PANEL DISCUSSION

# Combination Locoregional and Immunotherapy in Practice

Beau B. Toskich, MD, leads Rony Avritscher, MD; Kirema Garcia-Reyes, MD; and Nora Tabori, MD, through a series of questions about their approaches to combining local therapy with immunotherapy, how/if recent data have impacted their decision-making, preferences on type of immunotherapy, emerging applications, and more.


**MODERATOR**
**Beau B. Toskich, MD, FSIR**
Director of Interventional Oncology
Professor of Radiology
Mayo Clinic
Jacksonville, Florida
toskich.beau@mayo.edu

**Rony Avritscher, MD**
Department of Interventional Radiology
University of Texas/MD Anderson Cancer Center
Houston, Texas
rony.avritscher@mdanderson.org

**Kirema Garcia-Reyes, MD**
Assistant Professor, Interventional Radiology
Associate Program Director, IR/DR Residency
Icahn School of Medicine at Mount Sinai
New York, New York
kirema.garcia-reyes@mountsinai.org

**Nora Tabori, MD**
Associate Professor of Radiology
MedStar Georgetown University Hospital
Chief of Interventional Radiology
MedStar Washington Hospital Center
Washington, DC


The oncology landscape has been changed by the advent of immunotherapy. Locoregional therapies are now a standard-of-care and indispensable treatment for many cancers. There has been considerable enthusiasm in the potential of combining these therapies, yet data in support of their interaction are only beginning. We have reached out to leading interventional oncology experts for their opinion on how to best treat patients while our understanding of combining local therapy and immunotherapy matures.

### Dr. Toskich: Are you currently combining local therapy with immunotherapy in your practice? If so, what evidence in your experience has prompted you to consider this approach?

**Dr. Avritscher:** Yes, in our current practice, we often combine locoregional therapies with systemic immunotherapy. The results of both IMbrave150 and HIMALAYA trials established the role of immunotherapy in advanced hepatocellular carcinoma (HCC), and we commonly employ locoregional modalities to help consolidate therapy for those patients.

**Dr. Garcia-Reyes:** Yes, we currently combine locoregional therapies such as yttrium-90 (Y90) radioembolization with immunotherapy, particularly in high-risk patients. Our experience has shown that patients receiving this combination therapy demonstrate improved imaging responses and, in some cases, better disease control compared to those on monotherapy. We have observed promising out-

comes in these high-risk populations, which encourages us to continue implementing this approach. As clinical evidence continues to grow, we hope it will further inform and support our practice, demonstrating that combining locoregional therapies with immunotherapy can provide significant benefits for these patients.

**Dr. Tabori:** The answer is yes, but in who, is the real question. Intermediate-stage HCC as defined by Barcelona Clinic Liver Cancer (BCLC) includes everything from well-defined disease just outside of transplant criteria to diffuse bilobar infiltrative disease.[1] Although the BCLC would suggest that the latter category receives systemic therapy alone, we know from animal and human studies that a lower primary tumor load leads to a more favorable response from multikinase inhibitors and immunotherapies. Promising results found in several studies, including LAUNCH where the combination of lenvatinib with transarterial chemoembolization (TACE), demonstrated a significant improvement in overall survival (OS) compared to lenvatinib alone may be explained by this concept of debulking.[2] However, additional mechanisms of synergy must also be considered. Locoregional therapies create in an ischemic environment resulting in the upregulation of proangiogenic factors that may lead to future recurrence, so it stands to reason that targeting this with tyrosine kinase inhibitors (TKIs) will result in a more durable result.

This hypothesis is further supported by the recent data from the EMERALD-1 trial. EMERALD-1 found that the combination of durvalumab (anti–programmed cell death ligand 1 [PD-L1]) plus bevacizumab (anti–vascular endothelial growth factor [VEGF]) plus TACE significantly improved progression-free survival (PFS) compared to TACE alone with no new safety signal, while the addition of durvalumab alone did not have a highly significant effect on the importance of the anti-VEGF effect.[3] There is also promising data emerging in the use of Y90 in combination with immune checkpoint inhibitors. Yu et al found that prembrolizumab with Y90 therapy resulted in PFS of 9.5 months and OS of 27.3 months in patients with advanced-stage disease with a manageable safety profile.[4] Similar efficacy and safety have been seen in two studies combining nivolumab and locoregional therapy including Y90, although larger studies are needed to confirm these results.[5,6]

So, to finally answer the question, I work in conjunction with my tumor board to select highly functional patients who have preserved liver function and either intermediate-stage HCC with poor prognostic features like high tumor burden, or infiltrative appearance or advanced-stage HCC patients to undergo combination therapy while I eagerly await additional data from studies such as LEAP012, ROWAN, and EMERALD-Y90.

**Dr. Toskich: The recent IMbrave050 phase 3 randomized clinical trial studied HCC patients with high-risk features undergoing resection or ablation who received adjuvant atezolizumab and bevacizumab. How do you define high-risk HCC that may benefit from combination therapy?**

**Dr. Tabori:** The criteria set by the investigators in the study should be used: tumor > 5 cm, more than three tumors, microvascular invasion on explant, minor macrovascular invasion Vp1/Vp2, or grade 3/4 pathology. I also include infiltrative appearance on preprocedural imaging and alpha-fetoprotein (AFP) > 400.[7]

**Dr. Avritscher:** The most defining feature of high-risk patients is macrovascular invasion present on preprocedural imaging. Other important high-risk features include multifocality, tumor size, infiltrative nature, and central location encompassing multiple vascular watershed areas. Novel tools that can help us identify high-risk patients include detection of circulating tumor cells and circulating tumor DNA and emerging gene panels.

**Dr. Garcia-Reyes:** This is a crucial discussion point, as "high-risk HCC" encompasses more than just patients with macrovascular invasion or large tumors. High-risk patients are defined by tumor biology that suggests a poorer prognosis, indicating they may benefit from more aggressive treatment. Additional features to consider include infiltrative HCC, multinodular disease, and patients with significantly elevated serum AFP levels.

**Dr. Toskich: The EMERALD-1 phase 3 randomized controlled trial met its primary endpoint of PFS in patients with HCC treated with TACE plus durvalumab and bevacizumab. How have these data impacted decision-making in your tumor board and why?**

**Dr. Garcia-Reyes:** At our institution, we have been combining locoregional therapy, primarily radioembolization, with systemic therapies for some time and have observed promising internal results. Although this trial focused on TACE, it highlights combination therapy as a viable treatment approach. Although it hasn't significantly changed our daily practice—given that we continue to prioritize radioembolization due to its documented benefits over chemoembolization—we remain optimistic that upcoming trials involving radioembolization will further validate and reinforce our strategy. Additional data will strengthen our case for combination treatment and will be crucial for those seeking to introduce or expand clinical practice.

**Dr. Avritscher:** The preliminary results of EMERALD-1 are carefully being considered by our interdisciplinary tumor board, and we perform both TACE and Y90 for our HCC patients in the context of combination therapies. However, we have not yet incorporated any specific changes into our treatment algorithm. We are awaiting publication of additional data, such as time to progression and OS.

**Dr. Tabori:** Previously, systemic therapy had been siloed to unresectable HCC not amenable to local regional therapy. We are now integrating systemic therapy much earlier in our treatment algorithm.

**Dr. Toskich: The ROWAN and EMERALD-Y90 clinical trials are currently evaluating HCC patients across multiple BCLC stages with the combination of radioembolization plus tremelimumab and durvalumab or durvalumab and bevacizumab, respectively. Do you have a preference for which type of immunotherapy regimen your radioembolization patients receive with local therapy? If so, why?**

**Dr. Tabori:** Obviously, we do not know the answer here, which is why there is ongoing research, but dissecting the potential mechanisms of action is a worthwhile discussion. Tremelimumab is an antibody that binds cytotoxic T lymphocyte-associated antigen (CTLA-4). By blocking CTLA-4, tremelimumab helps prime the immune response by increasing T cell activation and proliferation. Radiation-induced cell death includes immunogenic cell death (ICD); however, the proimmunogenic effects of radiotherapy tend to be masked by overwhelming tumor immunosuppressive microenvironment. Golden et al found that introducing a CTLA-4 inhibitor in non–small cell lung cancer allowed immune-mediated tumor rejection to occur.[8] It stands to reason that CTLA-4 inhibition may be an important factor in radiation-induced cell death outside of the treatment area, the abscopal effect, in primary liver cancer as well.

Conversely, bevacizumab is a recombinant humanized monoclonal antibody that binds to VEGF, which inhibits the formation of new blood vessels and angiogenesis. This reduces the vascularization of tumors, which slows their growth. The early data from EMERALD-1 and the results of LAUNCH both support the hypothesis that VEGF inhibition is critical to a synergistic effect with locoregional therapies. I look forward to seeing how the data play out.

**Dr. Garcia-Reyes:** Although we do not have a strict preference for a specific immunotherapy regimen to combine with radioembolization, our decision is based on individual patient characteristics, tumor biology, and emerging clinical data. The combination of tremelimumab and durvalumab explored in the ROWAN trial targets multiple immune pathways, while the durvalumab and bevacizumab combination assessed in the EMERALD-Y90 trial offers a dual approach through immune checkpoint inhibition and antiangiogenic effects. I am eager to see the results from these trials.

It is also important to note that certain criteria can exclude patients from specific therapies. For instance, the presence of varices may preclude the use of bevacizumab. Additionally, VEGF inhibitors can alter tumor vasculature, necessitating a washout period to optimize the effectiveness and safety of transarterial therapies. Ultimately, treatment choices are tailored to each patient to optimize outcomes while minimizing potential adverse effects.

**Dr. Avritscher:** The preferred immunotherapy regimen is truly determined on a case-by-case basis. However, based on standards of care, in our current practice, unless the patient is diagnosed with varices or does not have access to upper gastrointestinal endoscopy, we will most commonly initiate combination of PD-L1 inhibitor with bevacizumab first. For patients undergoing systemic therapy at the time of radioembolization, an effort is made to optimize the interval between systemic injection and local intervention to reduce the impact of VEGF inhibitor at the time of minimally invasive procedure.

**Dr. Toskich: Outside of liver transplantation, recurrence rates of HCC remain high after curative-intent treatments. Although immunotherapy has shown a disease control benefit and is well tolerated by most patients, rare adverse events can be serious. What evidence would make you consider the addition of immunotherapy for most HCC patients?**

**Dr. Avritscher:** This is a critical concept. Immunotherapy is well tolerated, but adverse events certainly occur and can be devastating. There are HCC subtypes less likely to respond to immunotherapy. A combination of imaging, tissue, and serum biomarkers is sorely need to help identify these patients and avoid potentially harmful exposure.

**Dr. Tabori:** Although liver transplantation is the goal we seek for most patients, livers are a highly limited resource, and transplantation is not without risk. Ultimately, what we are all looking for is a way to spare the host organ while maximizing cancer-free survival. If combination therapy allows for PFS and OS similar to resection and/or transplantation, we will have found the next gold standard of care for primary liver cancer.

**Dr. Garcia-Reyes:** Although disease control is crucial in any cancer intervention, I firmly believe that safety is paramount when evaluating combination therapy in this patient population. In a study conducted at our institution assessing the safety and efficacy of combination therapy, we found that patients with intermediate- to advanced-stage HCC receiving radioembolization combined with immunotherapy exhibited better imaging responses and fewer regimen-altering adverse events compared to those treated with TKIs. Importantly, our study also showed that no significant adverse events associated with the combination therapy could be attributed to the radioembolization itself, highlighting its safety within the combined treatment regimen.

**Dr. Toskich: Other than HCC, what additional malignancies are you treating with combination therapy?**

**Dr. Garcia-Reyes:** We utilize radioembolization alongside systemic therapies for patients with intrahepatic cholangiocarcinoma, colorectal cancer, and other solid tumors that have metastasized to the liver.

**Dr. Tabori:** We have used combination therapy in patients with metastatic colorectal cancer, non–small cell lung cancer, and thymic cancer.

**Dr. Avritscher:** The second most common is cholangiocarcinoma. We have also been treating a subset of metastatic melanoma patients.

**Dr. Toskich: An emerging application of local therapy has been in its use as a potential adjuvant to systemic therapy. Although the probability of abscopal events is historically low, and predictive biomarkers have been challenging to identify, its effects can be life-changing for patients with limited options. Is there a role for local therapy in this capacity and does this affect your approach?**

**Dr. Tabori:** The abscopal effect is the Holy Grail for every type of cancer, and locoregional therapy is primed to be in the pathway to stimulate it, as the denatured cancer tissue is left behind for the immune system to interact with and potentially now recognize as foe rather than friend. It also raises the question of how much of the tumor immune microenvironment needs to be left behind to allow for such an effect. Until we have data and predictive markers, I continue to treat based on the best clinical practice data we have to optimize OS and local tumor control, including data from LAUNCH, DOSISPHERE-01, LEGACY, TRACE, RASER, and many more.

**Dr. Garcia-Reyes:** Yes, local therapy plays a significant role as an adjuvant to systemic therapy, particularly in improving outcomes for patients with limited options. Even though the probability of abscopal effects is low, integrating local therapies like radioembolization with systemic treatments can offer meaningful benefits, especially for patients with advanced disease.

This combination may create a more favorable tumor microenvironment and sensitize tumors to systemic therapies, enhancing treatment responses. Although identifying predictive biomarkers remains a challenge, incorporating local therapy into a multimodal strategy broadens our treatment options for high-risk patients. Ultimately, recognizing the potential for these local therapies to induce systemic responses, although infrequent, encourages us to explore their use alongside systemic interventions, potentially leading to better outcomes and improved quality of life for our patients.

**Dr. Avritscher:** We have seen isolated cases of abscopal effect in metastatic melanoma patients undergoing local therapy. It is a rare but truly dramatic phenomenon. It is a therapeutic option we consider for patients with metastatic melanoma to the liver resistant to immunotherapy, as local therapy may be able to reverse this resistance in isolated cases.

More commonly, we see HCC patients who demonstrate stability or partial response to systemic therapy in most lesions, but given the heterogeneity of the disease, single or a few lesions fail to respond, and we will pursue local therapy for these cases.

**Dr. Toskich: What data or study design do you feel will be the next critical step in advancing our knowledge of combining local therapy with immunotherapy?**

**Dr. Avritscher:** As discussed, there is a fundamental knowledge gap in prognostic biomarkers for combination therapies in HCC. I believe that upcoming trials must be designed to attempt to address this gap. Cutting-edge approaches are now available to analyze tissue and serum data from these patients, including liquid biopsy techniques, that can be integrated into these studies.

**Dr. Tabori:** A recent study by Kaya et al demonstrated a correlation between higher tumor mutation burden and response to combination of Y90 with nivolumab.[9] With the rapid expansion of systemic therapies on the market targeting different antitumorigenic pathways, we may need to choose our therapy based on molecular makeup of the tumor to optimize the re-

sponse. However, as you have previously mentioned, predictive biomarkers have been challenging to identify.

**Dr. Garcia-Reyes:** The next critical step in advancing our knowledge of combining locoregional therapy with immunotherapy will involve well-designed, multicenter randomized controlled trials that assess the safety and efficacy of these combinations across various cancer types. These studies should focus on defining optimal treatment sequences, timing, locoregional therapy type and technique, and the specific immunotherapy agents to maximize patient benefit. Identifying prognostic tumor markers will also be key to optimizing treatment response. ■

1. Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. J Hepatol. 2022;76:681-693. doi: 10.1016/j.jhep.2021.11.018
2. Peng Z, Fan W, Zhu B, et al. Lenvatinib combined with transarterial chemoembolization as first-line treatment for advanced hepatocellular carcinoma: a phase iii, randomized clinical trial (LAUNCH). J Clin Oncol. 2023;41:117-127. doi: 10.1200/JCO.22.00392
3. Lencioni R, Kudo M, Erinjeri J, et al. EMERALD-1: a phase 3, randomized, placebo-controlled study of transarterial chemoembolization combined with durvalumab with or without bevacizumab in participants with unresectable hepatocellular carcinoma eligible for embolization. J Clin Onc. 2024; 42:Suppl 3. doi: 10.1200/JCO.2024.42.3_suppl.LBA432
4. Yu S, Yu M, Keane B, et al. A pilot study of pembrolizumab in combination With Y90 radioembolization in subjects with poor prognosis hepatocellular carcinoma. Oncologist. 2024;29:270–e413. doi: 10.1093/oncolo/oyad331
5. Marinelli B, Cedillo M, Pasik SD, et al. Safety and efficacy of locoregional treatment during immunotherapy with nivolumab for hepatocellular carcinoma: a retrospective study of 41 interventions in 29 patients. J Vasc Interv Radiol. 2020;31:1729-1738.e1. doi: 10.1016/j.jvir.2020.07.009
6. Zhan C, Ruohoniemi D, Shanbhogue KP, et al. Safety of combined yttrium-90 radioembolization and immune checkpoint inhibitor immunotherapy for hepatocellular carcinoma. J Vasc Interv Radiol. 2020;31:25-34. doi: 10.1016/j.jvir.2019.05.023
7. Qin S, Chen M, Cheng AL, et al. Atezolizumab plus bevacizumab versus active surveillance in patients with resected or ablated high-risk hepatocellular carcinoma (IMbrave050): a randomised, open-label, multicentre, phase 3 trial. Lancet. 2023;402:1835-1847. doi: 10.1016/S0140-6736(23)01796-8
8. Golden EB, Demaria S, Schiff PB, et al. An abscopal response to radiation and ipilimumab in a patient with metastatic non-small cell lung cancer. Cancer Immunol Res. 2013;1:365-372. doi: 10.1158/2326-6066.CIR-13-0115
9. Kaya NA, Tai D, Lim X, et al. Multimodal molecular landscape of response to Y90-resin microsphere radioembolization followed by nivolumab for advanced hepatocellular carcinoma. J Immunother Cancer. 2023;11:e007106. doi: 10.1136/jitc-2023-007106

*Disclosures*

*Dr. Toskich: Advisor to Johnson & Johnson, Boston Scientific Corporation, Sirtex Medical, Terumo, AstraZeneca, Genentech, Delcath, Histosonics, Turnstone Biologics, Replimmune, VIVOS, Eisai, and Galvanize.*
*Dr. Avritscher: Consultant to Siemens Healthineers and Terumo; speaker's bureau for Boston Scientific; advisory board for Eisai Medical and Guerbet.*
*Dr. Garcia-Reyes: Consultant to Boston Scientific Corporation, Cook Medical, Johnson & Johnson, and AstraZeneca.*
*Dr. Tabori: Speaker for and consultant to Boston Scientific Corporation; consultant to BD.*