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Advances in HCC Treatment: Optimizing Care for Veterans from Diagnosis On

by Annette Boyle | Oct 25, 2025

Tamar Taddei, MD, Chief, Digestive Diseases, VA Connecticut Healthcare System Westhaven, Professor of Internal Medicine, Yale School of Medicine

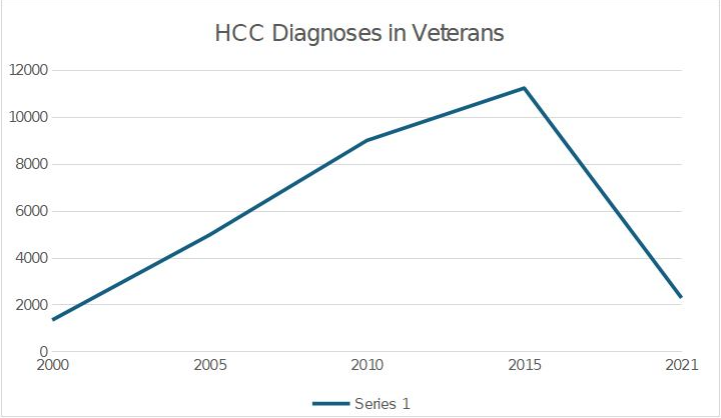
WEST HAVEN, CT — Hepatocellular carcinoma (HCC) remains one of the most lethal cancers worldwide and an urgent concern within the VA. The disease's landscape has shifted markedly in recent years with significant changes in etiology as well as rapid expansion of treatment options.

The widespread cure of hepatitis C virus (HCV) infection within the VA—one of the most striking public health achievements of the past decade—dramatically reduced HCV-related HCC. Yet as one risk factor has receded, another has risen sharply: metabolic dysfunction-associated steatotic liver disease (MASLD) and its progressive form, metabolic dysfunction-associated steatohepatitis (MASH).

For much of the past three decades, chronic HCV infection was the dominant risk factor for HCC in veterans. The department began aggressively screening veterans for HCV and monitoring them for cirrhosis and cancer in 1998, Kenneth Kizer, former VA under secretary for health told U.S. Medicine.

Aggressive VA screening and treatment programs using direct-acting antivirals cured more than 100,000 veterans, dramatically lowering progression to cirrhosis and HCC. But a new challenge has emerged.

"MASLD is now front and center," Tamar Taddei, MD, chief, digestive diseases, VA Connecticut Healthcare System in Westhaven and professor of internal medicine (digestive diseases) at the Yale School of Medicine, told U.S. Medicine.

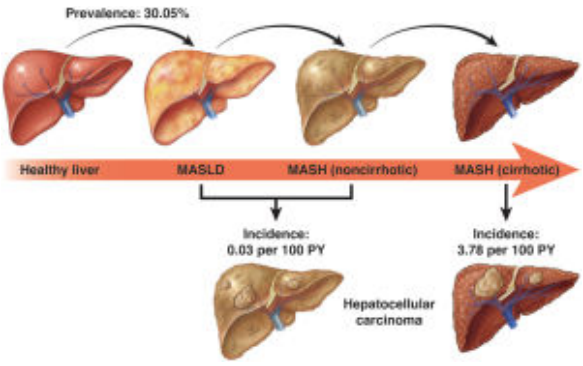


Click to Enlarge: *Data Source: VSSC Advanced Liver Disease Data Cube, VA reports (Graphic original to U.S. Medicine)*

National data support this observation. Up to 30% of U.S. adults have MASLD, with 20% of those progressing to MASH and 2% developing HCC, according to the American Liver Foundation. In veterans, prevalence is even higher given widespread obesity, diabetes, hypertension, and metabolic syndrome. The combination of metabolic and alcohol-related liver injury (MetALD) further increases risk.

Unlike HCV-related HCC, MASLD-related cancers often arise in non-cirrhotic livers, complicating screening strategies. "It's impossible to screen every person with MASLD—there are 100 million Americans at risk," Taddei added. "We're working on multivariable risk scores to identify who is most likely to develop HCC."

Candidate risk factors include genetic variants such as the gene PNPLA3, which plays a significant role in liver metabolism; common mutations increase fat accumulation in the liver and development of MASLD and MASH. Additional factors for HCC risk include environmental exposures, alcohol intake, and potentially some less well understood metabolic contributors. VA researchers are actively investigating these factors, recognizing that veterans represent a particularly high-risk cohort.



Click to Enlarge: Prevalence and incidence rates of metabolic dysfunction–associated steatotic liver disease (MASLD)/metabolic dysfunction–associated steatohepatitis (MASH) and hepatocellular carcinoma (HCC). PY, persons-year. *Source: Clinical Gastroenterology and Hepatology*

Heightened awareness among patients and across the health care system is critical for improving monitoring of liver disease. "I wish primary care physicians would think more about advanced liver

disease, calculate FIB-4 scores and refer patients when they were concerned about advanced fibrosis," Taddei said. "We have a lot of people walking around with liver disease who don't know they have it."

Unexpected and distressing findings on imaging

"Because so much hepatitis C has been cured—especially in the VA, where we've done a really great job of curing so many veterans of their hep C—we're now seeing much more non-cirrhotic HCC with the underlying etiology being MASLD or MASH," Taddei said.

"Patients may not know they have liver disease, and then they get imaging done for another indication, and we see a liver cancer. They're diagnosed with MASLD, advanced fibrosis and HCC all in one visit," Taddei explained. "A lot of these cancers are more advanced than we see in people who know they have cirrhosis and are being adherent to liver cancer surveillance recommendations for screenings every six months."

The lack of widely accepted screening protocols for MASLD/MASH and the insidious nature of HCC means many patients present at advanced stages, limiting those options and life expectancy.

Nationally, five-year survival for HCC improved modestly from 16% to 22% over the past decade. Digging in the details of survival highlights the cost of missed early detection.

"If you have early-stage HCC with preserved liver function, you should expect to live years—five years or more is very realistic," Taddei said. "Even at intermediate stage, two years is a reasonable expectation. I have one patient I've kept alive for 15 years. We ablate or TACE [transarterial chemoembolization] new tumors as they appear, and we just keep going."

Different etiologies, different treatment

Treatment for patients with HCC caused by MASLD may differ from that seen in patients with hepatitis C, too. "Many of these folks actually have well preserved liver function. We try to resect them if they're resectable at diagnosis, but again, if they're diagnosed very late in the game, then they may not have the benefits of loco-regional therapy, especially if they have vascular invasion or extrahepatic spread," Taddei noted.

For patients with early-stage disease, resection and ablation remain mainstays.

In veterans with locally advanced HCC, transarterial radioembolization (TARE) and transarterial chemoembolization (TACE) are recommended. Ablation, stereotactic body radiation therapy and proton-beam radiotherapy have also shown effectiveness.

Liver transplantation is unique in curing both HCC and cirrhosis. Milan criteria (one lesion ≤5 cm or up to three lesions ≤3 cm) remain the benchmark, but downstaging and salvage transplant approaches

have expanded eligibility. “Transplant offers the best chance of durable cure,” Taddei said.

Loco-regional therapies, expanding systemic options, and more flexible guidelines allow more patients a shot at that ‘best chance,’ she noted. By reducing tumor numbers and size, “we can downstage to transplant and we can do salvage transplant after resection. Coordination is everything.”

TACE has long dominated therapy for intermediate-stage HCC. But repeated sessions reduce viable parenchyma and harm hepatic reserve. “We need to recognize TACE refractoriness early,” Taddei said. “If patients are developing interval tumors between sessions or not achieving complete responses after one or two attempts, you’re better off preserving liver function and moving them to systemic therapy.”

This “preserve-to-treat” mindset supports a broader principle: sequencing matters. Protecting liver reserve up front can expand later options (including immunotherapy and transplant candidacy).

Exploring Combinations with Loco-regional Therapies

One option may be integrating loco–regional and systemic therapy to improve outcomes in nonresectable, non-metastatic HCC.

The LEAP-012 trial published earlier this year in The Lancet tested TACE with lenvatinib plus pembrolizumab against TACE with dual placebos.[1] “That really improved progression-free survival significantly to 14.6 months vs. 10 months for TACE alone, but again, it didn’t reach statistical significance for overall survival at the interim analysis, so we’re eager to see the final analysis,” Taddei said.

The increase translates into a 34% reduction in risk of progressionLEAP-012. Sixty-nine participants (29%) in the lenvatinib plus pembrolizumab group and 82 (34%) of those in the placebo group died for a 24-month overall survival rate of 75% (95% CI 68–80) in the lenvatinib plus pembrolizumab group and 69% (95% CI 62–74) in the placebo group (HR 0.80, 95% CI 0·57–1·11; one-sided p=0.087).

Another study published at the same time in The Lancet, the EMERALD-1 trial, examined TACE plus durvalumab plus bevacizumab in a three-arm study: TACE plus durva-bev, TACE plus durva and TACE plus placebo.[2] “The arm with durva-bev showed improvement in progression-free survival compared to TACE plus placebo, while the arm with durva alone did not show a significant progression-free survival benefit,” Taddei noted. “So we’re still waiting to see where the dust settles in overall survival before these become ready for prime time.”

The 616 patients evaluated were assigned 1:1:1 to the three arms. With a median follow-up for progression-free survival of 27.9 months, PFS in the combo arm was 15 months, 10 months for durvalumab and 8.2 months for sorafenib for a 23% reduction in progression risk for the combination

(HR 0.77, 95% CI 0.61–0.98; two-sided p=0.032) compared to placebo. Participants continue to be followed for overall survival.

Advanced HCC treatment emerging

For complex patients and those with advanced disease at diagnosis, "multidisciplinary tumor boards are still the mainstay of determining what we do. It still requires a pretty in-depth conversation and a great knowledge of the patient, their preferences and their underlying medical illnesses to know what they're eligible for and what they're not," Taddei explained.

While treatment options may be changing, some things remain the same. "What we know to be the concrete standard of care is that If a person has vascular invasion or extrahepatic metastases, that is when we consider systemic therapy."

In this area in particular, options have multiplied. For a decade, sorafenib reigned as the only therapy available for metastatic HCC. Since the approval of lenvatinib in 2017, however, multiple targeted therapies and immune checkpoint inhibitors (ICIs) have expanded the armamentarium, improving survival and changing practice guidelines.

The SHARP trial in 2008 established the tyrosine-kinase inhibitor (TKI) sorafenib as the first systemic therapy to extend survival in advanced HCC.[3] Patients lived a median of 10.7 months vs. 7.9 with placebo, with a hazard ratio for death of 0.69. Though modest, this three-month benefit was historic for a cancer long considered untreatable.

The phase 3 REFLECT trial posed the first successful challenge to sorafenib's dominance. It compared lenvatinib, a multi-targeted TKI of vascular endothelial growth factor (VEGF) receptors 1-3 and other receptor tyrosine kinases, including FGFR1-4, PDGFRα, cKIT, and RET, that also has some immunomodulatory effect, to sorafenib. The study evaluated 954 patients treated at 154 sites across 20 countries in four continents who were randomized on a 1:1 basis to lenvatinib (478) or sorafenib (476).[4]

Lenvatinib achieved non-inferior overall survival with a median of 13.6 months (95% CI 12.1-14.9) vs. 12.3 months for sorafenib (12.3 months, 10.4-13.9; hazard ratio 0.92, 95% CI 0.79-1.06). Lenvatinib proved superior in progression-free survival, however, with a median PFS of 7.4 months vs. 3.7 months for sorafenib. Lenvatinib also had much more robust response rates, with overall response of 18.8% vs. 6.5% for sorafenib.

A meta-analysis of 15 studies supported the initial findings, demonstrating a 37% improvement in progression-free survival for lenvatinib. The meta-analysis also highlighted significant differences in response rates between the two TKIs, finding them roughly five times higher for lenvatinib.[5]

The complete response (CR) rate was 3.22% for lenvatinib vs. 0.60% for sorafenib (OR = 5.61; 95% CI: 2.71–11.64; p < 0.00001). Partial response (PR) rates were 23.94% vs. 6.97% (OR = 4.62; 95% CI: 3.06–6.98; p < 0.00001) and overall response rate (ORR) of 25.74% vs. 6.4% (OR = 5.61; 95% CI: 3.90–8.09; p < 0.00001) for lenvatinib and sorafenib, respectively. The disease control rate was also significantly higher for lenvatinib at 71.54% compared to sorafenib at 51.59% (OR = 2.42; 95% CI: 1.79–3.28; p < 0.00001).

"In practice, lenvatinib seems to have a better side-effect profile than sorafenib," Taddei said. "Between the progression-free survival and tolerability, I rarely see patients on sorafenib anymore."

The IMbrave150 trial changed the landscape once again with the introduction of immune checkpoint inhibitors (ICIs). The trial evaluated 501 patients with HCC assigned 2:1 to atezolizumab plus bevacizumab (atezo-bev), a combination of an anti-PD-L1 ICI and a VEGF inhibitor, or sorafenib. Atezo-bev improved overall survival to 19.2 months vs. 13.2 for sorafenib, corresponding to a 34% reduction in mortality risk (HR 0.66, 95% CI 0.52–0.85). PFS was 6.8 months vs. 4.3 months (HR 0.65, 95% CI 0.53-0.81) and ORR 27.3% vs. 11.9%. Eighteen patients in atezo-bev group had a complete response vs. zero in the sorafenib group. The disease control rate was 73.6% for the combo vs. 55.3% for sorafenib. At a median of 15.6-month follow-up, there was no change in OS or PFS rates.[6,7]

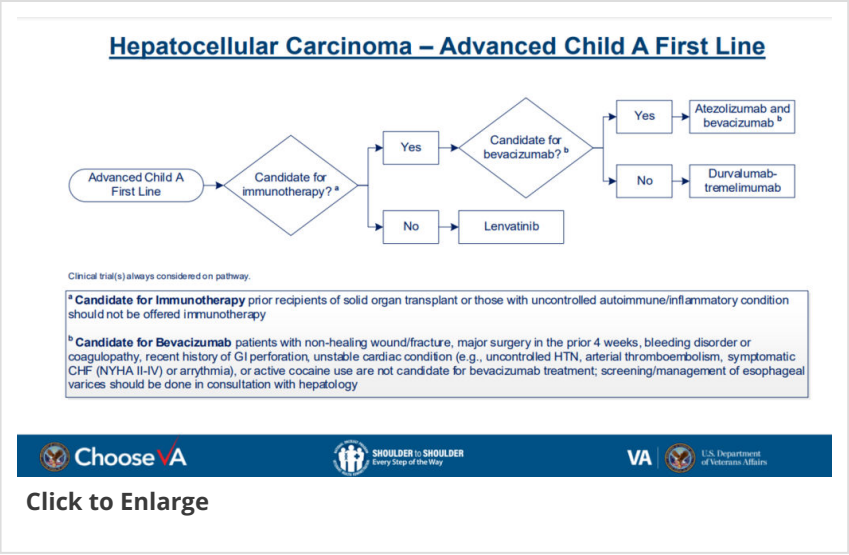
The HIMALAYA trial followed, comparing a combination of two ICIs, durvalumab plus tremelimumab (durva-treme) to durvalumab monotherapy and sorafenib monotherapy in 1171 patients assigned 1:1:1 to each arm. Durva-treme improved OS to 16.5 months vs. 13.8 for sorafenib (HR 0.78, 95% CI 0.65–0.92). ORR was 20.1% vs. 5.1%. Durvalumab alone was non-inferior to sorafenib. There was no difference in progression-free survival between the three arms. [8]

In a four-year follow-up of HIMALAYA, durva-treme (also called STRIDE, single tremelimumab regular interval durvalumab) continued to show a 22% reduction in mortality risk compared to sorafenib (HR 0.78, 95% CI 0.67-0.92). The 36-month OS rate for durva-treme was 30.7% versus 19.8% for sorafenib. At 48 months, the OS rate remained higher for the combination at 25.2% compared to 15.1% for sorafenib. The 103 long-term survivors who received the combo therapy included participants across clinically relevant subgroups and 57.3% of them reported no subsequent anticancer therapy.[9]

Matching Patient to Therapy

National guidelines from the VA, American Association for the Study of Liver Disease, the American Society of Clinical Oncology and the National Comprehensive Cancer Network (NCCN) recommend the ICI combinations as the preferred first-line therapies for most patients based on the longer overall survival compared to TKIs. The guidelines recommend sorafenib and lenvatinib in the first line for patients unable to tolerate immune therapies because of autoimmune disorders and for those who have received liver transplants.

The 2025 NCCN guidelines for HCC also include tislelizumab and durvalumab, as category 1 first-line therapies and nivolumab plus ipilimumab and pembrolizumab as other options.



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Choosing between the combinations is something of a toss up, with common patient comorbidities in the VA perhaps favoring atezo-bev. “The survival for atezo-bev seems to be superior to durva-treme, but both combinations are excellent when well tolerated,” Taddei said. And, the incidence of grade 3 or 4 adverse events are less than she has seen for TKIs.

Still, “there are some contraindications to the use of bevacizumab. So, for example, in the VA where you have a lot of hypertensive cardiovascular disease and risk for stroke or history of significant bleeding, you’re going to want to avoid bevacizumab,” she noted. Similarly, “if you have high risk esophageal varices you’re not going to get bevacizumab unless those varices are banded, which, of course, could delay treatment.”

“Now, if you can’t have immunotherapy, say, you have had a transplant or have autoimmune hepatitis or some other autoimmune condition where you know that giving a new checkpoint inhibitors will probably make that condition flare, then you want to be thinking about a TKI,” she noted.

Immune-related adverse events (irAEs) require vigilance across the board. “They can be subtle—you must keep patients in care and monitor closely,” Taddei stressed. Early recognition of colitis, hepatitis flares or endocrinopathies is crucial.

Immunotherapies and VEGF-blocking regimens increase the risk of proteinuria and all patients should be monitored for hypertension, renal insufficiency, and thyroid dysfunction as well as nutrition and frailty throughout treatment, particularly as therapies can cause loss of appetite, she noted.

Taddei tends to take a holistic view of the patient and disease progression.

“Overall survival is really the gold standard; it’s certainly the oncological standard. But I do know that the longer you can keep a person with liver disease from developing portal hypertension and consequences of their liver disease, which could be accelerated with growth of tumor, the longer they would have a good quality of life,” she observed. “It can be very difficult to determine the cause of

death in somebody who has cirrhosis and liver cancer, because when the liver cancer progresses, the liver function usually declines, and then they end up dying of what looks like liver-related death, as opposed to cancer-related death because they are so intimately intertwined."

At-a-Glance: Clinical Trial Data Highlights in Advanced HCC

Regimen / Trial	Median OS (comparator)	PFS	ORR	Key Notes
Sorafenib (SHARP3)	10.7 mo vs. 7.9 (placebo)	5.5 mo	2%	First systemic option (2007); modest OS benefit
Lenvatinib (REFLECT4)	13.6 mo vs. 12.3 (sorafenib)	7.4 vs. 3.7 mo	18.8% vs. 6.5%	Non-inferior OS; better PFS and ORR; generally better tolerated
Atezolizumab + bevacizumab (IMbrave1506)	19.2 mo vs. 13.2 (sorafenib)	6.8 vs. 4.3 mo	27% vs. 12%	34% mortality risk reduction; avoid in uncontrolled HTN, untreated varices, or bleeding risk
Durvalumab + tremelimumab (HIMALAYA8)	16.5 mo vs. 13.8 (sorafenib)	3.8 vs. 4.1 mo	20.1% vs. 5.1%	Improved OS and ORR; good option when bevacizumab contraindicated

Real-World Considerations, Patient Characteristics Factor into Selection

HCC treatment selection is inseparable from staging (e.g., BCLC) and liver function (Child-Pugh). "Most pivotal trials enrolled Child-Pugh A patients," Taddei noted. "But many real-world VA patients are

Child-Pugh B. Later studies suggest feasibility and relative safety in Child-Pugh B, but we have to be more careful. That's where the tumor board's judgment is critical."

The age at diagnosis and average age of veterans also affect treatment decisions. "With a median age at HCC diagnosis of 64, veterans often have multiple comorbidities—cardiovascular disease, renal impairment, diabetes—that influence choice at every step."

A deeper look at patient response

Recent studies suggest that the choice between ICIs and targeted therapies should be approached with greater nuance and with attention to the specific characteristics of both the patient and their disease. A meta-analysis in Digestive and Liver Disease explored whether the differences in the immunological microenvironment in viral cirrhosis and MASLD/MASH affected response to ICIs.[10]

"In the IMbrave150 trial, subgroup analyses were performed in three populations according to HCC: HBV, HCV and non-viral HCCs. The combination atezolizumab + bevacizumab was demonstrated to be superior as compared to sorafenib in patients with HBV-HCCs (HR = 0.58, 95% CI 0.40–0.83) and HCV-HCCs (HR = 0.43, 95% CI 0.25–0.73). By contrast, patients with non-viral HCC did not demonstrate a survival benefit from atezolizumab + bevacizumab compared to sorafenib (HR = 1.05, 95% CI 0.68–1.63)," the authors wrote in Digestive and Liver Disease.

A meta-analysis published in Nature reexamined the IMbrave150, KEYNOTE-240 and Checkmate 459 trials, totaling 1656 patients, based on etiology. The international team of researchers found that immunotherapy improved survival in the overall population by 23%. Digging into the data, patients with virus-related HCC who received ICIs had a significantly greater OS benefit compared to the group treated with sorafenib (HR = 0.64, 95% CI 0.50–0.83). On the flip side, patients with non-viral HCC who received ICIs did not have a significantly superior OS compared to the sorafenib group (HR = 0.92, 95% CI 0.77–1.11).[11]

"Our data identify a non-viral etiology of liver damage and cancer as a predictor of unfavorable outcome in patients treated with immune-checkpoint inhibitors. The better response to immunotherapy in patients with virus-induced HCC than in patients with non-viral HCC might be due to the amount or quality of viral antigens or to a different liver micro-environment, possibly one that does not impair immune surveillance," the European team noted. "Overall, our results provide comprehensive mechanistic insight and a rational basis for the stratification of patients with HCC according to their etiology of liver damage and cancer for the design of future trials of personalized cancer therapy."

A group of researchers at the Icahn School of Medicine at Mount Sinai observed that 20% to 40% of HCC patients treated with the ICI combination therapies demonstrated primary resistance. To determine whether etiology played a role, they enrolled 299 patients, 71.5% of whom had viral-

related HCC. Of those, 73.3% had HCV and 27.2 had hepatitis B. The non-viral group split 40.2% related to alcohol and 45.1% due to MASLD. The balance had mixed etiologies.[12]

Patients with non-viral HCC were on average older (68 vs. 63.5 years) and more likely to have cirrhosis (91.3% vs 75.6%) and more advanced disease (BCLC stage C), 78.2% for non-viral HCC vs. 59.8% for those with viral HCC.

With a median follow-up of 12.8 months, the median OS was 14 months. Patients with viral HCC had a median OS of 19 months and those with non-viral HCC had a median OS almost half that at 10 months. PFS was also worse for the non-viral group, three months, compared to five months for the viral HCC group. Looking at just the participants who had Child Pugh class A liver disease, at a median follow-up of 15.1 months, patients with viral HCC had a median OS of 24 months and a PFS of six months compared to 13 months and three months for OS and PFS, respectively, for those with non-viral HCC.

“Our own study found that non-viral HCC was associated with worse survival outcomes and response to front-line ICI therapy, but these effects were most prominent for patients with CP class A liver disease,” the Icahn authors noted. “We found that patients with [MASH]-induced HCC likely drove the negative prognostic effects seen in the non-viral HCC group, particularly in patients with preserved liver function. Nevertheless, the small number of [MASH] patients limits our ability to draw firm conclusions. Future studies, particularly clinical trials, should stratify patients into specific etiologies to clarify how [MASH] affects treatment outcomes.”

Othe patient characteristics might matter

In addition to etiology, a patient-specific characteristic might also influence response to ICIs and favor targeted therapies—sex. The liver is “an organ with recognized sexual dimorphism,” leading to marked differences between males and females and males throughout the natural history of liver diseases. Notably, males are less likely to spontaneously clear viral hepatitis infections, more likely to develop cirrhosis related to HCV or HBV infections, and two to five times more likely to develop all-cause HCC.[13]

A review published earlier this year indicated that the differences persist in treatment as well, with women responding more positively to immunotherapies, a factor important to VA clinicians who are treating rising numbers of female veterans. “Female patients, for instance, may experience better responses to therapies targeting PD-1/PD-L1, owing to the typically higher expression of immune checkpoints in females,” the authors said, while males may benefit more from alternative strategies.[14]

“One promising direction involves the development of personalized treatment strategies that take into account the unique immune landscapes in males and females,” the authors concluded.

“Specifically, patient stratification based on circulating sex hormone levels (e.g., estrogen, progesterone, testosterone) may help optimize immunotherapeutic response and minimize immune-related adverse effects. Integrating hormonal modulation with immune checkpoint inhibitors could potentially enhance the therapeutic response, especially in females, who often exhibit stronger immune responses due to estrogen-related pathways. Similarly, modulating testosterone in males could help balance immune responses without triggering excessive inflammation.”

If supported by additional research, stratifying by sex hormone levels such as estrogen, progesterone and testosterone and integrating hormonal modulation with ICIs could optimize response. With the VA serving more women veterans, considering dimorphism in response may improve outcomes.

On a molecular level, biomarkers have not emerged as important factors in selection of therapy in HCC, unlike it many other cancers. Currently, alpha fetoprotein of 400 ng/mL or greater is the only validated biomarker guiding therapy, identifying candidates for ramucirumab, which is not a first-line therapy. Tumor profiling occasionally reveals actionable mutations such as MSI-high, she said, but these are rare.

“That’s the only true biomarker-driven choice we have right now,” Taddei noted. “Beyond that, tumor profiling sometimes finds actionable mutations like microsatellite instability or certain fusion proteins, but these are rare. We don’t routinely profile tumors for HCC in practice because there aren’t many actionable mutations.”

That could change, given the expanding role of the VA National Precision Oncology Program, which offers tumor profiling to all veterans with cancer and incorporates clinical trials for targeted therapies as they become available. “We should keep looking,” Taddei added. “Genetics is always evolving. Things we thought were nonsense in the past are actually now very important.”

Integrated care provides best outcomes

The new therapies are steadily improving survival rates. Even with advanced disease, “checkpoint inhibitors have allowed some patients to live years,” said Taddei.

The key is frequent reassessment. “You have to bring patients back for frequent interval imaging, ablate or TACE new tumors, and not forget about transplant,” she added. “It’s a complex, ever-changing landscape that requires multidisciplinary work.”

Tight integration of hepatology and oncology leads to the best outcomes. “Too often patients do well on immunotherapy, live longer, and get close follow-up with oncology—but they fall out of liver care. That’s not a good thing,” Taddei said. “We still need to think about liver diseases, about clinically significant portal hypertension. We need to reassess our patients frequently and bring them back to tumor board. If we could run this like a well-choreographed musical, our patients would do better.”