Novel Agents and Targets in HCC

PROF. NAIMISH N. MEHTA

CO- CHAIRMAN & CHIEF TRANSPLANT SURGEON,

DEPT. OF SURGICAL GASTROENTEROLOGY,

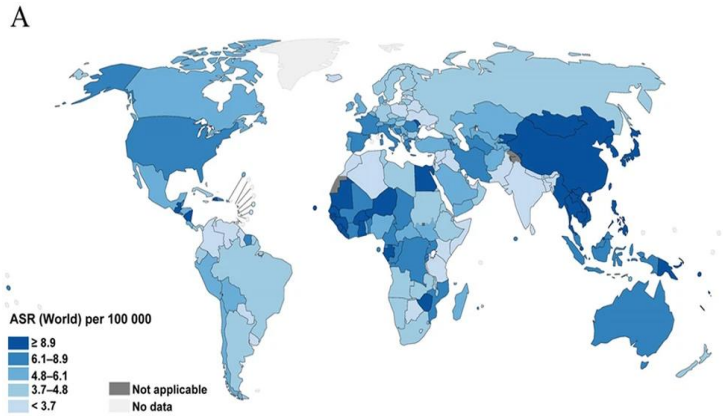
HPB SURGERY & LIVER TRANSPLANTATION

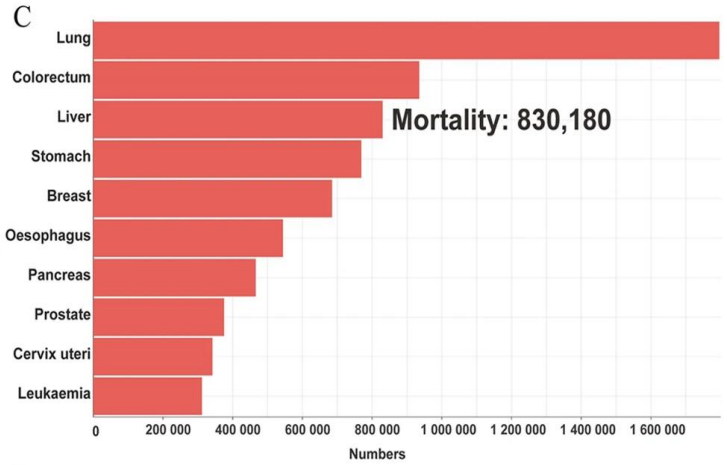
SIR GANGA RAM HOSPITAL, NEW DELHI

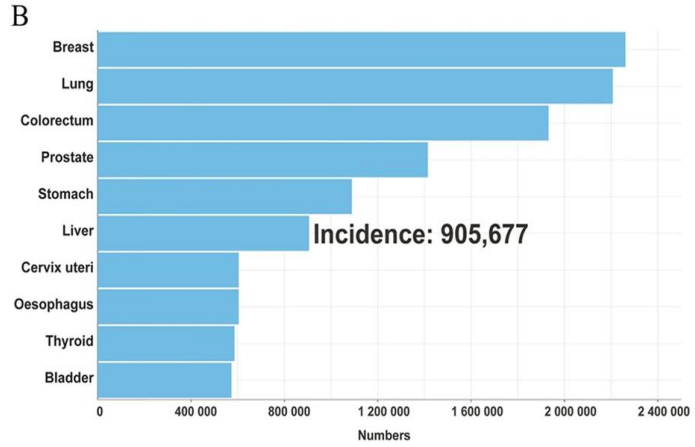
DIRECTOR, LIVER TRANSPLANTATION, MGUH, JAIPUR

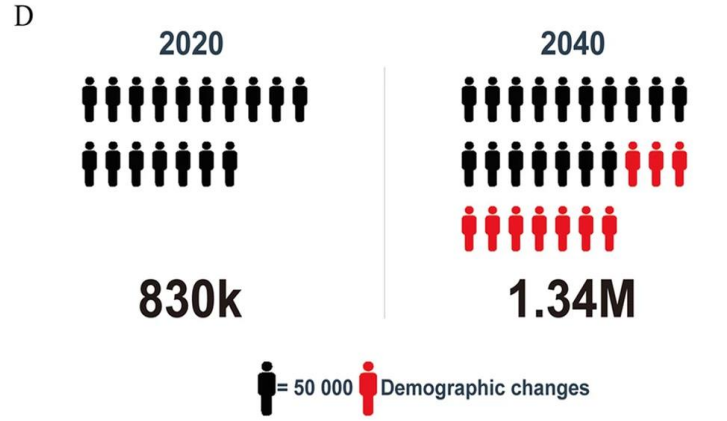
INTRODUCTION - Hepatocellular Carcinoma

- HCC is now the Sixth-mc cancer in the world and the fourth cause of cancer-related mortality
- Males : females - 2:1 to 4:1
- 5-year survival of HCC is typically less than 5% without treatment





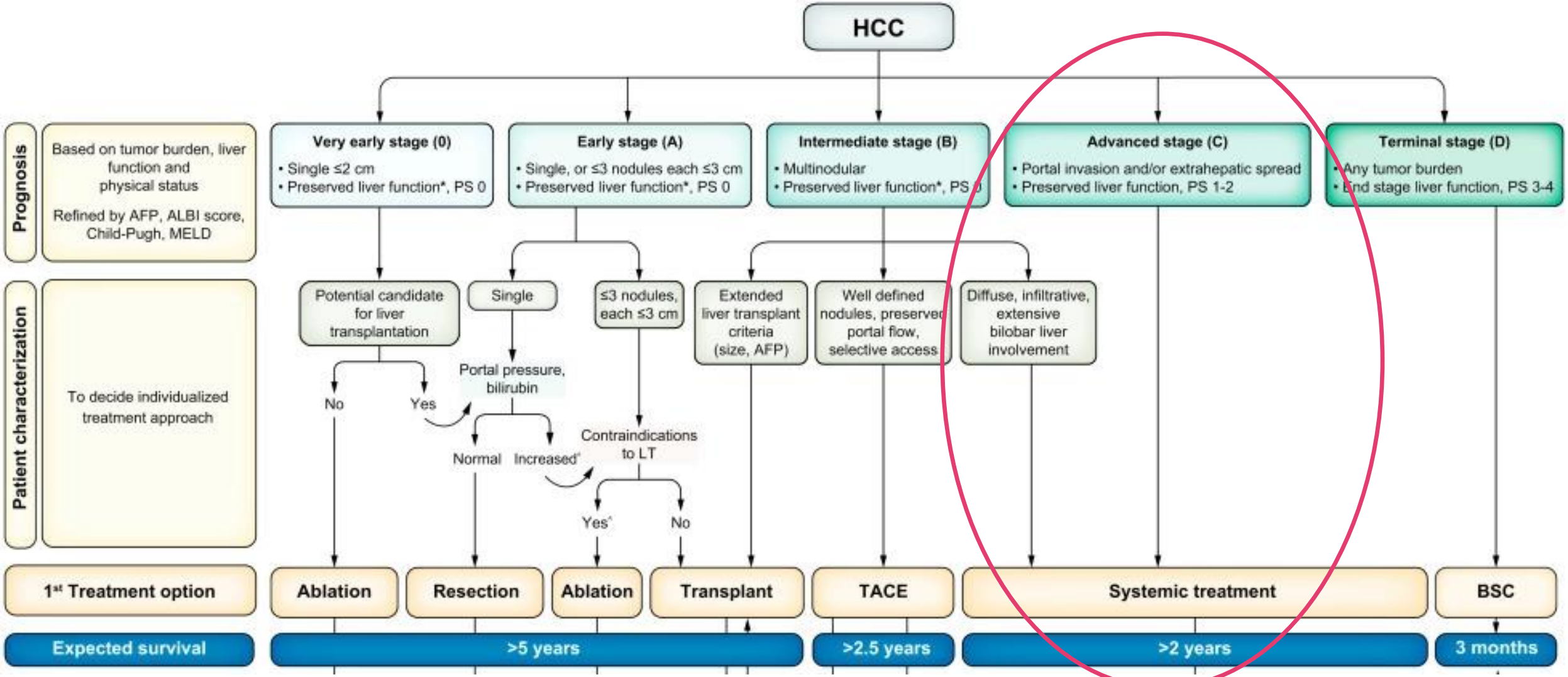




Advanced HCC

- At the time of clinical Dx, 60%-70% of HCC pts present with primary advanced, inoperable disease
- Moreover, tumor relapse (recurrence) following curative surgical Mx continues to be a substantial dilemma and is documented as high as approx 70% at 5 years postoperatively
- The standard of care Mx for Advanced HCC remains a dilemma

BCLC classification for HCC



Advanced HCC – Management options

- Systemic Chemotherapy
- Targeted molecular therapies
- Immune checkpoint inhibitors
- Combination therapies
- Novel drug therapies (future prospects)

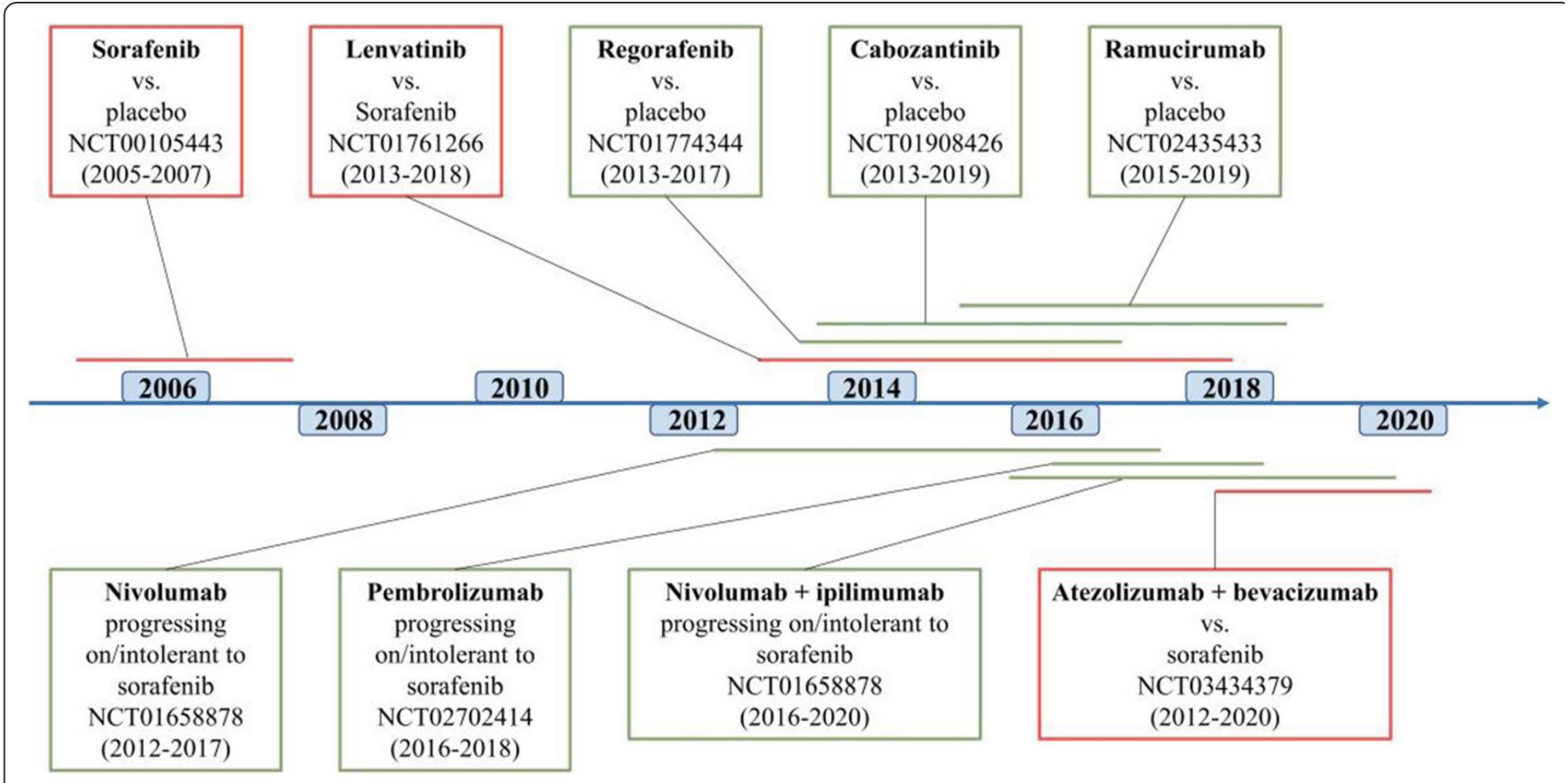


Fig. 2 Currently approved drugs for advanced HCC and timeline of pivotal clinical trials. The lines along the timeline indicate the time from the actual study start to FDA approval. The red boxes represent first-line therapies, and the green boxes represent second-line therapies

Sorafenib in Advanced HCC: SHARP TRIAL

Josep M. Llovet, Sergio Ricci, Vincenzo Mazzaferro. N Engl J Med 2008; 359:378-390

- Median OS was **10.7 mn** in the sorafenib group and **7.9 mn** in the placebo grp (HR in the sorafenib grp, 0.69; 95% CI, 0.55-0.87; **P<0.001**).
- The median time to symptomatic progression: 4.1 mn vs. 4.9 mn, P=0.77.
- The median time to radiologic progression: **5.5 mn Vs 2. 8 mn (P<0.001**).
- 7 pts in the sorafenib grp (2%) and 2 pts in the placebo grp (1%) had a PR; no CR in both
- The overall incidence of treatment-related A/E was 80% in the sorafenib group and 52% in the placebo group
- Diarrhea, wt loss, HFSR (Hand foot skin reaction), and hypophosphatemia were more frequent in the sorafenib grp.

Conclusion:

- In pts with advanced HCC, OS and time to **radiological progression was nearly 3 months longer** with Sorafenib than with placebo.

Targeted molecular therapies - Sorafenib

- Acts by inhibiting the serine–threonine kinases involved in RAF/MEK/ERK pathway, and the receptor tyrosine kinase activity of vascular endothelial growth factor receptors (VEGFRs) 1, 2, and 3 and platelet-derived growth factor receptor β (PDGFR-β)

- Cellular signaling that is mediated by the Raf-1 and VEGF pathways has been implicated in the molecular pathogenesis of HCC, providing a rationale for investigating sorafenib for this indication.

  - Inhibits tumor-cell proliferation
  - Inhibits Tumor angiogenesis
  - Increases the rate of apoptosis

Targeted molecular therapies Lenvatinib:

- Lenvatinib is an oral multikinase inhibitor that targets VEGFR1–3 and fibroblast growth factor receptor (FGFR)1–4, among others.
- Several phase III trials have been conducted to challenge sorafenib in front line (testing sunitinib, brivanib, erlotinib, linifanib or doxorubicin), but lenvatinib has shown non-inferior clinical efficacy.

Lenvatinib versus sorafenib in first-line treatment of patients with unresectable HCC: a randomised phase 3 non-inferiority trial/REFLECT

- Primary endpoint - mOS - lenvatinib 13.6 months vs sorafenib 12.3 months.
- Secondary endpoints such as PFS, TTP and Objective Response Rate (ORR) (24% vs 9.2% for sorafenib, mRECIST ORR) were significantly better for lenvatinib.
- Lenvatinib-related A/Es : HTN (42% vs 30%), diarrhoea (39% vs 45%) and HFSR (27% vs 52%).
- Conclusion – Lenvatinib demonstrated non-inferiority to sorafenib. This makes it a first line FDA approved therapy for advanced HCC

Targeted molecular therapies Regorafenib:

- Oral inhibitor of VEGFR1-3, TIE2, PDGFR-beta, FGFR1, B-RAF, RET and KIT.
- Approved as 2nd line therapy by FDA in 2017 based on results of RESORCE trial
- longer OS than placebo (mOS, **10.6 vs. 7.8 months**, p<0.0001)
- prolonged PFS and time to progression by mRECIST (**mPFS 3.1 vs. 1.5 months**, p<0.0001; **mTTP was 3.2 vs. 1.5 months**, p<0.0001)).
- **ORR of 11% versus 4%** compared to the placebo group (p=0.0047), and the **disease control rate (DCR) was 65% versus 35%** (p<0.0001).
- Of note, the RESORCE trial was performed in patients who had progressed on prior sorafenib treatment; thus, the efficacy of regorafenib among sorafenib-intolerant patients has not yet been determined.

Targeted molecular therapies Cabozatinib:

- small-molecule tyrosine kinase inhibitor of MET and VEGFR 1-3, RET, KIT, AXL, and FLT3
- Cabozantinib has remarkable antitumor activity in HCC through dual inhibition of MET and VEGFR2
- CELESTIAL trial –
- OS significantly improved (mOS 10.2 vs. 8.0 months, p=0.005)
- Improved the PFS and ORR according to RECIST v1.1 (mPFS was 5.2 vs. 1.9 months, p<0.001; ORR was 4% vs. < 1%, p=0.009)
- In 2019, the U.S. FDA approved cabozantinib for patients with HCC who had previously received sorafenib treatment

Targeted molecular therapies Ramicirumab:

- humanized recombinant IgG1 mono-clonal antibody, selectively binds to VEGFR-2, preventing activation of the VEGF pathway
- REACH-2 trial - OS was longer in the ramucirumab group (8.5 vs. 7.3 months, HR=0.71, p=0.0199); **increased PFS** (2.8 vs. 1.6 months, p<0.0001); **increased time to radiographic progression** (3.0 vs. 1.6 months, p<0.0001), and **increased disease control rate** (59.9% vs. 38.9%, p=0.0006)
- But in subgroup with **high AFP (>400ng/ml) → prolonged OS (7.8 mn vs 4.2 mn)**
- 2019, the U.S. FDA authorized ramucirumab as a 2nd -line treatment for HCC patients whose AFP > 400 ng/mL

Immune checkpoint inhibitors - Nivolumab

- monoclonal antibody, blocks the PD-1 signaling pathway and restores the anti-tumor immune activity
- CheckMate 040 trial → ORR was 20%, with 39 partial responses and 3 complete responses.
- The median duration of response was 9.9 months, and the mPFS was 4.0 months (95% CI, 2.9-5.4).
- 79 of 138 patients (57%) had their disease under control, with most disease stabilizations lasting for at least 6 months
- 2017, the U.S. FDA accelerated the approval of nivolumab to treat HCC patients who were first treated with sorafenib

Immune checkpoint inhibitors - Pembrolizumab

- monoclonal antibody blocking PD-1
- KEYNOTE-224 → 18 of 104 patients displayed an ORR (17%) as per RECIST v1.1, with 1 (1%) achieving a complete response and 17 (16%) achieving a partial response.
- mTTP and mPFS were both 4.9 months, mOS was 12.9 months, and 54% of responding patients had response durations over 12 months.
- Based on this, in 2018, pembrolizumab received accelerated approval by the U.S. FDA for patients with HCC progressing on sorafenib
- Being evaluated as a possible first line after the results of KEYNOTE 224 cohort 2.

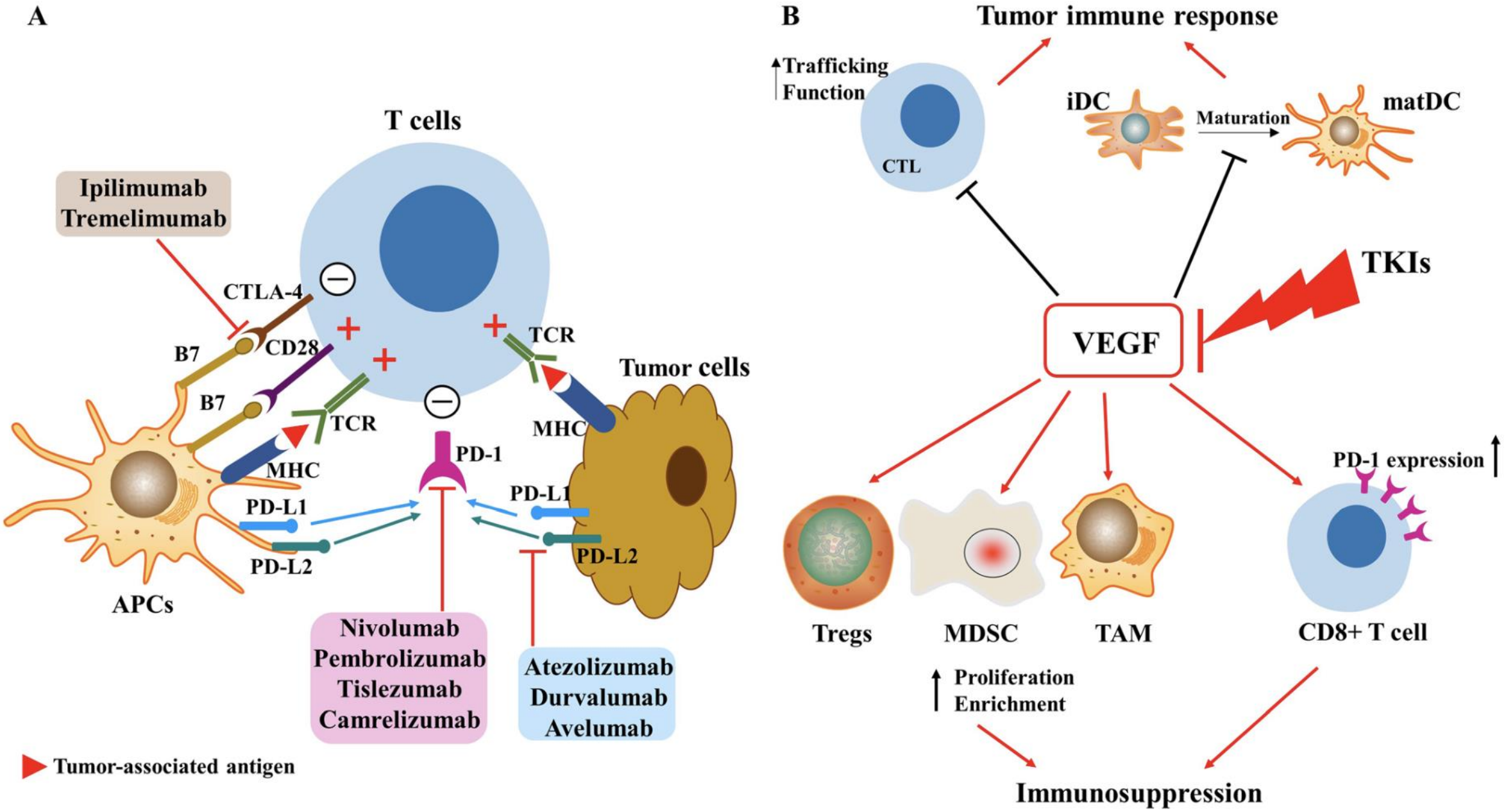
Combination therapy – Atezolizumab + Bevacizumab

- Atezolizumab (IgG1 monoclonal antibody) binds to PD-L1, interrupts its interaction with PD-1, thus reversing T cell suppression.
- Bevacizumab (humanized anti-VEGF monoclonal antibody) suppresses angiogenesis and tumor development
- At the 2021 ASCO GI Cancer Symposium, Finn et al. updated the OS analysis for IMbrave 150.
- **mOS → 19.2 months** in combination group vs **13.4 months** with sorafenib (HR= 0.66 [95% CI, 0.52–0.85], P=0.0009).
- **ORR** of **29.8%** (95% CI, 24.8-35) in combination group vs **11.3%** (95% CI, 6.9-17.3) in the sorafenib group, with CR= 7.7%
- This combination regimen has the **longest OS** ever seen in **first-line** phase III studies, and can serve as a **standard of care** for patients with advanced HCC who have not received any systemic therapy before.

Combination therapy – Nivolumab + Ipilimumab

- Ipilimumab blocks the CTLA-4 pathway → increases the activation and proliferation of T cells, leading to CD8+ T cell infiltration;
- Nivolumab blocks the PD-1/PD-L1 pathway → maintains the killing capacity of cytotoxic T lymphocytes (CTLs) and improves the ability of antigen-presenting cells to present tumor- associated antigens;
- given the high expression of CTLA-4 and PD-1 on T cells, the combination of these two inhibitors indirectly reduces the immunosuppressive tumor microenvironment (TME)
- CheckMate 040 → **mOS: 22.2 months; ORR → 32%; DCR →54%; median response duration →17.5 months (5 to 47+ months)**
- **Nivolumab + ipilimumab** as a **second-line treatment** continued to show clinical responses and long-term survival benefits

Mechanism of combination therapies



Novel therapies
1. VEGFR targeted therapies

- Tivozanib (VEGFR 1–3 TKI) with relatively lesser effects on KIT and PDGFRβ; has dose-dependent activity against HCC in vivo
- better **anti-tumor efficacy** than sorafenib (ORR **21% vs 6.5%**) and lenvatinib (ORR **21% vs 18%**) as first-line therapy
- In 1st line, donafenib (NCT02645981) had a significantly longer OS than sorafenib: 12.1 vs. 10.3 months (HR=0.831, p=0.0363)
- Apatinib (2nd -line therapy) is evaluated in phase III study AHELP (NCT02329860) → significantly longer OS (8.7 vs 6.8 mnths) and PFS (4.5 vs. 1.9 months) compared to placebo and exhibited a tolerable safety profile. ORR was 10.7% vs. 1.5% per RECIST v1.1.

Novel therapies
2. c-MET targeted therapies

- c-Met is a receptor tyrosine kinase for hepatocyte growth factor (HGF), and abnormalities in c-Met are found in approximately 50% of HCC patients
- Selective (tepotinib and capmatinib)and non selective (tivantinib and cabozantinib)c-MET inhibitors are being used in different trials for potential use in HCC as first- or second- line therapy.
- Selective c-MET inhibitors are more promising drug candidates and are thought to have reduced toxicity

Novel therapies – 3. TFG-beta targeted therapies

- Galunisertib (LY2157299) is a TGFβ receptor 1 inhibitor that has been studied as monotherapy and combined with sorafenib in extensive phase I/II trials for HCC
- TGFβ pathway has dual anti- and pro-tumoral activities in cancer cells:
- in the early stage, it is beneficial for promoting cell cycle arrest and apoptosis
- While in the advanced stage, it promotes tumor progression and metastasis by enhancing cell motility, epithelial-to- mesenchymal transition (EMT) and invasiveness

Novel therapies – 4. Endoglin targeted therapies

- Endoglin (CD105), a type 1 intact trans-membrane glycoprotein, is a co-receptor for TGF-β ligands and plays an important role in fibrogenesis and angiogenesis

- TRC105 (carotuximab) is an anti-endoglin antibody, Did not show adequate efficacy in the phase II trial for post-sorafenib HCC patients

- In 2019 ASCO GI, Raghav et al. reported that TRC105 and sorafenib combination (NCT01306058) showed an ORR of 21% per RECIST at all four dose levels, with a mOS of 15.5 months and a mTTP of 3.8 months.

Novel therapies – 5. FGF19/FGFR4 targeted therapies

- Among TKRs, fibroblast growth factor receptor 4 (FGFR4) is mostly expressed in the liver
- FGF19, one of the three endogenous FGFs, binds with the highest affinity to FGFR4
- In a phase I trial (NCT02508467), fisogatinib (BLU-554) produced a clinical re- response in FGF19-positive patients with advanced HCC: ORR - 17% (11 of 66 patients) in FGF19-positive patients and 0% in the FGF19-negative group
- This trial validates the effectiveness of blocking the FGF19/FGFR4 axis and the bio-marker potential of FGF19 to screen HCC patients.

Novel therapies – 6. CSF1/CSF-1R targeted therapies

- Colony-stimulating factor 1 (CSF-1) is a cytokine mainly produced by tumor cells that recruits macrophages under pathological conditions.
- When CSF-1/CSF- 1R is activated, tumor-associated macrophages (TAMs) secrete growth factors that contribute to tumor growth or metastasis, leading to a higher rate of recurrence.
- Ao et al. found that PLX3387 (CSF-1R inhibitor, also called pexidartinib) exhibited antitumor activity in both xenograft and allograft HCC models.

Novel therapies – PD-1 and PD-L1 inhibitors (immune checkpoint)

- PD-1 inhibitors → tislezumab versus sorafenib as first-line treatment (RATIONALE 301) camrelizumab (SHR-1210) as second-line treatment (NCT02989922)
- PD-L1 inhibitors → durvalumab (NCT01693562, NCT03847428), and avelumab (NCT03389126).
- Qin et al, ORR of camrelizumab was 14.7%, and the 6-month OS was 74.4%.
- Lee et al. reported the results of a phase II trial of avelumab monotherapy, ORR of 10%, DCR of 73.3%, mTTP of 4.4 months, and mOS of 14.2 months.

Novel therapies - Other immune checkpoint inhibitors

- Other immune checkpoints investigated include →
  1. Lymphocyte activation gene 3 (LAG-3)
  2. T cell immunoglobulin mucin-3 (TIM-3)/galectin- 9 (GLA-9)
  3. T cell immunoglobulin and ITIM domain (TIGHT)
  4. adenosine A2a receptor
- Zhou et al. found that a PD-L1 inhibitor in combination with a TIM-3, LAG-3, or CTLA-4 inhibitor results in a revitalization of in-vitro tumor-infiltrating lymphocyte (TIL) responses in most patients and further enhances its effect compared to PD-L1 monotherapy.

Novel therapies – Agonists of co-stimulatory pathways

Agonists of co-stimulatory checkpoint pathways such as →

1. OX40
2. GITR (Glucocorticoid-induced tumor necrosis factor receptor)
3. CD27
4. CD28

are under investigation

Novel therapies – Combination therapies in clinical trials

- Regorafenib and pembrolizumab as first-line treatment is being studied in a multicenter dose-escalation phase IIb trial
- Lenvatinib + pembrolizumab → promising antitumor activity and manageable toxicity in unresectable HCC through a phase Ib clinical trial (KEYNOTE-524)
- Multiple active trials are evaluating the efficacy of cabozantinib in combination with nivolumab/atezolizumab, including the COSMIC-312 phase III trial.
- VEGF Liver 100 is a phase Ib trial to evaluate the safety and efficacy of avelumab + axitinib (VEGFR in- inhibitor) as a first-line treatment.

Novel therapies – Combination therapies in clinical trials

- Camrelizumab + apatinib (VEGFR-2, RET, c-kit inhibitor) - in NCT029423
- Tivozanib (selective VEGFR 1–3 TKI) in combination with durvalumab for untreated advanced HCC updated its phase Ib data at the 2021 ASCO GI Conference
- HIMALAYA trial - durvalumab (D) + tremelimumab (T) investigated as 1st line therapy - reported at the 2020 ASCO Virtual Scientific Program → showed that ORR in T + D was 24% (95% CI, 14.9–35.3%), mOS was 18.7 mnths.
- phase III trial evaluating IBI310 (CTLA-4 in- inhibitor) plus sintilimab (PD-1 inhibitor) versus sorafenib as first-line treatment for advanced HCC is currently recruiting.

Future prospects - Antibody-drug conjugates (ADCs)

- It is a monoclonal antibody against a tumor-associated antigen (TAA) on the surface of cancer cells, conjugated to a cytotoxic drug (payload) through a chemical linker.
- Precise, directed targeting of antibody to antigens → effective cell-killing activity, reduced systemic exposure, reduced toxicity.
- The discovery of a series of HCC-specific TAAs provides the rationale for applying ADCs in HCC treatment:

1. glypican-3 (GPC3)
2. epithelial cell adhesion molecule (EpCAM)
3. NY- ESO-1
4. tumor endothelial marker 1 (TEM1, or endosialin)
5. AFP
6. MAGE-A
7. claudin-6 (CLDN6)

Future prospects – Bispecific T cell Engager (BiTE)

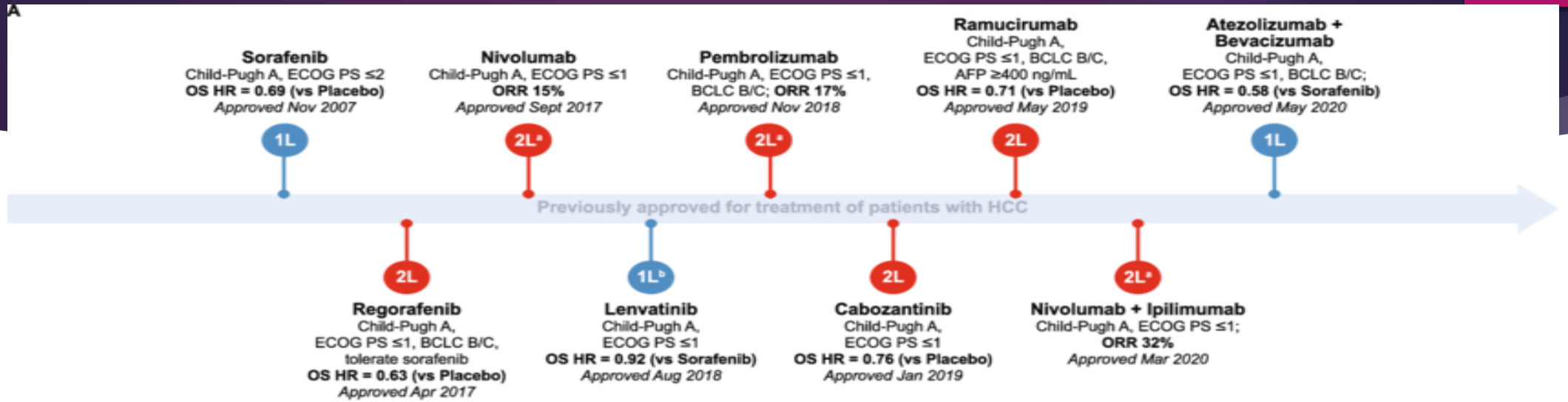
- Generated by two different fragments linked by small peptides, which are antigen binding domains of anti-CD3 and anti-TAA antibodies
- The ones under investigation are:

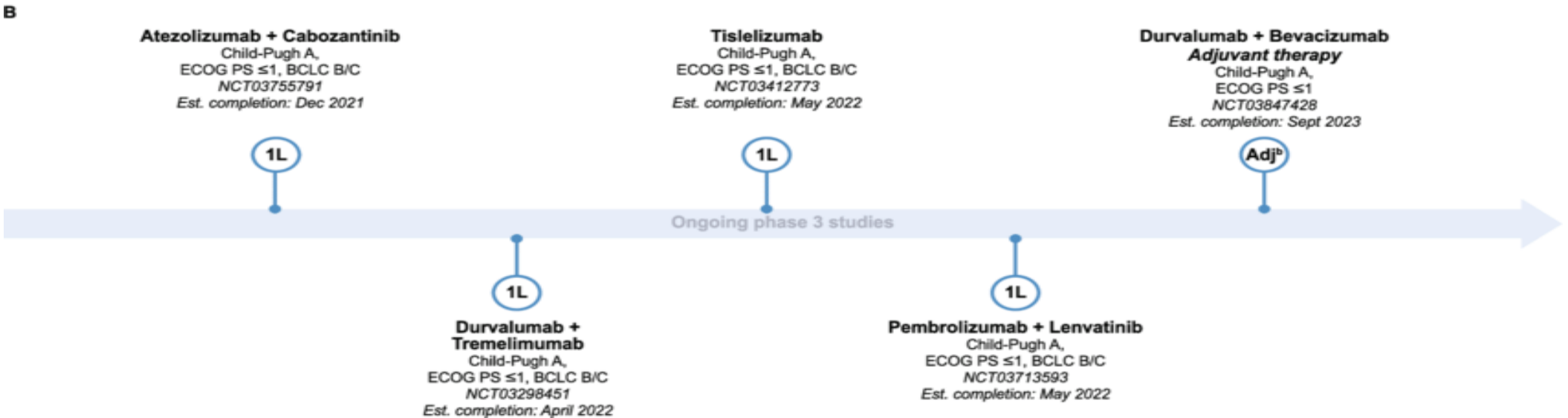
BiTE	TAA	T cell receptor	stage
1H8/CD3	EpCAM	CD3	preclinical
solitomab	EpCAM	CD3	phase I
ERY974	GPC3	CD3	phase I

Suggestions

- A meta- analysis of 14 clinical trials conducted by Sonbol et al. showed ***atezolizumab + bevacizumab*** was superior in the first-line setting compared to sorafenib, lenvatinib and nivolumab.
- In 1st-line therapies, ***atezolizumab + bevacizumab*** had the greatest OS benefit, while ***lenvatinib*** had the greatest ORR benefit.
- In 2nd-line therapies, ***cabozantinib*** had the greatest PFS benefit and ORR benefit compared to placebo.
- In the 2nd-line, all drugs showed PFS benefit (only ***regorafenib and cabozantinib*** converted to OS benefit)

Treatment landscape





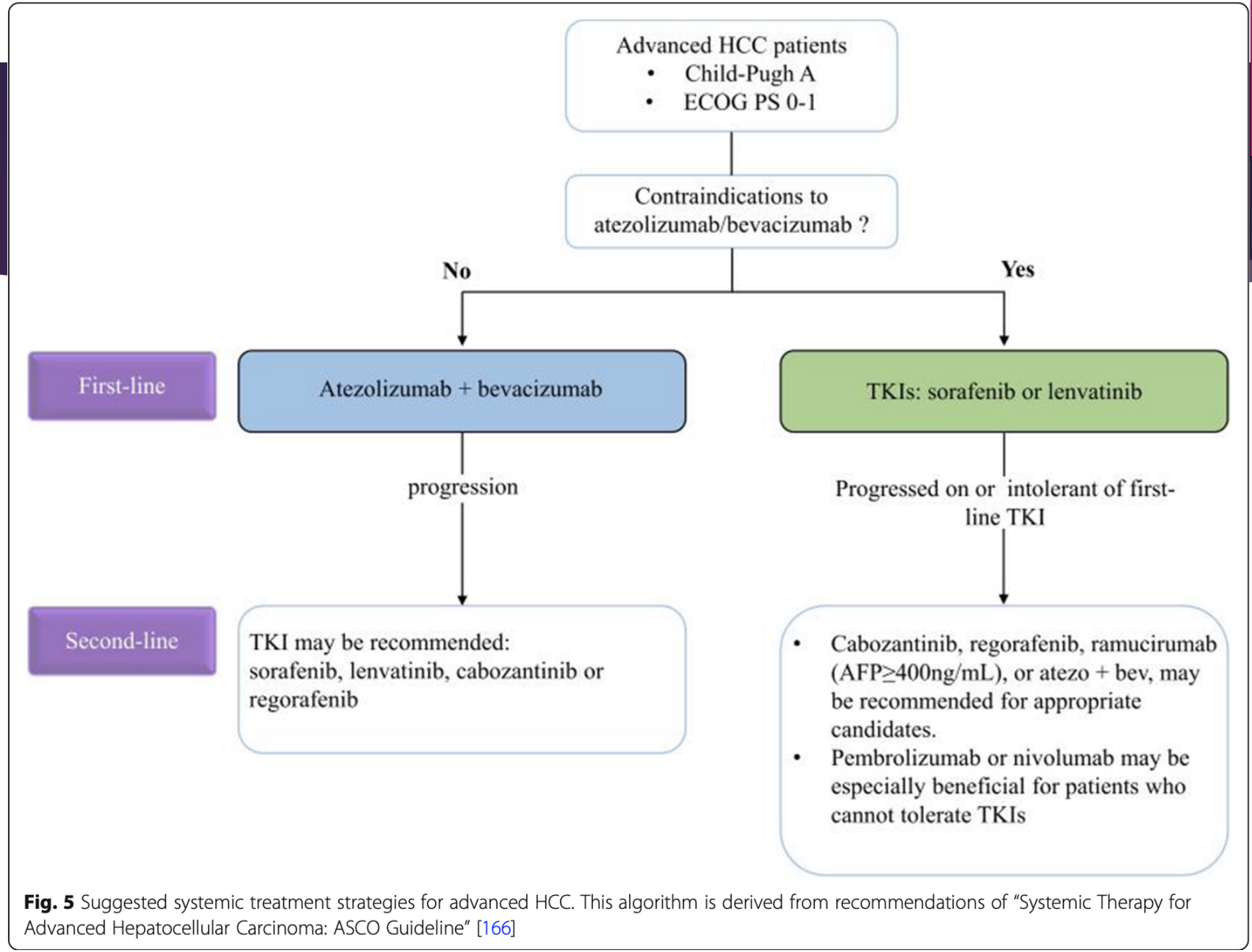


Fig. 5 Suggested systemic treatment strategies for advanced HCC. This algorithm is derived from recommendations of "Systemic Therapy for Advanced Hepatocellular Carcinoma: ASCO Guideline" [166]

Thank You