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STAGE-SPECIFIC DRUG THERAPIES AND TREATMENT STRATEGIES FOR HEPATOCELLULAR CARCINOMA

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ABSTRACT
Hepatocelluler cell cancer (HCC) is the top form of liver cancer & a key cause of death from cancer all over the world. What you can do to treat it rests much on how far it has gone, how the liver works, & how the sick one is doing. The Barcelona Clinic Liver Cancer (BCLC) list helps guide what to do in the clinic. Cures that can fix it, like cut out part of the liver, give a new liver, & small area burn are good for the start phase. For the mid phase, the go-to is TACE. For far-gone HCC, whole body drugs are key. Sorafenib was the first multi-use drug block to be okayed. It was top choice for a long time, though it has its limits due to not working after a bit & harm done. Since then, a lot more drugs like lenvatinib, regorafenib, cabozantinib, & ramucirumab have made more ways to treat. Also, drugs that block bad immune marks like nivolumab, pembrolizumab, & the mix of atezolizumab with bevacizumab have shown they help live longer for some. There are new study looks at mix of many drugs to block to fight the sickness in more ways & to do better overall. For the end stage HCC, the care aims to ease pain & help make life feel better. This text sums up the most recent ways to use drugs at each stage of HCC, shows the move from just one drug to many at once, & the hard tries still made to get the best out from treating it.

1 INTRODUCTION
Liver cancer is the sixth most found bad cell growth. It is the third top cause of death fromcancer. [1] Liver cell type (HCC) shows the main kind of liver ill. [2] Choice of care for HCC rests on how far it has spread.[3] For these with first-stage HCC, curing options are cut-off or whole liver cut-outs and liver swaps.[4] On the flip side, those with mid-stage HCC tend to get help with area-based care. Out of these, TACE stays as the top choice. [5][6] About half of all folks with HCC end up needing full body care. In the past, sorafenib was the main first pick. It hits many key spots in cells to stop growth. The U.S. Food & Drug Admin (FDA) said yes to it in 2007. It has big changed the care plan for bad HCC. [7] Sorafenib is known for its strong effects on blood vessel & cell growth control. Now, it is seen as a trigger for ferroptosis—a type of cell death tied to iron. It fights tumor cells in the liver by this way, which helps its healing effect. But, a big problem is that some patients don't react to sorafenib. This is mostly due to things like the tumor surroundings & change from skin-like to non-skin-like cells. [8][9][10]To fix these limits, more studies look at other care forms. Big in this group are more TKIs,including lenvatinib [11] , regorafenib [12] , and cabozantinib [13] , as well as epigenetic and multitargeted agents such as belinostat [14] and brivanib [15]. Also, they mix sorafenib with a lot of types. They check this join with real care.These include conventional chemotherapeutics (e.g., doxorubicin [16], 5-fluorouracil [17]), molecularly targeted agents (e.g., erlotinib [18] , everolimus [19]), and other pharmacological compounds (e.g., pravastatin [20] , vinorelbine [21]. New blend plans are

now in test. These mix drugs like sorafenib with TACE.[22] selective internal radiation therapy [23], and concurrent chemoradiotherapy [24]. All these clear plans show a great team push. They beat hard odds, raise cure rates, & help people with HCC live more.[25]

2 STAGES of Hepatocellular Carcinoma (BCLC)

The barcelona clinic liver cancer (BCLC) classification was first proposed by the Barcelona Clinic Liver Cancer group in 1999. [26] The BCLC stages HCC from 0 to D. It looks at tumor size, liver work (Child-Pugh), ECOG form, & signs. Each stage matches a set care plan. Many back it, but some critique it. They say it's too mixed in outcome, ECOG PS is too up in the air, & lacks give in true care use.[27]

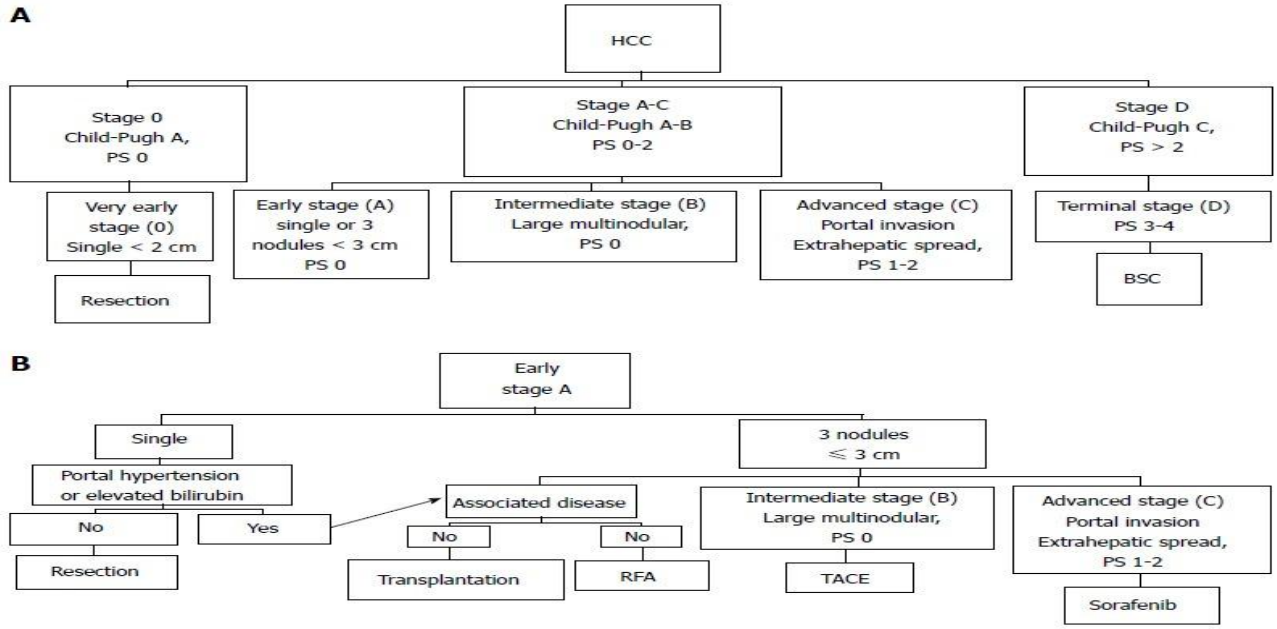

Figure 1. BCLC STAGES

TABLE 1 [28]

BCLC Stage	Tumor Characteristics	Liver Function & Patient Status	Recommended Treatment	Prognosis & Goal
Stage 0	Single tumor :-<2cm	Child-Pugh A, ECOG 0	Curative therapy: •Resection •Liver Transplant •Ablation	Best prognosis. Goal is to cure the patient.
Stage A	One tumor 2 cm or up to 3 tumors ≤3 cm	Child-Pugh A or B, ECOG 0	Curative therapy: •Resection •Liver Transplant •Ablation	Good prognosis. Goal is to cure the patient.
Stage B	Multiple tumors (usually >3) confined to the liver.	Child-Pugh A or B, ECOG 0	Transarterial Chemoembolization (TACE)	Palliative (non-curative). Goal is to slow disease progression and prolong life.
Stage C	Any tumor size with vascular invasion or extrahepatic spread (spread outside the liver).	Child-Pugh A or B, ECOG 1-2	Systemic Therapy (e.g., Sorafenib, Lenvatinib, Immunotherapy)	Palliative. Goal is to slow disease progression and extend life.
Stage D	Any tumor stage	Child-Pugh C, ECOG >2	Symptomatic Treatment and Best Supportive Care	Very poor prognosis. Goal is to maximize quality of life and manage symptoms.

3 Current Drug Strategies by Stage

3.1 Early-Stage HCC (BCLC 0–A)

First-phase HCC (BCLC 0 & A) is fixed by cure plans like surgery, transplant, or burn-off. Drug ways help or test to boost results & cut comebacks. [28]

3.1.1. Adjuvant Therapies

Adjuvant care in early HCC aims to cut the risk of a come-back after full fix jobs like cuts or heat kills. It aims at tiny left-over sick cells or free bad cells. While there is no set go-to adjuvant care, tests are looking at immune checkpoint blocks (like PD-1/PD-L1 blocks), aimed care (like sorafenib, lenvatinib), & mixed plans. The big test is to keep a good balance of care help with harm in folks who are well. Strong proof from hit-or-miss tests is a must before the day-to-day use of adjuvant cures. [29

3.1.2. Locoregional Therapies Combined with Drug Strategies

Local care for early HCC hits liver tumors hard. It's often mixed with drugs to up their power. “Transarterial Chemoembolization (TACE)” puts chemo right into the arteries that feed tumors. It then blocks blood flow to kill the tumor cells. Though it's mostly for mid-stage HCC, it can work for early-stage folks who can't have surgery or ablation. Key drugs are doxorubicin & cisplatin. “Radiofrequency Ablation (RFA)” or “microwave ablation (MWA)” is a top fix, it uses heat to wipe out tumors. Pairing RFA with new drugs or immune tricks, or using drug-filled beads, is a new way to cut back on tumor returns & hit left-over disease. [30]

3.1.3. Chemoembolization with Drugs

Chemoembolization has types like “TACE” & “drug-eluting bead TACE (DEB-TACE)”. It joins block of tumor blood flow with fixed chemo. Usual TACE uses chemo mixed with lipiodol to hold the tumor, while DEB-TACE has drug-full bits for long chemo use, cutting down harm to the full body. Though not first pick for early HCC, chemoembolization can work when cut or burn is not fit. Trials are to mix with full body drugs like sorafenib to boost care by hitting small left tumor cells. [31]

3.2 Intermediate-Stage HCC (BCLC B)

3.2.1. Transarterial chemoembolization (TACE) ± systemic drugs

In the mid-stage HCC (BCLC B), the main treatment is “Transarterial Chemoembolization (TACE). It sends chemo to the tumor's blood flow & makes it die. But low oxygen after TACE may help the tumor come back. To stop this, “drugs that block new blood cells” like sorafenib are used with TACE. The TACTICS trial showed this mix aids in stopping the tumor from getting worse. New drugs like “lenvatinib” & “immune checkpoint blockers” (e.g., atezolizumab) are being looked at too. They aim to boost tumor check & results in this tough stage. [31]

3.2.2. Drug-eluting beads (DEB-TACE)

“Drug-Bead Block (DEB-TACE)” uses small beads with chemo drugs like doxorubicin. They go in via a thin tube to stop tumor blood flow & give out drugs slow. This cuts full-body harm. Not like old TACE, DEB-TACE hits the mark well, has fewer ill effects, & works the same each time. The “PRECISION V study” had more good rates & less harm to the liver, especially in patients with compromised liver function. DEB-TACE is now tried with full-body drugs like sorafenib & lenvatinib to boost results in BCLC B HCC. [32]

3.3. Advanced-Stage HCC (BCLC C)

Advanced stage hepatocellular carcinoma(hcc) is characterized by portal vein invasion, extrahepatic spread, & cancer-related symptoms. At this point, therapeutic treatment plans like cut or swap won't work. Systemic therapies are the main way to treat.

3.3.1. First-line:

- **Sorafenib:** Sorafenib (Nexavar®) is the only OK drug for bad liver cancer (HCC). This is based on tests from the SHARP & Asia-Pacific groups. These tests show that sorafenib (400 mg two times a day) helps make folks live more. It slows down how fast the cancer gets worse. But does not change

when signs get worse. The drug works if the liver is still not too bad (Child-Pugh A). It may not be right for all. Data like that from the GIDEON test backs its use in some Child-Pugh B folks. The drug's side bits are known & are in check. Stuff like skin woes on hands & feet. [33]
Sorafenib hits top growth ways in liver cancer. It blocks RAF/MEK/ERK signs & stops growth. It hits keys like VEGFR, PDGFR-β, C-KIT, & FLT3. This stops the tumor & blood flow. It fights bad genes like RASSF1A & SOCS1 in HCC. First tests show it cuts blood to the tumor & kills cancer cells. This helps those with late HCC. [34][35]

The use of sorafenib in HCC care was first looked at in a big, global phase II test. It had 137 folk, & 73% of them had CP-A liver health. The test showed that the Time to Grow (TTP) was 4.2 months, & life span (OS) was 9.2 months. These scores were a bit more than with other care. Like doxorubicin & PIAF (cisplatin, drug that stops cells, doxorubicin, & drug that kills cells) plan, where the mid OS rates were 6.8 & 8.7 months. The 2008 SHARP test showed sorafenib worked well for bad HCC. It made life last longer (10.7 vs. 7.9 months) & put off sickness growth (5.5 vs. 2.8 months). It cut the risk of death in one year by 31%. Most side issues were small—bad guts, low strength, & hand-foot skin things. This test set sorafenib as the top first pick to treat bad liver sick. [36][37][38]

An in-depth look at two tests gave more clues on which signs will most favor the use of sorafenib. Folks with HCV had a mean life span of 426 days with sorafenib (HR 0.47 [0.32–0.69]). This is long next to 232 days for those with no HCV (HR 0.81 [0.66–0.99]). In the same way, folks with a less than 6 cm large growth got to live more in the sorafenib team. On the flip side, those with large blood vessel woes or a high white-to-red blood ratio got bad news. The look into also showed the bad life span in the Asia-Pacific group due to big growth woes & HBV roots. [39][40][41]

- **Lenvatinib:** Lenvatinib (Lenvima®) is a pill type drug. It stops many cell signals. It got the nod to be the first pick for big liver cancers you can't cut out. This is true in the USA, EU, Japan, & China. Its okay to use came from the REFLECT test. This test showed lenvatinib was as good as sorafenib in how long sick folks lived. It was better in other key points like how many had less cancer spread, how long they stayed free from worse cancer, & time till their cancer got worse. Its ill effects, such as high blood pressure, loose poop, less hunger, & less weight, are in check most times. Lenvatinib is a good pick to swap for sorafenib for late stage big liver cancers. [42]

Lenvatinib stops VEGF, FGF, PDGFRα, KIT, & RET paths. In the REFLECT test (2013–2015) with \~1,000 HCC patients (Child-Pugh A, ECOG 0–1), it tied sorafenib in full life time (13.6 vs. 12.3 months; HR 0.92). But it did more in free-from-disease life time (7.4 vs. 3.7 months), time to get worse (8.9 vs. 3.7 months), & fix rate (24.1% vs. 9.2%). Lenvatinib led to more high blood fix, runs, & weight drop; sorafenib led to more skin woes on hands & feet. More died with lenvatinib (11 vs. 4), but it stays a top first pick. [43][44]

A look back found that the Lenvatinib set who got CP-B soon had less OS (6.8 vs. 13.3) than CP-A did. It was seen that Grade 3 AEs were 71.7% (CP-B) vs. 54.7% (CP-A). Stops in use were 18.3% (CP-B) vs. 7.5% (CP-A). Two more looks back spoke of those who got more care post-trial. Those who got first Lenvatinib & then more anti-cancer drugs had 25.7 months OS. Those on first Sorafenib & then drugs had an OS of 22.3 months. Those who had steps (like TACE or HIAC) saw that first Lenvatinib set had an OS of 27.2 months (Sorafenib set had too few to count OS). These facts show that OS can go up for those who take to Lenvatinib & get more steps or drugs. In 2018, Lenvatinib was okayed for big HCC, with new rules to use it in HCC with CP-A only. [45][46][47]

- **Atezolizumab and Bevacizumab:** Atezolizumab, which blocks PD-L1, & bevacizumab, which aims at VEGF, are used to treat bad liver cancer (HCC). In the IMbrave150 test, this mix made life & health last more than with sorafenib. From these facts, the FDA said yes to it as a first fix for HCC that can't be cut out. This plan is now a new care rule, more so for those who can't have surgery or a

new liver. Big bad side effects are high blood flow, feeling tired, bad runs, & health tie-ups caused by the body's guard system. [48]

PD-L1/PD-L2 halt T-cell work by tying up PD-1, so tumors hide from body guards. High PD-L1 in HCC ties to bad ends. Atezolizumab stops PD-L1 & frees up T-cells, while Bevacizumab cuts VEGF & drops blood to tumors. In the GO30140 test, the Atezolizumab-Bevacizumab mix got more time free from disease (5.6 vs. 3.4 months) than Atezolizumab on its own. The IMbrave150 phase 3 test put Atezolizumab-Bevacizumab up against Sorafenib in fixed HCC. With a 2:1 pick rate, key aims were full life span & time free from disease. The mix did well & became a top first pick. Docs checked for varices, & folks with fresh heart woes or both HBV/HCV were left out. Care went on till bad side stuff or disease got worse. [52][53]

This work showed that the OS got better with Atezolizumab & Bevacizumab. At 6 months & 12 months, the rates were 84.8% & 67.2% vs. 72.2% & 54.6% in the Sorafenib group. PFS was longer with Atezolizumab & Bevacizumab too. The mean was 6.8 months vs. 4.3 months for Sorafenib. Bad side things were more with Atezolizumab-Bevacizumab than Sorafenib. Stomach side blows were the top cause to stop. Stomach blood loss was more in Atezolizumab & Bevacizumab vs. Sorafenib (7% vs. 4.5%). The top side blow was high slow blood move in Atezolizumab & Bevacizumab (15%). Other bad things to note were skin odds, high ALT, more bilirubin, more pee blood stuff, & low plate bits. In this test, it was found that the mix of two drugs gave better life span & health. The mix was Atezolizumab & Bevacizumab. This duo also cut down on loss of hunger, loose bowels, tiredness, & hurt. The test showed that putting PD-L1 with a VEGF stopper may work well to treat tough HCC. As the mix works, the FDA said it was good as first help for hard HCC. [54][55]

TABLE 2 [33-55]

Drug/Regimen	Mechanism of Action	Key Clinical Trial(s)	Key Efficacy Findings	Key Efficacy Findings
Sorafenib	Blocks multiple signaling pathways, including RAF/MEK/ERK, and receptors like VEGFR and PDGFR-β. This inhibits tumor proliferation and angiogenesis (new blood vessel formation).	SHARP & Asia-Pacific trials	SHARP trial: Increased overall survival (OS) (10.7 vs. 7.9 months) and time to tumor progression (TTP) (5.5 vs. 2.8 months) compared to placebo.	Hand-foot skin reaction, diarrhea, fatigue, low strength.
Lenvatinib	Multikinase inhibitor that targets VEGFR, FGF, PDGFRα, KIT, and RET pathways. It inhibits tumor growth and angiogenesis.	REFLECT trial	Non-inferiority to sorafenib: OS (13.6 vs. 12.3 months). Superiority: Progression-free survival (PFS) (7.4 vs. 3.7 months), TTP (8.9 vs. 3.7 months), and objective response rate (24.1% vs. 9.2%).	Hypertension (high blood pressure), diarrhea, decreased appetite, weight loss.
Atezolizumab + Bevacizumab	Atezolizumab: A PD-L1 inhibitor that "frees up" T-cells to attack tumor cells. Bevacizumab: A VEGF inhibitor that reduces the tumor's blood supply.	IMbrave150 trial	Superiority to sorafenib: Improved OS (at 6 and 12 months) and PFS (6.8 vs. 4.3 months).	Hypertension, fatigue, diarrhea, hemorrhage (bleeding), and immune-related adverse events.

3.3.2 Second-line and beyond:

➢ **Regorafenib:** Regorafenib (Stivarga®) is a drug made to halt many cell growths. It got the OK for liver cancer cases who get worse post-sorafenib care. The OK came from a big phase III RESORCE test. The test showed that regorafenib made life span, disease-free time, & time to get worse, all last more. It had a safe use mark, with mild bad effects like skin sores, tired feel, loose bowels, & high blood flares. Of note, no fatal liver fails did happen. Regorafenib is a key pick for bad liver cancer. [56]

Regorafenib is a drug you take by mouth. It stops many key growth points in bad cells. It aims at blood vessel growth, cell frame, & growth cues. It's much like Sorafenib in its build. It acts by blocking VEGF cues 1-3, KIT, PDGFR-alpha, PDFR-beta, RET, FGFR1 & 2, TIE2, DDR2, TrkA, Eph2A, RAF-1, BRAF, BRAF V600E, SAPK2, PTK5, & Abl. The study phase III RESORCE looked at regorafenib in sick folks with liver cancer (HCC) who got worse on sorafenib. All had good liver health & stage B or C of the disease. They took 160 mg of regorafenib each day for 21 days in 28-day times until they got worse or the side effects were too much. Regorafenib made folks live longer on the whole (10.6 vs. 7.8 months; HR 0.63; $p < 0.001$), cutting the risk of death by 37%. It also made the time without the disease get worse slower (3.1 vs. 1.5 months), the time to get worse (3.2 vs. 1.5 months), rate of disease control (65% vs. 36%), & clear good change rate (11% vs. 4%) than fake med. Bad sides were okay to deal with, like high blood press, skin issues on hands & feet, lack of get-up-&-go, & loose bowels. Regorafenib worked well as a next step help post-sorafenib. More news from the RESORCE test says Regorafenib is good no matter the last Sorafenib use. In 2017, the FDA said yes to Regorafenib for HCC if Sorafenib did not stop the sick. Take it as 160 mg by mouth. Do this each day for the first 21 days of a 28-day span. [57][58][59]

➢ **Cabozantinib:** Cabozantinib (Cabometyx®) is a drug that stops many kinases. It got the nod in the EU & USA to treat big liver cancer (HCC) in ones who tried sorafenib first. The okay came from the phase III CELESTIAL test. This study had folks whose sickness got worse after one or two tries of past drugs. Cabozantinib made life last longer & slowed the cancer more than a fake drug did. It worked well in all types of sick folks & cancer forms. Its safety was okay & much like other RTK stoppers. Side effects were kept in check by fixing the dose & extra care. Cabozantinib is a good pick for round two in treating big HCC if sorafenib does not work. [60]

Cabozantinib stops bad cells from moving to new sites. It works on many types of cell triggers like AXL, FLT-3, KIT, & more. In the phase III CELESTIAL trial, it helped those with HCC who had taken Sorafenib before. In this trial, sick folks got 60 mg of Cabozantinib a day or a fake drug. They took it till their disease got worse or the side effects were too much to bear. In the test, sick folks with bad HCC & Child-Pugh A liver work, plus those with hep B or C, spread of disease, or past care, got cabozantinib or a fake pill. Cabozantinib upped life span (10.2 vs. 8.0 months) & time with no worse signs (5.2 vs. 1.9 months). It cut the risk of death & disease get worse. Bad side parts were skin woes on hands & feet, high blood press, tired feel, & loose stools, hitting 68% of cabozantinib users vs. 36% on fake pills. Gains were the same for all test signs. In 2019, the FDA said yes to cabozantinib for use after sorafenib, as a 2nd or 3rd pick. It comes in 20, 40, & 60 mg pills, with a tip to take 60 mg a day. [61][62][63]

➢ **Ramucirumab:** Ramucirumab (Cyramza®) is an anti-VEGFR-2 drug. It is okayed for use in liver cancer (HCC) care. This is for folks who used sorafenib before & have high AFP (≥ 400 ng/mL). In the REACH-2 study, phase 3, it made life last more & made sick time less than with no drug. The gains were the same in all kinds of sick folks. It was safe to use, with fewer & mild bad effects. Ramucirumab is the sole pick checked in HCC folks with high AFP. They tend to do worse, so this is a key next care for this hard sick group.[64]

Ramucirumab is a lab-made drug that stops VEGFR-2, a key part in making blood paths that help tumors grow. In liver cancer (HCC), high alpha-protein (AFP ≥ 400 ng/mL) means more blood flow

& worse ends. First tests of Ramucirumab in the REACH phase I/II trial took place with 42 sick folks with bad HCC who had tried & failed with sorafenib. The life gain (9.2 vs. 7.6 months) was not big, but a group with high AFP showed a good life boost (7.8 vs. 4.2 months), so more tests were done.The REACH-2 phase III trial then looked at 292 folks with bad HCC, all with high AFP & past sorafenib use. They set folks 2:1 to get either ramucirumab or a fake drug each two weeks. The test went on till the disease grew worse or side effects got too bad. Ramucirumab led to longer life (8.5 vs. 7.3 months) & slow disease growth (2.8 vs. 1.6 months), with a 29% cut in death risk. More folks got better in the ramucirumab group. The drug was mostly easy to take. Main side effects were being tired, not hungry, upset guts, loose bowel runs, belly pain, sore hands & feet, & head pain. Bad but rare side effects were high blood press, low salt, & some deadly cases linked to bad kidneys or liver-kidneys.In May 2019, the FDA said yes to ramucirumab as a solo fix for sick folks with bad HCC & high AFP who got worse with or post sorafenib. It was the first fix just for this high-AFP group. [65][66][67]

- **Nivolumab:** Nivolumab, a drug to fight PD-1, aids in more folk with cancer to live. The FDA said yes to use nivolumab & ipilimumab (another drug) for tough liver cancer. Nivolumab by itself also works in Taiwan for this cancer. But, it costs a lot. This makes it hard to get in places with less cash, with few Asian spots paying for it. So, low-dose nivolumab is now seen as a way to save cash. Tests show this small dose works in lung, kidney, & blood cancer. In a test, they tried out different doses for liver cancer. The FDA set the dose at 240 mg every two weeks for all uses, no matter the body size. [68]

Nivolumab is a drug that helps boost the body's fight against cancer. It sticks to PD-1 on T cells. The CheckMate 040 trial checked how safe & good it is for folks with bad liver cancer (HCC). They also had B or C hepatitis, Type A or B liver health, & some had used sorafenib before.There were two parts in the study. A small group (48 folks) got 0.1-10 mg/kg every two weeks. A big group (214 folks) got 3 mg/kg every two weeks. The big group had 20% react well. The small group had 15% react. Bad side stuff hit 25% of the small group, not tied to dose. Folks with PD-L1 at 1% or more saw better rates (26%) than those below 1% (19%).The CheckMate 459 trial had 743 folks. They got nivolumab (240 mg IV every two weeks) or sorafenib (400 mg by mouth, twice a day). The mid time they lived was 16.4 months with nivolumab & 14.7 months with sorafenib. The gap was small (p=0.0419). Nivolumab was nicer to use, with fewer skin issues (14% vs. more with sorafenib), and less liver harm & high blood pressure. Bad side stuff was near same (12% nivolumab vs. 11% sorafenib).Nivolumab got a yes from FDA in 2017 for HCC folks post sorafenib. But it was pulled back in the U.S. for solo use as it did not show sure help. [69][70]

- **Pembrolizumab:** Pembrolizumab worked well & was okay in folks with bad liver cancer who had previously been treated with sorafenib. These facts show pembrolizumab could be a choice for these folks. This drug gets more looks in two phase 3, short run tests as a back-up fix in those with liver cancer. Pembrolizumab, which is another monoclonal antibody against PD-1. This second-line treatment can also be considered in those who were unsuccessfully treated in first-line by Sorafenib. Keynote-240 demonstrated that benefits of pembrolizumab were diminishing over the course of time (30).The effect of CP is something that first is noticed in phase II Keynote-224 in advanced HCC patients who had previous failure of Sorafenib to exactly know level of influence of liver function on the immunotherapy. A total of 47 medical centers and hospitals in 10 countries were involved in the study. One hundred and four patients were included in the study across January 2016 to February 2018. [71][72]

The Phase III KEYNOTE-240 trial looked at pembrolizumab as a plan B PD-1 stopper for worse liver growth (HCC). In this masked test, 413 sick were split 2:1 to pembrolizumab or fake drug. Pembrolizumab had a better hit rate (18.3% vs. 4.4%) & full fix rate (6 vs. 0 sick). Most on pembrolizumab (96.4%) had bad signs, with 48 quit care due to bad side hits like gut swell (4.3%) & high liver stuff (1.4%). Care breaks were in 84 due to high bile or AST. Seven deaths were tied to bad

signs in the pembrolizumab team, four in fake. Big bad signs were high liver stuff, tired feel, & itch. Body fight bad signs were mostly gland mess up & lung swell, in 18.3% of pembrolizumab sick. Liver woes hit 3.6%, with most got well & no virus burst. Drugs to ease side signs were used in 8.2% of pembrolizumab sick. Pembrolizumab (200 or 400 mg IV) got the ok for sick first treated with sorafenib. [73]

TABLE 3 [56-73]

Drug/Regimen	Mechanism of Action	Key Clinical Trial(s)	Key Efficacy Findings	Key Efficacy Findings
Regorafenib	A multi-kinase inhibitor similar to Sorafenib, it blocks a wide range of kinases including VEGFR 1-3, KIT, PDGFR, and RAF, thereby inhibiting angiogenesis and tumor cell proliferation.	RESORCE (Phase III)	Improved overall survival (OS) (10.6 vs. 7.8 months) and progression-free survival (PFS) (3.1 vs. 1.5 months) compared to placebo. It reduced the risk of death by 37%.	Hand-foot skin reaction, fatigue, diarrhea, and hypertension. Export to Sheets
Cabozantinib	A multi-kinase inhibitor that targets a broad spectrum of receptor tyrosine kinases (RTKs) involved in tumor growth, angiogenesis, and metastasis, including VEGFR, MET, and AXL.	CELESTIAL (Phase III)	Improved OS (10.2 vs. 8.0 months) and PFS (5.2 vs. 1.9 months) compared to placebo in patients who had failed prior Sorafenib treatment.	Hand-foot skin reaction, hypertension, fatigue, and diarrhea. Export to Sheets
Ramucirumab	A monoclonal antibody that specifically targets and blocks the vascular endothelial growth factor receptor 2 (VEGFR-2), crucial for tumor angiogenesis.	REACH-2 (Phase III)	The only drug approved specifically for HCC patients with a high alpha-fetoprotein (AFP) level (≥400 ng/mL) after Sorafenib. It showed improved OS (8.5 vs. 7.3 months) and PFS (2.8 vs. 1.6 months) compared to placebo.	Fatigue, decreased appetite, and gastrointestinal issues. Export to Sheets
Nivolumab	An immune checkpoint inhibitor that blocks the PD-1 protein on T-cells. This "releases the brakes" on the immune system, allowing it to recognize and attack cancer cells.	CheckMate 040 (Phase I/II) & CheckMate 459 (Phase III)	CheckMate 040 showed a 20% objective response rate. CheckMate 459 did not meet its primary endpoint for statistically significant OS improvement (16.4 vs. 14.7 months), but it had a more favorable safety profile than Sorafenib. It was approved in 2017 but was voluntarily withdrawn in the U.S. for solo use due to lack of confirmed clinical benefit.	Fatigue, rash, and immune-related adverse events (e.g., colitis, hepatitis). Export to Sheets
Pembrolizumab	Another immune checkpoint inhibitor that targets the PD-1 pathway, similar to Nivolumab, to enhance the anti-tumor immune response.	KEYNOTE-240 (Phase III) & KEYNOTE-224 (Phase II)	KEYNOTE-240 showed a better objective response rate (18.3% vs. 4.4%) compared to placebo. It demonstrated promising efficacy but did not meet its primary endpoints for OS	Fatigue, pruritus (itching), and immune-related adverse events affecting various organs.

			or PFS. It was granted accelerated approval but was later withdrawn for a similar reason to Nivolumab.	

3.4 Terminal-Stage HCC (BCLC D) [74][75]

Lots of folks get palliative care wrong. They think it's just for those near death or when no more cures are left— mainly for those waiting for liver swaps. This wrong view puts off early help from palliative care, which could ease pain & signs while other cures go on. UK, Canada, & USA studies show that many cut from liver swap lists got palliative care just days before they died. In the past, talks on palliative care for liver disease were few, even though strong proof from other sick states shows it aids life quality, mood, & help for both sick folks & carers. One study tried out a palliative care plan for liver patients up for swap review. This method eased signs in half of the patients & lifted mood in 43% after three months. The act had one meet with a palliative care pro. It dealt with pain, mood, social help, & soul care, with the most hurt getting the most aid. Early use of palliative care can truly boost results in liver disease.

In towns & care spots, nurses help those with liver woes & their help-mates. They lead to a better life. In deep care spots (ICUs), plans to chat with kin about what lies ahead & what the sick one wants got a test run. They spoke of when to end life aid. This way led to more time with kin, less time in ICU & on life aid. Yet, the end was much the same. This shows it’s as safe as the norm. To set up tests for more care in liver ills, we need fresh ways & aims. Plus, deep ties with those ill & their aides to make sure the results mean more than just how long they live or stay in a care home. About 15-20% with liver cancer (HCC) are in a bad spot (ECOG 3-4, Child-Pugh C) & may not live more than 3-4 months. For them, care aims at ease from pain, good food, & mind help not at the cancer. They tend not to be in new trials. This text looks at last-days care for those with bad HCC.

3.5 PALLIATIVE DRUG

Liver disease in ER care is on the rise. The virus made it worse. Even with good care for bad liver scars, many die in 6 to 12 months post-diagnosis. Care at end of life is poor & has few facts on it. It's from what docs see. Many get late or no end of life care & face big blocks to help. Help for pain is bad, as signs are seen late & talks on what may come are not had soon. More folks in the UK care about end of life care for liver cases, & more experts are there. This look at the topic says we must make the care better & gives tips on how to add this care into plans for liver health. [74]

HCC folks in the last part of their sickness may show with a mix of signs tied to bad liver health. This can mean fluid in the belly, blood loss from veins, swelling in arms & legs, and brain issues from liver failure. On top of these signs, belly pain is the most seen (near 2/3 of those sick). It comes from big tumor mass & is told as a deep gut pain. Lots of folks have said they feel tired or weak. Some have swelling at their feet or hands. Weight loss, fluid in the belly, hard breaths, loss of hunger, & vomiting are also reported. Those with HCC show high rates of sad or stressed minds. This is the third most in 14 other cancer types. [76][77][78]

The idea of symptom groups is now well-known. Such groups have 2 or more signs that link to each other & show up at the same time. The groups are made up of steady sets of signs. They stand alone from other groups. They may show clear root sides of signs. Signs in a group may or may not have the same cause. The link among signs in a group is more of a tie than a cause. It is key to look for likely group of signs in HCC patients. This helps make good ways to deal with their signs. It's well-known that not eased signs hurt how patients turn out. This counts in how they work, feel, & their life's quality. Knowing this is very key when we care for end stage HCC patients. [79][80][81]

Pain is a key part of liver cancer (HCC), caused by the illness or its care. It shows as deep, sore, sharp, or sharp pain in the upper right side, sent to the right arm. Gut pain is oft deep, from organ swell,

cramp, or spread. Good care starts with full checks, oft with a pain scale. As it comes & goes, HCC-linked pain must be checked all the time to keep hurt at bay. [74]

LIST OF PALLIATIVE DRUG

- Nonselective NSAIDs
- Selective COX-2 Inhibitors
- Opioids
- Acetaminophen(Paracetamol)
- Corticosteroids

4.0 Mechanism of Action of Major Drug Classes

4.1 Tyrosine kinase inhibitors (TKIs)

Blood flow is key for liver lump growth. VEGFR is in high use in HCC. It leads to bad blood lines & less air flow. It ties to bad ends. VEGFR may aid liver lump birth. It is a main fix spot. Tyrosine kinases turn on a lot of growth bits in a cell. Tyrosine kinase blockers stop these signs. They block VEGFR & EGFR2. They cut off lump cell chat & speed up lump cell death. [82][83]

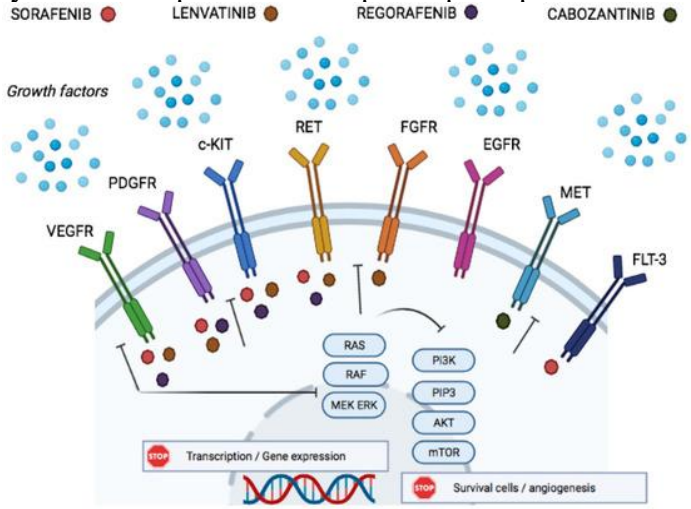

Figure 2. Tyrosine kinase inhibitors and molecular pathways in hepatocellular carcinoma.

The drug Sorafenib, made in 2007, was the first pill that took on many kinases in late-stage HCC (BCLC B & C). It hit targets like VEGFR2/3 & PDGFR. The 2008 SHARP test (602 folk, Child–Pugh A, no past full-body fix) said folk lived more with the drug (10.7 vs. 7.9 months, HR 0.69, $p < 0.001$). Yet, signs got bad at the same pace (4.1 vs. 4.9 months). But, a slow down in the scans was seen (5.5 vs. 2.8 months, $p < 0.001$). Big side woes were skin issues on hand & foot (7%), lack of zip (7.4%), & loose runs (13.1%), leading up to 44% to quit the drug. In 2009, a trial in Asia-Pacific backed these facts, noting better life spans (6.5 vs. 4.2 months, HR 0.68) & slow bad times (2.8 vs. 1.4 months, $p = 0.005$). [84][85]

For ten years, sorafenib was the sole first-line care. It was the only one to boost life span in high-level HCC. This was for folk with good liver work. All the big tryouts of new drugs did not work to add to life span. This was in the first test (sunitinib, linifanib, or doxorubicin). [86][87][88] or second-line settings (Brivanib or ADI peg 20) There are many causes for these fails. Most are tied to poor focus on the liver's ill state. Take sunitinib. It had big harm to the liver at the dose used (37.5 mg once per day). The root cause of the liver's ill state (alcohol, fat liver ill called NAFLD, virus in liver), blood vein spread, or spread to other parts were all small rated parts. These led to the fail of the care in these tests. [89][90]

The RESORCE test looked at regorafenib, a pill, on late HCC folk who grew worse on sorafenib. This stage 3 test was set up with a choice on a fake pill & had folk with good liver work. Regorafenib helped folk live more (10.6 vs. 7.8 months; HR 0.63, $p < 0.0001$). The dose was 160 mg each day for 3 weeks in a 4-week span. From this, regorafenib was the top pick for use after sorafenib did not help.

A key side effect, hand-foot skin woes, tied to much more life span (14.1 vs. 6.6 months; HR 0.52), like with sorafenib. [91]

Lenvatinib, a pill TKI that hits VEGF, FGF, PDGF, RET, & KIT, was checked as a first pick for bad HCC as there were few choices. In the 2018 phase III REFLECT test, lenvatinib did just as well as sorafenib in how long folks lived (13.6 vs. 12.3 months; HR 0.92). It did better in time with no worse signs (8.9 vs. 3.7 months) & how well it worked. But, lenvatinib led to more high blood press (23% vs. 14%), it gave less hand-foot skin woes (3% vs. 11%). These facts made it a top pick for HCC that can't be cut out. Lenvatinib may be a good fit for those with past skin probs from sorafenib or some heart risks, giving a strong choice with a clear set of side woes. [92][93][94]

Cabozantinib, which stops VEGFR & c-MET, was in a big test. It was in the CELESTIAL phase III trial. 707 HCC folks who got worse after sorafenib were in the test. They had 60 mg cabozantinib each day or a fake pill. It helped them live more (10.2 vs. 8.0 months; odds 0.76, $p = 0.005$). It also slowed the sick spread (5.2 vs. 1.9 months; odds 0.44, $p < 0.001$). Usual bad effects made a need for dose changes. These included skin issues on hands & feet (22%), runny stools (10%), tired feel (7%), & high blood push (7%). Cabozantinib is a strong pick for round two for those who got worse on or can’t bear sorafenib. [95]

4.2 Immune checkpoint inhibitors (ICIs)

Anti-VEGF aids link to key spots (VEGFR1 or VEGFR2) & stop new blood lines in tumor cells. Key cell types show PD-L1 & link to a match (PD-1) on T-Cells. This link cuts down the work of T-cells.[fig] Systemic immune checkpoint inhibitors, such as atezolizumab (anti-PD-L1) or nivolumab (anti-PD-1), prevent this binding and increase T-cell activation to restore antitumoral activity. Various immune checkpoint inhibitors have been evaluated for the treatment of advanced HCC. [96][97][98]

Nivolumab is a form of drug. It fights some sick cells. The CheckMate 040 trial was done. Nivolumab was tried on sick folk. It was given at 3 mg per kg. It worked with about 20% of them. These folk had bad HCC & still good liver work. This was after sorafenib did not work.[99] In this test, the rate of disease stop was 64%. Life with no worse health was 4.1 months with nivolumab. Not long ago, the big phase III CheckMate 459 test put 743 sick ones to get nivolumab (240 mg in vein each 2 weeks) or sorafenib (400 mg by mouth two times each day). The mean full life time did not go up in the nivolumab group: 16.4 months vs 14.7 months with sorafenib (HR 0.85, CI 95% from 0.72 to 1.2, $p = 0.075$).[100] The safe mark was good, & the key bad effects were hand-foot skin snag (1%) & high enzyme in the liver (6%). They put Nivolumab up next to Regorafenib. This was for sick folks with bad HCC & failed first meds.[101] The safe mark was fine, & the key bad bits were skin snag on hand-foot (1%) & high liver enzyme (6%). They put Nivolumab up next to Regorafenib. This was for sick folks with bad HCC & failed first meds.

Pembrolizumab was tried in the KEYNOTE-240 test (413 sick HCC folk after sorafenib). It had a top check rate (18.3% vs. 6%) & more life span (13.9 vs. 10.6 months; HR 0.78) & more free time from progress (3.0 vs. 2.8 months; HR 0.71) than a fake cure. Yet, these perks were not big enough for green light, so pembrolizumab isn’t still okay as plan B care.On the flip side, the IMbrave150 test set atezolizumab & bevacizumab by sorafenib in 501 folk. At six months, life was up (84.8% vs. 72.2%) & free time from progress was more (6.8 vs. 4.3 months; HR 0.59). Death risk was less (HR 0.58), with top check rates (27.3% vs. 11.9%). High blood was the main bad mark, but bleed risk needs keen checks for varices. Atezolizumab-bevacizumab is now a lead first-line care for sick HCC.[102][103]

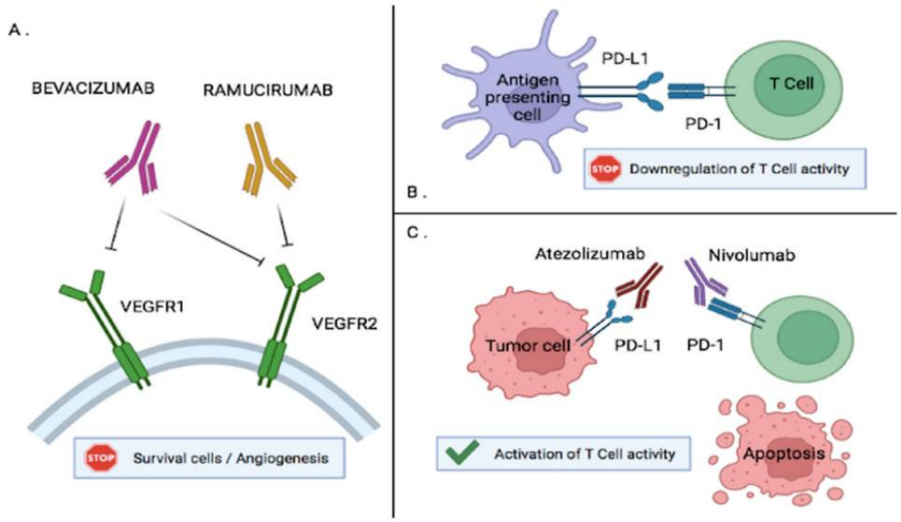

Figure 3. (A). Anti-VEGF and monoclonal antibody (ramucirumab) inhibit angiogenesis in tumor cell (B). Activated T-cells express P-1 that binds to its specific ligand PD-L1 on antigen presenting cell which inhibits T-cell activity (C). Anti PD-1 (Nivolumab) and anti-PD-L1 (Atezolizumab) prevent this binding and increase T-cell activation which allows apoptosis of tumor cells.

4.3 Combination therapies

Good results were seen when two care plans teamed up. A test phase checked the mix of two drugs. They showed great hope. The free run time with no bad growth was 9.5 months. The full life span was 22 months.[104] A phase III study comparing lenvatinib plus pembrolizumab to lenvatinib plus placebo is in progress (NCT03713593).The COSMIC-312 test in phase III looked at two drugs at once against just one. They had 837 sick folk with Child–Pugh A liver type & bad HCC. The mix of meds cut sick time to 6.8 months. By itself, the one drug did 4.2 months (HR 0.63, p = 0.0012). So, sickness slowed by about 37%. But, no big change was seen in how long all lived from start to end. They lived 15.4 months with two drugs & 15.5 months with one (HR 0.90, p = 0.438). The HIMALAYA phase III test looked at durvalumab alone or with tremelimumab vs. sorafenib for first-time, bad HCC. The mix made the mean life span go up (16.4 vs. 13.8 months; HR 0.78, p = 0.0035) & had fewer bad side effects (25.8% vs. 36.9%). This pair looks good as a new first pick. A like test for nivolumab & ipilimumab is still on. [105]

CONCLUSION

Liver cell cancer (HCC) is a big world health test. It has few cure choices in late phases. In the last ten years, care grew from one drug to lots. These include aimed drugs, body defense aids, & care help. Mix these aids with spot care brings new hope. It can lift life span & life worth. But, hard parts stay, like drug fight, picking the best aid for each one, fix side ills, & get to new aids, most in poor spots. The win ahead needs care fit to the one, good markers to see what will come, & care right to the tumor type & liver work. While cure is the aim for early stage, a mix plan with whole body aids, spot aids, & care help is key. It is to lift well feel & life span in all HCC stages. This mix, group way looks to add life & keep life worth through the sick road.

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