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POTENTIAL IMPACT OF IMbrave150 RESULTS IN THE EVOLVING TREATMENT LANDSCAPE OF ADVANCED HCC: A MULTIDISCIPLINARY EXPERT OPINION

Kulik L, et al. J Hepatocell Carcinoma. 2020;7:423-33

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FIRST LINE THERAPIES FOR ADVANCED HCC

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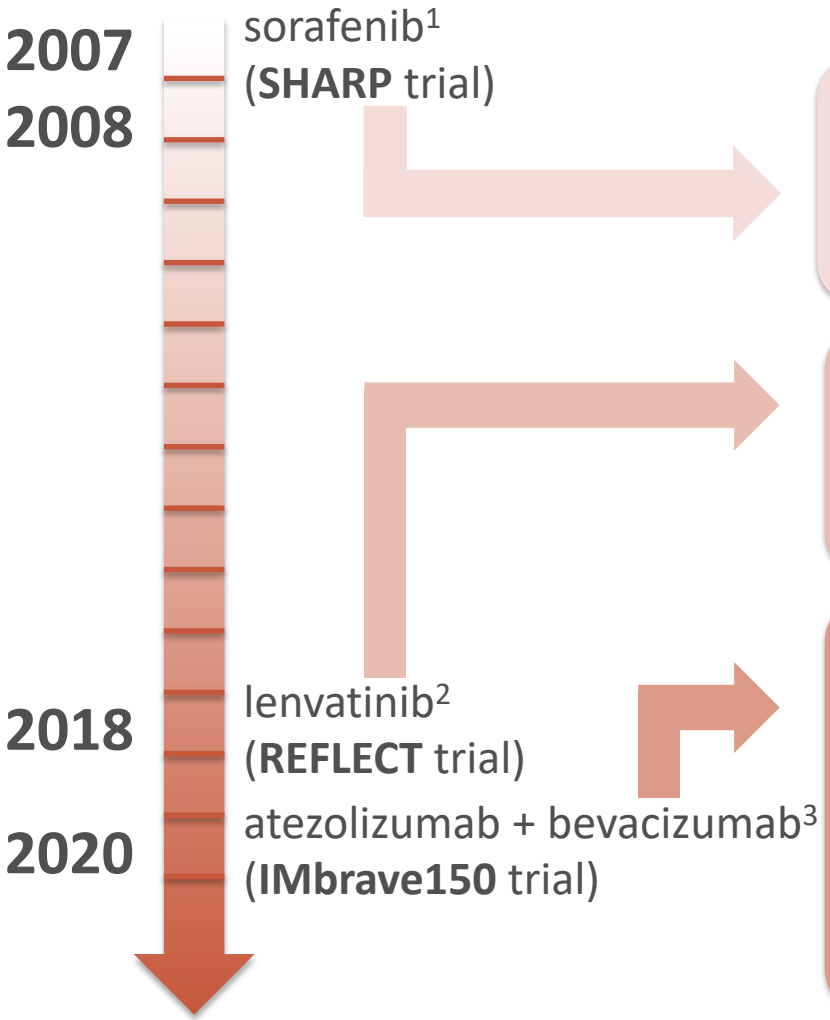

Clinical trial population	Randomized patients at baseline, %	mOS, months (95% CI)
Advanced-stage HCC Child-Pugh class A-B ECOG PS ≤2	BCLC stage A: 0 BCLC stage B: 17 BCLC stage C: 82 BCLC stage D: <1	sorafenib 10.7 (9.4-13.3) placebo 7.9 (6.8-9.1) HR 0.69 (95% CI 0.55 to 0.87) P<0.001
Unresectable HCC Child-Pugh class A ECOG PS 0-1	BCLC stage A: 0 BCLC stage B: 21 BCLC stage C: 79 BCLC stage D: 0	lenvatinib 13.6 (12.1-14.9) sorafenib 12.3 (10.4-13.9) HR 0.92 (95% CI 0.79-1.06) P=NS
Locally advanced metastatic or unresectable HCC Child-Pugh class A ECOG PS 0-1 Adequate hematologic and organ function	BCLC stage A: 3 BCLC stage B: 16 BCLC stage C: 82 BCLC stage D: 0	atezo + bev 19.2 (17.0-23.7)[4] sorafenib 13.4 (11.4-16.9)[4] HR 0.66 (95% CI, 0.52-0.85)[4] P=0.0009[4]

atezo, atezolizumab; BCLC, Barcelona Clinic Liver Cancer; bev, bevacizumab; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; HR, hazard ratio; mOS, median overall survival; NE, not evaluable; NS, not significant

1. Llovet JM, et al. N Engl J Med. 2008;359:378-90; 2. Kudo M, et al. Lancet. 2018;391:1163-73; 3. Finn RS, et al. N Engl J Med. 2020;382:1894-905; 4. Finn RS, et al. J Clin Oncol 39, 2021 (suppl 3; abstr 267)

DEVELOPMENT OF MULTIDISCIPLINARY EXPERT OPINION

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Seven experts from the Americas and European Union:

- Five physicians (representing hepatology, oncology, and radiology) with expertise in the treatment of HCC,
- An HCC patient advocate, and
- A payer systems and health economics expert

were invited to participate in the virtual HCC Experts Round Table, an independent medical education programme

The experts' opinions on the following topics were assessed by questionnaire:

- Current first-line standard of care in advanced HCC
- Management of advanced HCC patients
- IMbrave150 trial outcomes and their anticipated impact on clinical practice in the expert's region

Aggregate questionnaire outcomes were shared with the experts and used to facilitate their discussion during the virtual roundtable

These insights from an international and multidisciplinary group of experts in advanced HCC have been captured in this opinion statement

HCC, hepatocellular carcinoma

KEY CLINICAL CONSIDERATIONS FOR SELECTION OF FIRST-LINE TREATMENT OF HCC IN THE AMERICAS AND EUROPEAN UNION

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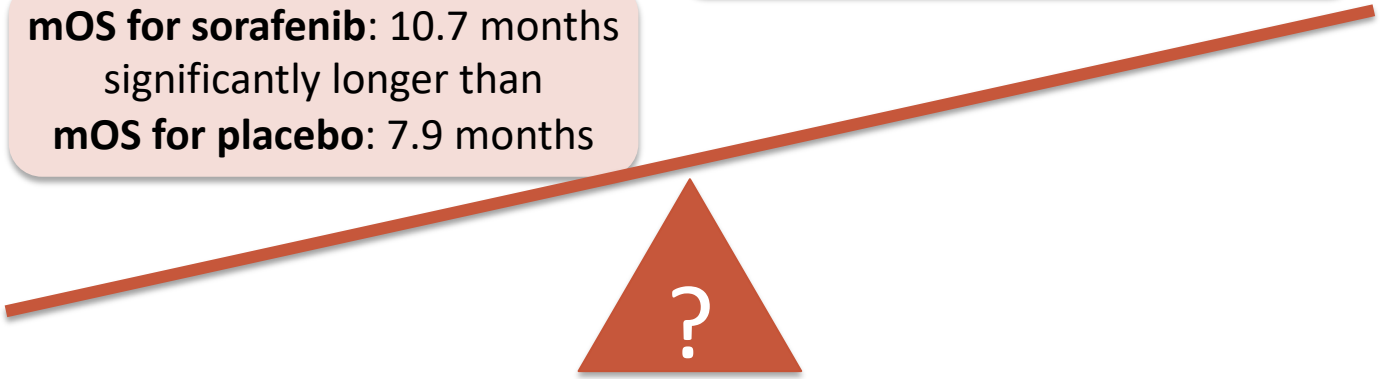
lenvatinib[2]

mOS for lenvatinib: 13.6 months
Non inferior to
mOS for sorafenib: 12.3 months

sorafenib[1]

mOS for sorafenib: 10.7 months
significantly longer than
mOS for placebo: 7.9 months



Factors that may influence prescribing decision

- Limited availability and insurance coverage for lenvatinib
- Physicians' long-term experience using sorafenib and associated comfort level
- The noninferiority of lenvatinib compared with sorafenib in the REFLECT trial
- sorafenib provides a greater benefit in patients infected with hepatitis C virus*

- **Modest improvement in mOS with sorafenib or lenvatinib (around 3 months)**
  - Need more effective first-line treatment options for patients with HCC
- **Identify subsets of patients that could benefit from sorafenib or lenvatinib**
  - Biomarkers required

* The data regarding efficacy according to viral aetiology are based on *post hoc* analyses (for progression-free survival)
HCC, hepatocellular carcinoma; mOS, median overall survival
1. Llovet JM, et al. N Engl J Med. 2008;359(4):378-90; 2. Kudo M, et al. Lancet. 2018;391 (10126):1163-73

IMPLICATIONS OF THE IMbrave150 TRIAL RESULTS FOR CLINICAL PRACTICE

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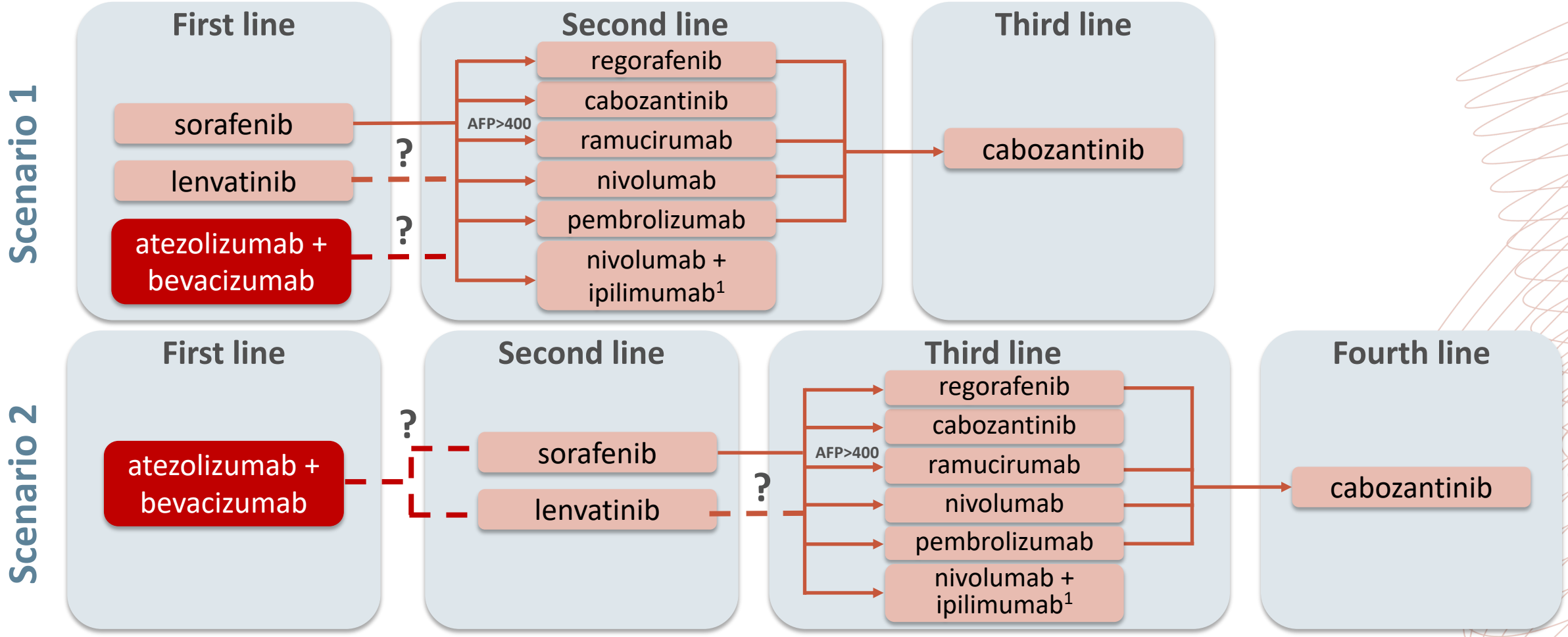
PROPOSAL FROM EXPERTS ON THE IMPACT IN DECISIONS REGARDING THE SEQUENCING OF TREATMENTS:



[1]nivolumab + ipilimumab combination was approved by the US FDA on March 2020 (refer to the US Prescribing Information of the respective drugs)[2,3]
AFP, alpha-fetoprotein; FDA, Food and Drug Administration; US, United States
Adapted from 1. Bruix J, et al. Nat Rev Gastroenterol Hepatol 2019;16:617-30; 2. OPDIVO (nivolumab) injection, for intravenous use. US Prescribing Information. Revised October 2020; 3. YERVOY (ipilimumab) injection, for intravenous use. US Prescribing Information. Revised October 2020

PATIENTS' AND PAYERS' INFLUENCE ON CLINICAL DECISION-MAKING FOR THE SELECTION OF FIRST-LINE THERAPIES IN HCC

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Extending life and returning to regular activities represent the most important concerns for patients

PRO data can help clinicians to select treatments that will align with individual patient goals

PRO data from the IMbrave150 trial collected with the EORTC QoL Questionnaire for Cancer instrument

Treatment with atezo + bev compared to sorafenib showed:

- clinically meaningful delays in deterioration in patient-reported quality of life, physical functioning, and role functioning
- delayed deterioration in key HCC-related patient-reported symptoms (appetite loss, diarrhoea, fatigue, and pain)

Payers weigh benefits of interventions vs cost

The criteria for evaluating benefits of atezolizumab plus bevacizumab may be based on:

- efficacy, tolerability, effects on quality of life assessed by PROs
- ability to manage AEs
- downstaging opportunities
- route of administration (oral vs infusion)
- Impact on treatment adherence and satisfaction
- the size of the eligible patient population
- degree of additional survival benefit
- health insurance setup
- competing financial pressures

AEs, adverse events; atezo, atezolizumab; bev, bevacizumab; EORTC, European Organisation for Research and Treatment of Cancer; HCC, hepatocellular carcinoma; PRO, patient-reported outcome; QoL, Quality-of-Life

THE ROLE OF TUMOUR BOARDS IN SELECTING TREATMENTS FOR PATIENTS

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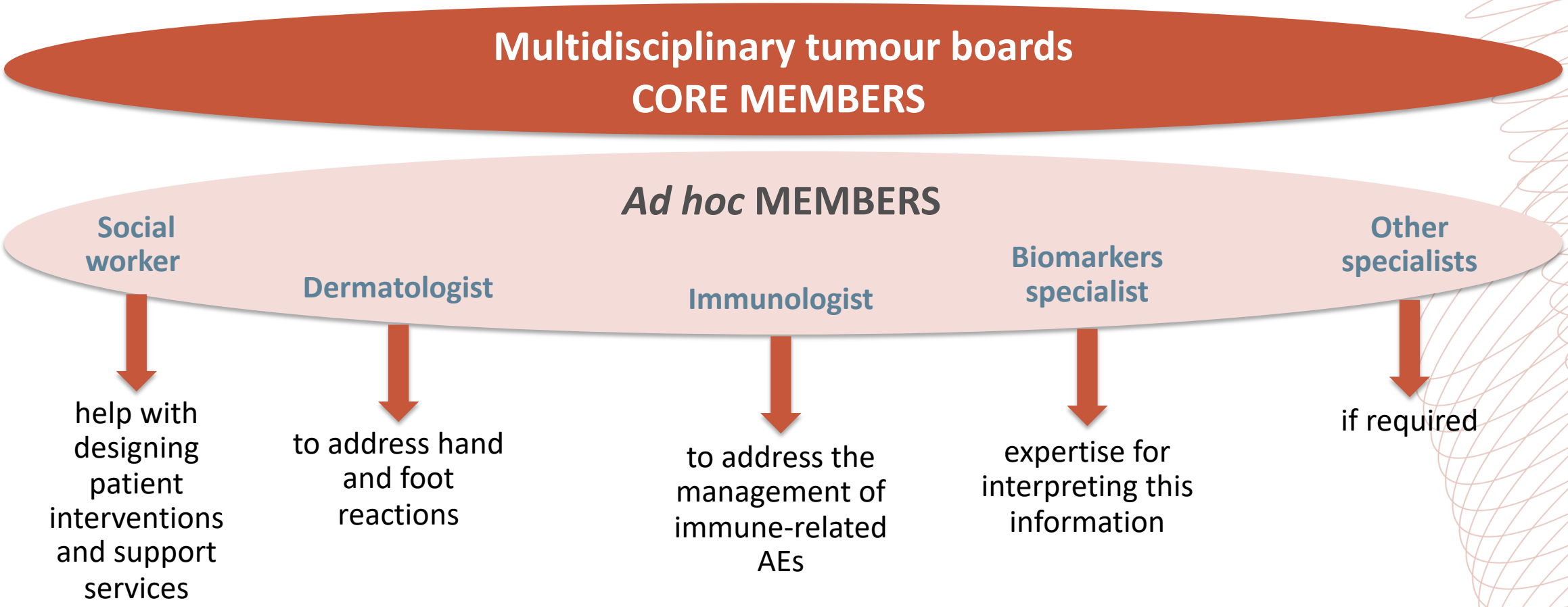
Multidisciplinary tumour boards (MTB) are essential for selecting treatment approaches for individual patients.
→ There is a need to extend the MTB to additional specialities as proposed by experts below:



AEs, adverse events

CONCLUSION

- The treatment of advanced HCC is rapidly evolving and treatment decisions are becoming more complex
- The clinically significant efficacy data and the manageable safety profile associated with atezolizumab plus bevacizumab, compared with sorafenib, indicate that this immunotherapy approach will play an important role in clinical practice

BUT

- Treatment choices should be individualised based on patient characteristics and preferences
- Third-party payer coverage will have an important impact on patient access to treatment options

WHAT'S NEXT?

- Identification of biomarkers before therapeutic decisions would be useful, to allow individualised treatment

HCC, hepatocellular carcinoma

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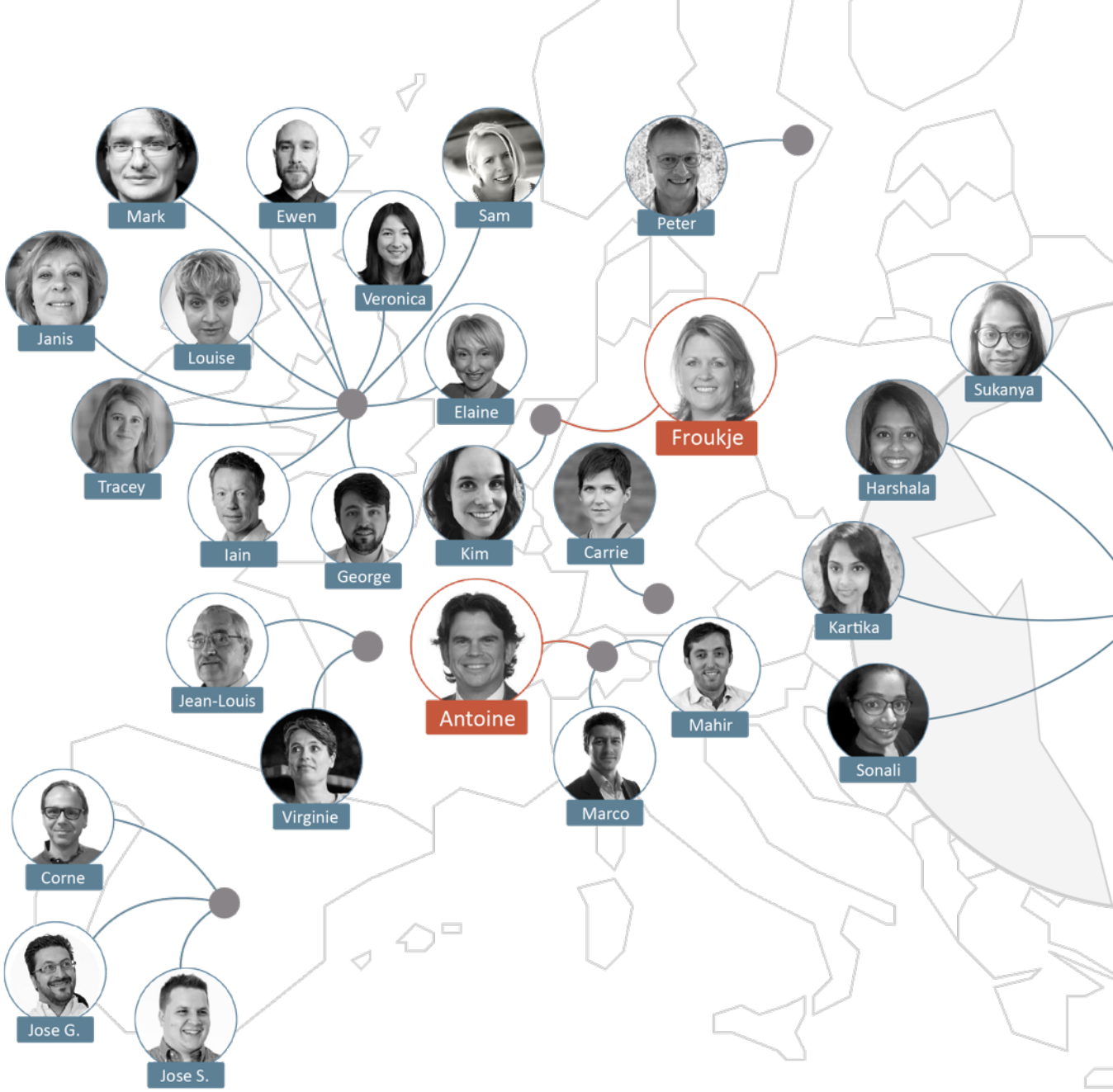

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