentage (%) of Patients			
Chemistry				
Increased LDH	84	9	29	2
Increased ALT	73	12	37	6
Increased AST	73	24	46	19
Hypoalbuminemia	51	1	32	1
Increased ALP	43	8	38	6
Hypophosphatemia	25	9	8	4
Hypokalemia	23	6	6	1
Hypomagnesemia	22	3	3	0
Increased amylase	16	2	9	2
Hypocalcemia	8	2	0	0
Hematology				
Decreased platelets	54	10	16	1
Neutropenia	43	7	8	1
Increased hemoglobin	8	0	1	0

[1] Includes laboratory abnormalities with a between-arm difference of ≥5% (all grades) or ≥2% (Grade 3-4)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, blood lactate dehydrogenase

Differentiated Thyroid Cancer

The safety of CABOMETYX was evaluated in COSMIC-311, a randomized, double-blind, placebo-controlled trial in which 187 patients with advanced differentiated thyroid cancer were randomized to receive CABOMETYX 60 mg orally once daily (n=125) or placebo (n=62) with supportive care until disease progression or unacceptable toxicity. At the time of the primary efficacy analysis, the median duration of treatment was 4.4 months (range 0.0 – 15.7) for patients receiving CABOMETYX and 2.3 months (range 0.3 – 11.6) for patients receiving placebo. The median age was 66 years (range 32 to 85 years), 55% were female, 70% were White, 18% were Asian, 2% were Black, 2% were American Indian or Alaska Native, and 63% received prior lenvatinib.

Adverse reactions occurring in ≥25% of CABOMETYX-treated patients, in order of decreasing frequency were: diarrhea, PPE, fatigue, hypertension, and stomatitis. Grade 3-4 adverse reactions which occurred in ≥5% of patients were PPE, hypertension, fatigue, diarrhea, and stomatitis. Serious adverse reactions occurred in 34% of patients who received CABOMETYX. Serious adverse reactions in ≥2% included diarrhea, pleural effusion, pulmonary embolism and dyspnea. Fatal adverse reactions occurred in 1.6% of patients in the CABOMETYX arm, including arterial hemorrhage (0.8%) and pulmonary embolism (0.8%).

The median average daily dose was 42.0 mg for CABOMETYX. The dose was reduced in 56% of patients receiving CABOMETYX; 22% of patients required a second dose reduction. The most frequent adverse reactions (≥5%) leading to dose reduction of CABOMETYX were PPE, diarrhea, fatigue, proteinuria, and decreased appetite. Dose interruptions occurred in 72% patients receiving CABOMETYX. Adverse reactions requiring dosage interruption in ≥5% of patients were PPE, diarrhea, dyspnea, hypertension, decreased appetite and proteinuria. Adverse reactions leading to permanent discontinuation of CABOMETYX occurred in 5% of patients.

Table 8. Adverse Reactions Occurring in ≥5% of CABOMETYX-Treated Patients in COSMIC-311[1]

Adverse Reaction	CABOMETYX (N=125)		Placebo (N=62)	
	All Grades[2]	Grade 3-4	All Grades[2]	Grade 3-4
	Percentage (%) of Patients			
Gastrointestinal				
Diarrhea	51	7	3	0
Nausea	24	3	2	0
Vomiting	14	1	8	0
Stomatitis[3]	26	5	3	0
Dry mouth	10	1	2	0
General				
Fatigue[4]	42	10	23	0
Metabolism and Nutrition				
Decreased appetite	23	3	16	0
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia	46	10	0	0
Vascular				
Hypertension[5]	30	10	5	3
Investigations				
Weight decreased	18	1	5	0
Nervous System				
Dysgeusia	10	0	0	0
Headache	10	2	2	0
Respiratory, Thoracic, and Mediastinal				
Dysphonia	10	0	2	0
Pulmonary embolism	5	2	0	0
Renal and Urinary				
Proteinuria	15	1	3	0

[1] Includes terms that are more frequent in the CABOMETYX arm and have a between-arm difference of ≥5% (all grades) or ≥2% (Grade 3-4)
[2] NCI CTCAE Version 5.0
[3] Includes the following terms: mucosal inflammation, stomatitis
[4] Includes the following terms: fatigue, asthenia
[5] Includes the following terms: hypertension, blood pressure increased, hypertensive crisis

Table 9. Laboratory Abnormalities Occurring in ≥10% of CABOMETYX-Treated Patients in COSMIC-311[1]

Laboratory Abnormality	CABOMETYX N=125		Placebo N=62	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
	Percentage (%) of Patients			
Chemistry				
LDH increased[2]	90	10	32	3
AST increased	77	1	18	0
ALT increased	66	2	11	0
Hypocalcemia	36	9	10	2
ALP increased	34	0	15	0
GGT increased	26	2	21	2
Hypomagnesemia	25	2	5	0
Hypoalbuminemia	19	1	7	0
Hypokalemia	18	1	3	0
Hyponatremia	15	0	10	2
Hyperbilirubinemia	12	0	5	0
Hematology				
Leukocytes decreased	38	2	7	2
Neutrophils decreased	31	2	5	2
Platelets decreased	26	0	5	0

[1] Includes laboratory abnormalities that are more frequent in the CABOMETYX arm and have a between-arm difference of ≥5% (all grades) or ≥2% (Grade 3-4)
[2] Sponsor-defined grades for LDH were as follows: Grade 1 (>ULN to ≤2 × ULN), Grade 2 (>2 × ULN to ≤3 × ULN), Grade 3 (>3 × ULN).
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; LDH, blood lactate dehydrogenase

Neuroendocrine Tumors

Pancreatic Neuroendocrine Tumors (pNET)

The safety of CABOMETYX was evaluated in adult patients with unresectable, locally advanced or metastatic, well-differentiated neuroendocrine tumors in the CABINET trial. Patients received CABOMETYX 60 mg (n=63) or placebo orally (n=31) once daily until disease progression or unacceptable toxicity. Patients with pNET were required to have disease progression after prior treatment with at least one FDA approved therapy (everolimus, sunitinib or lutetium Lu 177 dotatate), other than somatostatin analogs. The median duration of treatment was 8.3 months (range: 0.1 to 37.8) for patients receiving CABOMETYX and 2.9 months (range: 0.1 to 11.2) for patients receiving placebo.

The median age of patients who received CABOMETYX was 60 years (range: 29 to 79), 57% were male, 86% were White, 6% were Asian, 3.2% were Black, 1.6% were American Indian or Alaska Native, 1.6% were Native Hawaiian or Other Pacific Islanders, and 3.2% were Hispanic or Latino.

Serious adverse reactions occurred in 46% of patients who received CABOMETYX. Serious adverse reactions in ≥2% of patients included thromboembolic events (10%), vomiting (6%), sepsis (4.8%), nausea (4.8%), hypoxia (4.8%), hemorrhage (3.2%), abdominal pain (3.2%), musculoskeletal pain (3.2%), blood bilirubin increased (3.2%), fatigue (3.2%), hyperkalemia (3.2%), and hypertension (3.2%).

Permanent discontinuation of CABOMETYX due to an adverse reaction occurred in 19% of patients. Adverse reactions which resulted in permanent discontinuation of CABOMETYX included thromboembolic events, acute kidney injury, rash, dyspnea, fistulas, hemorrhage, cardiac arrest, musculoskeletal pain, COVID-19 infection, Cushing's syndrome, pneumonia, proteinuria, and myocardial infarction.

The median average daily dose was 41.4 mg for CABOMETYX. Dosage interruptions of CABOMETYX due to an adverse reaction occurred in 83% of patients. Adverse reactions which required dosage interruption in ≥5% of patients included rash, diarrhea, fatigue, thromboembolic events, nausea, hypertension, increased ALT, blood bilirubin increased, musculoskeletal pain, stomatitis, vomiting, and increased AST.

Dose reductions of CABOMETYX due to an adverse reaction occurred in 49% of patients. Adverse reactions which required dose reductions in ≥5% of patients included rash, fatigue, hypertension, and stomatitis.

The most common adverse reactions occurring in ≥20% of CABOMETYX-treated patients were fatigue, increased AST, increased ALT, hypertension, diarrhea, rash, stomatitis, musculoskeletal pain, hyperglycemia, nausea, platelet count decreased, dysgeusia, neutrophil count decreased, abdominal pain, decreased appetite, hemoglobin decreased, dizziness, hypophosphatemia, hypothyroidism, vomiting, increased ALP, and lymphocyte count decreased.

Table 10 summarizes the adverse reactions in patients with pNET in CABINET.

Table 10. Adverse Reactions (≥15%) in Patients with pNET Who Received CABOMETYX in CABINET

Adverse Reaction	CABOMETYX (N=63)		Placebo (N=31)	
	All Grades[1]	Grade 3-4	All Grades[1]	Grade 3-4
	Percentage (%) of Patients			
General				
Fatigue[2]	79	14	61	6
Vascular				
Hypertension[3]	67	25	55	16
Thromboembolic events[4]	19	11	3.2	0
Gastrointestinal				
Diarrhea[5]	63	6	23	0
Stomatitis[6]	49	6	10	0
Vomiting	25	6	16	0
Nausea	37	8	32	3.2
Abdominal pain[7]	25	3.2	16	6
Dyspepsia[8]	16	0	6	0
Skin and Subcutaneous Tissue				
Rash[9]	57	11	23	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[10]	41	1.6	19	0
Nervous System				
Dysgeusia[11]	30	0	6	0
Dizziness[12]	25	0	3.2	0
Endocrine disorders				
Hypothyroidism[13]	25	0	3.2	0
Metabolism and Nutrition				
Decreased appetite	25	3.2	19	0
Investigations				
Weight decreased	19	3.2	10	0
Respiratory, Thoracic, and Mediastinal				
Dyspnea[14]	16	0	3.2	0

[1] NCI CTCAE Version 5.0
[2] Includes fatigue, asthenia
[3] Includes hypertension, blood pressure increased, blood pressure systolic increased, systolic hypertension
[4] Includes thromboembolic event, pulmonary embolism, embolism, deep vein thrombosis, vena cava thrombosis, embolism venous, embolism arterial
[5] Includes diarrhea, colitis
[6] Includes stomatitis, aphthous ulcer, mucosal inflammation, cheilitis, glossitis
[7] Includes abdominal pain, abdominal pain lower, abdominal pain upper, gastrointestinal pain, abdominal discomfort, hepatic pain
[8] Includes dyspepsia, gastroesophageal reflux disease
[9] Includes rash, palmar-plantar erythrodysesthesia syndrome, dermatitis acneiform, skin exfoliation, erythema multiforme, rash macular, rash maculo-papular, rash pustular, dermatitis, dermatitis bullous, dermatitis contact, erythema, dermatitis psoriasiform
[10] Includes musculoskeletal pain, non-cardiac chest pain, back pain, arthralgia, pain in extremity, myalgia, bone pain, arthritis, neck pain, musculoskeletal chest pain, musculoskeletal stiffness, chest discomfort
[11] Includes dysgeusia, taste disorder, ageusia, anosmia
[12] Includes dizziness, vertigo
[13] Includes hypothyroidism, blood thyroid stimulating hormone increased
[14] Includes dyspnea, dyspnea exertional

Clinically relevant adverse reactions in <15% of patients who received CABOMETYX included peripheral neuropathy, hemorrhage, cardiac arrhythmia, hypotension, alopecia, and hair color changes.

Table 11 summarizes the laboratory abnormalities in patients with pNET in CABINET.

Table 11: Select Laboratory Abnormalities (≥10%) Reported as Adverse Reactions in Patients with pNET Who Received CABOMETYX in CABINET

Laboratory Abnormality	CABOMETYX (N=63)		Placebo (N=31)	
	All Grades[1]	Grade 3-4	All Grades[1]	Grade 3-4
Chemistry				
Increased AST	76	1.6	48	0
Increased ALT	75	1.6	39	3.2
Hyperglycemia[2]	37	3.2	48	3.2
Hypophosphatemia[3]	25	0	6	0
Increased ALP[4]	22	3.2	23	0
Hypocalcemia[5]	17	0	3.2	0
Hyponatremia[6]	16	1.6	16	0
Blood bilirubin increased[7]	14	4.8	6	3.2
Hyperkalemia[8]	14	1.6	10	0
Hypoalbuminemia[9]	14	0	10	0
Hypoglycemia[10]	11	0	6	0
Hypomagnesemia[11]	11	0	6	0
Hypokalemia[12]	10	1.6	3.2	0
Hematology				
Platelet count decreased[13]	37	0	19	0
Neutrophil count decreased[14]	27	1.6	6	0
Hemoglobin decreased[15]	25	1.6	32	0
Lymphocyte count decreased[16]	22	8	16	0
White blood cell count decreased[17]	19	1.6	3.2	0

[1] NCI CTCAE Version 5.0
[2] Includes hyperglycemia, blood glucose increased
[3] Includes hypophosphatemia, blood phosphorus decreased
[4] Includes blood alkaline phosphatase, blood alkaline phosphatase increased
[5] Includes hypocalcemia, blood calcium decreased, adjusted calcium decreased
[6] Includes hyponatremia, blood sodium decreased
[7] Includes blood bilirubin increased, hyperbilirubinemia
[8] Includes hyperkalemia, blood potassium increased
[9] Includes hypoalbuminemia, blood albumin decreased
[10] Includes hypoglycemia, blood glucose decreased
[11] Includes hypomagnesemia, blood magnesium decreased
[12] Includes hypokalemia, blood potassium decreased
[13] Includes platelet count decreased, thrombocytopenia
[14] Includes neutrophil count decreased, neutropenia
[15] Includes hemoglobin decreased, anemia
[16] Includes lymphocyte count decreased, lymphopenia
[17] Includes white blood cell count decreased, leukopenia

Extra-Pancreatic Neuroendocrine Tumors (epNET)

The safety of CABOMETYX was evaluated in adult patients with unresectable, locally advanced or metastatic, well-differentiated neuroendocrine tumors in the CABINET trial. Patients received CABOMETYX 60 mg (n=132) or placebo (n=67) orally once daily until disease progression or unacceptable toxicity. Patients with epNET were required to have disease progression after prior treatment with at least one FDA approved therapy (everolimus or lutetium Lu 177 dotatate), other than somatostatin analogs. The median duration of treatment was 5.4 months (range 0.1 to 32.4) for

patients receiving CABOMETYX and 2.8 months (range 0.5 to 22.8) for patients receiving placebo.

The median age was 66 years (range 28 to 86), 55% were female, 86% were White, 7% were Black, 2.3% were Asian, 5% had unknown race or race not reported, and 6% were Hispanic or Latino.

Serious adverse reactions occurred in 44% of patients who received CABOMETYX. Serious adverse reactions in ≥2% included hypertension (6%), abdominal pain (5%), musculoskeletal pain (5%), diarrhea (3.0%), vomiting (3.0%), blood bilirubin increased (3.0%), thromboembolic events (3.0%), nausea (2.3%), hemoglobin decreased (2.3%), muscular weakness (2.3%), fatigue (2.3%), sepsis (2.3%), and syncope (2.3%). Fatal adverse reactions occurred in 4.5% of patients who received CABOMETYX, including hepatic failure, multi-organ dysfunction, gastrointestinal hemorrhage, cardiac arrest, ruptured ascending aortic aneurysm, and sudden death not otherwise specified, occurring in one patient each.

Permanent discontinuation of CABOMETYX due to an adverse reaction occurred in 28% of patients receiving CABOMETYX. Adverse reactions which resulted in permanent discontinuation of CABOMETYX included diarrhea, fatigue, increased AST, increased ALT, blood bilirubin increased, rash, thromboembolic events, hypertension, increased ALP, nausea, and stomatitis.

The median average daily dose was 42.9 mg for CABOMETYX. Dosage interruptions of CABOMETYX due to an adverse reaction occurred in 81% of patients. Adverse reactions which required dosage interruption in ≥5% of patients included diarrhea, fatigue, rash, hypertension, nausea, stomatitis, abdominal pain, increased AST, vomiting, and musculoskeletal pain.

Dose reductions of CABOMETYX due to an adverse reaction occurred in 38% of patients. Adverse reactions which required dose reductions in ≥5% of patients included rash, fatigue, diarrhea, and hypertension.

The most common adverse reactions occurring in ≥20% of CABOMETYX-treated patients were fatigue, increased AST, diarrhea, hypertension, increased ALT, platelet count decreased, rash, stomatitis, nausea, white blood cell count decreased, neutrophil count decreased, musculoskeletal pain, dysgeusia, hypothyroidism, decreased appetite, hemoglobin decreased, hyperglycemia, abdominal pain, increased ALP, lymphocyte count decreased, weight decreased, blood creatinine increased, hypoalbuminemia, blood bilirubin increased, hypocalcemia, hypokalemia, and hypomagnesemia.

Table 12 summarizes the adverse reactions in patients with epNET in CABINET.

Table 12. Adverse Reactions (≥15%) in Patients with epNET Who Received CABOMETYX in CABINET

Adverse Reaction	CABOMETYX (N=132)		Placebo (N=67)	
	All Grades[1]	Grade 3-4	All Grades[1]	Grade 3-4
	Percentage (%) of Patients			
General				
Fatigue[2]	73	14	58	9
Edema[3]	16	1.5	10	0
Gastrointestinal				
Diarrhea[4]	65	11	42	4.5
Stomatitis[5]	40	3.8	10	0
Nausea	39	2.3	21	0
Abdominal pain[6]	29	9	43	8
Vomiting	17	2.3	10	1.5
Vascular				
Hypertension[7]	64	27	37	6
Skin and Subcutaneous Tissue				
Rash[8]	50	3.0	10	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[9]	36	8	33	1.5
Endocrine System				
Hypothyroidism[10]	34	0	4.5	0
Metabolism and Nutrition				
Decreased appetite	33	1.5	15	1.5
Nervous System				
Dysgeusia[11]	35	0	1.5	0
Dizziness[12]	17	0	6	0
Investigations				
Weight decreased	27	4.5	8	0
Respiratory, Thoracic, and Mediastinal				
Cough[13]	17	0	10	0

[1] NCI CTCAE Version 5.0
[2] Includes fatigue, asthenia
[3] Includes edema, edema peripheral, generalized edema, localized edema, periorbital edema, face edema, eye edema
[4] Includes diarrhea, colitis
[5] Includes stomatitis, aphthous ulcer, mucosal inflammation, cheilitis, glossitis
[6] Includes abdominal pain, abdominal pain lower, abdominal pain upper, gastrointestinal pain, abdominal discomfort, hepatic pain
[7] Includes hypertension, blood pressure increased, blood pressure systolic increased, systolic hypertension
[8] Includes rash, palmar-plantar erythrodysesthesia syndrome, dermatitis acneiform, skin exfoliation, rash macular, rash pustular, dermatitis bullous, dermatitis, erythema multiforme, rash maculo-papular, dermatitis contact, erythema, dermatitis psoriasiform
[9] Includes musculoskeletal pain, non-cardiac chest pain, back pain, arthralgia, pain in extremity, myalgia, bone pain, arthritis, neck pain, musculoskeletal chest pain, musculoskeletal stiffness, chest discomfort
[10] Includes hypothyroidism, blood thyroid stimulating hormone increased
[11] Includes dysgeusia, taste disorder, ageusia, anosmia
[12] Includes dizziness, vertigo
[13] Includes cough, upper-airway cough syndrome, productive cough

Clinically relevant adverse reactions in <15% of patients who received CABOMETYX included cardiac arrhythmia, hemorrhage, thromboembolic events, kidney injury, proteinuria, hypotension, peripheral neuropathy, reversible posterior leukoencephalopathy syndrome, alopecia, hair color changes, and cardiac failure.

Table 13 summarizes the laboratory abnormalities in patients with epNET in CABINET.

Table 13: Select Laboratory Abnormalities (≥10%) Reported as Adverse Reactions in Patients with epNET Who Received CABOMETYX in CABINET

Laboratory Abnormality	CABOMETYX (N=132)		Placebo (N=67)	
	All Grades[1]	Grade 3-4	All Grades[1]	Grade 3-4
Chemistry				
Increased AST	70	3.8	21	1.5
Increased ALT	63	0.8	18	1.5
Hyperglycemia[2]	30	0.8	39	1.5
Increased ALP[3]	29	4.5	30	6
Blood creatinine increased	23	0	12	1.5
Blood bilirubin increased[4]	20	3	10	6
Hypoalbuminemia[5]	20	0.8	9	0
Hypocalcemia[6]	20	0	4.5	0
Hypokalemia[7]	20	2.3	10	1.5
Hypomagnesemia[8]	20	0.8	4.5	0
Hypophosphatemia[9]	19	0.8	4.5	0
Hyponatremia[10]	16	2.3	7	1.5
Hematology				
Platelet count decreased[11]	55	1.5	13	1.5
White blood cell count decreased[12]	37	3	4.5	0
Neutrophil count decreased[13]	36	3	6	0
Hemoglobin decreased[14]	30	2.3	19	0
Lymphocyte count decreased[15]	28	9	18	1.5

[1] NCI CTCAE Version 5.0
[2] Includes hyperglycemia, blood glucose increased
[3] Includes blood alkaline phosphatase, blood alkaline phosphatase increased
[4] Includes blood bilirubin increased, hyperbilirubinemia
[5] Includes hypoalbuminemia, blood albumin decreased
[6] Includes hypocalcemia, blood calcium decreased, adjusted calcium decreased
[7] Includes hypokalemia, blood potassium decreased
[8] Includes hypomagnesemia, blood magnesium decreased
[9] Includes hypophosphatemia, blood phosphorus decreased
[10] Includes hyponatremia, blood sodium decreased
[11] Includes platelet count decreased, thrombocytopenia
[12] Includes white blood cell count decreased, leukopenia
[13] Includes neutrophil count decreased, neutropenia
[14] Includes hemoglobin decreased, anemia
[15] Includes lymphocyte count decreased, lymphopenia

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on CABOMETYX

Strong CYP3A4 Inhibitors

Coadministration of a cabozantinib capsule formulation with a strong CYP3A4 inhibitor increased the exposure of cabozantinib, which may increase the risk of exposure-related adverse reactions. Avoid coadministration of CABOMETYX with strong CYP3A4 inhibitors. Reduce the dosage of CABOMETYX if coadministration with strong CYP3A4 inhibitors cannot be avoided. Avoid grapefruit or grapefruit juice which may also increase exposure of cabozantinib.

Strong or Moderate CYP3A Inducers

Coadministration of a cabozantinib capsule formulation with a strong CYP3A4 inducer decreased the exposure of cabozantinib, which may reduce efficacy. Avoid coadministration of CABOMETYX with strong or moderate CYP3A4 inducers. Increase the dosage of CABOMETYX if coadministration with strong or moderate CYP3A4 inducers cannot be avoided. Avoid St. John's wort which may also decrease exposure of cabozantinib.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, CABOMETYX can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal developmental and reproductive toxicology studies administration of cabozantinib to pregnant rats and rabbits during organogenesis resulted in embryofetal lethality and structural anomalies at exposures that were below those occurring clinically at the recommended dose. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In an embryo-fetal development study in pregnant rats, daily oral administration of cabozantinib throughout organogenesis caused increased embryo-fetal lethality compared to controls at a dose of 0.03 mg/kg (approximately 0.12-fold of human area under the curve [AUC] at the recommended dose). Findings included delayed ossification and skeletal variations at a dose of 0.01 mg/kg/day (approximately 0.04-fold of human AUC at the recommended dose).

In pregnant rabbits, daily oral administration of cabozantinib throughout organogenesis resulted in findings of visceral malformations and variations including reduced spleen size and missing lung lobe at 3 mg/kg (approximately 1.1-fold of the human AUC at the recommended dose).

In a pre- and postnatal study in rats, cabozantinib was administered orally from gestation day 10 through postnatal day 20. Cabozantinib did not produce adverse maternal toxicity or affect pregnancy, parturition or lactation of female rats, and did not affect the survival, growth or postnatal development of the offspring at doses up to 0.3 mg/kg/day (0.05-fold of the maximum recommended clinical dose).

8.2 Lactation

Risk Summary

There is no information regarding the presence of cabozantinib or its metabolites in human milk, or their effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with CABOMETYX and for 4 months after the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating CABOMETYX.

Contraception

CABOMETYX can cause fetal harm when administered to a pregnant woman.

Females

Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the final dose.

Infertility

Females and Males

Based on findings in animals, CABOMETYX may impair fertility in females and males of reproductive potential.

8.4 Pediatric Use

The safety and effectiveness of CABOMETYX for the treatment of differentiated thyroid cancer (DTC) and neuroendocrine tumors (NETs) have been established in pediatric patients aged 12 years and older.

Use of CABOMETYX in pediatric patients aged 12 years and older with DTC and NETs is supported by evidence from adequate and well-controlled studies of CABOMETYX in adults with additional population pharmacokinetic data demonstrating that cabozantinib exposure is within the same range between adults and pediatric patients aged 12 years and older at the recommended dosages.

Physeal widening has been observed in children with open growth plates when treated with CABOMETYX. Based on the limited available data of the effects of CABOMETYX on longitudinal growth, physeal and longitudinal growth monitoring is recommended in children with open growth plates.

The safety and effectiveness of CABOMETYX in pediatric patients less than 12 years of age have not been established.

Juvenile Animal Toxicity Data

Juvenile rats were administered cabozantinib at doses of 1 or 2 mg/kg/day from Postnatal Day 12 (comparable to less than 2 years in humans) through Postnatal Day 35 or 70. Mortalities occurred at doses ≥1 mg/kg/day (approximately 0.16 times the clinical dose of 60 mg/day based on body surface area). Hypoactivity was observed at both doses tested on Postnatal Day 22. Targets were generally similar to those seen in adult animals, occurred at both doses, and included the kidney (nephropathy, glomerulonephritis), reproductive organs, gastrointestinal tract (cystic dilatation and hyperplasia in Brunner's gland and inflammation of duodenum; and epithelial hyperplasia of colon and cecum), bone marrow (hypocellularity and lymphoid depletion), and liver. Tooth abnormalities and whitening as well as effects on bones including reduced bone mineral content and density, physeal hypertrophy, and decreased cortical bone also occurred at all dose levels. Recovery was not assessed at a dose of 2 mg/kg (approximately 0.32 times the clinical dose of 60 mg based on body surface area) due to high levels of mortality. At the low dose level, effects on bone parameters were partially resolved but effects on the kidney and epididymis/testis persisted after treatment ceased.

8.5 Geriatric Use

In CABOSUN and METEOR, 41% of 409 patients treated with CABOMETYX were age 65 years and older, and 8% were 75 years and older. In CELESTIAL, 49% of 467 patients treated with CABOMETYX were age 65 years and older, and 15% were 75 years and older. In COSMIC-311, 50% of 125 patients treated with CABOMETYX were age 65 years and older, and 12% were 75 years and older. In CABINET, 38% of 63 patients treated with CABOMETYX were age 65 years and older, and 5% were 75 years and older in the pNET cohort, and 55% of 132 patients treated with CABOMETYX were age 65 years and older, and 13% were 75 years and older in the epNET cohort.

No overall differences in safety or effectiveness were observed between these patients and younger patients.

Of the 320 patients with RCC treated with CABOMETYX in combination with nivolumab in CHECKMATE-9ER, 41% were 65 years or older and 9% were 75 years or older.

No overall difference in safety was reported between older and younger patients receiving both CABOMETYX and nivolumab.

8.6 Hepatic Impairment

Increased exposure to cabozantinib has been observed in patients with moderate (Child-Pugh B) hepatic impairment. Reduce the CABOMETYX dose in patients with moderate hepatic impairment. Avoid CABOMETYX in patients with severe hepatic impairment (Child-Pugh C), since it has not been studied in this population.

8.7 Renal Impairment

No dosage adjustment is recommended in patients with mild or moderate renal impairment. There is no experience with CABOMETYX in patients with severe renal impairment.

10 OVERDOSAGE

One case of overdosage was reported following administration of another formulation of cabozantinib; a patient inadvertently took twice the intended dose for 9 days. The patient suffered Grade 3 memory impairment, Grade 3 mental status changes, Grade 3 cognitive disturbance, Grade 2 weight loss, and Grade 1 increase in BUN. The extent of recovery was not documented.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

- Hemorrhage: Instruct patients to contact their healthcare provider to seek immediate medical attention for signs or symptoms of unusual severe bleeding or hemorrhage.
- Perforations and fistulas: Advise patients that gastrointestinal disorders such as diarrhea, nausea, vomiting, and constipation may develop during CABOMETYX treatment and to seek immediate medical attention if they experience persistent or severe abdominal pain because cases of gastrointestinal perforation and fistula have been reported in patients taking CABOMETYX.
- Thromboembolic events: Venous and arterial thromboembolic events have been reported. Advise patients to report signs or symptoms of an arterial thrombosis. Venous thromboembolic events including pulmonary embolus have been reported. Advise patients to contact their health care provider if new onset of dyspnea, chest pain, or localized limb edema occurs.
- Hypertension and hypertensive crisis: Inform patients of the signs and symptoms of hypertension. Advise patients to undergo routine blood pressure monitoring and to contact their health care provider if blood pressure is elevated or if they experience signs or symptoms of hypertension.
- Cardiac Failure: Advise patients that CABOMETYX can cause cardiac failure. Advise patients to immediately contact their healthcare provider for signs or symptoms of cardiac failure.
- Diarrhea: Advise patients to notify their healthcare provider at the first signs of poorly formed or loose stool or an increased frequency of bowel movements.
- Palmar-plantar erythrodysesthesia: Advise patients to contact their healthcare provider for progressive or intolerable rash.
- Hepatotoxicity: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding.
- Adrenal insufficiency: Advise patients receiving with nivolumab to contact their healthcare provider immediately for signs or symptoms of adrenal insufficiency.
- Proteinuria: Advise patients to contact their healthcare provider for signs or symptoms of proteinuria.
- Osteonecrosis of the jaw: Advise patients regarding good oral hygiene practices. Advise patients to immediately contact their healthcare provider for signs or symptoms associated with osteonecrosis of the jaw.
- Impaired wound healing: Advise patients that CABOMETYX may impair wound healing. Advise patients to inform their healthcare provider of any planned surgical procedure.
- Reversible posterior leukoencephalopathy syndrome: Advise patients to immediately contact their health care provider for new onset or worsening neurological function.
- Thyroid dysfunction: Advise patients that CABOMETYX can cause thyroid dysfunction and that their thyroid function should be monitored regularly during treatment. Advise patients to immediately contact their healthcare provider for signs or symptoms of thyroid dysfunction.
- Hypocalcemia: Advise patients that CABOMETYX can cause low calcium levels and that their serum calcium levels should be monitored regularly during treatment. Advise patients to immediately contact their healthcare provider for signs or symptoms of hypocalcemia.
- Embryo-fetal toxicity:
  - Advise females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy.
  - Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the final dose.
- Lactation: Advise women not to breastfeed during treatment with CABOMETYX and for 4 months following the last dose.
- Drug interactions: Advise patients to inform their healthcare provider of all prescription or nonprescription medications, vitamins or herbal products. Inform patients to avoid grapefruit, grapefruit juice, and St. John's wort.
- Important administration information
  Instruct patients to take CABOMETYX on an empty stomach, at least 1 hour before or at least 2 hours after eating.

This brief summary is based on the CABOMETYX Prescribing Information

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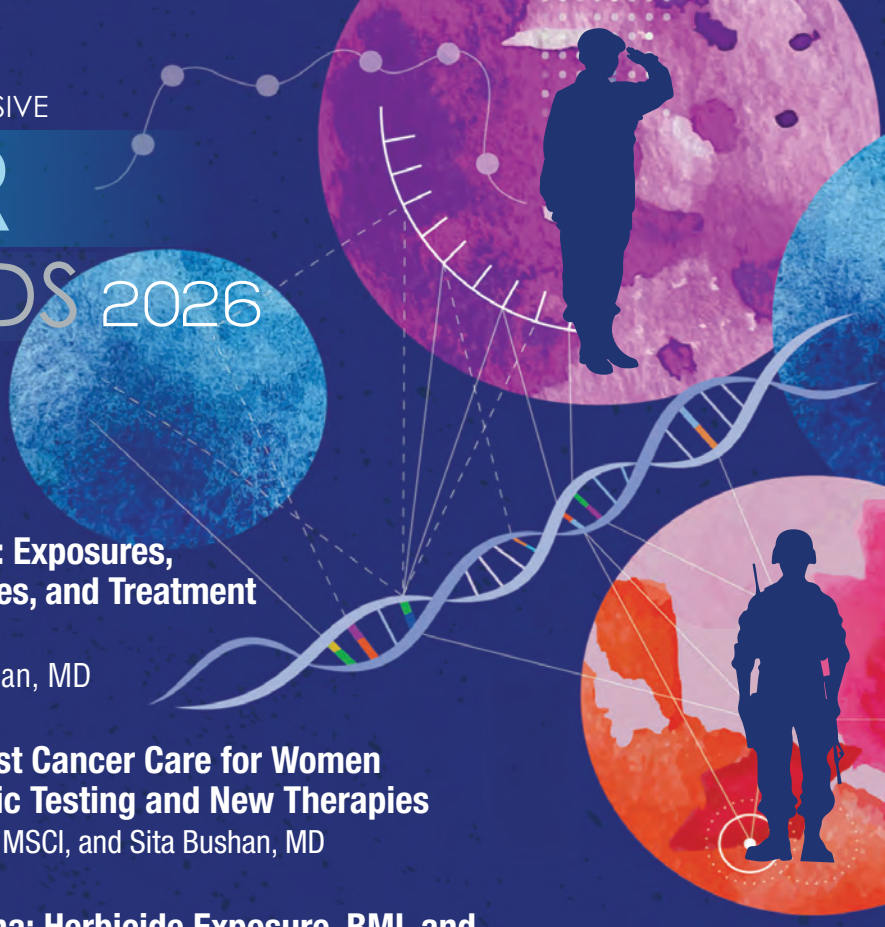
CANCER DATA TRENDS 2026



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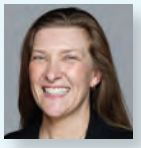

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Common abbreviations used throughout this issue:

VA, Veterans Affairs; VHA, Veterans Health Administration

Prostate Cancer: Exposures, Racial Differences, and Treatment Trends

Michael M. Goodman, MD

Prostate cancer is the most common solid tumor cancer diagnosed within the VHA.[1] Veterans who are diagnosed with prostate cancer and have certain environmental exposures or who were in specified deployment locations are awarded disability compensation based on the presumptive link.[2,3] Agent Orange specifically has also been shown to increase incidence of metastases and prostate cancer mortality in veterans.[2]

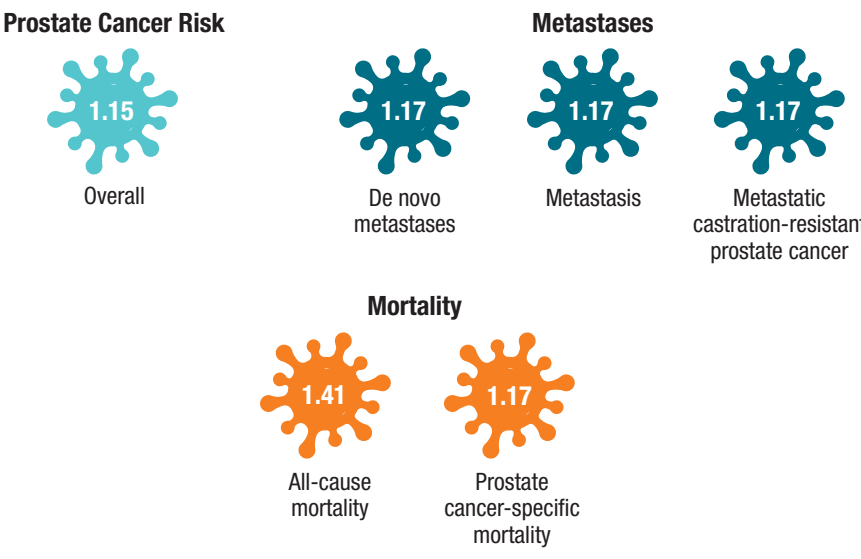
Precision oncology is key to improving outcomes in veterans with prostate cancer. Recent studies have shown that genetic alterations in prostate cancer are affected by race and ethnicity; specifically, different mutations correlate with survival and treatment outcomes in non-Hispanic Black and White veterans.[4] Within the VA healthcare system, while these differences in genetic alterations exist, survival is similar in both groups, showing the effect of equitable healthcare on prostate cancer outcomes in veterans.[4]

For metastatic hormone-sensitive prostate cancer (mHSPC), the standard treatment has evolved in recent years to combination therapy, with an androgen receptor pathway inhibitor (ARPI) with or without docetaxel added to the standard protocol of androgen deprivation therapy (ADT).[5] Combination therapy has been shown to improve overall survival in veterans with mHSPC compared with just ADT alone.[5] Prostate cancer care is a key concern in the VHA system, but promising new treatments and genetic advances are on the horizon.[2,4,5]

Agent Orange and Prostate Cancer Outcomes[2]

Of the 2.6 million veterans who served in Vietnam, 30% were exposed to Agent Orange.

Displayed as hazard ratios; compared to those who served in Vietnam but were not exposed to Agent Orange

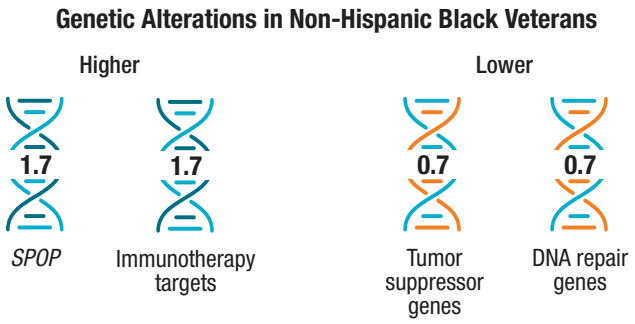


The association between Agent Orange exposure and prostate cancer risk in Vietnam veterans may not be causal, but Agent Orange exposure marginally increases prostate cancer risk in this population.

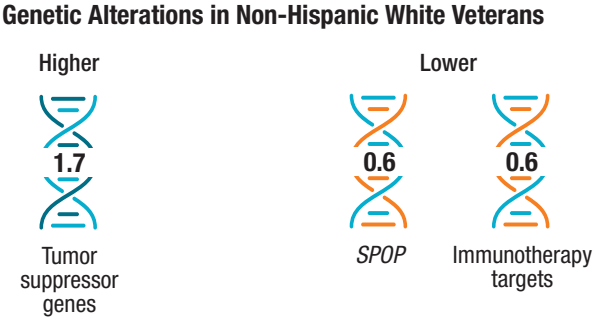
Racial Differences in NGS for Metastatic Disease[4]

A study of about 5000 men who underwent next-generation sequencing (NGS) for metastatic prostate cancer through the VA from 2019 to 2023 compared genetic alterations in non-Hispanic Black and non-Hispanic White veterans. In these two groups, nine of the 10 most commonly altered genes were the same, but there were differences in the frequency of these genetic alterations in each group.

Displayed as odds ratios; odds of genetic alteration compared to Non-Hispanic White veterans



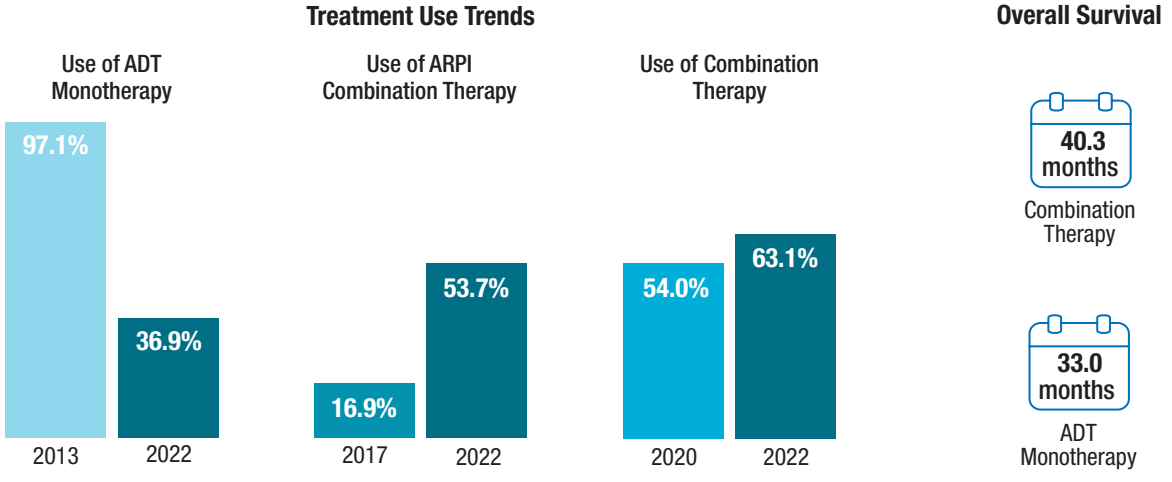
Compared to Non-Hispanic Black veterans



Immunotherapy targets include MSI-high, mismatch repair pathway, and *CDK12* alterations.

Treatment Use and Survival Trends in mHSPC[5]

Approximately 6000 veterans with de novo mHSPC treated at the VHA from 2013 to 2022 were assessed for treatment use and survival patterns. Combination therapy was defined as docetaxel or an ARPI (eg, abiraterone, enzalutamide, apalutamide, or darolutamide) within 120 days of ADT.



Expanding Breast Cancer Care for Women Veterans: Genetic Testing and New Therapies

Sarah Colonna, MD, MSCI, and Sita Bushan, MD

Since 2000, the number of women veterans using VA healthcare services has tripled, heightening focus on breast cancer care.[1] Breast cancer accounts for 30% of cancers in this group, making it the most prevalent cancer diagnosis.[1]

The Making Advances in Mammography and Medical Options for Veterans Act of 2022 (MAMMO Act) mandated that the VA conduct a study on the availability of and access to germline genetic testing for veterans diagnosed with breast cancer.[1,2] A recent study aimed to gain insight into how many veteran women with breast cancer were offered germline genetic testing through the VHA.

In 2025, the FDA broadened targeted breast cancer treatment with approvals of fam-trastuzumab deruxtecan-nxki across multiple human epidermal growth factor receptor 2 (HER2) settings, datopotamab deruxtecan-dlnk as the first trophoblast cell-surface antigen 2-targeted antibody-drug conjugate, and imlunestrant for estrogen receptor-positive, estrogen receptor 1-mutated disease with companion diagnostics. Fam-trastuzumab deruxtecan-nxki also received FDA Breakthrough Therapy Designation for post-neoadjuvant high-risk HER2-positive early breast cancer based on the DESTINY-Breast05 trial.[3-7]

These findings highlight critical progress in breast cancer care for women veterans — from improved access to genetic testing under the MAMMO Act to new FDA-approved targeted therapies that expand treatment options and personalize care.

Germline Genetic Testing in Veterans With Breast Cancer[1,2,8]

Despite advances that make germline genetic testing more accessible and actionable, its uptake in clinical practice remains limited. A recent study (n = 200) implemented a natural language processing (NLP)-assisted review of electronic health records to identify documentation of germline genetic testing offers, referrals, or results for patients with breast cancer in the VHA.

The VHA recommends offering germline testing to all veterans with breast cancer.

59%
medical records reviewed

94.5%
seen by oncology

62.4%
offered/received genetic testing

Why it matters

- 5%-10% of breast cancers are hereditary
- Lifetime risk
  - *BRCA1* → 44%-78%
  - *BRCA2* → 31%-56%
- Identifying pathogenic variants can guide early screening and prevention

Implication

- Improve adherence to testing
- Embeds workflows in VA process

The VA Clinical Cancer Genetics Service and Comprehensive Genetics Service provide cancer risk assessment, hereditary germline genetic counseling, and genetic testing for veterans, while supporting clinicians with testing pathways and result interpretation.

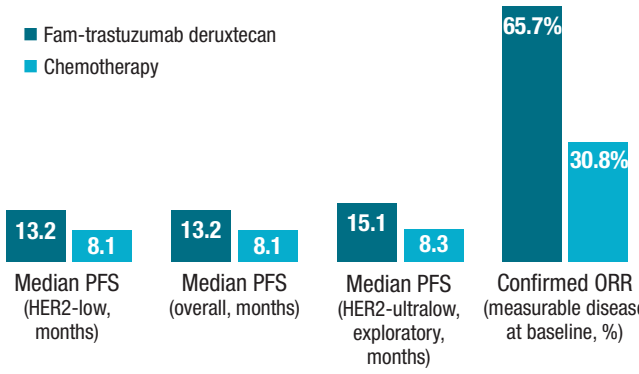
Recent FDA Approvals/Expansions for Breast Cancer Treatments[3-7]

Drug	Indication	Approval Date/Type	Details
Fam-trastuzumab deruxtecan-nxki	Unresectable/metastatic HR+ HER2-low/-ultralow BC after endocrine therapy progression	Jan-Mar 2025/Expanded	ADC targeting HER2; expands options for HR+ cases
Datopotamab deruxtecan-dlnk	HR+/HER2-negative, unresectable/metastatic BC after prior endocrine therapy and chemotherapy	Jan-Mar 2025/New	TROP2-targeting ADC; offers new therapy for pretreated advanced disease
Imlunestrant	ER+, HER2-negative, *ESR1*-mutated advanced/metastatic BC which has progressed after ≥ 1 line of endocrine therapy	Sep 2025/New	Oral SERD/antagonist; provides a new, all-oral option
Fam-trastuzumab deruxtecan-nxki + pertuzumab AND PATHWAY anti-HER2/neu (4B5) rabbit monoclonal primary antibody and HER2 dual ISH DNA probe cocktail	First-line treatment; unresectable or metastatic HER2+ (IHC 3+ or ISH+) BC	Dec 2025/Simultaneously approved	Companion diagnostic devices to identify patients eligible for therapy with this combination
Fam-trastuzumab deruxtecan-nxki	High risk early HER2+ disease with residual invasive BC after neoadjuvant therapy	Dec 2025/Breakthrough Therapy Designation	ADC targeting HER2 expressing cells

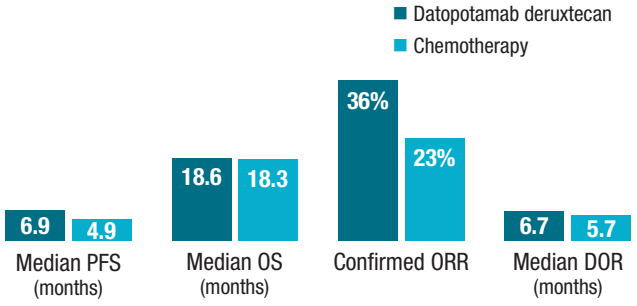
ADC, antibody-drug conjugate; BC, breast cancer; ER+, estrogen receptor–positive; ESR1, estrogen receptor 1; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ICH 3+, immunohistochemistry high, uniform overexpression of the HER2; ISH+, in situ hybridization positive; SERD, selective estrogen receptor degrader; TROP2, trophoblast cell-surface antigen 2

Recent FDA Approvals/Expansions for Breast Cancer Treatment: Cont.[3-7]

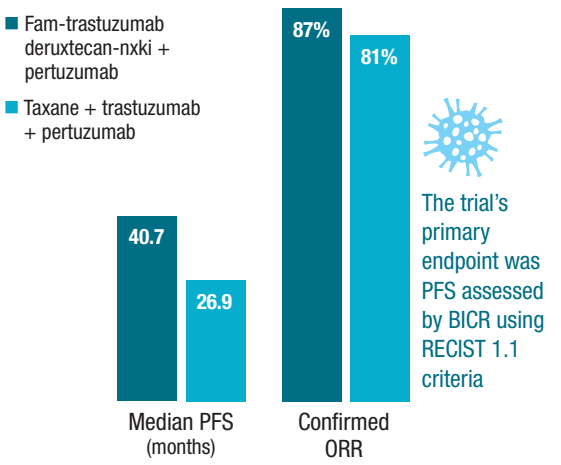
DESTINY-Breast06: HR+/HER2-low or -ultralow BC



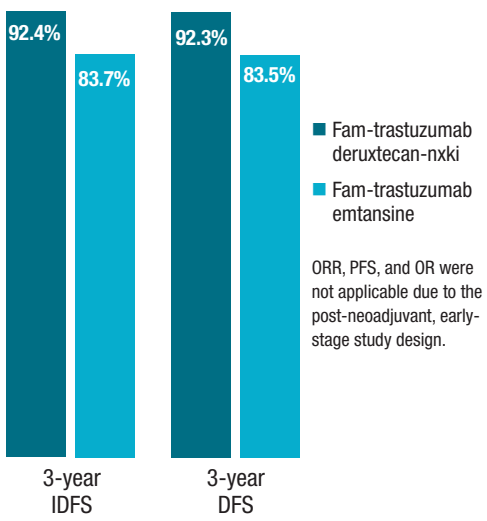
TROPION-Breast01: HR+/HER2- BC



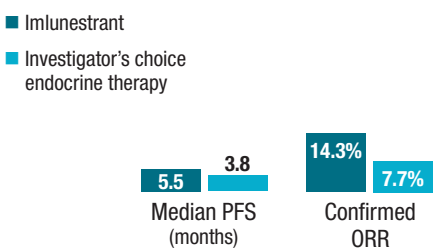
DESTINY-Breast09: Unresectable/metastatic HER2+ (IHC 3+ or ISH+) BC



DESTINY-Breast05: Post neoadjuvant HER2+ early BC



EMBER-3: ER+, HER2-, *ESR1*-mutated advanced/metastatic BC



BICR; blinded independent central review; DFS, disease-free survival; DOR, duration of response; ESR1, estrogen receptor 1; IDFS invasive disease-free survival; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RECIST; response evaluation criteria in solid tumors

Multiple Myeloma: Herbicide Exposure, BMI, and Novel Quadruplet Regimens

Maxwell M. Krem, MD, PhD

Multiple myeloma (MM) is the world's second most common blood cancer, and its diagnosis rates are rising.[1] Most MM cases are diagnosed in individuals older than 50 years, with frailty and comorbidities more common in veteran cohorts.[2] MM displays substantial genetic diversity, which contributes to treatment resistance. In most patients, MM eventually relapses or stops responding to available therapies, even as newer treatments improve remission.[1]

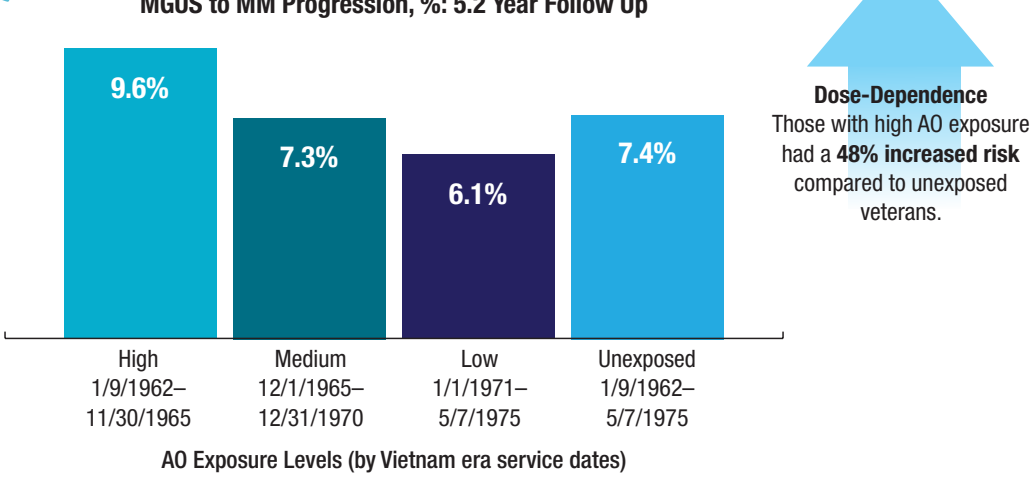
A study of Vietnam War-era veterans with high Agent Orange (AO) exposure found a heightened risk of progressing from monoclonal gammopathy of undetermined significance (MGUS) to MM compared with those without exposure, highlighting a critical link between herbicide contaminants and cancer progression risk.[3] Further, in a large VHA cohort of veterans with MGUS, higher cumulative BMI (> 25) was significantly associated with increased risk of progression to MM. Among patients with healthy BMI at diagnosis (18.5 to < 25), each 1-unit increase in excess BMI per year raised progression risk by 21%.[4]

Evidence from a meta-analysis supports quadruplet regimens with anti-cluster of differentiation 38 (CD38) antibodies for veterans with newly diagnosed MM, showing longer survival and deeper, more durable responses than triplet therapies. Given that many veterans have higher myeloma risk due to prior exposures and older age at diagnosis, these regimens could potentially improve outcomes and quality of life for veterans with MM.[5]

AO Exposure and Progression From MGUS to MM in Vietnam War-Era Veterans[3]

High exposure to AO was associated with a significantly higher risk of progression to MM compared with no AO exposure. Vigilant monitoring among patients with MGUS with documented AO exposure might be warranted.

Study Sample
10,847 Vietnam War-era veterans with MGUS
26.3% with documented AO exposure

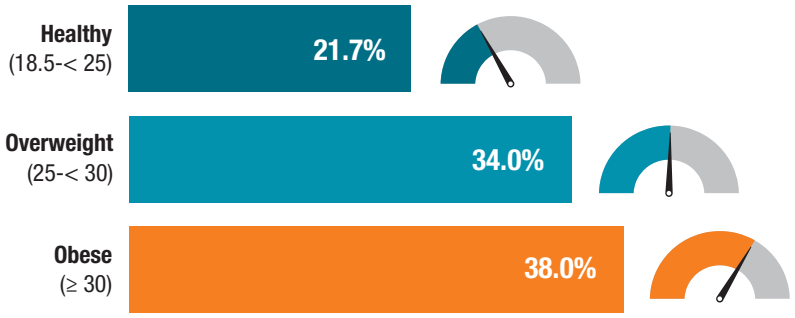


Dose-Dependence
Those with high AO exposure had a **48% increased risk** compared to unexposed veterans.

Preventing MM in Veterans Through Weight Management[4]

Quadruplet regimens incorporating anti-CD38 antibodies outperform triplet therapies in veterans with newly diagnosed MM, supporting their use as a new standard of care. In a nationwide cohort of 22,429 veterans with MGUS, higher BMI at diagnosis and greater cumulative exposure to excess BMI were associated with an increased risk of progression to multiple myeloma. These findings suggest that obesity burden over time is an important, potentially modifiable risk factor for MGUS progression.

BMI Distribution at MGUS Diagnosis



Key Findings

Overweight
aHR 1.17
(95% CI, 1.03-1.34)

Obese
aHR 1.27
(95% CI, 1.09-1.47)

...compared to healthy weight patients

aHR = adjusted hazard ratio

For healthy-weight patients:
Each +1 unit* of excess BMI/year **+21% higher MM risk**
(aHR 1.21; 95% CI, 1.04-1.40)

Patients with MGUS and baseline BMI ≥ 25:
17%-27% higher risk of MM
compared with patients with baseline BMI within the reference range

*A +1 unit increase in BMI corresponds to gaining enough weight to raise BMI by one point—for example, about 5–7 lb (2–3 kg) for an average-height adult (≈5'9").

Interpretations

Higher and prolonged BMI exposure **increases** MM progression risk.

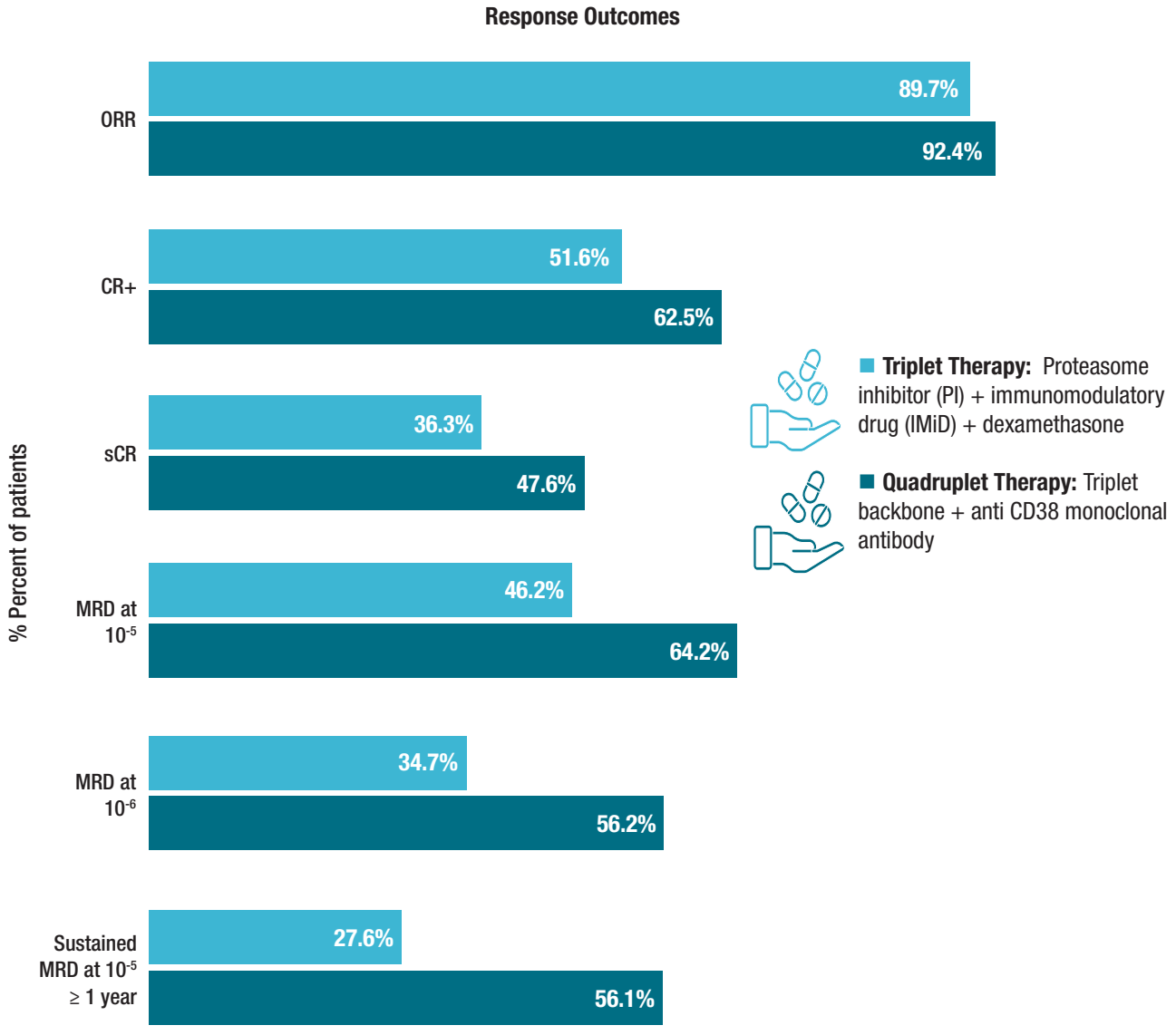
Maintaining a stable, healthy weight post-MGUS diagnosis may **reduce the risk of disease progression.**

Quadruplet Therapy Provides a New Highly Effective Frontline Treatment Option in MM[5]

Findings from a recently published meta-analysis may lead to increased use of quadruplet induction regimens, including anti-CD38 antibodies, among veterans with newly diagnosed MM (NDMM), as these regimens offer longer survival potential and deeper, more durable responses than prior triplet therapies.

Overview

Quadruplet Therapy Provides a New Highly Effective Frontline Treatment Option in MM: Cont.[5]



CR+, complete response or better; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; sCR, stringent complete response.

MRD 10^{-5} and 10^{-6} numbers refer to how deeply MRD is measured, ie, how sensitive the test is at detecting remaining myeloma cells after treatment. Deeper MRD negativity correlates with longer progression-free survival and overall survival in MM.

Conclusions

PFS: Quadruplets reduced risk of progression or death by 45% vs triplets

OS: Quadruplets reduced risk of death by 35% vs triplets

Quadruplets = Superior efficacy (deeper and more durable responses) with manageable toxicity, particularly in **transplant-eligible NDMM**

Melanoma in Veterans: Higher Risk, Delayed Diagnosis, and Evolving Solutions

Soo J. Park, MD

Veterans face a markedly higher risk of melanoma than civilians.[1] Prevalence is estimated to be 2.2% in veterans versus 0.6% in civilians.[1] Veterans are also more likely to be diagnosed with regional or distant (stage III/IV) disease, contributing to lower survival rates compared to civilians.[1,2]

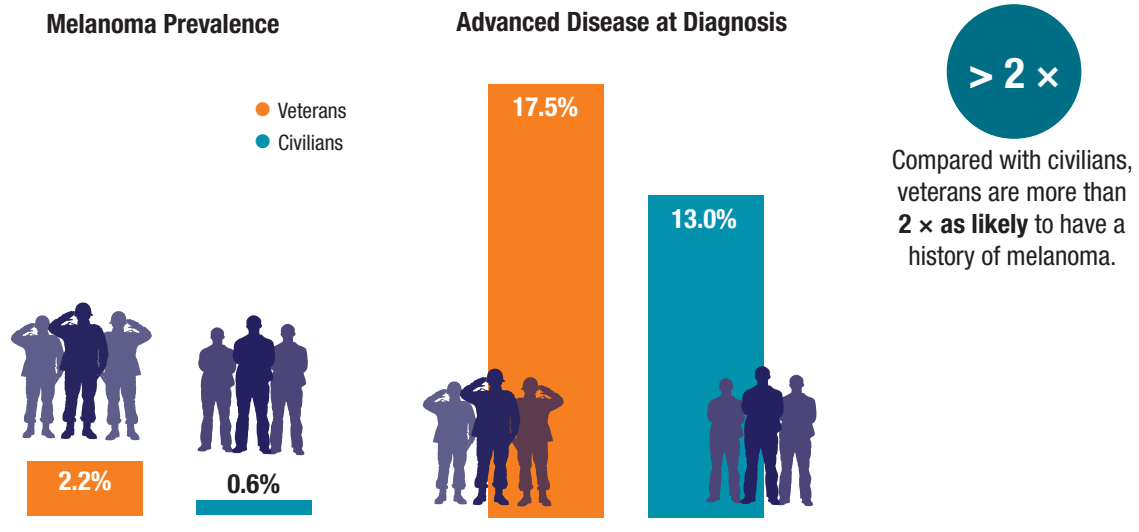
A 2025 study of teledermatology for melanoma care in the VHA demonstrated that remote consultations substantially expand access and support early evaluation for many patients. While face-to-face dermatology continues to provide the most rapid treatment pathway, teledermatology effectively connects patients to specialty input and timely intervention, especially for those in underserved or rural areas. Both care models play important roles in melanoma management as part of an evolving system of dermatologic care.[3]

Further, recent treatment breakthroughs include cellular therapy to fight melanoma with lifileucel, a personalized form of immunotherapy which has been in research and development for nearly four decades. On the heels of that arrived the two-year update on neoadjuvant nivolumab plus ipilimumab, which highlights that neoadjuvant immunotherapy is superior to adjuvant therapy alone for resectable stage III melanoma.[4-6]

For veterans, who face disproportionately higher rates of melanoma (eg, from service-related UV exposure), these advances translate to VHA-accessible therapies and response-adaptive protocols that increase cure rates, lessen treatment burden, and provide hope for formerly untreatable cases. With ongoing VA-funded research into risk factors for clinically aggressive melanoma in veterans, targeted interventions are enhancing early detection and improving outcomes in this high-risk population.[7]

Melanoma in Veterans: Higher Risk and Worse Outcomes[1,2]

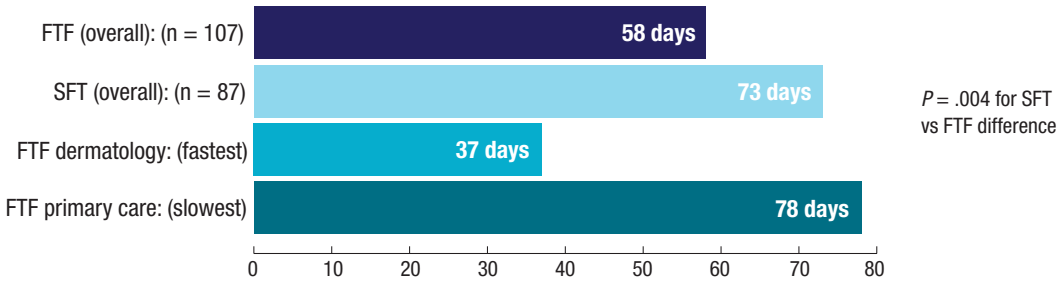
Veterans have a higher prevalence of melanoma and are more likely to be diagnosed with advanced-stage disease compared with civilians. After adjusting for demographic factors, veterans showed a significantly increased likelihood of melanoma diagnosis and lower melanoma-specific survival rates.



Evaluating Process Timing for Melanoma Care for Veterans: Teledermatology vs In-Person Visits[3]

This study analyzed whether store-and-forward teledermatology (SFT) offers melanoma patients the same timeliness of treatment as traditional face-to-face (FTF) care. While SFT improved access, FTF dermatology—especially when first consulted—provided the fastest timelines to melanoma excision, and process enhancements could help reduce delays in SFT care.

Median Timeline for Melanoma Treatment: Entry to Definitive Excision

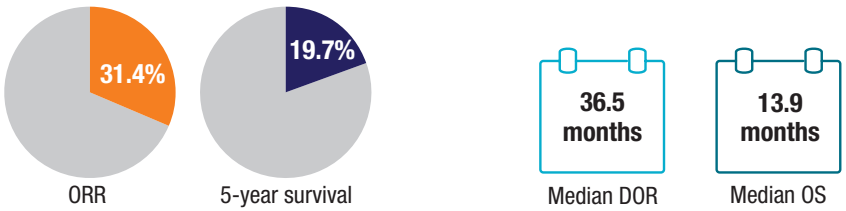


FTF dermatology care provided faster access to melanoma treatment compared to SFT with a median of 15 days of delay. Handoff efficiency within the SFT process is vital in closing the gap in treatment timelines.

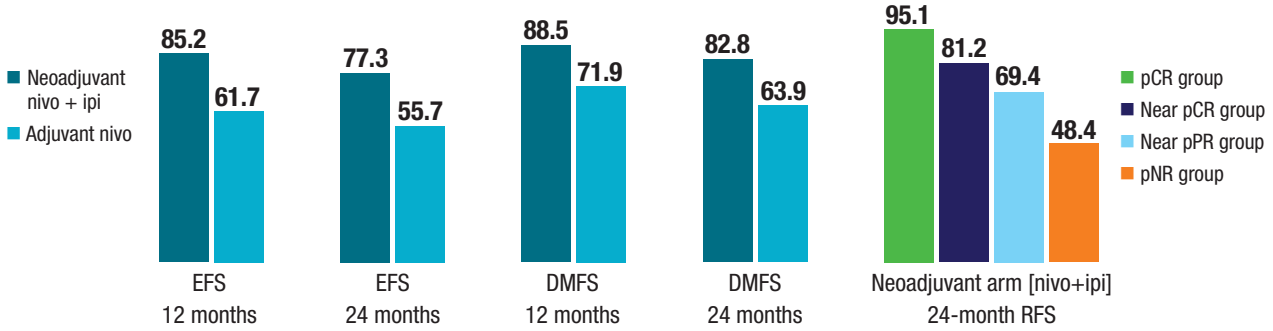
Long-Term TIL Therapy Survival and Neoadjuvant Immunotherapy Optimization[4-6]

Lifileucel, the first FDA-approved autologous TIL therapy, delivers long-term benefit for advanced melanoma after checkpoint or BRAF/MEK inhibitor failure as seen in the C-144-01 TIL trial, with manageable, short-term adverse effects. The NADINA trial established neoadjuvant nivolumab plus ipilimumab as another standard of care option for resectable, macroscopic stage III melanoma, with sustained benefits in event-free survival at 2 years of follow-up compared to adjuvant therapy. **Together, these advances improve outcomes and survival across melanoma stages.**

C-144-01 TIL Trial



NADINA Trial: 2 Year Follow Up: Core Efficacy, %



BRAF/MEK, B-Raf proto-oncogene/mitogen-activated protein kinase; DMFS, distant metastatic free survival; DOR, duration of response; EFS, event-free survival; IPI, ipilimumab; NIVO, nivolumab; ORR, objective response rate; OS, overall survival; pCR, pathologic complete response; pPR, pathologic partial response; pNR, pathologic non-response; RFS, recurrence-free survival; TIL, tumor-infiltrating lymphocytes

Colorectal Cancer Trends and Digital Interventions in Veterans

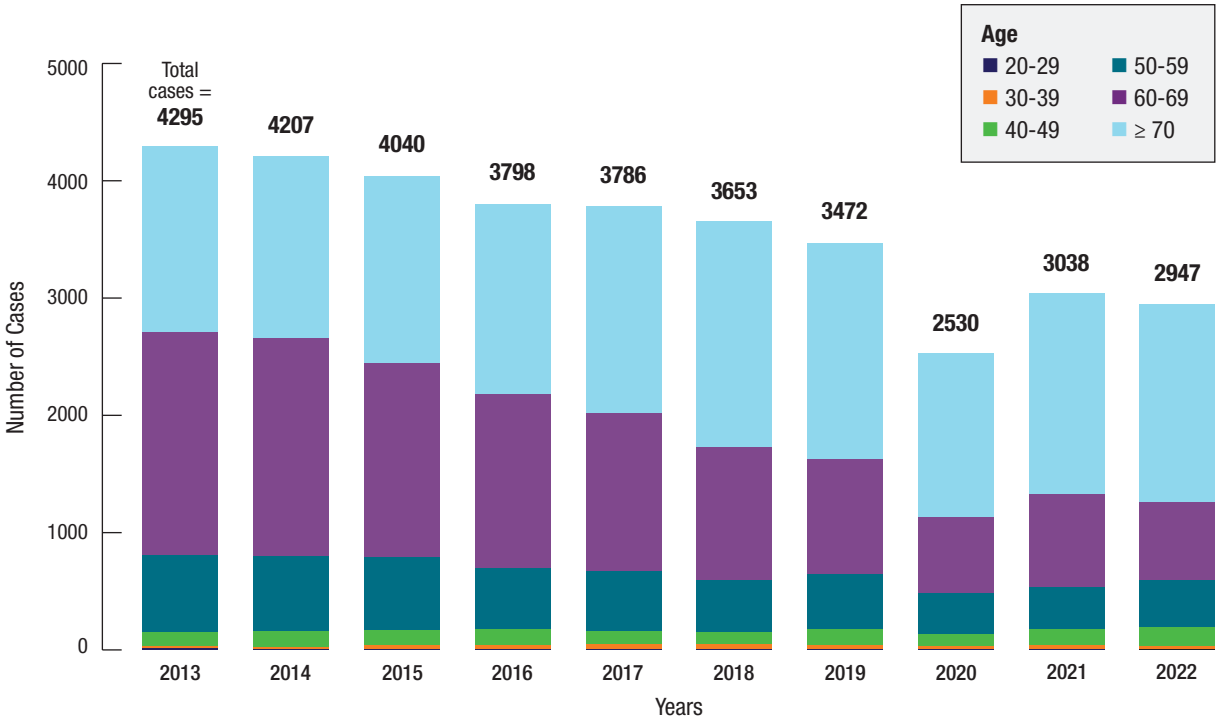
Aasma Shaukat, MD, MPH

Colorectal cancer (CRC) is one of the most commonly diagnosed cancers among US veterans, despite declining rates since 2013.[1,2] Screening is key to reducing risk, and veterans have higher CRC screening rates and less racial disparities in CRC screening compared to civilians.[1-3] This is potentially due to equal healthcare coverage within the VA.[2,3] Although most cases of CRC have been shown to occur in average-risk individuals within the guideline-designated screening age range, more than 12% of cases occur in high-risk individuals and those outside the recommended age range, highlighting a significant minority not covered by conventional screening.[4]

Screening quality is also important for lowering CRC rates. A large VA study recently found that within 3 years, the postcolonoscopy CRC (PCCRC) rate was 6.4%.[5] This finding was mainly due to missed lesions and incomplete resection during colonoscopy.[5]

The VA has strived to create programs to increase screening completion and improve bowel prep and surveillance rates.[6-8] Interventions, such as Annie, an informational texting app, aim to improve bowel preparation for screening colonoscopy, as well as adherence to repeat colonoscopies.[7,8] Other interventions have used phone calls or text messages to improve the fecal immunochemical test (FIT) screening return rate among veterans.[6,9]

Prevalence of CRC in Veterans by Age[1]



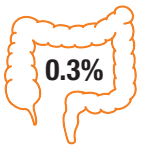
The COVID-19 pandemic affected cancer reporting which could explain significantly lower rates during 2020.[10,11]

From 2013 to 2022, overall CRC cases in veterans have decreased by 31.4%. The most significant decrease in cases was seen in veterans aged 60-69 (-65.2%), while cases increased in veterans aged 30-49 years (+> 31%). Cases remain generally highest in veterans aged ≥ 70, rising 6.8% overall during this time.

PCCRC Rates in FIT-Positive Individuals[5]

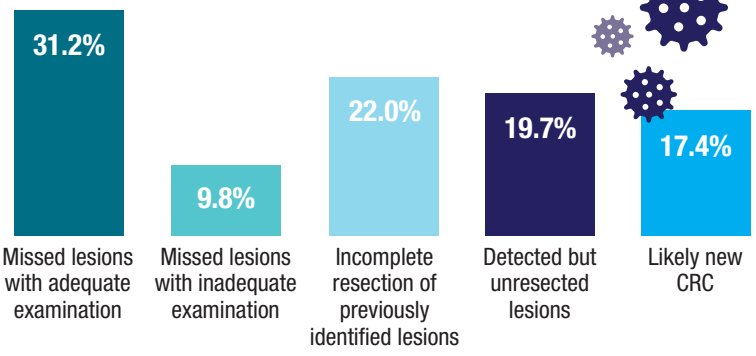
A study with > 52,000 VA patients, who were FIT-positive and had a colonoscopy from 2015 through 2022, assessed PCCRC rates and causes. PCCRC was defined as CRC found ≥ 6 months after colonoscopy.

PCCRC Prevalence



3-Year PCCRC Rate

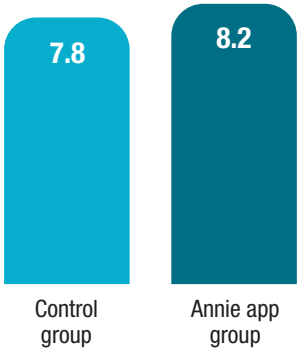
Causes of PCCRC



Digital Interventions to Improve Bowel Preparation and FIT Return Rate[7,9]

A study with 640 veterans at the Minneapolis VA assessed the effectiveness of a texting application, Annie, on bowel preparation quality and patient satisfaction between 2019 and 2020. Annie provided a 6-day bowel preparation protocol via text message. Bowel preparation quality was measured by the Boston Bowel Preparation Scale, in which scores of 0 to 3 are given for each segment of the colon: left, transverse, and right. A total score of ≥ 6 with a minimum score of 2 per segment is considered adequate preparation; higher scores can facilitate better detection of small or flat polyps.

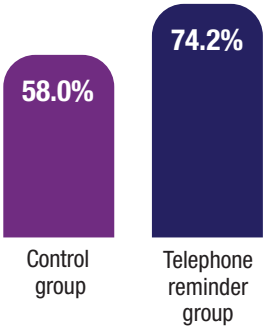
Bowel Preparation Quality Score

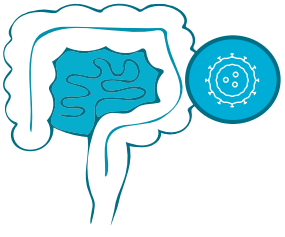


Differences were still present in bowel preparation scores after controlling for age and mental health diagnoses.

Another study of 800 patients at the Minneapolis VA in 2020 evaluated the effect of a telephone call reminder on FIT completion rates.

FIT Completion Rate





Advancing HCC Management: Updated Guidelines and VHA's Innovative Screening Trial

Tamar H. Taddei, MD

Hepatocellular carcinoma (HCC) accounts for ~90% of liver cancers worldwide.[1] Population-based data indicate that in many regions 60% or more of HCC cases are diagnosed at intermediate or advanced stages, reflecting a high proportion with local extension or distant metastases at presentation—limiting curative options.[2] Posttreatment recurrence reaches 70% within 5 years after resection (higher after ablation) but ~10% after liver transplantation.[1] Veterans in VHA care face 4 to 5 times higher HCC incidence than the general United States population due to elevated cirrhosis prevalence; however, the VHA's integrated system and population health focus enables higher screening rates.[3,4]

The VHA 2023 PREMIUM trial is comparing abbreviated MRI (aMRI) with standard ultrasound screening, aiming to detect HCC earlier, increase curative treatments, and reduce mortality in high-risk veterans. If the study is successful, aMRI could become the new VA screening standard.[5] These advancements reflect ongoing efforts to improve HCC outcomes through refined guidelines and innovative screening tailored to high-risk veterans.

The American Association for the Study of Liver Disease (AASLD) updated HCC Practice Guidance (2025) advises against systemic adjuvant therapies outside clinical trials, prioritizing surveillance and salvage transplantation or liver-directed therapies for recurrence.[6] This change in guidance is based on updated findings from the IMbrave050 trial, but many more regimens are being studied that could further impact treatment recommendations in this setting.

VA PREMIUM Study: aMRI and Ultrasound for Early HCC Detection[5]

Rationale

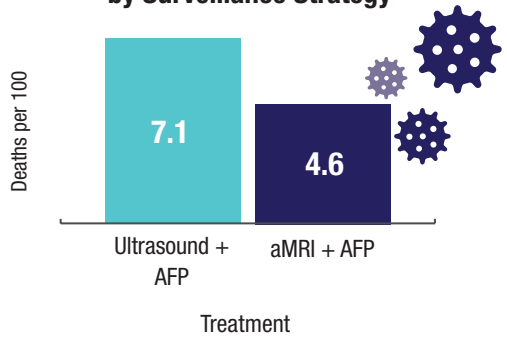
- Early detection boosts curative treatment, reducing mortality
- aMRI protocols are brief, cost-effective, and available at VA sites

This 8-year, 2-arm study compares aMRI + alpha-fetoprotein (AFP) screening versus ultrasound + AFP in patients with cirrhosis at high risk for HCC.

A total of 2350 participants per group will undergo screening every 6 months, HCC-related mortality is the primary endpoint.

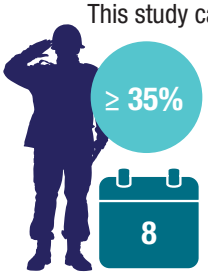
Proven mortality benefits could position aMRI as the new screening standard.

Projected 8-Year HCC Mortality by Surveillance Strategy



Hypothesized Power Calculation

This study can detect a



reduction in HCC-related mortality at 8 years

AASLD HCC Guidance Update: Adjuvant Therapy and Recurrence Management[6]

AASLD advises against adjuvant and neoadjuvant systemic therapies for patients with HCC undergoing resection/local ablation (level 1, strong recommendation)

Management post-resection/ablation with complete response by clinical scenario

- Recurrence within Milan criteria
  - Salvage liver transplantation
- Liver-localized recurrence within downstaging criteria
  - Liver-directed therapy, consider transplantation if downstaged or systemic therapy if disease progresses
- Recurrence with vascular invasion, extrahepatic spread, or unsuitable or locoregional therapy
  - First-line systemic therapy

Current Standard

Surveillance post-resection/ablation, even for high-risk patients

Ongoing Trials

Adjuvant (Phase III)
- ✓ Pembrolizumab (KEYNOTE-937)
- ✓ Nivolumab (CheckMate-9DX)
- ✓ Durvalumab + bevacizumab (EMERALD-2)
- ✓ Camrelizumab + apatinib

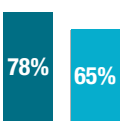
Neoadjuvant (Phase II)
- ✓ Atezolizumab + bevacizumab
- ✓ Nivolumab + ipilimumab
- ✓ Lenvatinib + pembrolizumab

Although the initial analysis of IMbrave050 showed promise, atezolizumab plus bevacizumab lacked sustained recurrence-free survival (RFS) benefit for HCC, with immature overall survival (OS) data in a second interim analysis. No FDA-approved adjuvant or neoadjuvant HCC therapies exist; surveillance remains standard post-treatment. Early interim analyses may overestimate benefits due to nonproportional hazards, underscoring the need for robust trial designs. Ongoing trials may identify effective therapies, but current practice relies on surveillance and established recurrence management.

Initial Analysis
Median follow-up: 17.4 months

RFS
HR 0.72

12-month RFS
78% vs 65%
(Treatment vs placebo)



Treatment duration
11 months

Adverse events
34.9%
grade 3-4

Second Interim Analysis
Median follow-up: 35.1 months

RFS
HR 0.90

OS
HR 1.26; >80% alive in both arms

Subgroups
No difference

Safety
No new concerns

HR, hazard ratio

Mental Health Care in Veterans With Cancer

Kaitlin N. Ohde, PhD

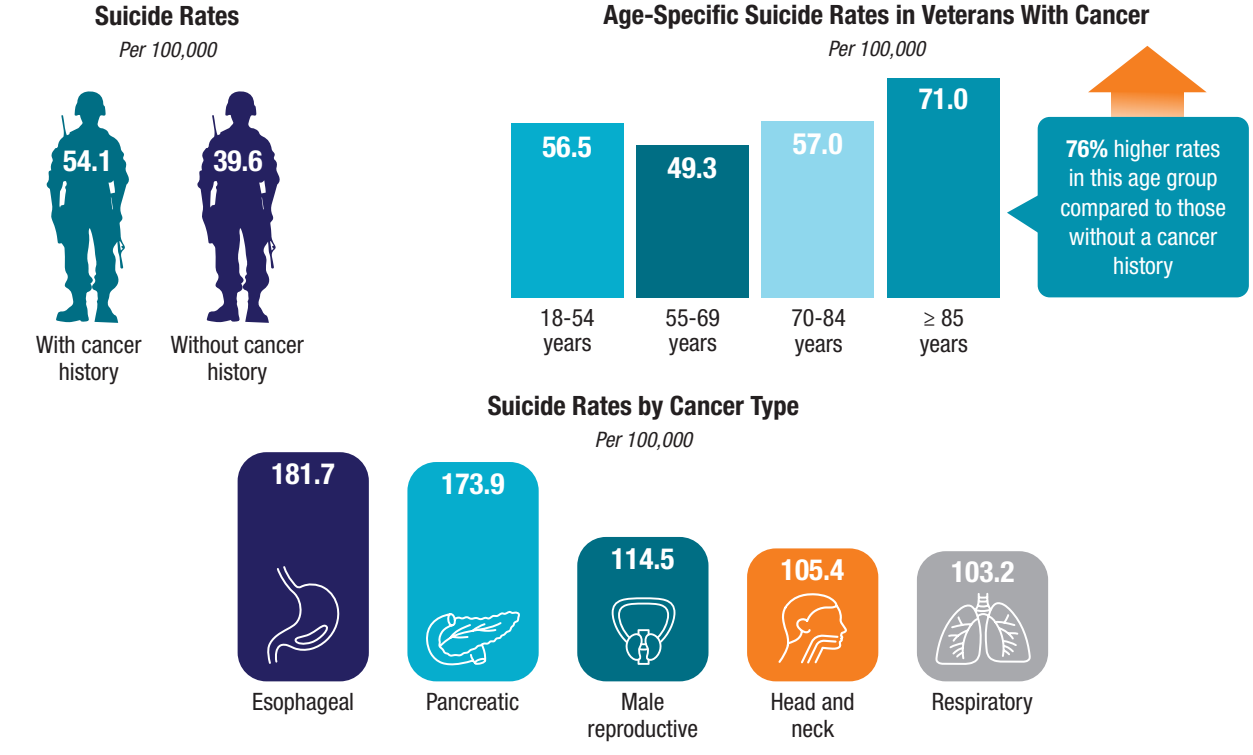
A cancer diagnosis can lead to a complex emotional experience, with increased risk for depression, anxiety, posttraumatic stress disorder (PTSD), eating disorders, and suicide.[1-3] In veterans — who are already at increased risk of suicide compared with civilians — cancer diagnoses represent a time of susceptibility to mental health challenges that healthcare professionals should be aware of.[2,4] Veterans with cancer have 37% higher suicide rates compared with veterans without cancer; esophageal, pancreatic, male reproductive, head and neck, and respiratory cancers confer the most risk.[2] Throughout the cancer treatment process, two time periods reflect the highest suicide risk: right after diagnosis, and early survivorship, making risk assessment crucial throughout treatment and after treatment ends.[2]

The evaluation of mental health status during cancer is complex. Depression and anxiety can stem from the psychosocial factors related to having cancer, as well as from the cancer medications themselves.[1,5] Identifying if mental health symptoms are related to the cancer itself or psychosocial factors is important for management.[5] A cancer diagnosis is a time for veteran healthcare professionals to assess mental health frequently, especially for suicide risk.

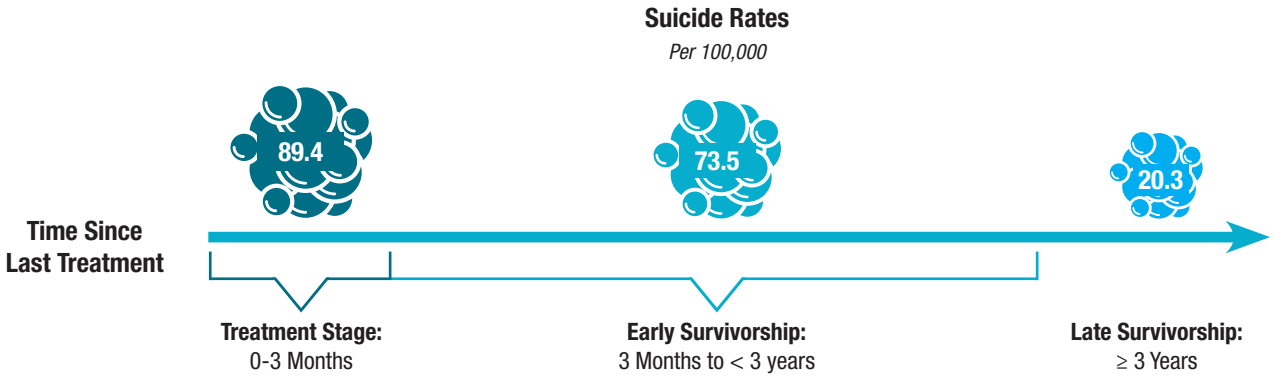
If you or someone you know is having thoughts of suicide, **call or text 988 to reach out to the National Suicide Prevention Lifeline, or contact the Veterans Crisis Line: www.veterancrisisline.net**

Suicide Rates in Veterans With Cancer[2]

Approximately 440,000 veterans with cancer were compared with an age-matched cohort of veterans without cancer to assess suicide rates. The cohort was predominantly male and White, with a mean age of 67.2 years.

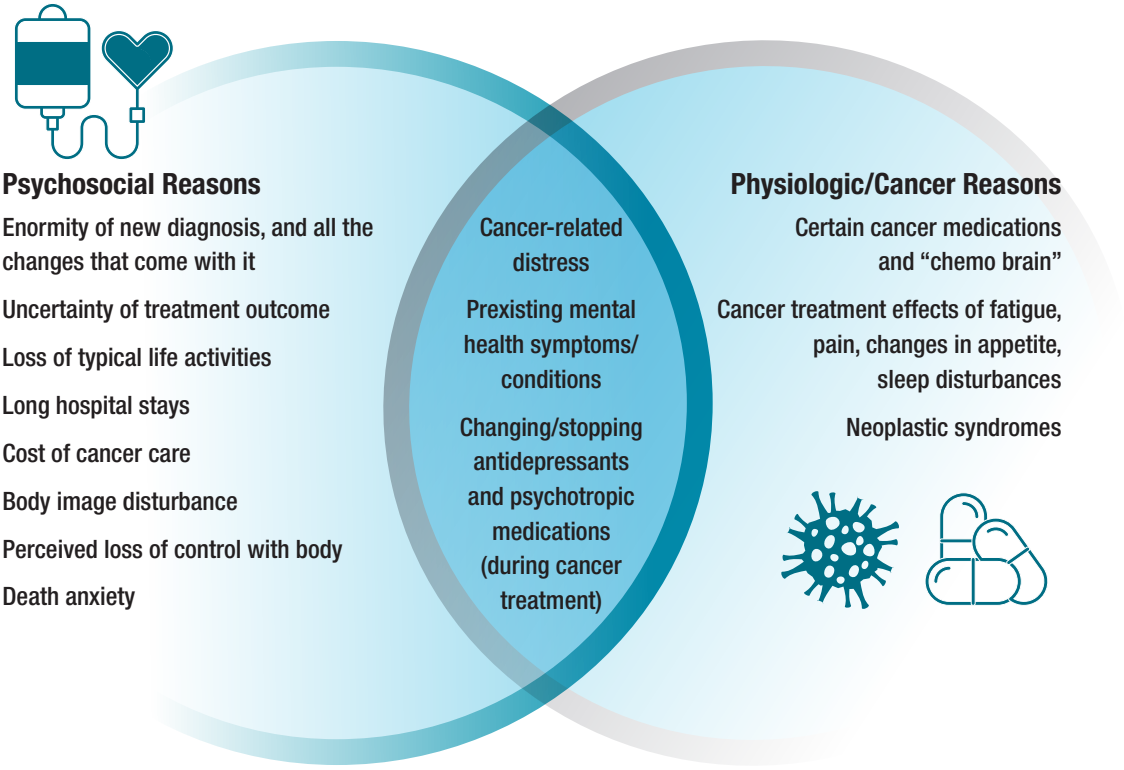


Timeline of Suicide Risk in Veterans With Cancer[2]



During the first year since diagnosis, **the hazard rate of suicide was 86% higher in veterans with cancer** compared to veterans without cancer. Hazard rates declined in years 2-5 and leveled out after year 5.

Possible Causes of Depression and Anxiety in Cancer[1,5-7]



It is important to assess if mental health symptoms in cancer are caused by psychosocial factors or by cancer physiology and cancer medications. Mental health screening tools should be used to assess mental health symptoms, and asking tailored questions can help differentiate the origin of symptoms.

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