



CASES

INSIGHTS INTO HEPATOCELLULAR CARCINOMA

Virtual Platform

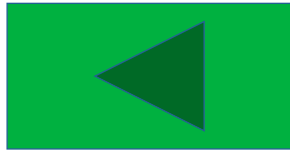
March 15, 2021

Insights From Community Oncologists From the
Pacific Northwest, USA







HOW TO NAVIGATE THIS REPORT



Click to move to topic of interest or ARS supporting data



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Topic	
Report Objectives	
Report Snapshot	
<ul style="list-style-type: none">• Session overview• Attendee overview• Agenda	
Topline Takeaways and Strategic Recommendations	
Key Insights and Discussion Summary	
<ul style="list-style-type: none">• First-line treatment for advanced HCC• First-line discussion overview• Second- or subsequent-line treatment for advanced HCC• Second-line discussion overview	
Advisor Key Takeaways	
ARS Data	

STUDY OBJECTIVES

To gain advisors' perspectives on

- > Current treatment practices regarding therapy of unresectable advanced HCC
- > Current treatment practice attitudes toward recently introduced and upcoming agents

REPORT SNAPSHOT: SESSION OVERVIEW



A moderated roundtable discussion was held with community oncologists from the Pacific Northwest region of the United States in a virtual setting on **March 15, 2021**

Disease state and data presentations were led by **Dr Tanios Bekaii-Saab** from the Mayo Clinic in Phoenix, Arizona, in conjunction with content developed by the Aptitude Health clinical team

Insights on **first-line and subsequent therapies for advanced HCC** in the community setting and impact on patient management were obtained

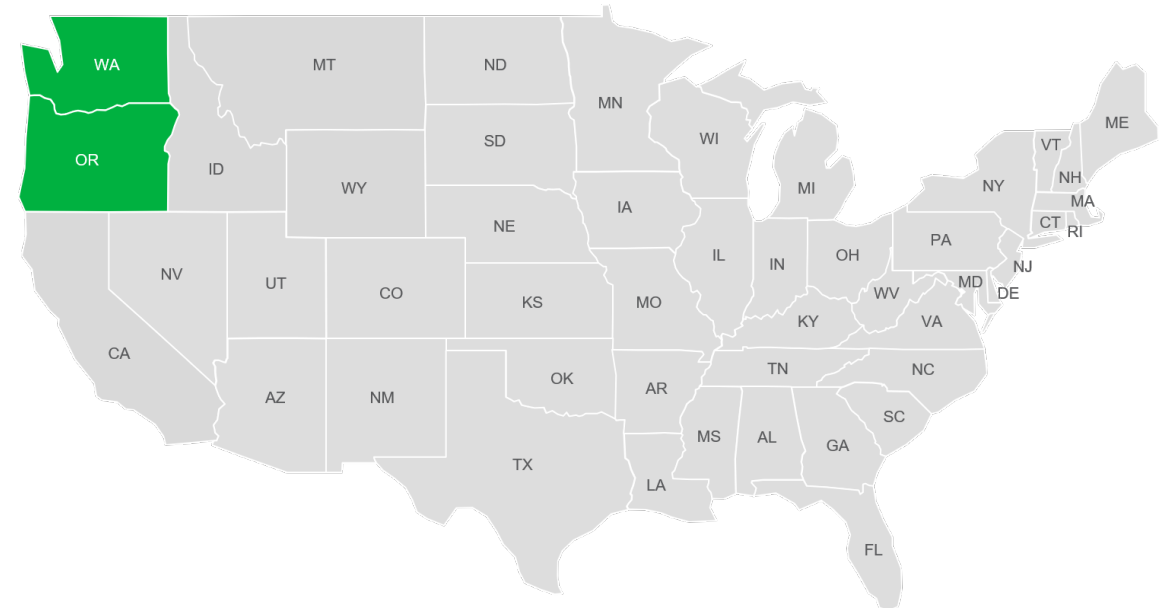
Data collection was accomplished through use of audience response system (ARS) questioning and in-depth moderated discussion

REPORT SNAPSHOT: ATTENDEE OVERVIEW



- > The group of advisors comprised 9 community oncologists from the Pacific Northwest region of the United States
 - Attendees of the roundtable represented community oncologists from Washington and Oregon

INSTITUTION	CITY	STATE
North Star Lodge, Yakima Valley Memorial	Yakima	WA
Virginia Mason Medical Center	Federal Way	WA
UW Medicine-Valley Medical Center	Renton	WA
Compass Oncology	Portland	OR
Swedish Cancer Institute	Issaquah	WA
Swedish Cancer Institute	Seattle	WA
Washington Permanente Medical Group	Tacoma, Silverdale	WA
Providence Regional Cancer Partnership	Everett	WA
Vancouver Clinic	Vancouver	WA



REPORT SNAPSHOT: AGENDA



Time (EST)	Topic
6.00 PM – 6.15 PM (15 min)	Introduction and ARS Questions <ul style="list-style-type: none">• Program overview• Round-robin introductions• ARS questions
6.15 PM – 7.10 PM (55 min)	First-Line Treatment in Advanced HCC <ul style="list-style-type: none">• Overview of current data: Factors guiding first-line therapy<ul style="list-style-type: none">– Sorafenib vs lenvatinib– Incorporation of checkpoint inhibitors<ul style="list-style-type: none">▪ Atezolizumab▪ Nivolumab• Reaction and discussion
7.10 PM – 8.45 PM (95 min)	Second-Line and Subsequent Therapy for Advanced HCC <ul style="list-style-type: none">• ARS questions• Overview of current data<ul style="list-style-type: none">– Subsequent-line therapy<ul style="list-style-type: none">▪ Cabozantinib▪ Nivolumab vs pembrolizumab▪ Ramucirumab (high AFP)▪ Regorafenib▪ Ipilimumab + nivolumab▪ Pembrolizumab• Reaction and discussion
8.45 PM – 9:00 PM (15 min)	Key Takeaways and Meeting Evaluation



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Topline Takeaways and Strategic Recommendations

INSIGHTS INTO HCC

MEETING OBJECTIVES WERE ACHIEVED: TOPLINE TAKEAWAYS



OBJECTIVE

PROCESS

INSIGHTS

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[Faded text describing insights]



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**Key Insights and
Discussion Summary**

KEY INSIGHTS: FIRST-LINE TREATMENT OF ADVANCED HCC (1/2)



How and when is MRD assessed by community oncologists, and does it impact use of immunotherapy in the frontline setting?

MRD is mainly assessed at complete response (CR) by either molecular PCR, MRD or multicolor flow. Immunotherapy is used to treat MRD+ patients in the frontline by about half of the addressors (50%)

- MRD is assessed at CR by half of addressors (50%). The other reports assess MRD at CR and 3 months from induction, and every 3 months thereafter (20%). Only a few reports (10%) assess MRD monthly
 - The more routine approach is performed either by the pathologists in the treatment centers, or by the addressors themselves, depending on the hospital
 - Most of the addressors were aware of the importance of sending the first sample of tumor response samples for MRD assessment
- MRD assessment methods mostly used by the addressors are molecular PCR (20%), and MRD (20%). The multicolor flow is used by 20% of addressors
 - Although MRD is considered more precise in detecting MRD when compared with PCR, its use is limited by the cost, which is considered still too expensive by most addressors
- Generally, when patients are MRD+ following induction, the induction therapy is extended, followed by consolidation
 - However, at least 3 addressors are using immunotherapy to induce MRD negatively after induction (1 addressor in the consolidation of addressors). The remaining addressors would refer their patients to treatment departments

KEY INSIGHTS: FIRST-LINE TREATMENT OF ADVANCED HCC (2/2)



How and when is MRD assessed by community oncologists, and does it impact use of immunotherapy in the frontline setting?

MRD is mainly assessed at complete response (CR) by either molecular PCR, MRD or multicolor flow. Immunotherapy is used to treat MRD+ patients in the frontline by about half of the addressors (50%).

- MRD is assessed at CR by half of addressors (50%). The other reports assess MRD at CR and 3 months from induction, and every 3 months thereafter (20%). Only a few reports (10%) assess MRD monthly.
 - The time response approach is performed either by the pathologists in the transplant centers, or by the addressors themselves, depending on the hospital.
 - Most of the addressors were aware of the importance of sending the first sample of time response approach for MRD assessment.
- MRD assessment methods mainly used by the addressors are molecular PCR (20%), and MRD (20%). The multicolor flow is used by 20% of addressors.
 - Although MRD is considered more precise in detecting MRD when compared with PCR, its use is limited by the cost, which is considered still too expensive by most addressors.
- Generally, when patients are MRD+ following induction, the induction therapy is continued, followed by consolidation.
 - However, at least 3 addressors are using immunotherapy to reduce MRD negatively after induction (1 addressor is after consolidation of addressors). The remaining addressors would refer their patients to transplant departments.

FIRST-LINE TREATMENT – INSIGHTS AND DATA

“For HCC it is always a merging of both the liver function as well as the extent of disease. It really comes down to the best

1. Treatment success in Sorafenib vs Placebo

The overall survival benefit was modest. This is not unexpected because this is a chronic disease, so we need chronic therapy. I think what is really important here is that we have a significant improvement in overall survival with a treatment approach that is using SO as a first-line agent. The overall survival benefit was modest, but it is a significant benefit. I think what is really important here is that we have a significant improvement in overall survival with a treatment approach that is using SO as a first-line agent.

2. Data needed to confirm that SO is effective

That's all a lot of things have been done, getting a better idea of SO and how it works. It really helps with how to use SO and how to use it. I think what is really important here is that we have a significant improvement in overall survival with a treatment approach that is using SO as a first-line agent. The overall survival benefit was modest, but it is a significant benefit. I think what is really important here is that we have a significant improvement in overall survival with a treatment approach that is using SO as a first-line agent.

FIRST-LINE TREATMENT – INSIGHTS AND DATA

"I have not yet used this combination, but I think it is going to be a huge tool for my practice in the future."

1. Treatment success in frontline HCC

Overall survival data was presented. This is an important metric for a cancer therapy, as it measures overall survival. The data showed that the combination of nivolumab and ipilimumab significantly improved overall survival compared to nivolumab monotherapy. The hazard ratio was 0.78, indicating a 22% reduction in the risk of death. The p-value was 0.0004, which is highly significant. The median overall survival was 13.8 months for the combination group versus 11.6 months for the monotherapy group. The 95% confidence interval for the hazard ratio was 0.61 to 1.00. The data suggests that the combination of nivolumab and ipilimumab is a more effective first-line treatment for advanced HCC compared to nivolumab monotherapy.

2. Data needed to confirm front-line HCC in practice

The data presented here is very helpful in making a decision about whether to use nivolumab and ipilimumab. The overall survival data is a key metric for a cancer therapy, and the data shows that the combination of nivolumab and ipilimumab significantly improved overall survival compared to nivolumab monotherapy. The hazard ratio was 0.78, indicating a 22% reduction in the risk of death. The p-value was 0.0004, which is highly significant. The median overall survival was 13.8 months for the combination group versus 11.6 months for the monotherapy group. The 95% confidence interval for the hazard ratio was 0.61 to 1.00. The data suggests that the combination of nivolumab and ipilimumab is a more effective first-line treatment for advanced HCC compared to nivolumab monotherapy. This data is very helpful in making a decision about whether to use nivolumab and ipilimumab. The overall survival data is a key metric for a cancer therapy, and the data shows that the combination of nivolumab and ipilimumab significantly improved overall survival compared to nivolumab monotherapy. The hazard ratio was 0.78, indicating a 22% reduction in the risk of death. The p-value was 0.0004, which is highly significant. The median overall survival was 13.8 months for the combination group versus 11.6 months for the monotherapy group. The 95% confidence interval for the hazard ratio was 0.61 to 1.00. The data suggests that the combination of nivolumab and ipilimumab is a more effective first-line treatment for advanced HCC compared to nivolumab monotherapy.

KEY INSIGHTS: SECOND-LINE AND SUBSEQUENT THERAPY IN TREATMENT OF ADVANCED HCC



How and when is MRD assessed by community oncologists, and does it impact use of immunotherapy in the frontline setting?

MRD is mostly assessed at complete response (CR) by either molecular PCR, MRD is molecular free. Immunotherapy is used to treat MRD+ patients in the frontline by about half of the addressors (42%)

- MRD is assessed at CR by half of addressors (42%). The other reports assess MRD at CR and 3 months from induction, and every 3 months thereafter (48%). Only a few reports (11%) assess MRD monthly
 - The time interval approach is performed either by the pathologists in the treatment centers, or by the addressors themselves, depending on the hospital
 - None of the addressors were aware of the importance of sending the first sample of tumor response approach for MRD assessment
- MRD assessment methods mostly used by the addressors are molecular PCR (48%) and MRD (48%). The molecular free is used by 20% of addressors
 - Although MRD is considered more precise in detecting MRD when compared with PCR, its use is limited by the cost, which is considered still too expensive by most addressors
- Generally, when patients are MRD+ following induction, the induction therapy is extended, followed by consolidation
 - However, at least 3 addressors are using immunotherapy to induce MRD negatively after induction (1 addressor) or after consolidation (2 addressors). The remaining addressors would refer their patients to treatment departments

KEY INSIGHTS: SECOND-LINE AND SUBSEQUENT THERAPY IN TREATMENT OF ADVANCED HCC



How and when is MRG assessed by community oncologists and does it impact use of immunotherapy in the frontline setting?

MRG is mainly assessed at complete response (CR) by either radiologic (CR) or molecular flow. Immunotherapy is used to treat MRG+ patients in the frontline by about half of the advanced HCC.

- MRG is assessed at CR by half of advanced HCC. The other reports assess MRG at CR and 2 months from induction, and every 2 months thereafter (20%). Only a few reports (17%) assess MRG monthly.
 - The best response approach is performed either by the pathologists in the oncology centers, or by the patients themselves, depending on the center.
 - Most of the patients were aware of the importance of sending the first sample of best response approach for MRG assessment.
- MRG assessment methods mainly used by the patients are radiologic (CR) (20%) and MRG (20%). The molecular flow is used by 20% of patients.
 - Although MRG is considered more precise in detecting MRG when compared with CR, its use is limited by the cost, which is considered still too expensive by most patients.
- Generally, when patients are MRG+ following induction, the induction therapy is extended, followed by consolidation.
 - However, at least 3 patients are using immunotherapy to induce MRG negatively after induction or after consolidation of patients. The remaining patients would refer their patients to oncology departments.

DISCUSSION: SECOND-LINE AND SUBSEQUENT THERAPY IN ADVANCED HCC (1/2)



SECOND-LINE AND SUBSEQUENT TREATMENT – INSIGHTS AND DATA

“Radiographic progression is, in my mind, the gold standard. Tumor marker progression is also a reference.”

1. Treatment outcomes in Sorafenib (SOF) vs Placebo (PLC)

The overall survival benefit was modest. This is not necessarily surprising given the complex disease. In our head-to-head comparison, we saw a significant improvement in overall survival with SOF vs PLC, and we would say that the disease-free rate at 1 year is probably an even better indicator of significant benefit with the treatment, and overall being more compelling.

2. Data needed to justify SOF vs PLC in practice

There are a lot of things that have been done, including a better than SOF and SOF vs SOF, but we really need to see SOF vs SOF in the real world. I would be a SOF advocate. I would not be one of the first ones to move beyond SOF vs anything else that I don't see something that's been done and we know that SOF is better. If the benefits are not very modest, I think a benefit rate of 10% or better would be something that I would be looking at. Overall survival data, that's what we're looking at. SOF is better overall, but we do need to see some surrogate of efficacy. So, I do think that a 10% or higher response rate would be a good indicator of benefit, and I think that's going to be the case in the future. SOF is SOF overall.

DISCUSSION: SECOND-LINE AND SUBSEQUENT THERAPY IN ADVANCED HCC (2/2)



SECOND-LINE AND SUBSEQUENT TREATMENT – INSIGHTS AND DATA

“Overall survival is number 1, progression-free survival is number 2. The side effects profile would be my number 3.”

<p>1. Treatment outcomes in patients 18-74.</p>	<p>Overall survival (OS) was the primary endpoint. The secondary endpoints were progression-free survival (PFS) and quality of life (QoL). OS was significantly improved in the treatment group compared to the control group. PFS was also significantly improved in the treatment group. QoL was significantly improved in the treatment group. The most common side effect was fatigue, which was managed with supportive care. The overall side effect profile was favorable.</p>
<p>2. Data needed to inform your HCC in practice.</p>	<p>The data needed to inform your HCC in practice includes OS, PFS, and QoL. OS is the most important outcome for patients and clinicians. PFS is also an important outcome for patients and clinicians. QoL is an important outcome for patients and clinicians. The overall side effect profile is also an important outcome for patients and clinicians. The overall side effect profile is favorable.</p>



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Advisor Key Takeaways

ADVISOR KEY TAKEAWAYS (1/2)



ADVISOR

ADVISOR

> The network analysis provided here showed me why it makes a

- There is a better understanding of sequencing therapy
- I really want to talk further with professional and
- I think I can have a better understanding of
- These things and have a better idea of when to use
- What is my priority

- There is a better understanding of some of my other
- options
- I'm particularly interested in the educational and how
- that will and how much it would be considered to a secondary
- option for my own therapy options
- There's a lot more information to suggest therapy
- and to things the professional that may offer some
- other advice

- It was good to hear about innovations and what's
- coming down the pipeline for immunotherapy

- There's a lot of good options for second line that just
- I think I can manage with second line other people
- and good response rate
- Immunology is an issue

- The immunotherapy options are not to have
- different options besides PD-1 and what is going to
- work?

- In hoping that some of these immunotherapy agents will
- get added into practice and hopefully improve the
- look up

- This interesting to learn about all these
- immunotherapy treatments, especially the
- specific antibodies
- It's a lot of options coming up in the future. The only issue
- will be to learn how to sequence these drugs

- Not too much of the standard

ADVISOR KEY TAKEAWAYS (2/2)



ADVISOR

ADVISOR

> This is a very troublesome disease, and the winner is clear for

- There is a better understanding of sequencing therapy
- There is a better understanding of the role of the immune system
- There is a better understanding of the role of the immune system
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- There is a better understanding of the role of the immune system



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**INSIGHTS INTO
HEPATOCELLULAR CARCINOMA**

**ARS RESULTS: FIRST-LINE TREATMENT OF
ADVANCED HCC**

MOST ADVISORS' PATIENT POPULATION COMPRISES 4%–10% OF PATIENTS WITH ADVANCED OR UNRESECTABLE HCC (N = 9)

Approximately what percentage of your patients have advanced/unresectable HCC?

FOR EXAMPLE PURPOSES ONLY

MOST ADVISORS PREFER THE COMBINATION OF ATEZOLIZUMAB AND BEVACIZUMAB AS FIRST-LINE THERAPY FOR UNRESECTABLE HCC (N = 9)

In general, my preferred first-line systemic therapy for unresectable HCC is:

FOR EXAMPLE PURPOSES ONLY

ADVISORS CITE PROVEN EFFICACY AS THE MAIN DRIVER OF FIRST-LINE THERAPY SELECTION (N = 9)

My first-line therapy selection for unresectable HCC is mainly driven by:

FOR EXAMPLE PURPOSES ONLY

THE MAJORITY OF ADVISORS HAVE EXPERIENCE WITH ATEZOLIZUMAB + BEVACIZUMAB IN THE FIRST-LINE SETTING (N = 9)

In how many advanced HCC patients have you ever used atezolizumab + bevacizumab in the first-line setting?

FOR EXAMPLE PURPOSES ONLY

CASE 1

- > A 68-year-old man whose past medical history is significant only for diabetes

- > [Blurred text]

MOST ADVISORS WOULD RECOMMEND ATEZOLIZUMAB + BEVACIZUMAB AS FIRST-LINE TREATMENT FOR THIS PATIENT (N = 9)

What would you recommend for this patient?

FOR EXAMPLE PURPOSES ONLY

 A large, stylized sunburst graphic composed of thick, dark teal lines radiating from the center, positioned on the left side of the slide.

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INSIGHTS INTO HEPATOCELLULAR CARCINOMA

ARS RESULTS: SECOND-LINE AND
SUBSEQUENT THERAPY FOR ADVANCED
HCC

PREFERRED SECOND-LINE THERAPY VARIED GREATLY AMONG ADVISORS (N = 9)

In general, my preferred second-line therapy for unresectable HCC is:

FOR EXAMPLE PURPOSES ONLY

PROVEN EFFICACY AS SECOND-LINE THERAPY WAS CITED AS THE MAIN DRIVER FOR SELECTION (N = 9)

My second-line therapy selection for unresectable HCC is mainly driven by:

FOR EXAMPLE PURPOSES ONLY

> A 41-year-old white male presents with chronic HBV infection. His

[Blurred text block]

[Blurred text block]

MOST ADVISORS WOULD RECOMMEND CABOZANTINIB AS THE NEXT LINE OF THERAPY FOR THIS PATIENT (N = 9)

What would you recommend for this patient now?

FOR EXAMPLE PURPOSES ONLY

ALL ADVISORS CONSIDER AFP SOMEWHAT IMPORTANT WHEN DETERMINING SECOND-LINE THERAPY (N = 9)

How important is AFP level when determining second-line therapy for your HCC patients?

FOR EXAMPLE PURPOSES ONLY

MOST ADVISORS HAVE USED RAMUCIRUMAB AS SECOND-LINE THERAPY IN PATIENTS WITH UNRESECTABLE HCC (N = 9)



In how many unresectable HCC patients have you ever used the drug ramucirumab in the second-line setting?

FOR EXAMPLE PURPOSES ONLY



ALL ADVISORS HAVE USED CABOZANTINIB AS SECOND-LINE THERAPY IN PATIENTS WITH UNRESECTABLE HCC (N = 9)

In how many unresectable HCC patients have you ever used the drug cabozantinib in the second-line setting?

FOR EXAMPLE PURPOSES ONLY