Combine and Conquer

Minimizing the Impact of Toxicity Associated with Novel Immunotherapy-Angiogenesis Inhibitor Combinations

Hepatocellular Carcinoma Tweetorial

References

1/ 📣#OncTwitter #TumorBoardTuesday HCPs
✅#HCC #MedTweetorial 🧵
🔎#HCC AA/IO combos

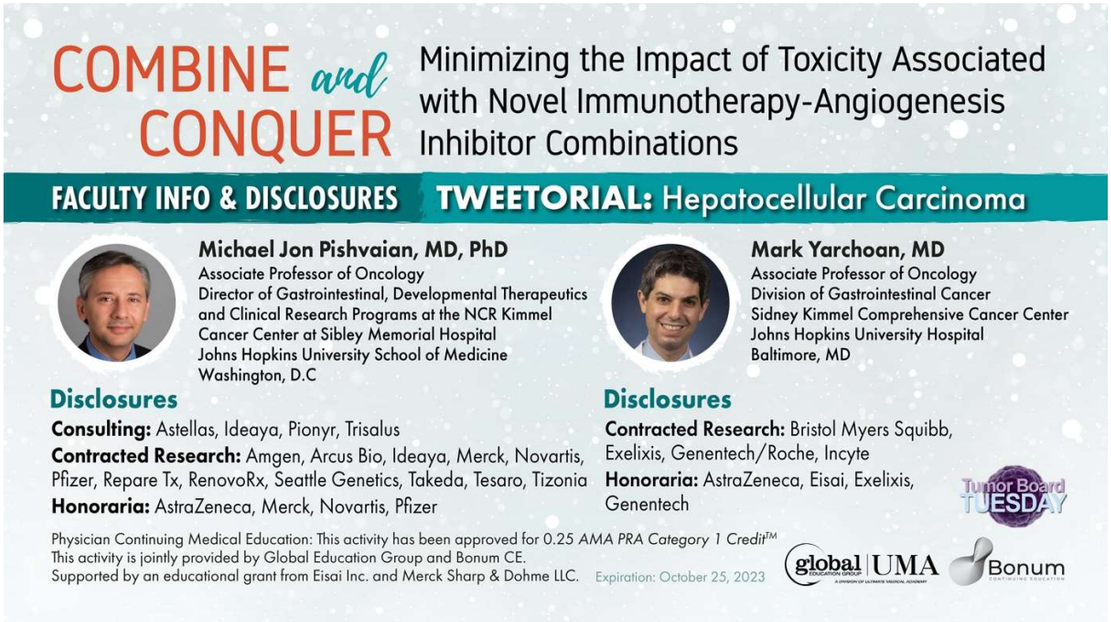
⭐Latest data
⭐Tox to👀for
⭐Tox impact on tx💊choice

1st🆙@MarkYarchoan & @MPishvaian

🆓#CME🔗bit.ly/3MS9Ocs
Supported by edu grants from Eisai, @Merck

2/ 🆓CME 👉 bit.ly/3MS9Ocs
✅& full ref list🗒️

⭐ The critical elements👇



3/ #TumorBoardTuesday
@US_FDA approvals in 1st line #HCC

TKIs:
🔹 sorafenib
🔹 lenvatinib

ICI:
🔸 durvalumab (PD-L1mAb)

Combo:
🔸 atezolizumab (PD-L1mAb) + bevacizumab (VEGF mAb)
🔸 durvalumab (PD-L1mAb) + tremelimumab (CTLA4 mAb)

Ref #

3

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4/ #TumorBoardTuesday #BonumCE #HCC #OncTwitter #LiverTwitter #MedTwitter

14

🟢#PreTest Q 1️⃣
📊 Which of the following is TKI toxicity not generally observed with bevacizumab?

- ☐ Bleeding
- ☐ Proteinuria
- ☐ Hypertension
- ☐ Diarrhea

5/ Anti-VEGFs: sorafenib, lenva, bev AEs

Ref #

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🔧Largely related to MOA=predictable
⚠️Some shared class tox➡️HTN, proteinuria
⚠️Some distinct based on diff 💊🎯s
💊Sorafenib ⬆️PPES (HFS)
💊Lenva⬆️HTN
⚠️Bev⬆️bleeding

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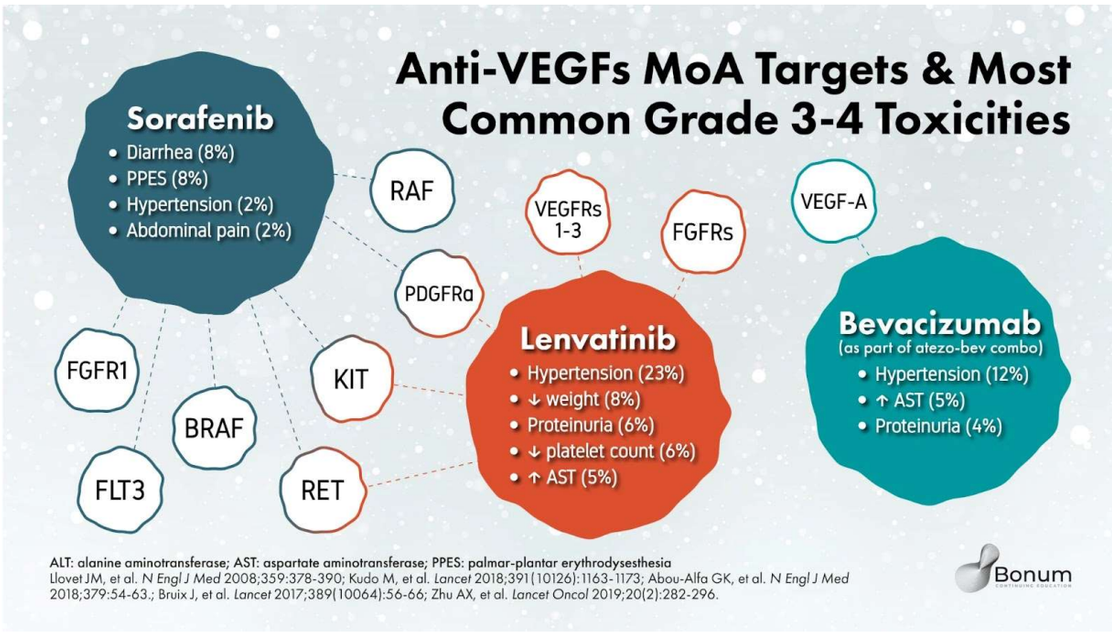

6/ #TumorBoardTuesday #LiverCancer #GITwitter

Ref #

14
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ICI AEs
🔧Largely related to MOA=immune-related
⚠️Can become severe/fatal if not promptly Dx & Tx
Can impact virtually any bodily system 👇

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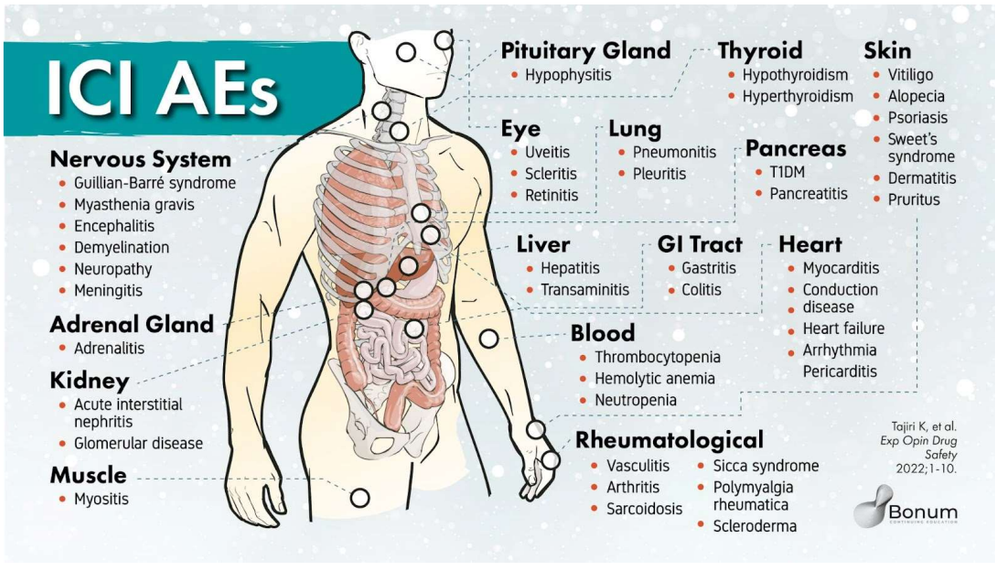


7/ #TumorBoardTuesday #BonumCE #HCC #OncTwitter #LiverTwitter #MedTwitter

Ref # 14

🟢 #PreTest Q 2️⃣

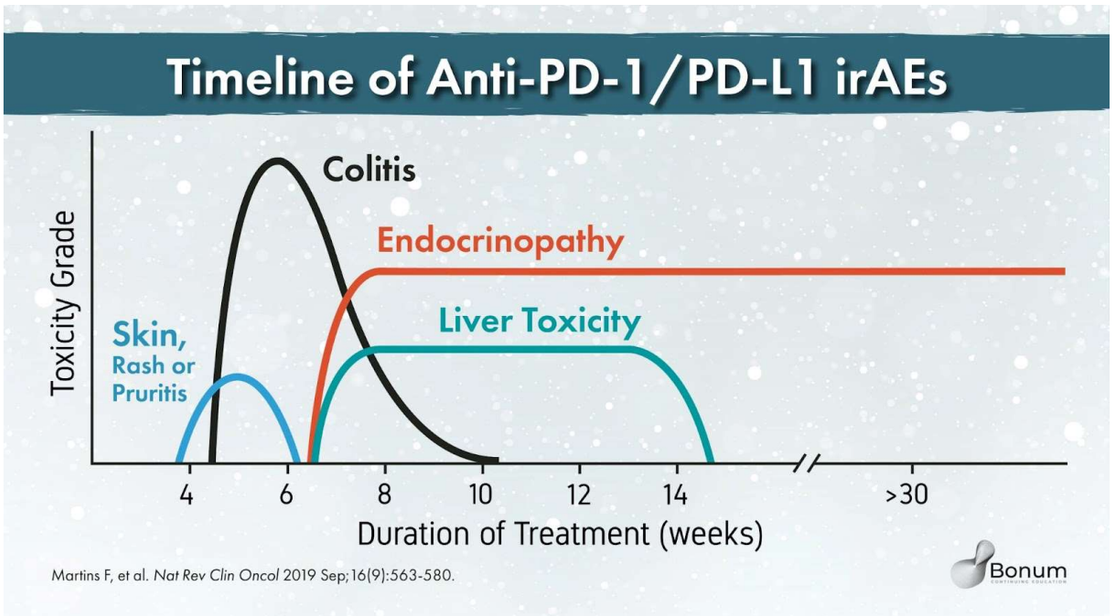
📊 Which of the following is classically a late ICI toxicity (usually occurring >3 months after treatment initiation)?

- ☐ Adrenal insufficiency
- ☐ Colitis
- ☐ Hepatitis
- ☐ Pneumonitis

8/ #TumorBoardTuesday #BonumCE #LiverCancer #GITwitter

Ref # 19

🕛While most ICI toxicities occur “early” (<14 wks after starting therapy), endocrinopathies (eg type 1 diabetes, adrenal insuf, etc) often occur many months after starting tx📅



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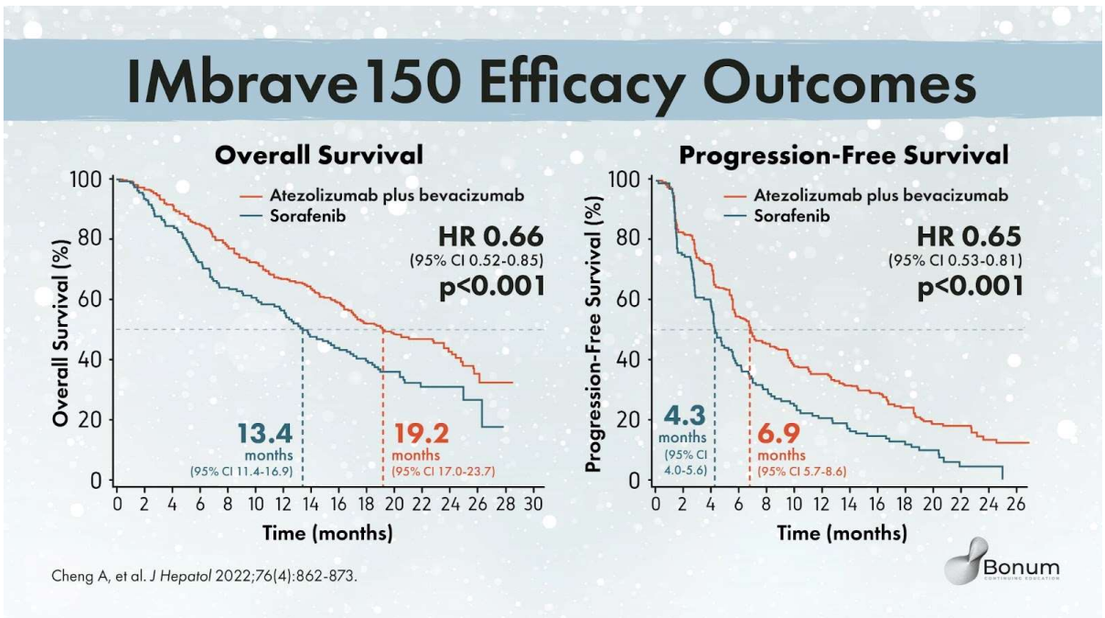
9/ ✅Combo atezo + bev

Ref # 5

🆕SOC in advanced #HCC

Approved 05/20 based on P3 #IMbrave150 trial
🔼mOS by 5.8m vs sorafenib per latest published data 🔗bit.ly/3yesKfi



10/ #IMbrave150 Safety🦺
Atezo-Bev v Sorefenib
⚠️Similar rate TRAEs overall & G3/4 TRAEs
⚠️AEs leading to discont of either drug: 22% v 12%
⚠️AEs leading to dose interruption: 59% v 44%
⚠️irAEs req systemic corticosteroids use: 12%

Ref # 5

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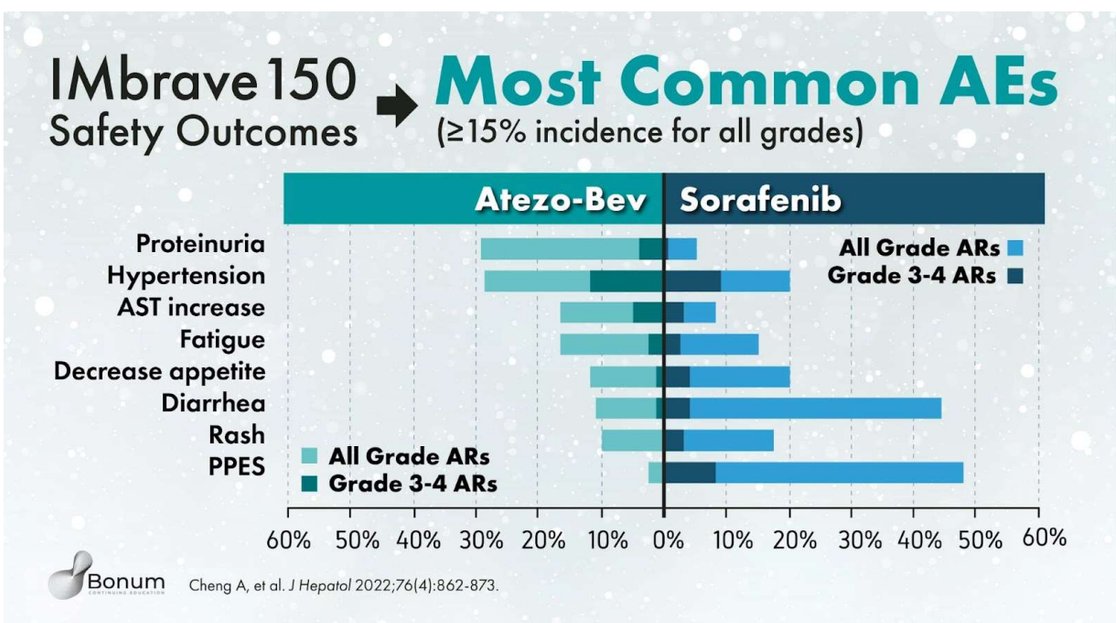

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🟢#PreTest Q 3️⃣
📊 58 y/o M w/ recurrent #HCC 2 years after a liver transplant, with multiple lesions to the lung. Which of the following is the most suitable therapeutic choice for this pt?

- ☐ Atezolizumab + bevacizumab
- ☐ Durvalumab + tremelimumab
- ☐ Lenvatinib
- ☐ Lenvatinib + pembrolizumab

12/ 🔬TKI-ICI combos also in late-stage clinical trials of doublets in the 1st line setting in unresectable #HCC

🧪 Recent P3 trial readouts: imBRAVE150, COSMIC312, LEAP002, STUDY310

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#LiverCancer #GITwitter

Ref #
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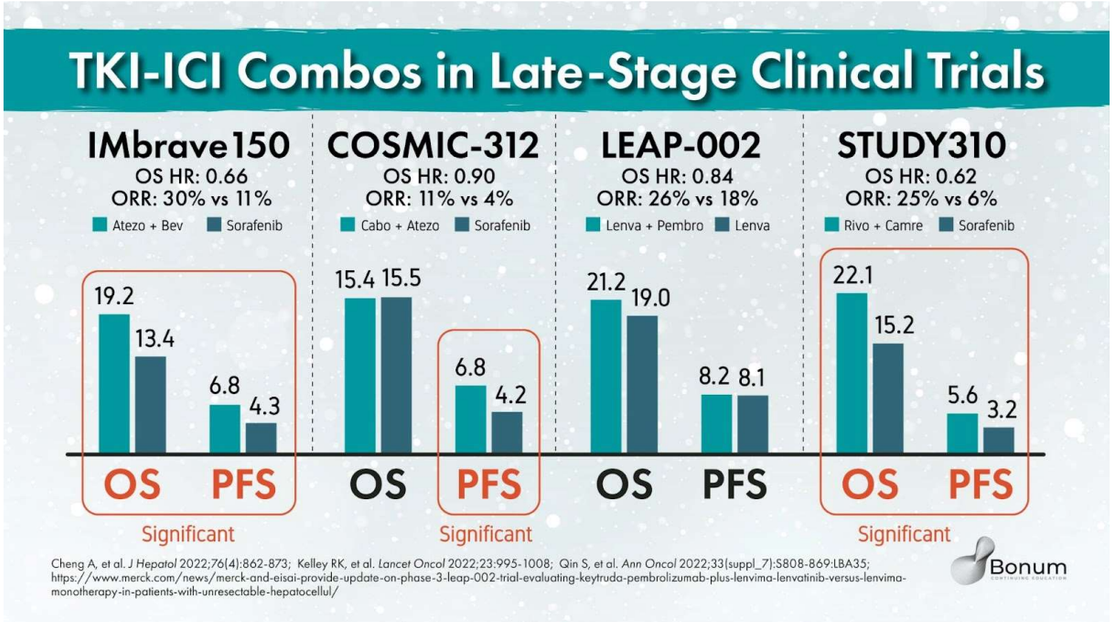

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#LEAP002 - lenva + pembro
#ESMO22 – ⬆️ PFS/OS trends but not stat sig
Control arm (lenva monotx) performed better than anticipated
Combo = longest mOS ever reported 4 1st line HCC (21.2 mos)

⚠️G3-5 TRAEs: 62.5% vs 57.5%
Common TRAEs 👇

Ref #
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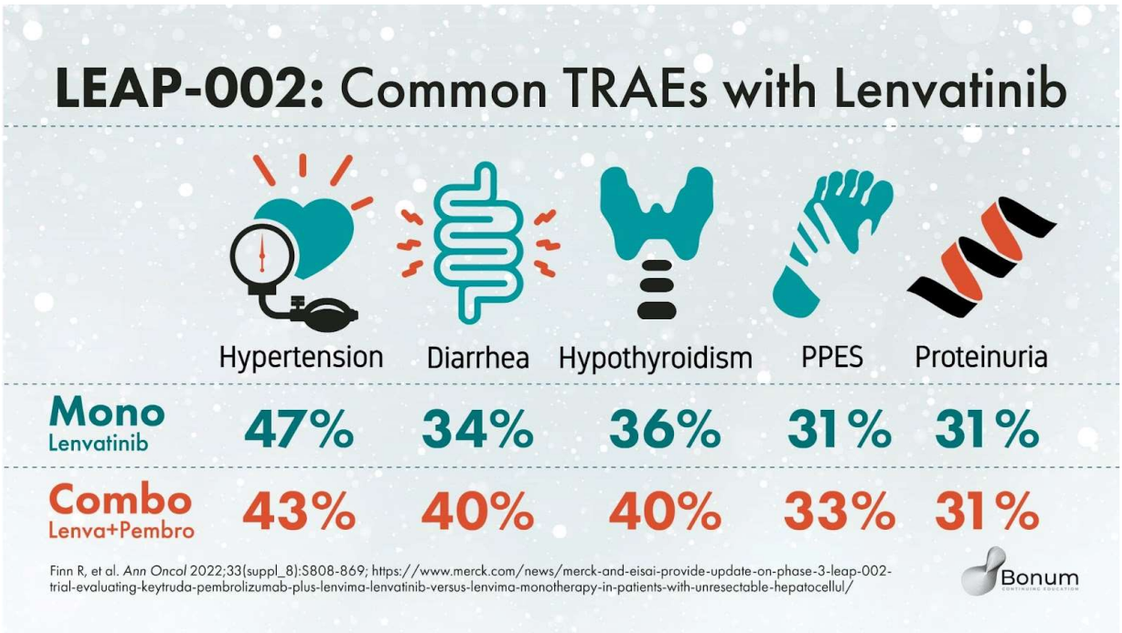
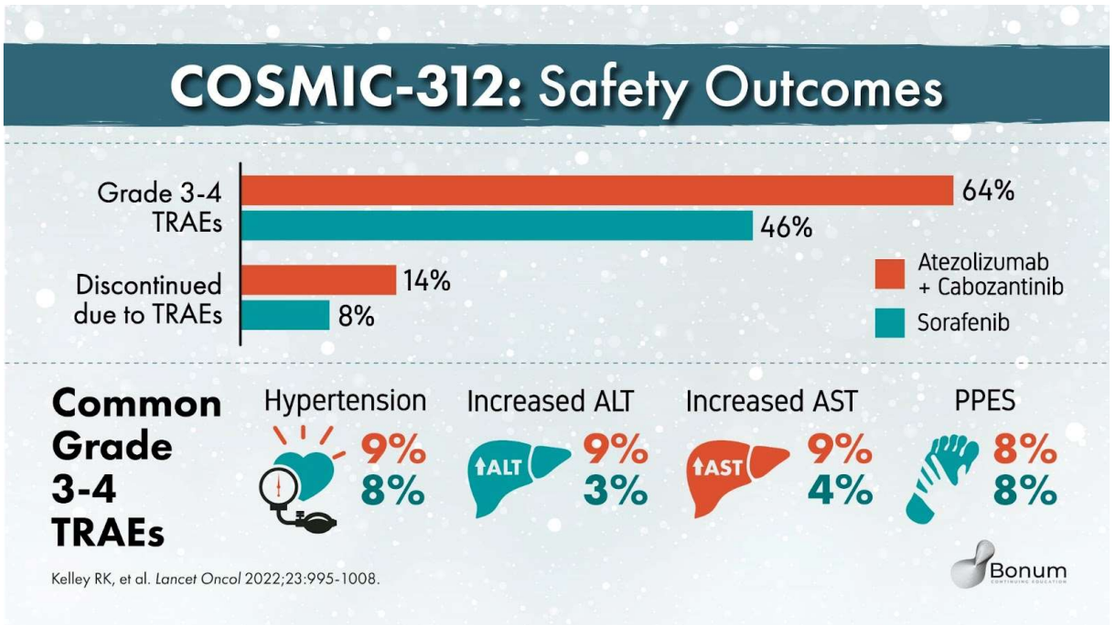


14/ #TumorBoardTuesday

Ref # 10

#COSMIC312 - cabo + atezo vs sorafenib
⬆️ in PFS but not OS

⚠️ G3/4 TRAEs: 64% vs 46%
⚠️ Discont due to TRAEs: 14% vs 8%
⚠️ No excess of serious bleeding events in cabo arm despite no requirement for endoscopy prior to enrollment
⚠️ Common G3/4 TRAEs 👇



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15/#HCC
SHR1210-III-310 - rivoceranib + camrelizumab vs sorafenib

Ref # 20

#ESMO22 ⬆️PFS & OS

Only ~20% tx outside Asia

⚠️ G3/4 TRAEs: 80.9% RC vs 52.4% sorafenib
⚠️ Most common: HTN, ⬆️AST & ALT, PPES, & platelet ⬇️
⚠️ Combo tox led 2 discont in 1/4 pts & dose mods/ints in 80.5%

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Ref # 8 12

🟢#PreTest Q 4️⃣
📊 A pt treated with the combination of lenvatinib and pembrolizumab develops grade 1-2 diarrhea.

How might you diagnose which drug is causing this toxicity?

- ☐ Discontinue lenvatinib
- ☐ Withhold lenvatinib
- ☐ Withhold pembrolizumab
- ☐ Discontinue both drugs

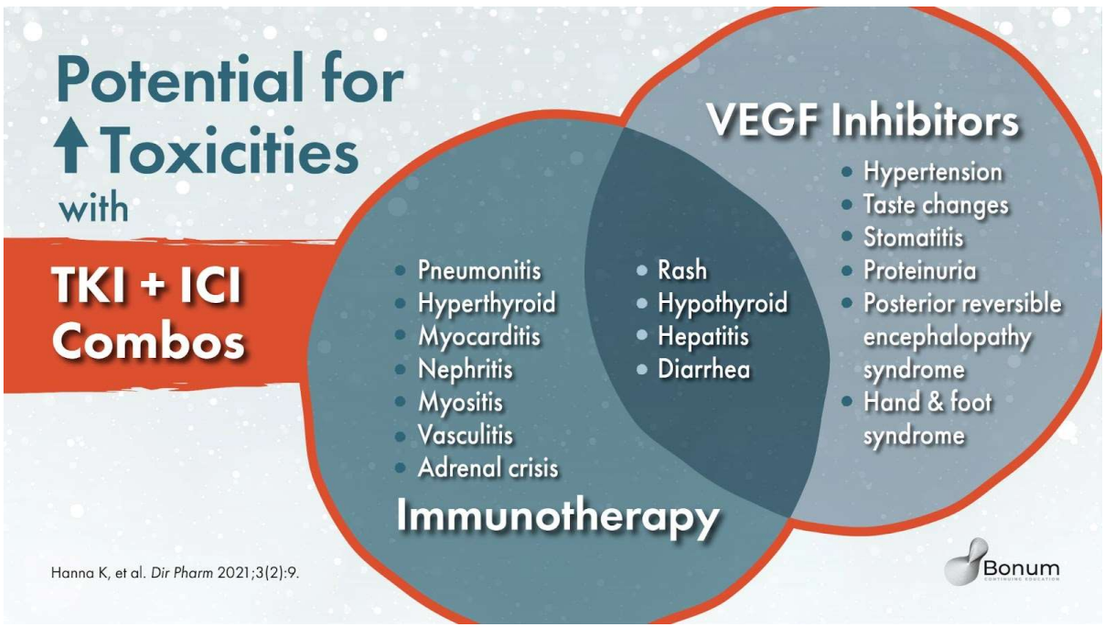
17/ #HepatocellularCarcinoma #MedTwitter

Ref # 19

⚠️⬆️ potential for overlapping tox w TKI + ICI combos

Diarrhea & rash common to both 💊 classes – BUT require distinct mgmt strategies – dose reduction/withhold vs initiate corticosteroids

Timing & severity is 💉 to diagnosis



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#OncTwitter #LiverTwitter #MedTwitter

Ref # 5 6 18

🟢#PreTest Q 5️⃣
📊 Which of these tests is recommended prior to initiating therapy with atezolizumab + bevacizumab?

- ☐ PD-L1 testing
- ☐ Next-gen sequencing
- ☐ Endoscopy
- ☐ Colonoscopy

19/ #TumorBoardTuesday #HCC
Esophageal varices common in adv liver dis ➡️ portal HTN

Ref # 1 5 23

#IMBRAVE150 9% G3/4 bleeding despite pt exclusions:
- 🔹 variceal 🩸 w/in 6m prior to Tx
- 🔹 untreated/incompletely treated varices w 🩸
- 🔹 high risk of 🩸

#Endoscopy recommended to evaluate 🩸 risk

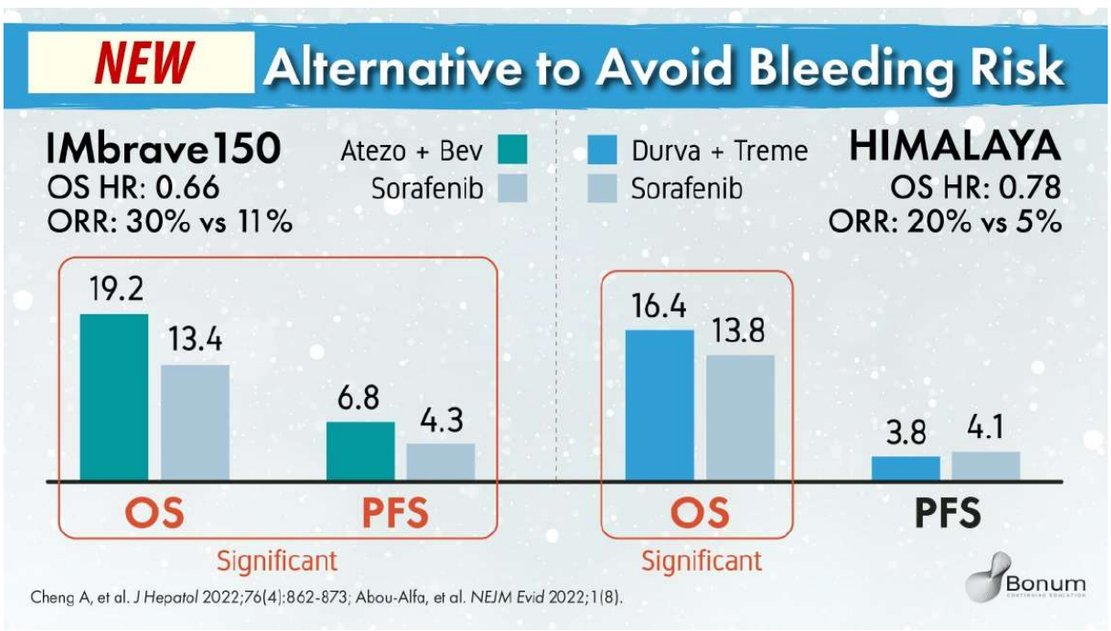
20/#TumorBoardTuesday
Alternative to atezo-bev for pts w ⬆️ bleeding risk?
✅ Lenvatinib
✅ Sorafenib

Ref # 1

⏩ Durvalumab+tremelimumab is a new 1L option

P3 #HIMALAYA study demonstrated efficacy of this combo
⬆️ mOS and mPFS vs sorafenib

#HIMALAYA vs #IMbrave150 👇



Cheng A, et al. *J Hepatol* 2022;76(4):862-873; Abou-Alfa, et al. *NEJM Evid* 2022;1(8).

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21/ Durva-Treme Tox
w 2X ICI combos ⬆️risk of irAEs
Novel dosing strategy 2 combat risk
➡️STRIDE (Single Treme Regular Interval Durva)
➡️Treme 300mg, 1 dose + durva 1500 mg Q4W

G3/4 irAEs in 12% pts treated w Durva-Treme
Common: hepatic events, dermatitis/rash, diarrhea/colitis

22/ #TumorBoardTuesday #HCC
Key points:
🔑Atezo+Bev= SOC for 1st line HCC
🔑Pt-specific factors guide Tx choice 4 pts can't tolerate/ineligible Atezo+Bev
🔑**Durva+Treme ICI combo a new 1st line option**
🔑AA & ICIs distinct tox profiles & nuance among drugs w/in class

Claim your CME credit by completing the post-survey and evaluation. Link provided👉

🆓 #CME 🔗 bit.ly/3SvVbNm
Thanks for joining me & @TumorBoardTuesday!

References 👇

1. Abou-Alfa GK, Lau G, Kudo M, et al. Tremelimumab plus Durvalumab in Unresectable Hepatocellular Carcinoma. *NEJM Evid.* 2022;1(8). doi: 10.1056/EVIDoa2100070.
2. Abou-Alfa GK, Meyer T, Cheng A-L, et al. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. *N Engl J Med.* 2018;379:54-63
3. Akce M, El-Rayes BF, Bekaii-Saab TS. Frontline therapy for advanced hepatocellular carcinoma: an update. *Ther Adv Gastroenterol.* 2022;15: 17562848221086126.
4. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017;389(10064):56-66
5. Cheng A-L, Qin S, Ikeda M, et al. Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs sorafenib for unresectable hepatocellular carcinoma. *J Hepatol*. 2022;76:862-873. doi: 10.1016/j.jhep.2021.11.030.
6. Finn R, Kudo M, Merle P, et al. Primary results from the phase III LEAP-002 study: Lenvatinib plus pembrolizumab versus lenvatinib as first-line (1L) therapy for advanced hepatocellular carcinoma (aHCC). *Ann Oncol.* 2022;33(suppl_8):S808-869.
7. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *N Engl J Med.* 2020;382:1894-1905. doi: 10.1056/NEJMoa1915745.
8. Hanna K, Barlow A, Barlow B. Updates in Renal Cell Carcinoma Management. *Dir Pharm.* 2021;3(2):9.
9. Hapani S, Sher A, Chu D, Wu S. Increased risk of serious hemorrhage with bevacizumab in cancer patients: a meta-analysis. *Oncology* 2010;79(1-2):27-38.
10. Kelley RK, Rimassa L, Cheng A-L, et al. Cabozantinib plus atezolizumab versus sorafenib for advanced hepatocellular carcinoma (COSMIC-312): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2022;23:995-1008.
11. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018;391(10126):1163-1173
12. Leucht K, Ali N, Foller S, et al. Management of Immune-Related Adverse Events from Immune-Checkpoint Inhibitors in Advanced or Metastatic Renal Cell Carcinoma. *Cancers* 2022;14:4369. doi: 10.3390/cancers14184369.

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13. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in Advanced Hepatocellular Carcinoma. *N Engl J Med.* 2008;359:378-390
14. Martins F, Sofiya L, Sykiotis GP, et al. Adverse effects of immune checkpoint inhibitors: epidemiology, management and surveillance. *Nat Rev Clin Oncol.* 2019;16:563-579. doi: 10.1038/s41571-019-0218-0.
15. Massey PR, Okman JS, Wilkerson J, Cowen EW. Tyrosine kinase inhibitors directed against the vascular endothelial growth factor receptor (VEGFR) have distinct cutaneous toxicity profiles: a meta-analysis and review of the literature. *Support Care Cancer* 2014;23(6):1827-1835.
16. Medina P, Jeffers KD, Trinh VA, Harvey RD. The Role of Pharmacists in Managing Adverse Events Related to Immune Checkpoint Inhibitor Therapy. *J Pharm Practice* 2020;33(3):338-349. doi:10.1177/0897190019885230.
17. Merck. Merck and Eisai Provide Update on Phase 3 LEAP-002 Trial Evaluating KEYTRUDA® (pembrolizumab) Plus LENVIMA® (lenvatinib) Versus LENVIMA Monotherapy in Patients with Unresectable Hepatocellular Carcinoma. Press Release. August 3, 2022. https://www.merck.com/news/merck-and-eisai-provide-update-on-phase-3-leap-002-trial-evaluating-keytruda-pembrolizumab-plus-lenvima-lenvatinib-versus-lenvima-monotherapy-in-patients-with-unresectable-hepatocellul/. Accessed October 19, 2022.
18. Meseeha M, Attia M. Esophageal Varices. [Updated 2022 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK448078/. Accessed October 19, 2022.
19. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Hepatobiliary Cancers. Version 2.2022. July 15, 2022. https://www.nccn.org/login?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf. Accessed October 18, 2022.
20. Qin S, Chan LS, Gu S, et al. Camrelizumab (C) plus rivoceranib (R) vs. sorafenib (S) as first-line therapy for unresectable hepatocellular carcinoma (uHCC): A randomized, phase III trial. *Ann Oncol.* 2022;33(suppl_7):S808-869:LBA35.
21. Rimassa L, Danesi R, Pressiani T, Merle P. Management of adverse events associated with tyrosine kinase inhibitors: improving outcomes for patients with hepatocellular carcinoma. *Cancer Treatment Rev.* 2019;77:20-28.
22. Saito K, Fujii H, Kono K, et al. Changes in blood pressure during treatment with the tyrosine kinase inhibitor lenvatinib. *Clin Kid J.* 2021;14(1):325-331.
23. Stuart KE. Systemic treatment for advanced hepatocellular carcinoma. May 2, 2022. https://www.uptodate.com/contents/systemic-treatment-for-advanced-hepatocellular-carcinoma. Accessed October 18, 2022.
24. Tajiri K, Ieda M. Cardiac Complications in Immune Checkpoint Inhibition Therapy. *Front Cardiovasc Ther.* 2019;6(3). *doi: 10.3389/fcvm.2019.00003*
25. Takahashi S. Fatigue and its management in cancer patients undergoing VEGFR-TKI therapy. *Exp Opin Drug Safety* 2021; Aug 30;1-10. doi: 10.1080/14740338.2021.1969360. Online ahead of print.
26. Zhu AX, Kang Y-K, Yen C-J, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2019;20(2):282-296.

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