HBV Forum: Safety Panel Webinar

A general discussion of the Springbank Catalyst Study

K Agarwal, Institute of Liver Studies, Kings College Hospital, London

NB Late Breaker Abs upcoming ILC 2020

Authors: Agarwal, Afdhal, Coffin, Fung, Dusheiko, Foster, Elkhashab, Tam, Ramji, Iyer, Kennedy

Disclosures:

Arbutus/ Assembly/ Aligos/ Biotest/ Gilead/ Immunocore/ Roche/ Merck/ Springbank/ Shinoigi/ Sobi/ Vir

Acknowledgements:

Patients

Trial teams

Springbank

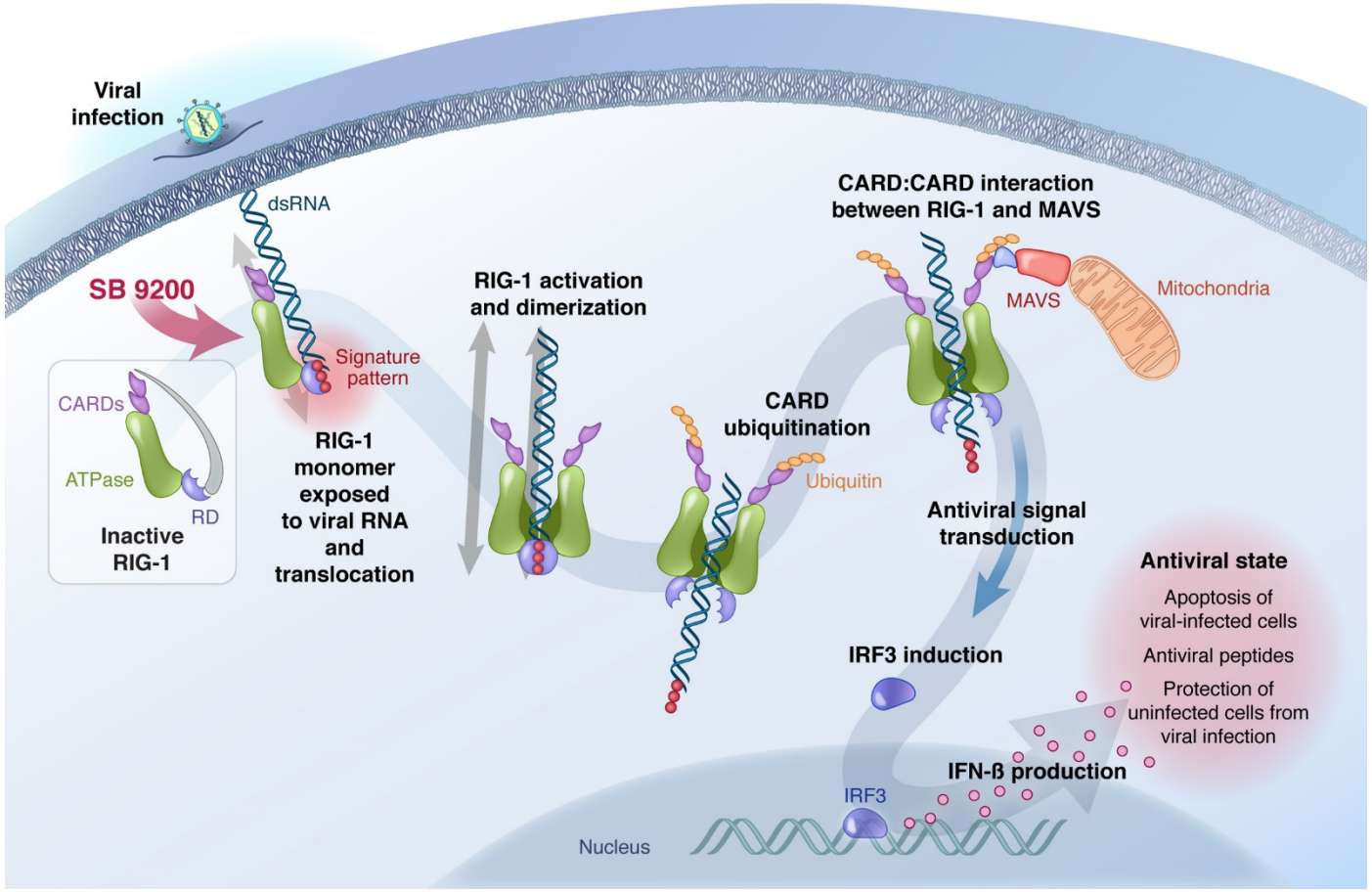
Esp: Afdhal, Dusheiko, Foster, Kennedy

Accept that some days you are the bird and some days you are the buffalo…

SB 9200, a Novel Dinucleotide Activates RIG-I and Modulates the Innate Immune System

Novel mechanism of action

- Binds to RIG-I – sentinel protein in the body's innate defense system
- Restores intrahepatic immunity through IFN production
- Has direct antiviral activity by inhibiting HBV replication complex
- Synergistic with Nucs, IFN
- Active against drug resistant HBV Variants
- High barrier to viral resistance
- Antiviral activity against HCV, RSV, influenza, Norovirus

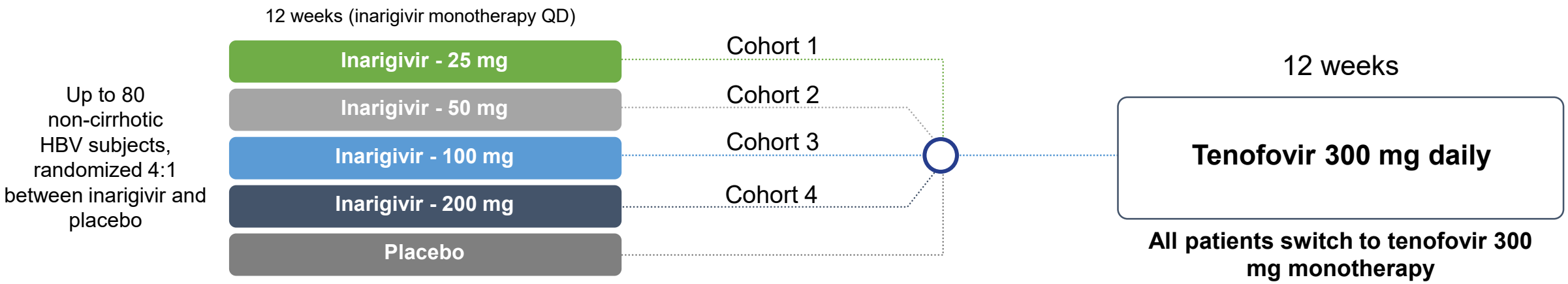


- **SB 9200 is a prodrug which converts to the active metabolite SB 9000 in vivo**

Interesting data

ACHIEVE Phase 2 Dose Escalation Study

Inarigivir monotherapy 12 weeks followed by switch to Tenofovir 300 mg for 12 weeks



PRIMARY ENDPOINT

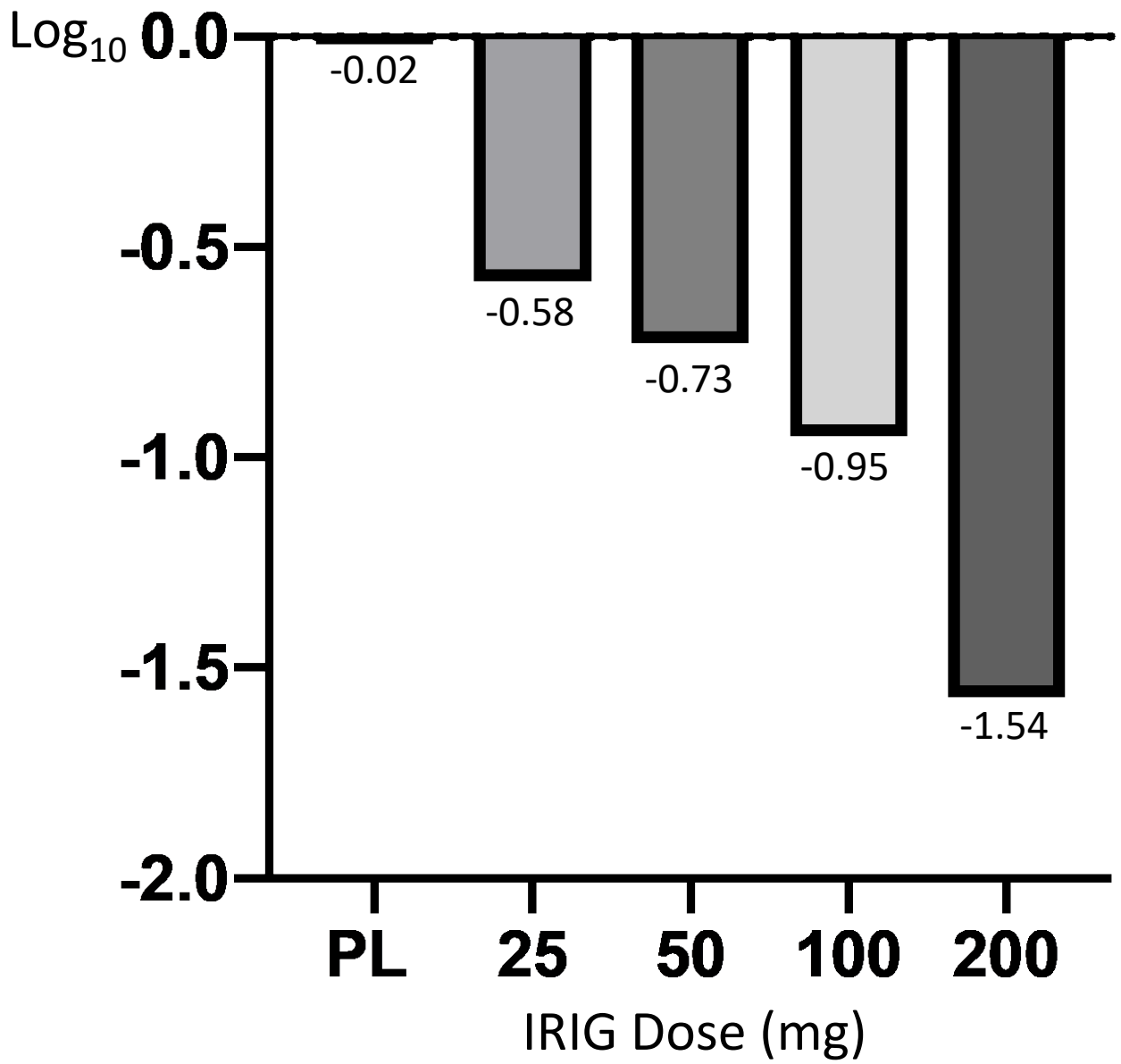
Safety and HBV DNA reduction at 12 weeks

SECONDARY ENDPOINTS

PK, change in serum HBV DNA, HBsAg, HBV RNA, HBcrAg and HBeAg from baseline to weeks 12 and 24

MF Yeun et al EASL 2019

Primary Endpoint: Mean Change from Baseline in HBV DNA to Week 12 in Placebo (PL) and IRIG cohorts



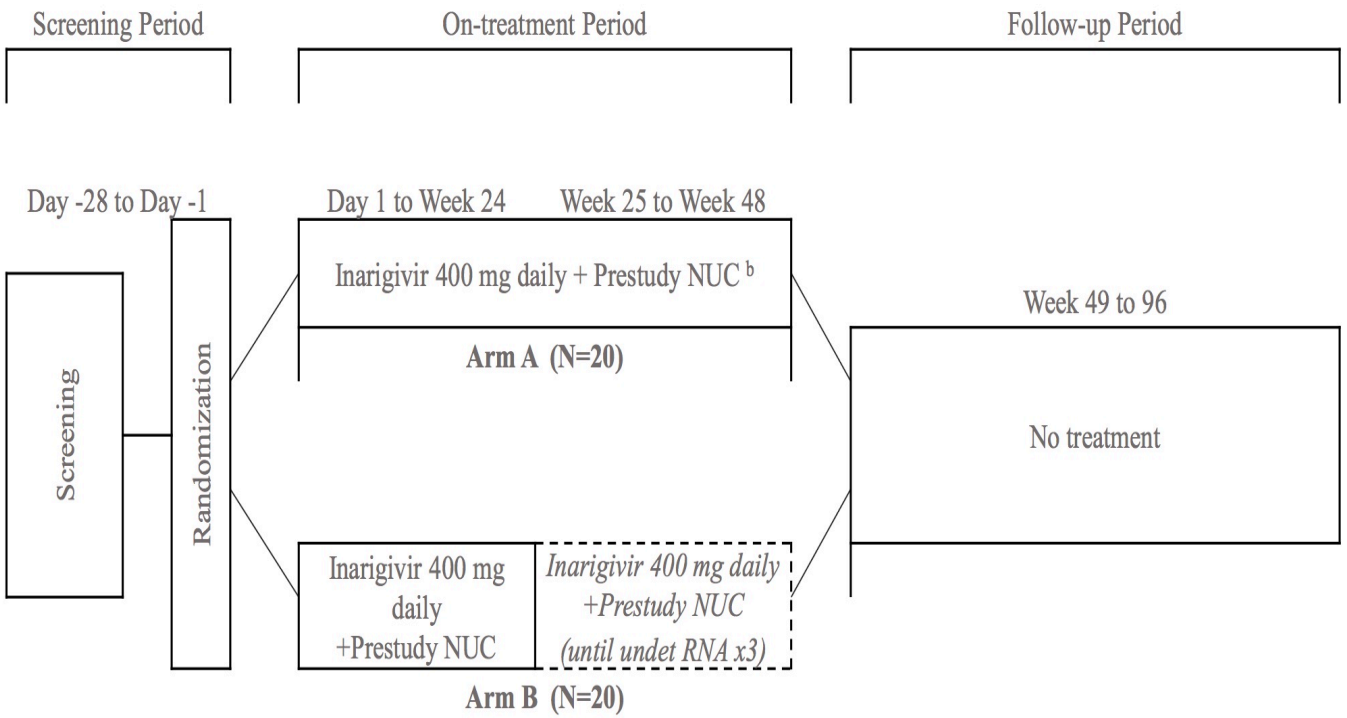
Catalyst study

eAg-ve NUC suppressed
Non- cirrhotic

C1 – stop and shock
C2 – suppress and watch

Study Design by Cohort

Cohort 2: Subjects Continuing NUC Treatment (N=40)

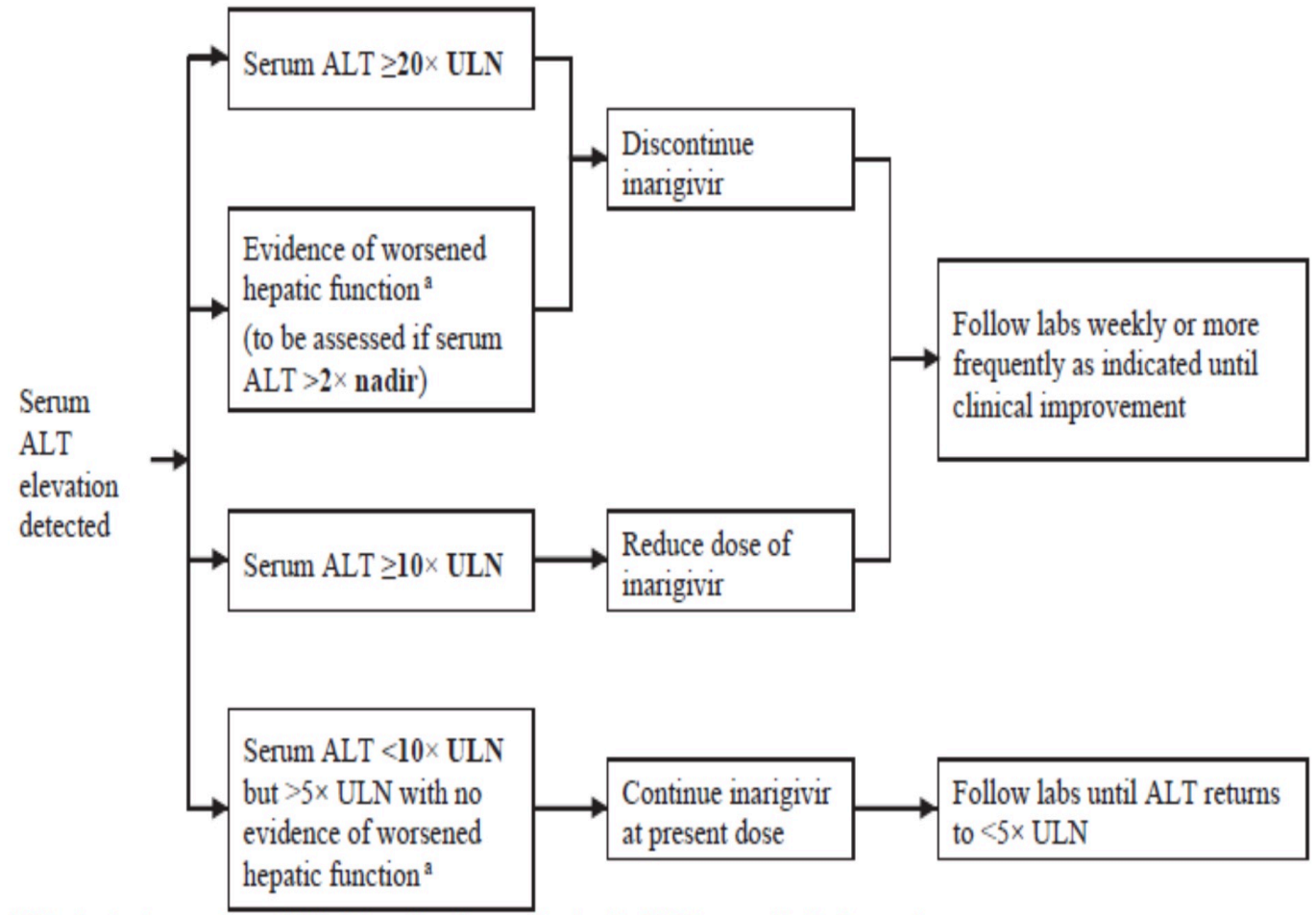


During follow-up, subjects who have a clinical relapse of HBV defined as HBV DNA >2000 IU and elevated ALT >2× ULN will restart the NUC.

a Subjects in Cohort 1 will discontinue NUC therapy and be observed for 4 to 6 weeks off NUCs. Subjects without early viral flare during the Off-NUC Period will proceed into the On-treatment Period.

b Subjects in Cohort 2, Arm A will receive their prestudy NUC and inarigivir 400 mg daily for 48 weeks, then enter the Follow-up Period (no treatment) for an additional 48 weeks.

Dose Reduction Due to ALT Elevation



ALT=alanine transaminase; INR=international normalized ratio; ULN=upper limit of normal

a Examples of evidence of worsened hepatic function include total bilirubin >2 mg/dL in the absence of Gilbert's disease, elevated INR ≥1.7 or >0.5 over Baseline, or abnormal serum albumin >1 g/dL decrease from Baseline.

Catalyst Springbank Phase 2

- Up to 250 pts dosed between 25-900mg between 1-12 weeks previously
- Flare ‘Stop and Shock’ C1 vs ‘Suppress and watch’ C2
- 42 pts
- Gradual slow increase alt – approx 40% week 8 up to 88% week 16
- 3 aesi elevated alt
- 19 dec – London pt sick, trial halted: lactic acidosis, pancreatitis, liver failure
- 7 pts admitted, 1 death- heterogenous lfts, abdo pain, vomiting
- Continued to evolve post cessation of dosing
- Cholestasis and coagulopathy in 2 - yikes
- Significant time to resolve
- (at least 3 cleared SAg – cohort 1)
- Last DSMB – trial discontinued

Discussion

- Standard development – no flags
- Immunomodulatory agent – novel MOA
- Dosing duration in prior studies – likely DILI duration related
- Flare vs DILI – the rules are there are no rules…? heterogenous
- Grumbling low level ALT ‘might be a good thing…??’
- More biopsies?
- Duration of follow up?
- Fialuridine analogy NEJM 1995…