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Saudi Society for the Study of Liver Disease and Transplantation

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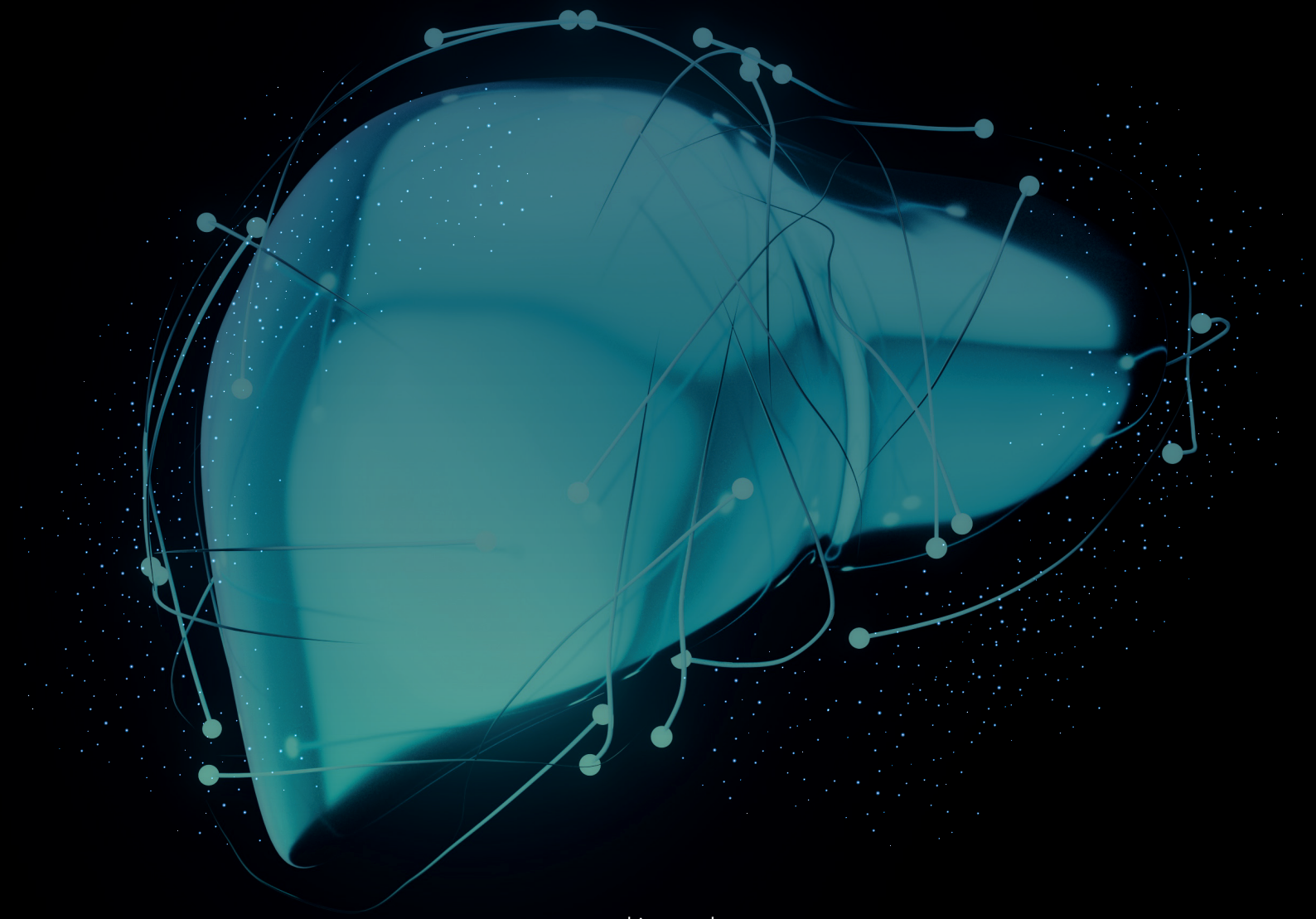

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BIOGRAPHY

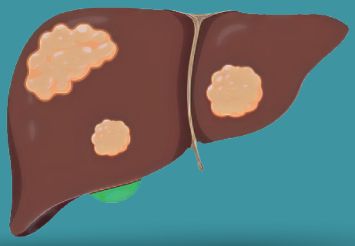
Dr Abdelrahim is a gastrointestinal medical oncologist, and transplant oncologist where he is taking care of patients with upper and lower GI malignancies in addition to malignancies treated by liver transplantation. He is the section chief of GI medical oncology leading the GI cancer care at Houston Methodist Neal Cancer Center with focus on clinical trial Phase II/III in GI malignancies. Dr. Abdelrahim serves as the Director of Cockrell Center for Advanced Therapeutics where he is oversees Phase I program at Houston Methodist Hospital and Neal Cancer Center. He is a principal investigator on multiple clinical trials with focus on chemotherapy, targeted therapy and Immunotherapy in GI malignancies.

His research is focused on developing new mechanism-based drugs for the treatment of gastrointestinal cancers. He has identified for the first time a new structural class of compounds that can target selective transcription factor that are now recognized as targets for the development of new anticancer drugs. The lead compound of this class reached Phase I Clinical Trial to treat patients with GI cancers. Dr Abdelrahim has published more than 130 original research articles, review articles and book chapters in prestigious journals and publishing groups. Dr. Abdelrahim is a member of the American Society of Clinical Oncology, American Association of Cancer Research and International Liver Transplant Society. He is the site Principal Investigator for Southwest Oncology cooperative Group at Houston Methodist Neal Cancer Center. He is on the Editorial Boards of several medical journals where he serves as Editor-in Chief of “Transplant Oncology and Cancer Nursing Care” section of Cancers and associate Editor of Frontiers in oncology.

Dr. Abdelrahim completed his pharmacy degree followed by Doctor of Philosophy and graduate work in the field of pharmacology and toxicology from Texas A &M University, College Station, Texas. He obtained his Medical Degree from Texas A&M University then Residency from Baylor College of Medicine. He then Moved to North Carolina where he finished his Medical Oncology fellowship at Duke University.

1. What is the role of immunotherapy in Hepatocellular carcinoma (HCC)?

Recently there was a huge milestone in the immunotherapy era for HCC indications. Immunotherapy increases survival rates and provides long-term cancer control in subsets of HCC patients while also minimizing side effects.IMbrave150 was the first successful Phase III trial of a cancer immunotherapy combination of atezolizumab plus bevacizumab in unresectable or metastatic HCC[1]. Moreover, the HIMALAYA trial has been approved as first-line tremelimumab plus durvalumab that improves overall survival in unresectable HCC[2]. This has resulted in radical changes in HCC therapy, especially for patients who failed to respond to local treatments and those with advanced-stage disease who are suitable for first-line treatment.



2. What type of ICPI agents are being used for HCC treatment?

The rapid evolution of immunotherapy over the years has shown to have a crucial role in the development of HCC outcomes. Programmed death/ligand 1 (PD-1; including nivolumab and pembrolizumab/PD-L1; including atezolizumab and durvalumab) and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4; including ipilimumab and tremelimumab) receptors work to induce the host's natural immune response by recognizing receptors on HCC tumors allowing facilitating a pathway and T cell response [4 ,3].

3. What about liver transplantation for HCC indication?

Unlike other solid organ transplants, LT is considered an exception in the field of transplant oncology which has shown promising results in radically curing HCC. Although HCC has multiple treatment options including chemotherapy, radiotherapy, and immunotherapy, the fact that almost %90 of HCC cases occur under the setting of cirrhosis, makes LT the ideal treatment option with 5-year survival rates of approximately %80. Hence, treatments like ICPIs would be ideal for bridging patients to LT.

4. Is it safe to use ICPI in liver-transplanted candidate/recipient patients for HCC treatment?

This has become an inadvertently controversial topic in transplant oncology, and there are a multitude of conflicting reports because of conflicting data [8-5]. Actually, there is little opportunity to confidently say an oncology treatment is safe- any intervention that induces the host's immune system will receive different responses. Though, presently, there is an increasing number of published research that evaluate ICPI utilization in HCC patients' post-LT with reported success in elongating survival and beneficial outcomes overall.

5. Can we use ICPI pre-liver transplant?

Although LT in HCC shows promising results, it is only applicable to a small ratio of patients who meet the standards of the Milan criteria. Therefore, neoadjuvant therapies may be useful to downstage the tumor and hinder its progression. ICPIs have demonstrated significant success in improving outcomes and evolving treatment regimens of a wide range. Recently a case report reported an excellent response with significant downstaging in a safe manner after neoadjuvant treatment with atezolizumab and bevacizumab in a patient diagnosed with poorly differentiated HCC. As a result of the significant response observed with safe outcomes, the patient was listed for orthotopic liver transplant (OLT) evaluation and transplanted successfully with no evidence of clinical rejection. The viability of administering ICPI prior to liver transplantation will be further clarified by ongoing clinical investigations conducted in United State (NCT05185505).

6. What about using ICPI post-liver transplant?

Immune checkpoint (ICPI) therapy in the palliative setting is a controversial topic in not only HCC treatment but also transplant oncology in its entirety [11-9]. Recent research has published several conflicting reports and case series both praising and condemning utilization [13 ,12 ,8 ,7]. Though an investigation of the specific clinical factors that could play a role in raising the rate of allograft rejection may facilitate greater interest and generate the literature necessary to truly improve outcomes in this setting [14]. A recently reported PubMed review of 16 varying publications describing HCC cases that had received immunotherapy, ICPI, in the post-LT setting were evaluated for intervention safety and efficacy [15]. The results of the review demonstrated most of the safety and efficacy [15]. The results of the review demonstrated most of the safety concerns associated with ICPI treatment in post-LT patients. There was a %32 rejection rate and %56 of those reported organ failure and early mortality, other adverse clinical cases were treated with interventions that resulted in reversible malignancies. These negative results to the intervention of ICPIs in the post-transplant setting are not singular and certainly cause for concern, as well as further study into the clinical factors associated to cause of rejection and early recurrence. Though these are the very safety concerns that have inevitably stifled literature because often transplant patients are excluded from studies involving ICPIs on palliative therapy.

7. What is the primary concern of ICPI use in the transplant setting?

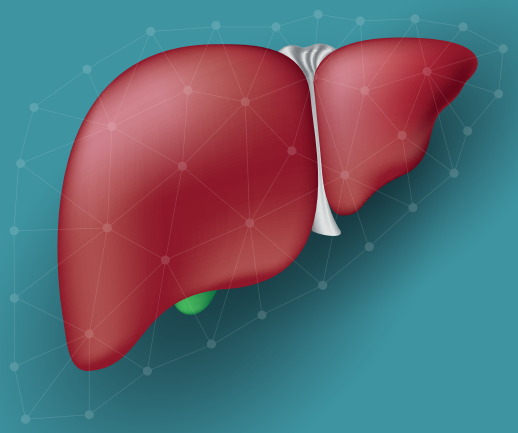
The chance of graft rejection is the main concern while using ICPI peri-transplant. The immunological tolerance of the graft is thought to be facilitated by PD-1 and CTLA-4 pathways; PD-L1 is expressed in post-transplant liver allografts, and PD-1 is substantially expressed on graft infiltrating T-cells. The CTLA-4 binding to its counter-receptor B7 on T-cells produces an inhibitory signal that stops T-cell responses [16 ,9]. As a result, blocking these pathways may cause these T-cells to become more active, resulting in T-cell-mediated graft rejection.

8. Does immunosuppression affect the efficacy of ICPIs?

Wide studies have been conducted on the efficacy of concomitant use of immunosuppressants/steroids and ICPIs, and they have shown that despite almost opposite mechanisms of action, simultaneous use of immunosuppressants with ICPIs does not necessarily decrease the ICPI efficacy [17]. ICPI pathways limit T-cell activation and shorten the duration of the immune response, they also have a crucial role in the resolution of inflammation. While immunosuppressants act on levels of the immune response acting on preventing allograft rejection by inhibiting cell proliferation and cytokine production [19 ,18]. Noteworthy that a recent study reported that is death-censored rejection-free survival was higher in patients who received at least one drug other than corticosteroids however it is hard to draw a firm conclusion from small uncontrolled trials.

9. Is there ICPI class safer than another?

Despite the differences in ICPI mechanisms of action, there is not enough data to support the safety of one ICPI over the other. However, several studies have been conducted for investigation Nevertheless, further studies are needed to produce definite conclusions [,8 22-20].



10. Is there a biomarker for graft rejection (safety biomarker)?

Immunological monitoring after LT is crucial for proper post-transplant management and tailoring personalized immunosuppressive therapy. Therefore, the ideal diagnostic biomarker should be highly sensitive and specific, non-invasive, and rapidly available [23]. Although identifying potential biomarkers is a growing area of interest, only a few biomarkers are used in clinical practice. In addition, it can be challenging to find specific biomarkers for graft rejection due to overlap with other clinical conditions [25 ,24]. In a recent retrospective study from the Mayo Clinic, Arizona, 5 patients who

received PD-1 inhibitors following liver transplant underwent graft biopsy. Of these 5 patients, 2 developed graft rejection, and the biopsy at the time of rejection also showed PD-L1– positive cells, the other 3 patients who did not develop graft rejection had liver biopsies without evidence of PD-L1 expression[26]. In a prospective single-arm study of anti-PD-1 immunotherapy for patients with recurrent malignancy following liver transplantation whose grafts were shown to lack PD-L1 expression, 18 patients with posttransplant tumor recurrence received screening biopsies, only 9 patients reported negative PD-L1 expression, 5 patients were enrolled. All those 5 patients (%100) did not appear to experience graft rejection after infusion of the PD-1 inhibitor[27]. These available reports demonstrate the capability of liver biopsies to predict the prognosis of rejection but haven't been validated yet. In addition, they can help predict the possible response of ICPIs in some LT patients. Therefore, it was proposed that liver biopsies to determine the expression of PD-L1 can be considered before choosing the appropriate treatment. However, further investigation is warranted.

11. What is the importance of the timing of ICPI Peri-Transplant?

Studies have demonstrated that ICPIs can be used in either transplant candidates or recipients. In the setting of pre-transplant, ICPI activates the immune system and T-cell to attack and kill cancer cells. This state of the "hyperactive" immune system occurs in the absence of the allograft. Once ICPI is held, the immune system will "cool off" and return gradually to the normal body immune state at which a new liver transplant can be achieved safely. Additional immunosuppressants can be used to further inhibit the immune system and minimize the risks of graft rejection by the recipient's own immune system. The appropriate time interval between the last dose of immunotherapy and the liver transplant will further support the safety of ICPI before transplant. The ideal time is yet to be determined; however, 12-4 weeks have been reported. Hence, the timing of immune ICPIs administration is a critical factor that must be carefully considered to achieve favorable outcomes.

References:

1. Finn, R.S., et al., Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. New England Journal of Medicine, .2020 (20)382: p. 1905-1894.
2. Abou-Alfa, G.K., et al., Tremelimumab plus Durvalumab in Unresectable Hepatocellular Carcinoma. NEJM Evidence, (8)1 .2022: p. EVIDoa2100070.
3. Tanaka, K., et al., PDL1 is required for peripheral transplantation tolerance and protection from chronic allograft rejection. Journal of immunology (Baltimore, Md. : 1950), (8)179 .2007: p. 5210-5204.
4. Siu, J.H.Y., et al., T cell Allorecognition Pathways in Solid Organ Transplantation. Frontiers in immunology, 9 .2018: p. 2548-2548.
5. Kuo, J.C., L.B. Lilly, and D. Hogg, Immune checkpoint inhibitor therapy in a liver transplant recipient with a rare subtype of melanoma: a case report and literature review. Melanoma Res, (1)28 .2018: p. 64-61.
6. Larkin, J., F.S. Hodi, and J.D. Wolchok, Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med, .2015 (13)373: p. 1-1270.
7. Llovet, J.M., et al., Immunotherapies for hepatocellular carcinoma. Nat Rev Clin Oncol, (3)19 .2022: p. 172-151.
8. Ho, C.M., et al., Harnessing immunotherapy for liver recipients with hepatocellular carcinoma: a review from a transplant oncology perspective. Ther Adv Med Oncol, 11 .2019: p. 1758835919843463.
9. Kumar, V., et al., The Safety and Efficacy of Checkpoint Inhibitors in Transplant Recipients: A Case Series and Systematic Review of Literature. The oncologist, (6)25 .2020: p. 514-505.
10. Mazzaferro, V., et al., Liver Transplantation for the Treatment of Small Hepatocellular Carcinomas in Patients with Cirrhosis. New England Journal of Medicine, (11)334 .1996: p. 700-693.
11. Macek Jilkova, Z., J. Ghelfi, and T. Decaens, Immunomodulation for hepatocellular carcinoma therapy: current challenges. Current Opinion in Oncology, (2)34 .2022: p. 160-155.
12. Jin, X., et al., Low-dose PD-1 inhibitor combined with lenvatinib for preemptive treatment of recurrence after liver transplantation for hepatocellular carcinoma: Case report and literature review. Frontiers in Oncology, 12 .2022.
13. Hodi, F.S., Cytotoxic T-lymphocyte-associated antigen-4. Clin Cancer Res, 13 .2007(18 Pt 1): p. 42-5238.
14. Au, K.P. and K.S.H. Chok, Multidisciplinary approach for post-liver transplant recurrence of hepatocellular carcinoma: A proposed management algorithm. World J Gastroenterol, (45)24 .2018: p. 5094-5081.
15. Au, K.P. and K.S.H. Chok, Immunotherapy after liver transplantation: Where are we now? World J Gastrointest Surg, (10)13 .2021: p. 1278-1267.
16. Buchbinder, E.I. and A. Desai, CTLA-4 and PD-1 Pathways: Similarities, Differences, and Implications of Their Inhibition. American journal of clinical oncology, (1)39 .2016: p. 106-98.

References:

17. Mazzaferro, V., et al., The Long-Term Benefit of Liver Transplantation for Hepatic Metastases From Neuroendocrine Tumors. Am J Transplant, (10)16 .2016: p. 2902-2892.
18. McDermott, D.F., et al., Survival, Durable Response, and Long-Term Safety in Patients With Previously Treated Advanced Renal Cell Carcinoma Receiving Nivolumab. J Clin Oncol, (18)33 .2015: p. 20-2013.
19. Topalian, S.L., et al., Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med, (26)366 .2012: p. 54-2443.
20. Murakami, N., et al., A multi-center study on safety and efficacy of immune checkpoint inhibitors in cancer patients with kidney transplant. Kidney Int, (1)100 .2021: p. 205-196.
21. Munker, S. and E.N. De Toni, Use of checkpoint inhibitors in liver transplant recipients. United European Gastroenterology Journal, .2018 (7)6: p. 973-970.
22. Ranganath, H.A. and T.J. Panella, Administration of Ipilimumab to a Liver Transplant Recipient With Unresectable Metastatic Melanoma. Journal of Immunotherapy, (5)38 .2015.
23. Verhelst, X.P., et al., Biomarkers for the diagnosis of acute cellular rejection in liver transplant recipients: A review. Hepatol Res, (2)43 .2013: p. 78-165.
24. Nishimura, H., et al., Developmentally regulated expression of the PD-1 protein on the surface of double-negative (CD4-CD8-) thymocytes. Int Immunol, (5)8 .1996: p. 80-773.
25. Chemnitz, J.M., et al., SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol, (2)173 .2004: p. 54-945.
26. DeLeon, T.T., et al., Pilot evaluation of PD-1 inhibition in metastatic cancer patients with a history of liver transplantation: the Mayo Clinic experience. J Gastrointest Oncol, (6)9 .2018: p. 1062-1054.
27. Shi, G.-M., et al., Graft Programmed Death Ligand 1 Expression as a Marker for Transplant Rejection Following Anti–Programmed Death 1 Immunotherapy for Recurrent Liver Tumors. Liver Transplantation, .2021 (3)27: p. 449-444.

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New therapy in HCC

Hepatocellar carcinoma is deadly disease, cancer is not the only cause of death in theses patient as the disease started in very sick liver i.e cirrhosis.
So treatment of HCC very challenging if we take in consideration all the risk factor and patient comorbidity.

HCC is the fourth most common cancer affecting Saudi males and the ninth most common cancer affecting females with an overall age standardized rate of 000 100/5.3 population (000 100/7.5 for males and 000 100/3.1 for females.

Common cause viral related hepatitis based on the reports of The Ministry of Health in Saudi Arabia about Hepatitis A, B and C infections in all regions from the period of January 2006 to December 2010.

Hepatitis B virus (HBV) was the most predominant type, accounting for (%53) of the cases, followed by Hepatitis C virus (HCV) (%30) and HAV (%17).Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in Western countries, with an increasing prevalence associated with the rising prevalence of diabetes mellitus and obesity. The worldwide prevalence of NAFLD may be in the order of %25, but in the Middle East, it may be even higher.

In the past we have limited options of therapy in patient with HCC with evolving of immunotherapy treatment patient with HCC can live longer with better quality of life.
For better understanding treatment of HCC, we need to know more about pathophysiology of the disease and clinical classification. there was great effort of making molecular classification of HCC but unfortunately none of these classifications came in to clinical practice.
The main molecular subclasses of HCC is non-proliferation and proliferation HCC which more prognostic rather than predictive of therapy but there are some data toward effectiveness of immunotherapy in proliferation tumour, these molecular signatures have not been validated in prospective studies and are currently not used in clinical practice.

As we are going more toward therapy, we can divide therapy two categories.
First class of medication multikinase inhibitor, first drug to be discussed is sorafenib is active against vascular endothelial growth factor receptor (VEGFR) 2 and 3, fms like tyrosine kinase (FLT)3, KIT, platelet-derived growth factor receptor (PDGFR)β, RAF, BRAF WT, and BRAF V600E ,it is first approved as the

frontline standard of care in the sharp and Asian specific trial with modest efficacy in both progression free survival and overall survival.

The phase III SHARP trial showed that sorafenib conferred survival improvement (10.7 months in the treatment group vs. 7.9 in the placebo group, hazard ratio (HR), 0.69; p < 0.001) and higher disease control rate (patients with complete response, partial response, and stable disease for a period > 4 weeks, %43 vs. %32; p < 0.001)
Additional targeted therapies have recently demonstrated clinical benefits in phase III trials, including lenvatinib is a multikinase inhibitor active on VEGFR 3-1, fibroblast growth factor receptor (FGFR), KIT, RET, and PDGFR, the only TKI e showed superiority over Sorafenib with improvement of progression free survival and time to progression by 3 months , in phase III multicentre trial REFLECT Median overall survival was 13.6 months vs 12.3 (HR, %95 ;0.92 confidence interval (CI), 1.06-0.79). The surrogate endpoint progression-free survival (PFS) was significantly longer in the lenvatinib group (HR, %95 ;0.65 CI, 0.77-0.56; p < 0.001).

The are no predictives to choose one drug over the other but both option valid, some factors should be taken in consideration when we chose between both drugs, drug availability, toxicity and efficacy.

Regorafenib is anther TKI was approved only in second line after failure of Sorafenib in patient with good tolerance of sorafenib, in 2016, data from the RESORCE trial, a phase 3 study evaluating regorafenib in HCC patients who experience disease progression after first-line treatment with sorafenib, have shown a 2.8-month median survival benefit over placebo (10.6 versus 7.8 months)

Cabozantinib a multikinase inhibitor of VEGFR2, c-MET, AXL receptor tyrosine kinase (AXL), FLT3, c-KIT, and c-RET, also approved in second- and third-line therapy this approval was based on the results of phase 3 CELESTIAL trial, the median overall survival was 10.2 months (%95 CI, 12-9.1) in the cabozantinib group vs 8 months (%95 CI, 9.4-6.8) in the placebo group (HR, %95 ;0.76 CI, 0.92-0.63; p = 0.005). The median PFS was 5.2 months with cabozantinib and 1.9 with placebo (HR, %95 ;0.44 CI, 0.52-0.36; p < 0.001).

Ramucirumab s a monoclonal antibody active against VEGFR2. In the controlled phase 3 (REACH) trial, ramucirumab showed improvement in the overall survival, when compared to placebo in all enrolled patients had alpha-fetoprotein concentrations ≥ of 400 ng/mL .

The median survival time was 8.5 months (%95 CI, 10.6-7.0) in the experimental group vs 7.3 months (9.1-5.4) in the placebo group (HR, ;0.71 %95 CI, 0.949-0.531; p = 0.0199).

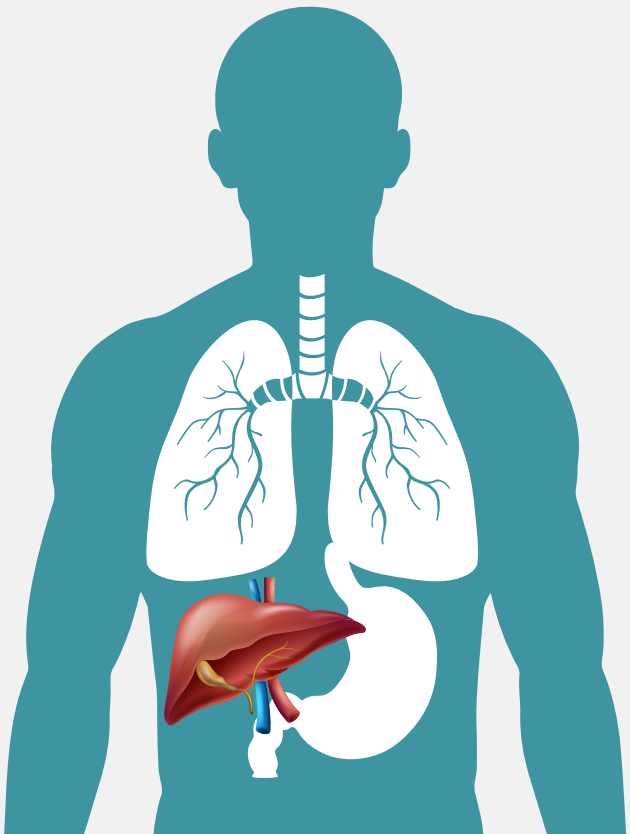
However, all these drugs only a modest extension in median survival (3–2 months) and low response rates, which underscores the need for predictive biomarkers to improve clinical management and also better patient profile to make better chose among these drugs.

Other class of drugs is immunotherapy single agent or in combination showed substantial benefit if we compare with TKI.

In recent years, immunotherapy that first approved Nivolumab and pembrolizumab which showed great benefit those results have led to an accelerated approval of these 2 checkpoint inhibitors by the FDA for the second-line treatment after failure of sorafenib in advanced HCC.

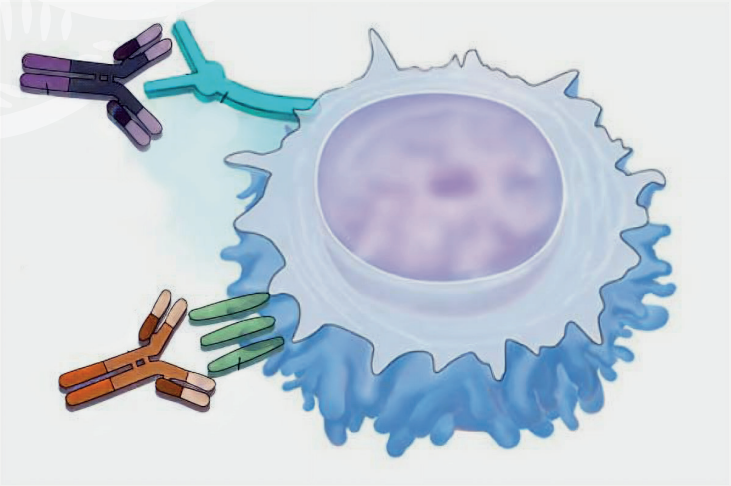
Pembrolizumab is a monoclonal humanized IgG4/K antibody active against PD-1. In phase 2 non-randomized open-label trial (Keynote 224), the drug showed promising activity in patients previously treated with sorafenib. Disease control was obtained in 64 of 104 patients. A subsequent phase III trial (Keynote 240) did not reach the pre-specified criteria of significance.

However, the median survival was 13.9 months in the pembrolizumab group vs. 10.6 months in the best supportive care group. Nivolumab is a fully human monoclonal IgG4 antibody active against PD-1, the open-label phase 2 trial Checkmate 040 showed an ORR of %15 in the dose-escalation phase the disease control rate was %58 (%95 CI, 72-43). The median duration of response was 17 months (%95 CI, 24-6). However, a recent press release reported that the phase III comparing nivolumab versus sorafenib in first line did not show benefit of nivolumab over sorafenib, this suggests that additional data are required to identify patients who will benefit from immunotherapy as single agents for both pembrolizumab and nivolumab.



Combination immunotherapy

More recently, the combination of durvalumab and tremelimumab has also been shown to be more active than sorafenib in terms of response rate (%20 versus %6) and overall survival (median: 16.4 months versus 13.8 months) but without effect on progression-free survival (median: 3.78 versus 4.07).



There is no direct head-to-head comparison of these two new standards of treatment, which are therefore valid first-line option. The combination of atezolizumab + bevacizumab is widely used and oncologists and hepatologists have learned to manage its toxicity. The combination of durvalumab and tremelimumab is easier to use in patients potentially at risk of gastrointestinal bleeding and also this combination had lower antidrug antibody (ADA) in comparison with Atezolizumab/Bevacizumab treatment Despite the evidence of the superiority of these two combinations with immunotherapy, there will still be %20-%15 of patients who will only receive tyrosine kinase inhibitors (sorafenib or lenvatinib), especially in patient with contraindication for immunotherapy or patient developed sever immune related toxicity, contraindication like autoimmune diseases, recurrence of HCC after transplantation in patients receiving immune suppressors.

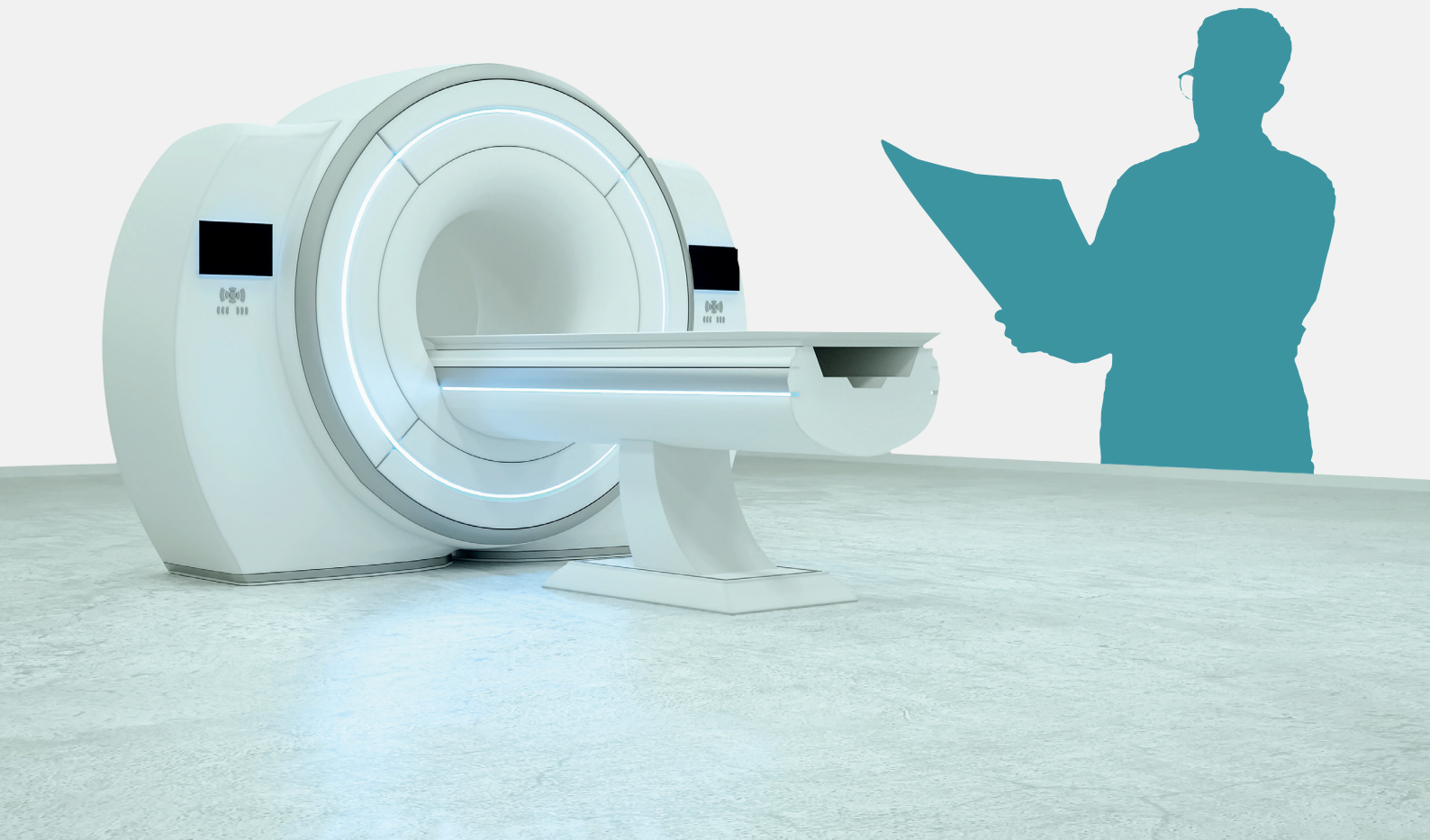
The question we need to ask the subsequent therapy post immunotherapy there is no clear data about second line therapy as all second line therapy post sorafenib. But still TKIs were the most common next line of therapy , in one trial showed the used of TKI post immunotherapy, sorafenib (%44.9) and regorafenib (%30.3).

A significant benefit in median OS was observed for those patients who received therapy following ICIs (HR ,0.4 %95 CI 0.5–0.3, p < 0.001), such that patients who received further treatment had a median OS following the cessation of ICIs of 12.2 months (%95 CI 15.0–9.3) compared with 3.2 months (%95 CI 4.5–1.8) in those who received BSC.

Second study of 40 patients with HCC and reported that lenvatinib achieved a high response rate (%81) in tumours with high expression of FGFR4 even in patients who do not respond well to previous treatment with atezolizumab plus bevacizumab due to β-catenin-activating mutations, subsequent treatment with lenvatinib would still provide better results due to potent inhibitory effect on FGFR4, lenvatinib following failure of PD-1/PD-L1 improved PFS (10 months) OS (15.8 months) (from the start of lenvatinib), ORR (%55.6), and disease control rate (%86.1)

In summery treatment of HCC now very complex too many options, sick patients and presence of other modality of treatment like locoregional therapy and radiation therapy, add to all this the value of neoadjuvant therapy and adjuvant which coming soon in the ongoing trials.

So I think the map of treating HCC getting bigger and more exciting, for now Immunotherapy is still standard of care in firs line unless there is contraindications.



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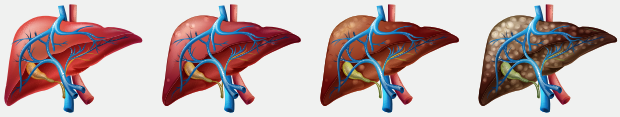
Hepatocellular Carcinoma in Non-alcoholic Steatohepatitis Without Cirrhosis

Nonalcoholic fatty liver disease (NAFLD) is a common complex, metabolic disease with an increasing incidence with the increase in obesity and diabetes worldwide. An important liver-related complication in NAFLD is the development of hepatocellular carcinoma (HCC). HCC accounts for %90 of primary liver cancers Worldwide, HCC being the sixth most common cancer, and is the second leading cause of cancer-related death.

The development of HCC occurs in both cirrhotic and non-cirrhotic patients with NAFLD. Liver tumorigenesis in NAFLD is unique as it is related to interacting mechanisms including environmental factors, oxidative stress, chronic inflammation, and the immune response. In the NAFLD population, there is significant higher proportion of HCC in non-cirrhotic to cirrhotic liver compared to other etiologies of liver diseases.

Previous data suggest that HCC occurrence in non-cirrhotic livers accounts for 20 to over %50 of all NAFLD associated HCC cases. Patients with non-cirrhotic NAFLD had a higher risk of HCC compared to the general population. Despite the increased risk of HCC development in non-cirrhotic NAFLD patients, the risk was less than that in cirrhotic and did not exceed the annual incidence threshold for surveillance.



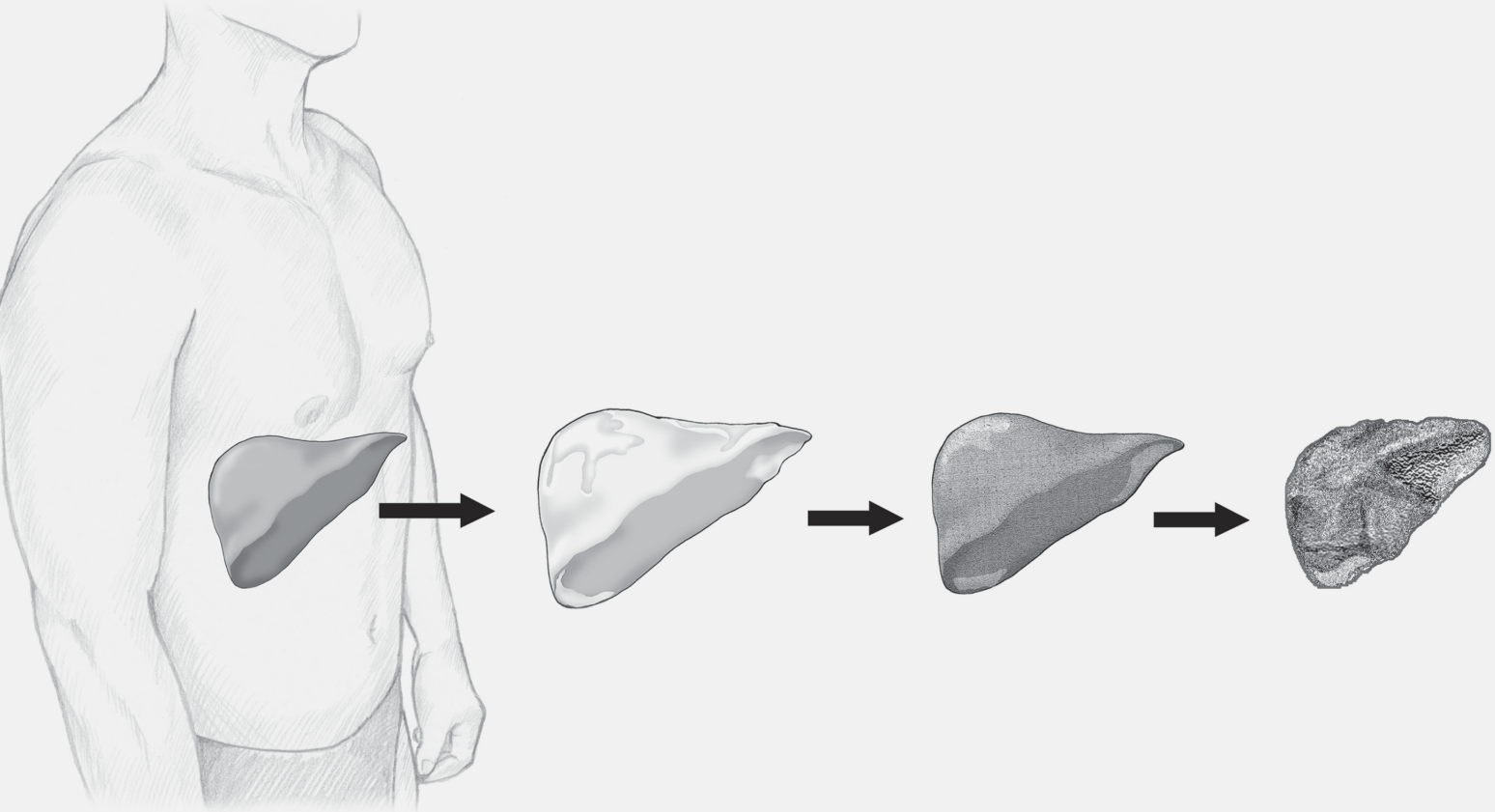
Although the risk of HCC in non-cirrhotic NAFLD is low overall, there is increased risk for HCC in some studies showed that obesity is a significant risk for the development of HCC particularly in patients with NASH, who have a higher predisposition for obesity. Obese (body mass index > 30 kg/m2) patients have a reported 1.93-fold higher risk of developing primary liver cancer. Obesity and excessive visceral adipose tissue has been associated with a chronic inflammatory state due to increased levels of leptin. Leptin, a profibrotic and proangiogenic cytokine, activates the Janus kinase (JAK) pathway, thereby initiating an intracellular signaling cascade of pro-inflammatory cytokines. Obesity has also been associated reduced level of adiponectin, an anti-inflammatory cytokine. Additionally, obesity has been associated with insulin resistance, increased hepatic lipid storage and alteration of intestinal microflora.

Also, other risk factors such as male patients over 65 with a history of smoking, an elevated ALT, and diabetes mellitus. In non-cirrhotic with all of these risk factors, there is a 9.9-fold increased risk for developing HCC compared to overall prevalence in non-cirrhotic NAFLD patients. Ethnicity may have a significant impact on the risk of HCC development in NAFLD population and Increased intrahepatic iron accumulation has been associated with NASH progression to HCC.

However, the current guidelines lack recommendations for surveillance of NASH patients without cirrhosis who are at risk for developing HCC. The lack of longitudinal data in the non-cirrhotic NASH population makes it difficult to develop good evidence - based screening guideline. There is a need for studies addressing the screening guidelines for surveillance of HCC in NASH particularly for non-cirrhotic individuals. We suspect that earlier screening may be needed in patients with NASH who have multiple risk factors for HCC.

Regular exercise and controlled caloric intake is the mainstay of therapy for NAFLD, however the extent to which these are effective to prevent the development of HCC is unclear.

Physical activity has been reported to have a preventive effect on development of HCC. A large prospective cohort study, which included over 400000 participants suggested that increased physical activity might have a role in HCC prevention that is independent of weight reduction. Data suggests that statins, metformin and S-Adenosylmethonine are potential chemopreventive agents. Patients with NASH have been found to be deficient in vitamin E and D; vitamin D deficiency is thought to play a role in hepatic carcinogenesis. Other dietary antioxidants such as vitamin C, selenium, coenzyme Q12 and certain phytochemicals have also been touted have chemopreventive potential.



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