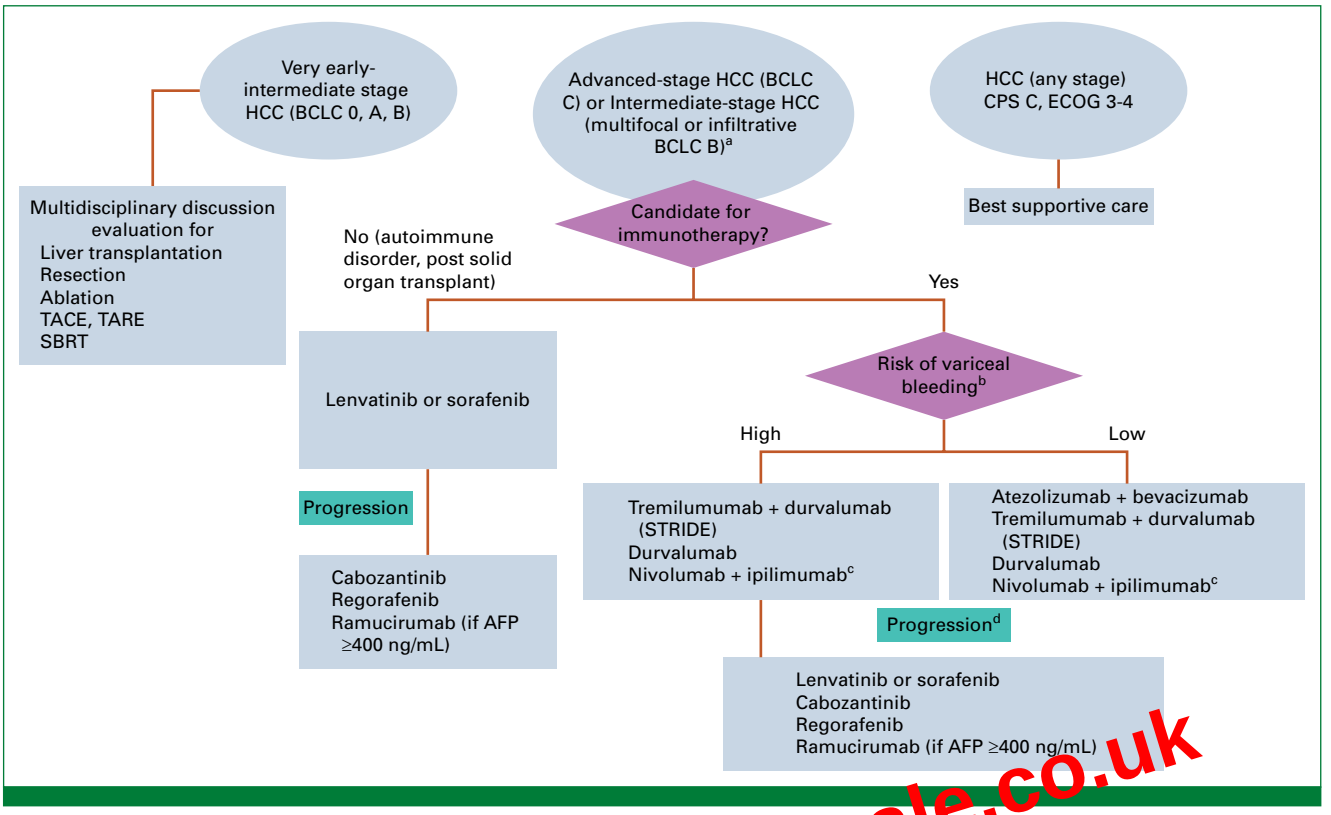

FIG 1. Approach to systemic therapy in advanced HCC. [a]Patients should be enrolled on clinical trials whenever feasible. [b]Risk of variceal bleeding high if untreated or incompletely treated varices on esophagogastroduodenoscopy within 6 months of treatment initiation. [c]Not currently approved for first-line use by the Food and Drug Administration. The role of atezolizumab/bevacizumab, durvalumab/tremelimumab, and nivolumab/ipilimumab in the second-line setting is unclear and decisions should be individualized in eligible patients. AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CPS, Child-Pugh score; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; SBRT, stereotactic body radiation; STRIDE, Single Tremelimumab Regular Interval Durvalumab; TACE, transarterial chemoembolization; TARE, transarterial radioembolization.

association with mortality than extrahepatic spread or performance status in untreated patients with HCC.[33]

The more recent CheckMate 9DW trial evaluated ipilimumab/nivolumab against lenvatinib or sorafenib as first-line systemic therapy for patients with unresectable HCC.[34] At a median follow-up of 35.2 months, the median OS was 23.7 months and 20.6 months, and objective response rate was 36% and 13% with the doublet ICI combination and lenvatinib/sorafenib groups, respectively. This combination is not currently FDA-approved.

Patients with CPS-B/C cirrhosis and/or Eastern Cooperative Oncology Group score 2 have traditionally been excluded from prospective clinical trials of systemic therapies for non–LRT-eligible HCC. However, sorafenib, atezolizumab/bevacizumab, and single-agent nivolumab have been shown in observational studies to have similar tolerability in patients with CPS-B7 to B9 cirrhosis but inferior OS when compared with patients with CPS-A cirrhosis. These benefits are modest, and treatment decisions should be made on a case-by-case basis, taking into account whether a patient's liver dysfunction is related to their tumor burden versus underlying cirrhosis.[35-38]

Other key trials evaluating first-line systemic therapy include LEAP 002,[39] ORIENT-32,[40] CARES-310,[41] RATIONALE-301,[42] and COSMIC-312.[43] LEAP 002 evaluated the superiority of pembrolizumab and lenvatinib against sorafenib in the first-line setting and did not meet its dual primary end points of progression-free survival (PFS) and OS.[39] ORIENT-32 evaluated sintilimab (anti–PD-1 antibody) and a bevacizumab biosimilar (IBI305); this combination showed a significant OS benefit when compared with sorafenib, but results have yet to be confirmed outside of China.[40] The COSMIC-312 trial evaluating first-line cabozantinib and atezolizumab versus sorafenib failed to show an OS benefit.[43] CARES-310 studied the combination of camrelizumab (anti–PD-1 antibody) and rivoceranib (VEGFR2 TKI) versus sorafenib in the first-line setting and median OS was 22.1 months and 15.2 months, respectively.[41] FDA approval for this combination is under review currently. The RATIONALE-301 trial demonstrated noninferiority of tislelizumab versus sorafenib in the first-line setting.[42] However, tislelizumab is unlikely to add to the established first-line combinations of atezolizumab/bevacizumab and the STRIDE regimen, which have demonstrated superiority versus sorafenib.