Highlights of New Data From EASL 2017

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Faculty Disclosures

Paul Y. Kwo, MD, has disclosed that he has received consulting fees from Abbott, AbbVie, Bristol-Myers Squibb, Caremark, Conatus, Gilead Sciences, Intercept, Merck, and Quest; has received funds for research support from AbbVie, Bristol-Myers Squibb, Conatus, Gilead Sciences, and Merck; and is a shareholder with Durect.

Nancy Reau, MD, has disclosed that she has received consulting fees from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Intercept, and Merck.

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Considerations for Chronic HBV Infection

Chronic HBV Infection: Updated EASL Recommendations

- Monotherapy with ETV, TAF, TDF recommended based on high barrier to resistance
  - PegIFN should only be considered as initial treatment for pts with mild/moderate CHB or selected pts with compensated cirrhosis (no portal hypertension)

ETV or TAF Preferred Over TDF When:
Older than 60 yrs of age
Bone disease ▪ Chronic steroids or other meds that affect bone ▪ History of fragility fracture ▪ Osteoporosis
Renal abnormalities ▪ eGFR < 60 min/mL/1.73 m^2 ▪ Albuminuria > 30 mg or moderate proteinuria ▪ Low phosphate (< 2.5 mg/dL) ▪ Hemodialysis
TAF over ETV if previous NA exposure *No dose adjustment required for kidney disease or hemodialysis with TAF; ETV needs dose adjustment for eGFR < 50 mL/min*

Management of NA Resistance	
LAM resistance	Switch to TDF or TAF
TBV resistance	Switch to TDF or TAF
ETV resistance	Switch to TDF or TAF
ADV resistance	**LAM naive** ▪ Switch to ETV or TDF or TAF **LAM-R** ▪ Switch to TDF or TAF
TDF or TAF resistance	**LAM naive** ▪ Switch to ETV **LAM-R** ▪ Add ETV
Multidrug resistance	Switch to ETV + TDF or TAF combination

EASL. HBV guidelines. 2017.

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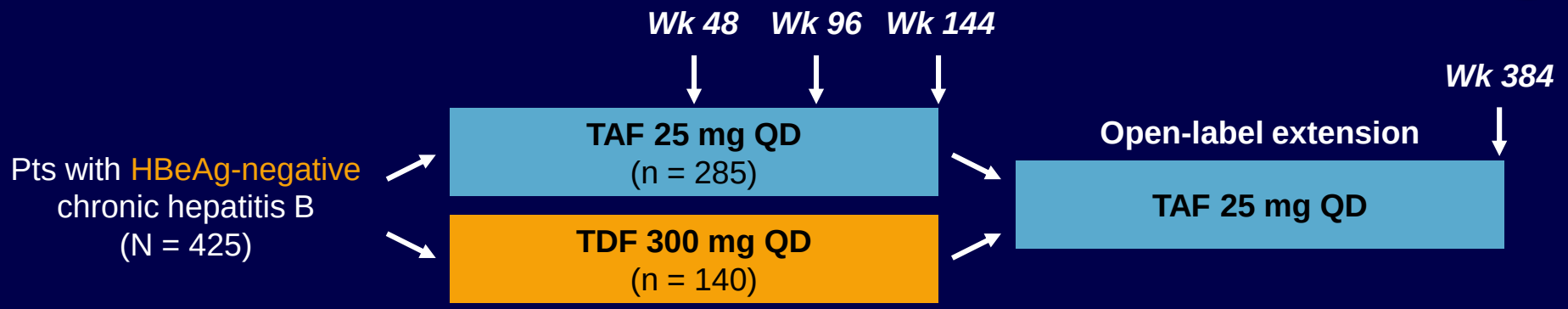
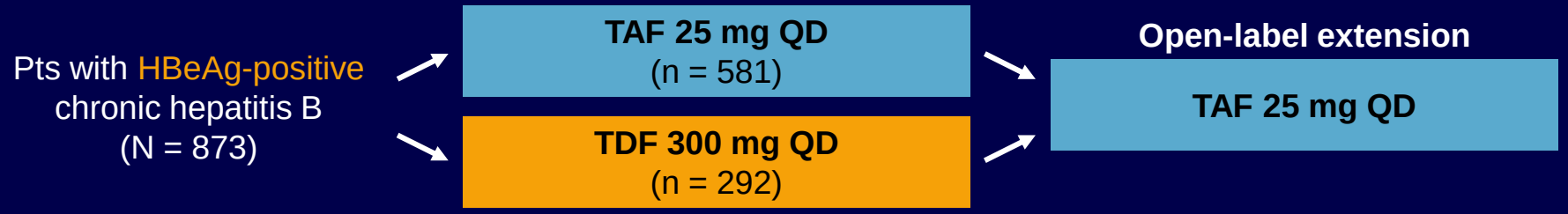
Studies 108 and 110: TAF vs TDF in HBeAg-Negative and HBeAg-Positive CHB

Study 108: randomized, double-blind, active-controlled phase III trial[1]



Study 110: randomized, double-blind, active-controlled phase III trial[2,3]



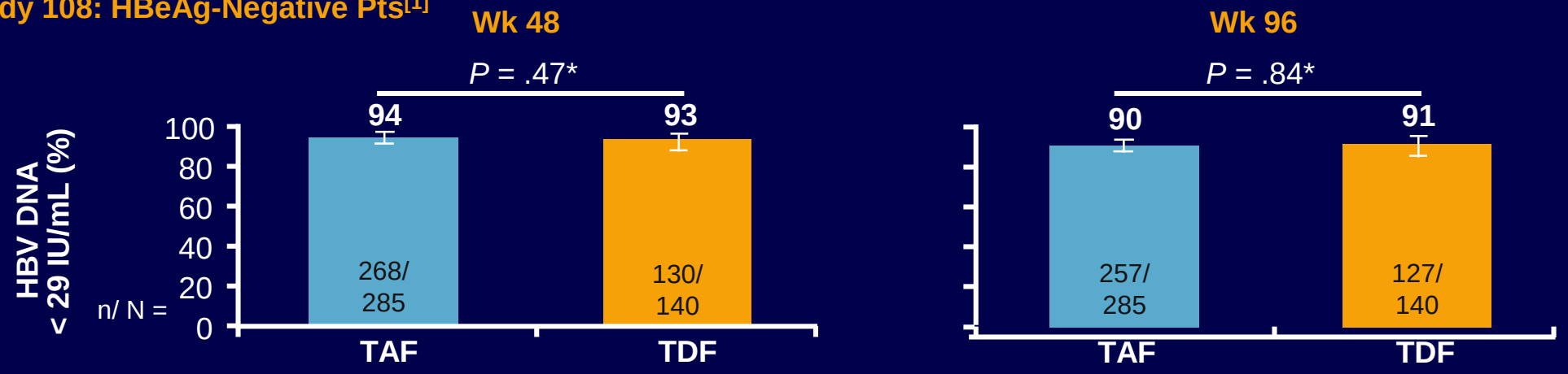
- Primary endpoint at Wk 48: HBV DNA < LLOQ (29 IU/mL)
- Secondary endpoints at Wk 96: HBV DNA < LLOQ, ALT normalization, serology

1. Brunetto M, et al. EASL 2017. Abstract PS-042. 2. Agarwal K, et al. EASL 2017. Abstract FRI-153. 3. ClinicalTrials.gov. NCT01940471.

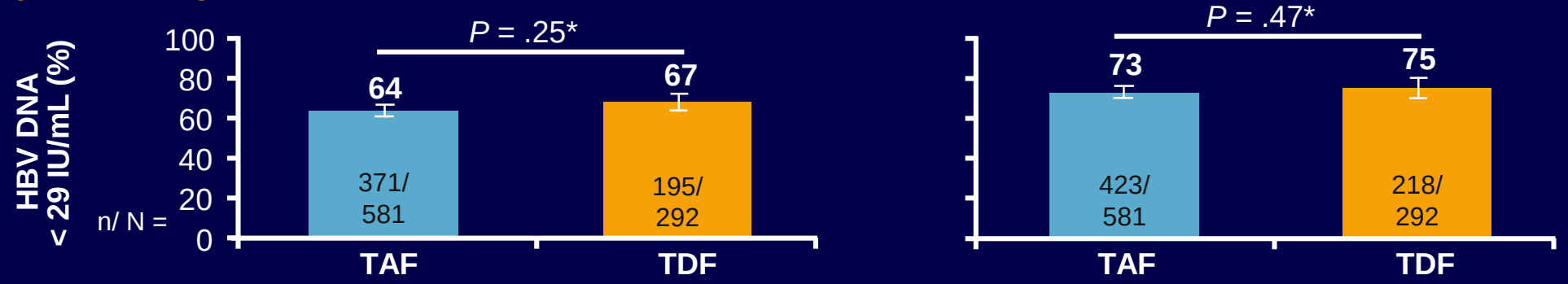
TAF vs TDF in HBeAg-Negative and HBeAg-Positive CHB: Wk 96 Efficacy

- TAF noninferior to TDF at Wks 48 and 96 in both studies; no resistance found in any arm

Study 108: HBeAg-Negative Pts[1]



Study 110: HBeAg-Positive Pts[2]



*Adjusted for BL HBV DNA and PO antiviral treatment status.

1. Brunetto M, et al. EASL 2017. Abstract PS-042. 2. Agarwal K, et al. EASL 2017. Abstract FRI-153. Reproduced with permission.

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TAF vs TDF in HBeAg-Negative and HBeAg-Positive CHB: Wk 96 Serology and ALT

- HBeAg-positive pts: higher rate of HBeAg seroconversion at Wk 96 vs Wk 48 in both arms[1]
  - Minimal decline in HBsAg in both arms for HBeAg-negative pts (1 TAF-treated pt with GT A had HBsAg loss and seroconversion)[2]

Serology in HBeAg-Positive Study, n/N (%)[1]	TAF (n = 581)	TDF (n = 292)	*P* Value
HBeAg by Wk 96			
▪ Loss	123/565 (22)	51/285 (18)	.20
▪ Seroconversion	99/565 (18)	35/285 (12)	.05
HBsAg by Wk 96			
▪ Loss	7/576 (1)	4/288 (1)	.88
▪ Seroconversion	6/576 (1)	0/288 (0)	.08

- In both studies, significantly higher rates at Wk 96 of ALT normalization with TAF

Wk 96 ALT Normalization, %	HBeAg Negative[2]			HBeAg Positive[1]		
	TAF	TDF	*P* Value	TAF	TDF	*P* Value
By central laboratory criteria*	81	71	.038	75	68	.017
By AASLD criteria†	50	40	.035	52	42	.003

*ULN for age < 69 yrs (≥ 69 yrs): men, ≤ 43 U/L (35 U/L); women, ≤ 34 U/L (32 U/L). †ULN: men, ≤ 30 U/L; women, ≤ 19 U/L.

1. Agarwal K, et al. EASL 2017. Abstract FRI-153. 2. Brunetto M, et al. EASL 2017. Abstract PS-042.

TAF vs TDF in HBeAg-Negative and HBeAg-Positive CHB: Wk 96 Safety

- Rates of treatment-emergent AEs and grade 3/4 laboratory abnormalities similar between arms, except for higher rates of LDL abnormalities for all pts on TAF (not adjusted for BL)
  - Improved renal and bone safety profiles for TAF vs TDF maintained through Wk 96

Safety Outcome	HBeAg Negative[1]			HBeAg Positive[2]		
	TAF (n = 285)	TDF (n = 140)	*P* Value	TAF (n = 581)	TDF (n = 292)	*P* Value
Any AE, n (%)	229 (80)	108 (77)	--	441 (76)	219 (75)	--
▪ Grade 3/4	18 (6)	8 (6)	--	40 (7)	14 (5)	--
▪ Serious AE	24 (8)	16 (11)	--	36 (6)	13 (4)	--
Death, n (%)	0	2*	--	2 (< 1)*	1 (< 1)*	--
Laboratory abnormalities in ≥ 2% pts						
▪ Grade 3/4, n/N (%)	95/282 (34)	39/140 (28)	--	214/577 (37)	106/288 (37)	--
▪ Fasting LDL, %	7	< 1	--	6	1	--
Change from BL to Wk 96						
▪ Mean spine BMD, %	-0.86	-3.06	< .001	-0.69	-2.34	< .001
▪ Mean hip BMD, %	-0.31	-2.96	< .001	-0.33	-2.30	< .001
▪ Median $eGFR_{CG}$, mL/min	-0.6	-3.6	.011	-1.8	-5.0	< .001

*Due to HCC in cirrhotic pt, multiorgan failure in pt with bilateral bronchopneumonia, H1N1 influenza, HCC unrelated to treatment, and cardiopulmonary arrest unrelated to treatment.

1. Brunetto M, et al. EASL 2017. Abstract PS-042. 2. Agarwal K, et al. EASL 2017. Abstract FRI-153.

Studies 108 and 110 Open-Label Extension: Switch to TAF vs TDF in CHB

- Analysis of open-label extension data from 2 phase III trials (Studies 108 and 110) in HBV-infected pts switching from TDF to TAF at Wk 96
  - 88% of pts achieved virologic suppression at Wk 96 (preswitch) and Wk 120 (post switch)
  - Significantly higher proportion of pts achieved ALT normalization after switch to TAF

Normalized ALT, n/N (%)	Pts Switching From TDF to TAF		*P* Value
	Wk 96: Preswitch	Wk 120: Post Switch	
By central laboratory criteria*	125/161 (78)	136/153 (89)	< .001
By AASLD criteria†	83/176 (47)	106/167 (63)	< .001

*ULN for age < 69 yrs (≥ 69 yrs): men, ≤ 43 U/L (35 U/L); women, ≤ 34 U/L (32 U/L). †ULN: men, ≤ 30 U/L; women, ≤ 19 U/L.

- Significant improvements in CrCl and change in hip and spine BMD at Wk 120

Chan HLY, et al. EASL 2017. Abstract PS-041.

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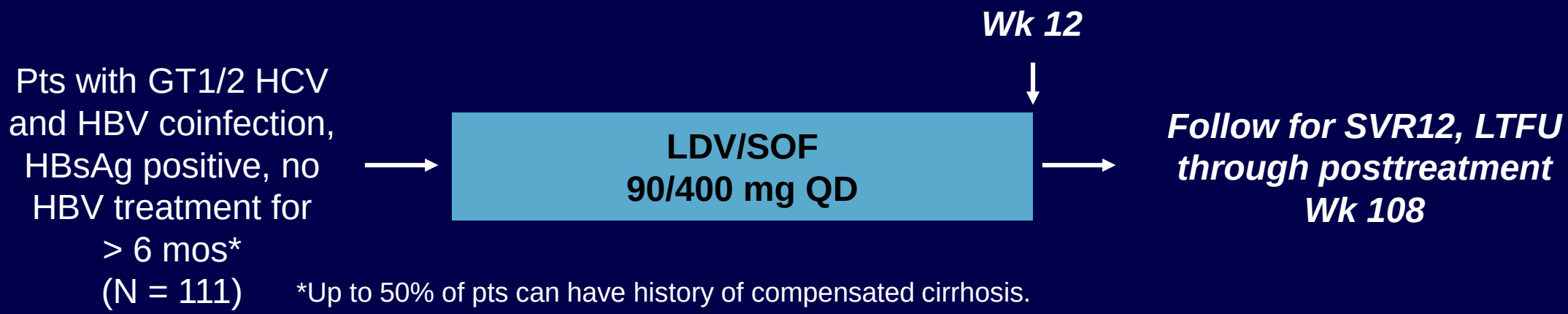
HBV Reactivation in Patients Receiving HCV DAA Therapy

LDV/SOF for 12 Wks in Pts With GT1/2 HCV and HBV Coinfection: Study Design

- Multicenter, single-arm, open-label phase III study in Taiwan of pts who are mostly HBeAg negative (99%), HCV treatment naive (67%)



*Up to 50% of pts can have history of compensated cirrhosis.

- Primary endpoints:
  - SVR12 (HCV RNA < 15 IU/mL)
  - AEs leading to discontinuation
- Secondary endpoints:
  - HBV DNA change from BL
  - Proportion of pts requiring HBV therapy per local guidelines

Liu CJ, et al. EASL 2017. Abstract PS-098.

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LDV/SOF for 12 Wks in Pts With GT1 or 2 HCV and HBV Coinfection: Results

- HCV SVR12: 100% (111/111)
- HBV DNA increased in 63% of pts (70/111)

HBV DNA Increase, n (%)	Overall (N = 111)	BL HBV DNA	
		< LLOQ* (n = 37)	≥ LLOQ* (n = 74)
≥ LLOQ	31 (28)	31 (84)	--
▪ ALT > 2 x ULN	0	0	--
> 1 to < 2 $\log_{10}$ IU/mL	37 (33)	11 (30)	26 (35)
▪ ALT > 2 x ULN	1 (< 1)	0	1 (1)
≥ 2 $\log_{10}$ IU/mL (any visit)	24 (22)	11 (30)	13 (18)
▪ ALT > 2 x ULN	4 (4)	0	4 (5)

*LLOQ = 20 IU/mL.

- 2 pts started HBV therapy (1 with GT1b HCV, cirrhosis; 1 with GT2 HCV, no cirrhosis)

- HBV DNA increase associated with higher BL ALT and HBV DNA

BL Factor, Mean (Range)	HBV DNA Increase		*P* Value
	No (n = 106)	Yes (n = 5)	
BL ALT, U/L	64 (17-281)	149 (40-228)	.0032
HBV DNA, $\log_{10}$ IU/mL	2.05 (1.28-5.83)	2.97 (1.54-5.46)	.0188

- No AE-related d/c, jaundice, liver failure/ transplant/decompensation; 1 pt with transient, asymptomatic grade 4 lipase (Wk 4)

AE, n (%)	Pts (N = 111)
Any AE	66 (60)
Grade 3/4 AE†	1 (< 1)
Serious AE†	4 (4)‡

†Deemed unrelated to LDV/SOF.
‡Included grade 1 duodenal ulcer, grade 2 meniscus injury, grade 3 optic neuritis, grade 2 postpolypectomy hemorrhage.

Liu CJ, et al. EASL 2017. Abstract PS-003.

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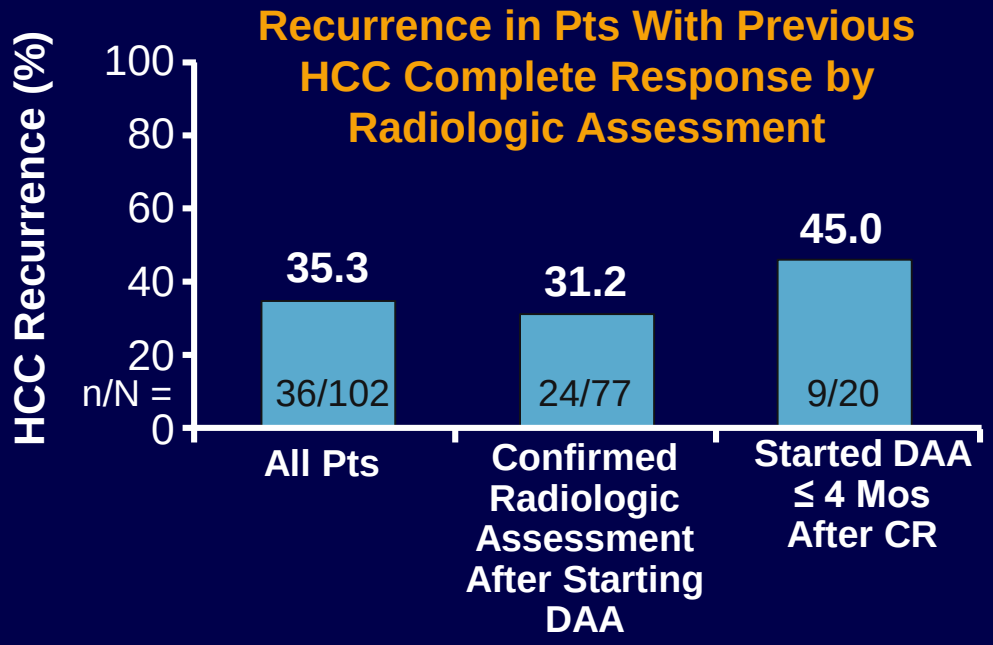
HCC Outcomes Following HCV DAA Therapy

HCC Recurrence Following HCV DAA Therapy

- Retrospective study of pts with history of HCC before starting HCV DAAs (N = 105)



- Among pts starting DAAs ≤ 4 mos after CR, 4 pts (20%) died
  - Deaths occurred in Months 9, 10, 15, 16 after starting DAA

- 10 pts had second HCC recurrence or progression

Endpoint	Pts With Recurrence (n = 24)*
Median time from DAA start to first recurrence, mos (IQR)	3.5 (2-7.6)
Median time from first to second recurrence/progression, mos (IQR)	6 (3.2-8.2)
▪ Within 6 mos of first recurrence, n/n (%)	6/20 (30)
▪ Death, n (%)	5 (20.8)

*Pts from cohort with confirmed radiologic assessment, no confounding factors.

Reig M, et al. EASL 2017. Abstract PS-031. Reproduced with permission.

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HCC Recurrence Equivalent With DAAs and IFN

- Meta-analysis and meta-regression analysis comparing risk of HCC after SVR with DAA- vs IFN-based therapy in 41 studies (N = 13,875)

Pts With First HCC Occurrence After SVR

Characteristic	DAA	IFN
Age, yrs	60	52
Cirrhosis, %	90	87
Child-Pugh score B/C, %	34	0
Follow-up, yrs	1.0	5.5

Pts With HCC Recurrence After SVR

Characteristic	DAA	IFN
Pts with previous curative HCC treatment, %	96	100
Follow-up, yrs	1.3	5.0

- After adjusting for these factors, no difference in risk of HCC occurrence (aRR: 0.75) or recurrence (aRR: 0.62) between DAAs and IFN

Dore G, et al. EASL 2017. Abstract PS-160.

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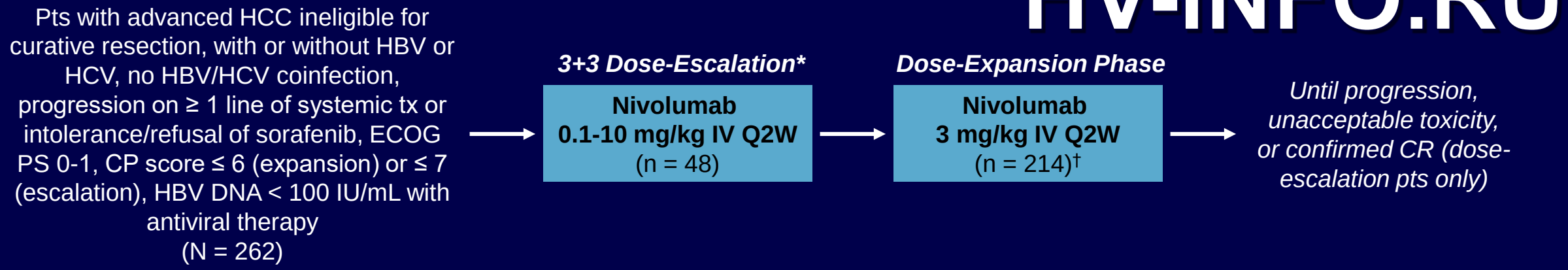
HCC Treatment

CheckMate 040: Nivolumab in Sorafenib-Experienced Pts With HCC ± HCV or HBV

- International, open-label, noncomparative phase I/II dose-escalation and multicohort dose-expansion study in sorafenib-naive and sorafenib-experienced pts
- Nivolumab: fully human IgG4 mAb and PD-1 checkpoint inhibitor



*3+3 design: 3 initial pts enrolled into given dose group. If no DLT, trial enrolls pts into next higher dose group. If 1 pt experiences DLT, additional 3 pts enrolled in same dose group; DLTs in > 1/6 pts suggests MTD exceeded.
†Includes 4 cohorts: sorafenib naive or intolerant without CVH, sorafenib progressor without CVH, HCV infected, HBV infected.

- Primary endpoints: objective response rate, safety (escalation only)
- Current analysis: sorafenib-experienced pts in dose-expansion phase (n = 145)

References in slidenotes.

Slide credit: clinicaloptions.com

Nivolumab in Sorafenib-Experienced Pts With HCC ± HCV or HBV: Efficacy

- Objective response of 14.5% (independent of PD-L1 expression), with 57% of responses in ≤ 3 mos

Outcome	Infection Status		
	HCV (n = 30)	HBV (n = 43)	Uninfected (n = 72)
Objective response, n (%)*	6 (20.0)	6 (14.0)	9 (12.5)
▪ Complete	1 (3.3)	1 (2.3)	0
▪ Partial	5 (16.7)	5 (11.6)	9 (12.5)
▪ Stable disease	9 (30.0)	14 (32.6)	37 (51.4)
▪ Progressive disease	11 (36.7)	22 (51.2)	23 (31.9)
▪ Not evaluable	4 (13.3)	1 (2.3)	3 (4.2)
Median time to response, mos (range)	2.1 (1.2-7.0)	2.0 (1.2-6.8)	4.0 (2.6-6.8)
1-yr OS, % (95% CI)	67.1 (46.2-81.4)	55.6 (39.6-69.0)	59.7 (47.4-70.0)

*By BICR using RECIST v1.1.

Sangro B, et al. EASL 2017. Abstract GS-010.

Slide credit: clinicaloptions.com

Nivolumab in Sorafenib-Experienced Pts With HCC ± HCV or HBV: Safety

- Safety profile consistent with other tumor types, with most ALT/AST elevations reversible

Endpoint, n (%)	Infection Status		
	HCV (n = 30)	HBV (n = 43)	Uninfected (n = 72)
Study treatment discontinuation	22 (73)	35 (81)	59 (82)
▪ Progression	17 (57)	34 (79)	51 (71)
▪ Toxicity	2 (7)	0	2 (3)
Treatment-related AE*	25 (83)	30 (70)	53 (74)
▪ Grade 3/4	9 (30)	4 (9)	11 (15)
Grade 3/4 ALT increase	1 (3)	0	2 (3)
Grade 3/4 AST increase	2 (7)	0	2 (3)

*In ≥ 5% pts: fatigue, pruritus, rash, diarrhea, nausea, dry mouth, decreased appetite.

- No SVR in HCV-infected pts
- No anti–HBs seroconversion in HBV-infected pts

Sangro B, et al. EASL 2017. Abstract GS-010.

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SARAH: Selective Internal Radiation vs Sorafenib in HCC

- Open-label, randomized phase III trial of SIRT with yttrium-90 microspheres vs sorafenib 400 mg BID in pts with HCC (N = 459)

Parameter	SIRT (n = 237)	Sorafenib (n = 222)	*P* Value
Median overall survival, mos	8.0	9.9	.179
Median progression-free survival, mos	4.1	3.7	.765
Response rate, %	19.0	11.6	.042
Treatment-related AEs			
▪ Overall, n	1297	2837	--
▪ Grade ≥ 3, n	230	411	--
▪ Pts with ≥ 1, n (%)	173 (76.5)	203 (94.0)	< .001
▪ Pts with ≥ 1 grade ≥ 3, n (%)	92 (40.7)	136 (63.0)	< .001

Vilgrain V, et al. EASL 2017. Abstract GS-012.

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Current Treatment of HCV Infection

Summary of Approved Direct-Acting Antivirals Discussed in This Slideset

Drug	Abbreviation	Class
Grazoprevir	GZR	NS3/4A protease inhibitor
Paritaprevir	PTV	NS3/4A protease inhibitor
Simeprevir	SMV	NS3/4A protease inhibitor
Daclatasvir	DCV	NS5A inhibitor
Elbasvir	EBR	NS5A inhibitor
Ledipasvir	LDV	NS5A inhibitor
Velpatasvir	VEL	NS5A inhibitor
Sofosbuvir	SOF	NS5B nucleotide polymerase inhibitor

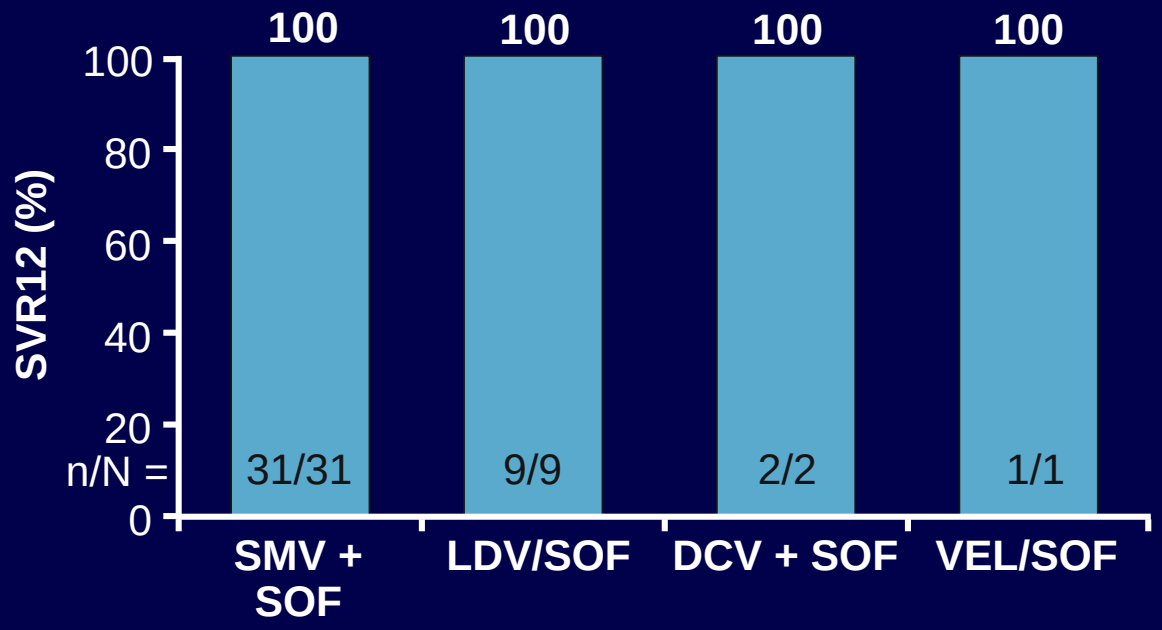
Summary of Investigational Direct-Acting Antivirals Discussed in This Slideset

Drug	Abbreviation	Class
Glecaprevir	GLE	NS3/4A protease inhibitor
Voxilaprevir	VOX	NS3/4A protease inhibitor
Pibrentasvir	PIB	NS5A inhibitor
Ruzasvir	RZR	NS5A inhibitor
Uprifosbuvir (formerly MK-3682)	UPR	NS5B polymerase nucleotide inhibitor

Slide credit: clinicaloptions.com

SOF-Based, RBV-Free DAAs in Pts With HCV Infection and ESRD

- N = 43 pts mostly on dialysis (93%), treatment naive (79%), genotype 1a (65%), noncirrhotic (51%)
  - Mean baseline hemoglobin: 11.1 g/dL (range: 8.9-13.8 g/dL)
- Most pts treated for 12 wks (n = 36)



Safety

- No hepatic decompensation
- No dose adjustment of any regimen

Nazario H, et al. EASL 2017. Abstract FRI-220. Reproduced with permission.

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TRIO, HCV-TARGET, VA: Real-World Efficacy of EBR/GZR

- Analyses of SVR12 rates in HCV-infected pts using specialty pharmacies and providers in US TRIO Network,[1] US and international clinical practices,[2] and US Veterans Affairs Healthcare System[3]

Source, n/N (%)	Pts With GT1 HCV	SVR12, %	
		Per Protocol	Evaluable
TRIO Network[1] (N = 462)	410/462 (89)	245/253 (97)	--
HCV-TARGET Study[2] (N = 319)*	319/319 (100)	135/139 (97)†	147/159 (92)†
VA Healthcare System*[3] (N = 2436)	2324/2436 (95)	2190/2257 (97)‡	2328/2436 (96)‡

*Included 22 pts treated with EBR/GZR + RBV. †For pts missing SVR12 outcome, data replaced with SVR4 outcome. ‡For pts missing SVR12 outcome, data replaced with HCV RNA test results obtained during posttreatment Wks 4-12.

- Safety evaluated in HCV-TARGET study[2]
  - AEs: EBR/GZR, 34%; EBR/GZR + RBV, 50% (serious AEs: 5% vs 0%, respectively)
  - Most common AEs in EBR/GZR-treated pts: fatigue (9%), headache (8%), nausea (5%), diarrhea (3%), influenzalike illness (3%), decreased appetite (3%), dizziness (2%), vomiting (3%), abdominal discomfort (2%), abdominal pain upper (2%)

1. Bacon B, et al. EASL 2017. Abstract THU-239. 2. Pearlman BL, et al. EASL 2017. Abstract THU-237. 3. Kramer JR, et al. EASL 2017. Abstract PS-095.

TARGET and TRIO: Real-World Efficacy of VEL/SOF

- SVR12 rates comparable between analyses of real-world pts with GT1-6 HCV treated with VEL/SOF ± RBV

Source	HCV Genotype, %				SVR12, n/N (%)	
	1	2	3	4-6	Per Protocol	Evaluable
TRIO Network[1] (n = 89)	100	--	--	--	29/30 (97)	--
TRIO Network[2] (n = 676)*	--	58	36	6	167/173 (97)	--
HCV-TARGET Study[3] (N = 495)†	19	34	42	6	119/126 (94)‡	121/128 (95)‡

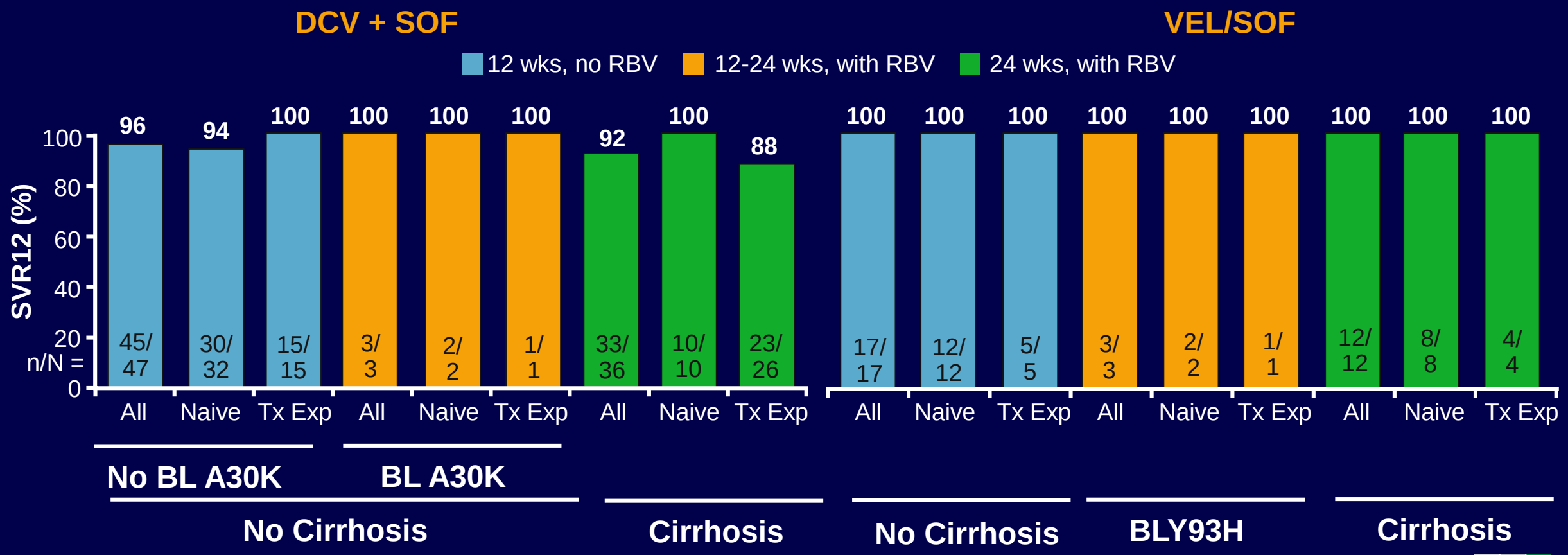
*Included 59 pts (8.7%) treated with VEL/SOF + RBV. †Included 108 pts (22%) treated with VEL/SOF + RBV. ‡For pts missing SVR12 outcome, data replaced with HCV RNA test results obtained during posttreatment Wks 4-12.

- Safety evaluated in HCV-TARGET study[3]
  - AEs: VEL/SOF, 55%; VEL/SOF + RBV, 80% (serious AEs: 2% vs 9%, respectively)
  - Most common AEs in VEL/SOF-treated pts: fatigue (12%), headache (14%), nausea (8%), anemia (1%), dizziness (3%), influenzalike illness (5%), arthralgia (4%), diarrhea (4%), vomiting (3%), abdominal pain (2%)

1. Tsai N, et al. EASL 2017. Abstract SAT-244. 2. Curry M, et al. EASL 2017. Abstract PS-102.
3. Khalili M, et al. EASL 2017. Abstract SAT-222.

DCV or VEL in Treatment-Experienced GT3 HCV Infection

- Real-world cohort of patients with GT3 HCV infection treated according to baseline NS5A RASs, previous treatment failure, and cirrhosis status (N = 167)



Vermehren J, et al. EASL 2017. Abstract PS-155. Reproduced with permission.

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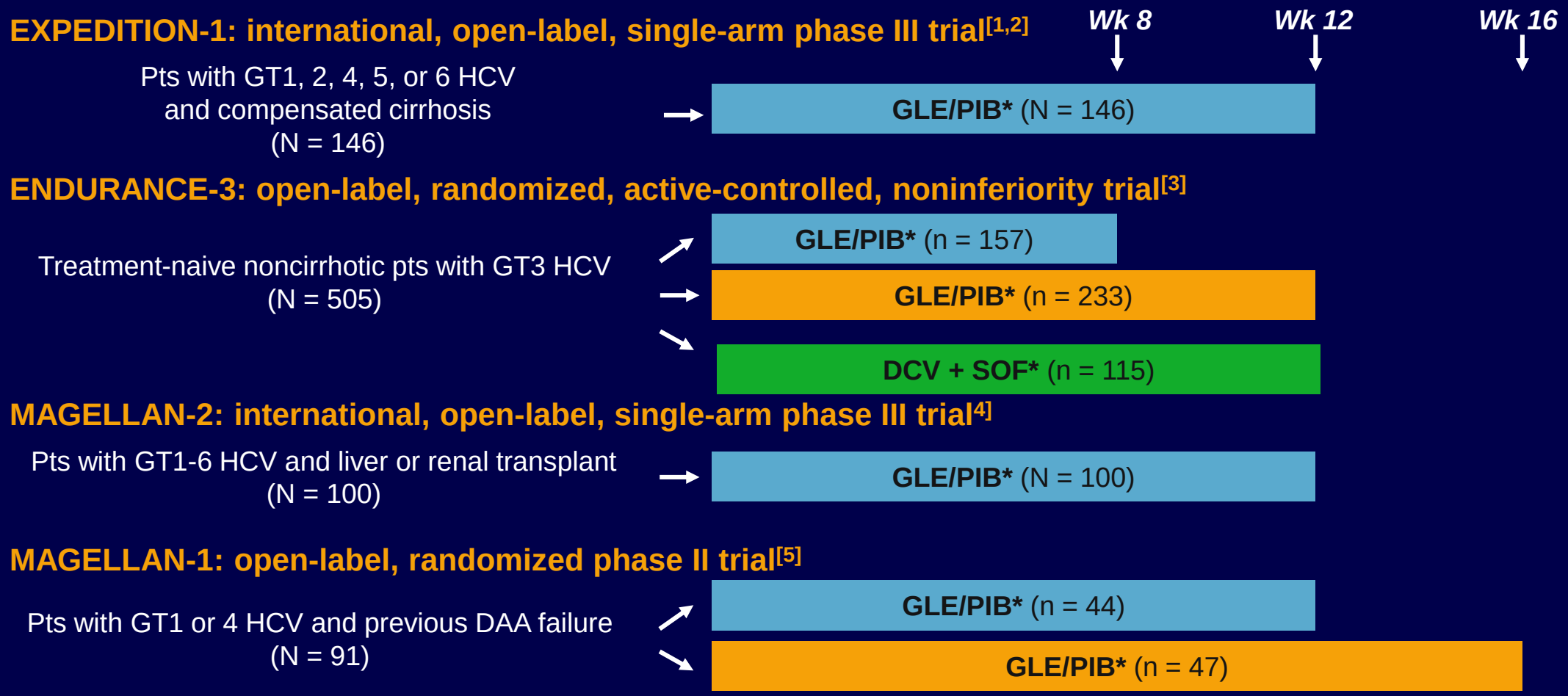
Investigational HCV Treatments

Glecaprevir/Pibrentasvir for Treatment of HCV

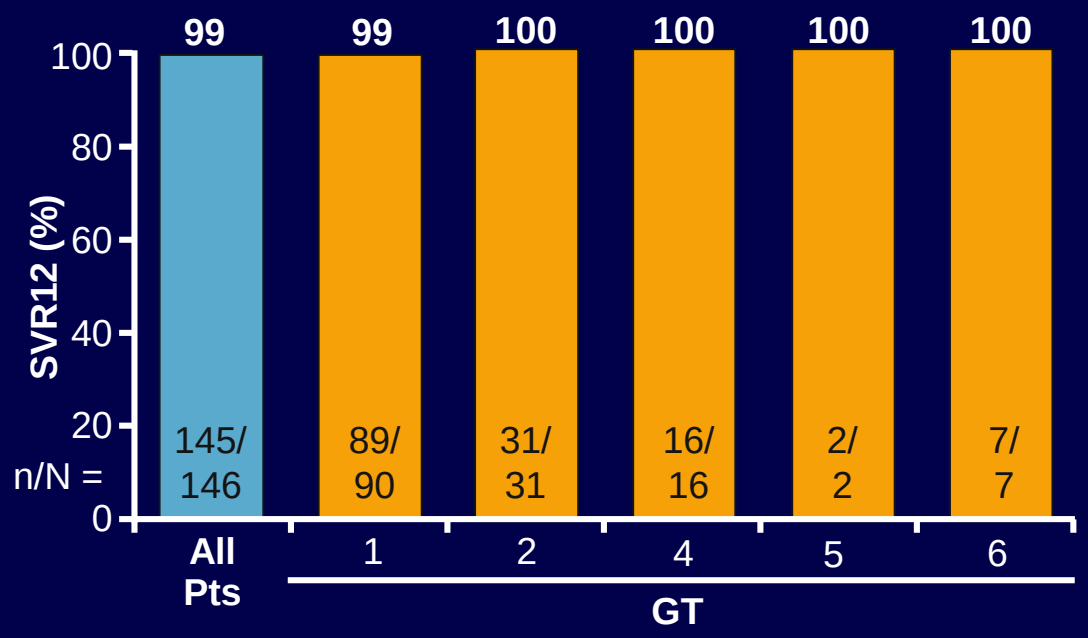


*Dosing: GLE/PIB, 300/120 mg. DCV + SOF, 60 mg + 400 mg QD.

References in slidenotes.

EXPEDITION-1: GLE/PIB in GT1, 2, 4, 5, or 6 HCV and Compensated Cirrhosis

SVR12 With GLE/PIB by Genotype



- 1 relapse in pt with GT1a HCV with new NS5A mutations (Q30R, H58D)

- No AE-related discontinuations or DAA-related serious AEs
  - 1 death due to cerebral hemorrhage in pt with history of hemophilia deemed unrelated to study drug

AE, n (%)	Pts (N = 146)
Any AE	101 (69)
Any serious AE	11 (8)
AEs occurring in ≥ 10% of pts	
▪ Fatigue	28 (19)
▪ Headache	20 (14)
▪ Pruritus	14 (10)
HCC	2 (1)

- Rare grade 3 laboratory abnormalities

Forns X, et al. EASL 2017. Abstract GS-006. ClinicalTrials.gov. NCT02642432.
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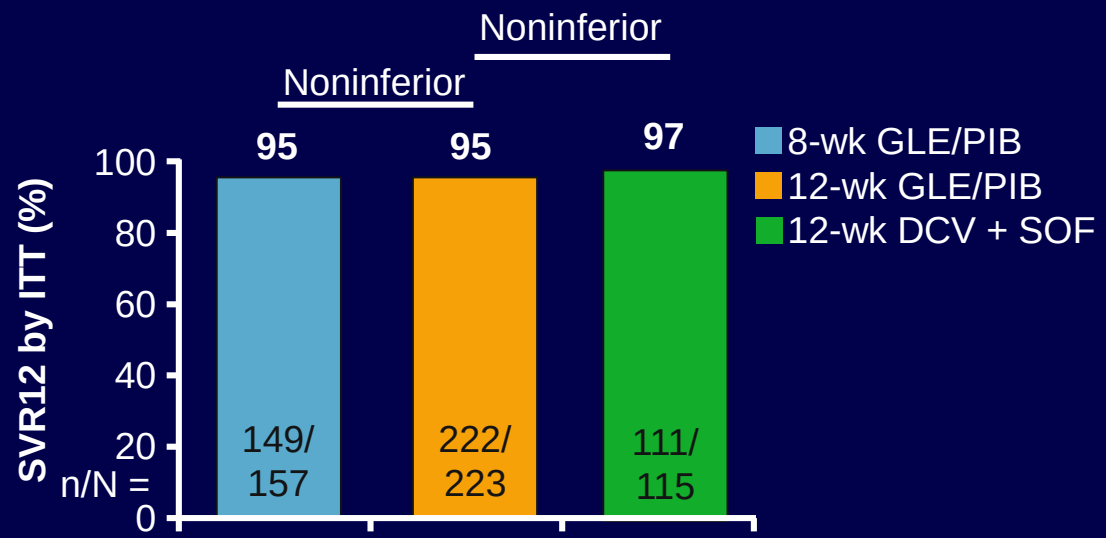
ENDURANCE-3: GLE/PIB in GT3 HCV Without Cirrhosis



Failure, n (%)			
Breakthrough	1 (1)	1 (< 1)	0
Relapse	5 (3)	3 (1)	1 (1)
AE-related d/c	0	1 (< 1)	1 (1)
LTFU	2 (1)	4 (2)*	2 (2)

*2 other failures due to consent withdrawal and noncompliance.

- Most pts had history of IDU (63% to 66%)

- No serious AEs deemed related to study drug

AE, n (%)	G/P 8 Wks (n = 157)	G/P 12 Wks (n = 233)	SOF + DCV (n = 115)
Any AE	98 (62)	177 (76)	80 (70)
▪ Possibly DAA related	63 (40)	112 (48)	50 (43)
Serious AE	3 (2)	5 (2)	2 (2)
AEs in ≥ 10% of pts			
▪ Headache	31 (20)	60 (26)	23 (20)
▪ Fatigue	20 (13)	44 (19)	16 (14)
▪ Nausea	19 (12)	32 (14)	15 (13)

- Grade ≥ 3 laboratory abnormalities: no clinically relevant ALT increases, 1 isolated bilirubin increase (G/P 8 wks), 1 isolated neutrophil count decrease (G/P 12 wks)

Foster GR, et al. EASL 2017. Abstract GS-007. Reproduced with permission.

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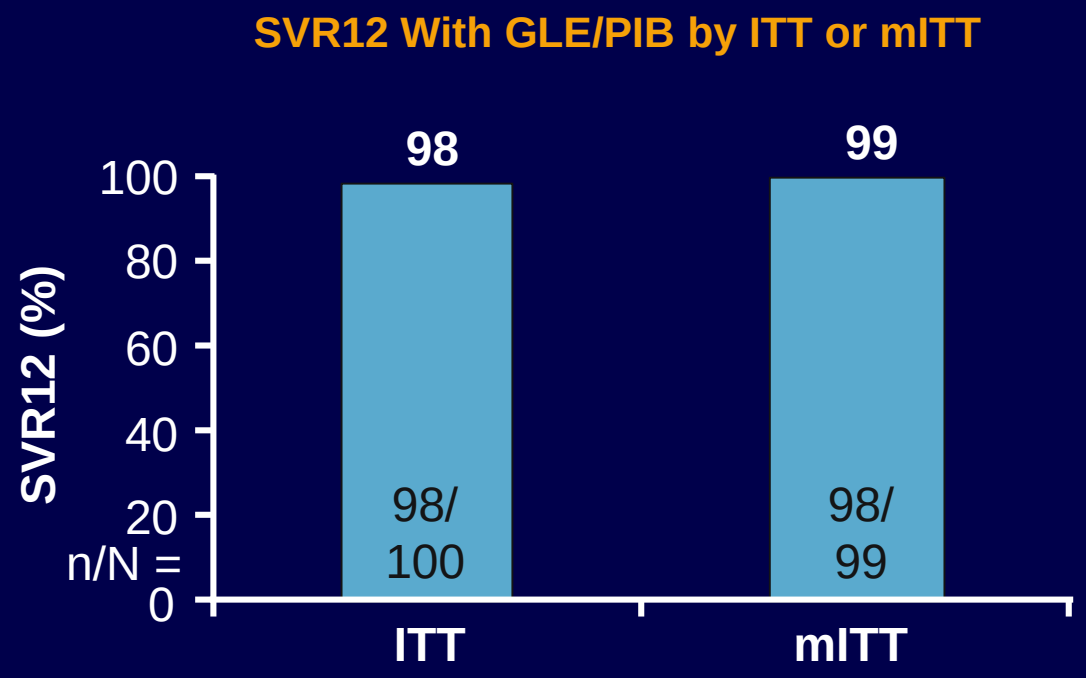
MAGELLAN-2: GLE/PIB in GT1-6 HCV With Liver or Renal Transplant



- 1 relapse in pt with GT3a HCV; 1 pt LTFU

- No deaths during study, 1 pt with transplant rejection (unrelated to DAA)

Safety Outcome, %	GLE/PIB (N = 100)
Any AE	85
Serious AE	8
▪ DAA related	2
AEs leading to d/c	1
▪ DAA related	0
AEs in ≥ 10% of pts	
▪ Headache	22
▪ Fatigue	22
▪ Nausea	12
▪ Pruritus	12
Grade ≥ 3 abnormality	
▪ AST	0
▪ ALT	1
▪ Total bilirubin	1
▪ CrCl	2

Reau N, et al. EASL 2017. Abstract LBO-03. Reproduced with permission.

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MAGELLAN-1: GLE/PIB in GT1 or 4 HCV With Previous DAA Failure

- Of pts with both NS3 and NS5a RASs, 9/9 had previous failure with PI + NS5A
  - 5/9 had SVR12 on GLE/PIB

SVR12, n/N (%)	GLE/PIB	
	12 Wks (n = 44)	16 Wks (n = 47)
Overall SVR12	39/44 (89)	43/47 (91)
SVR12 according to previous DAA class		
▪ PI only	14/14 (100)	13/13 (100)
▪ NS5A only	14/16 (88)	17/18 (94)
▪ PI + NS5A	11/14 (79)	13/16 (81)
SVR12 according to baseline RAS		
▪ None	13/13 (100)	13/13 (100)
▪ NS3 only	2/2 (100)	4/4 (100)
▪ NS5A only	20/24* (83)	22/23† (96)

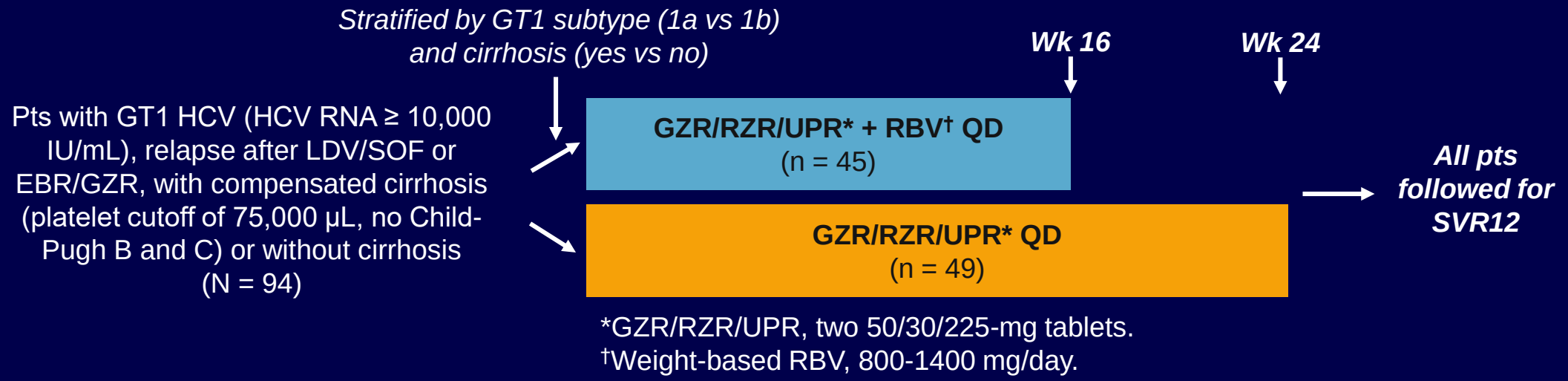
*Virologic failure: n = 3 relapse; n = 1 on treatment. †Virologic failure: n = 1 on treatment.

Poordad F, et al. EASL 2017. Abstract PS-156.

Slide credit: clinicaloptions.com

C-SURGE: GZR/RZR/UPR for GT1 HCV Pts Who Relapsed on Previous DAA Therapy

- Randomized, open-label phase II trial

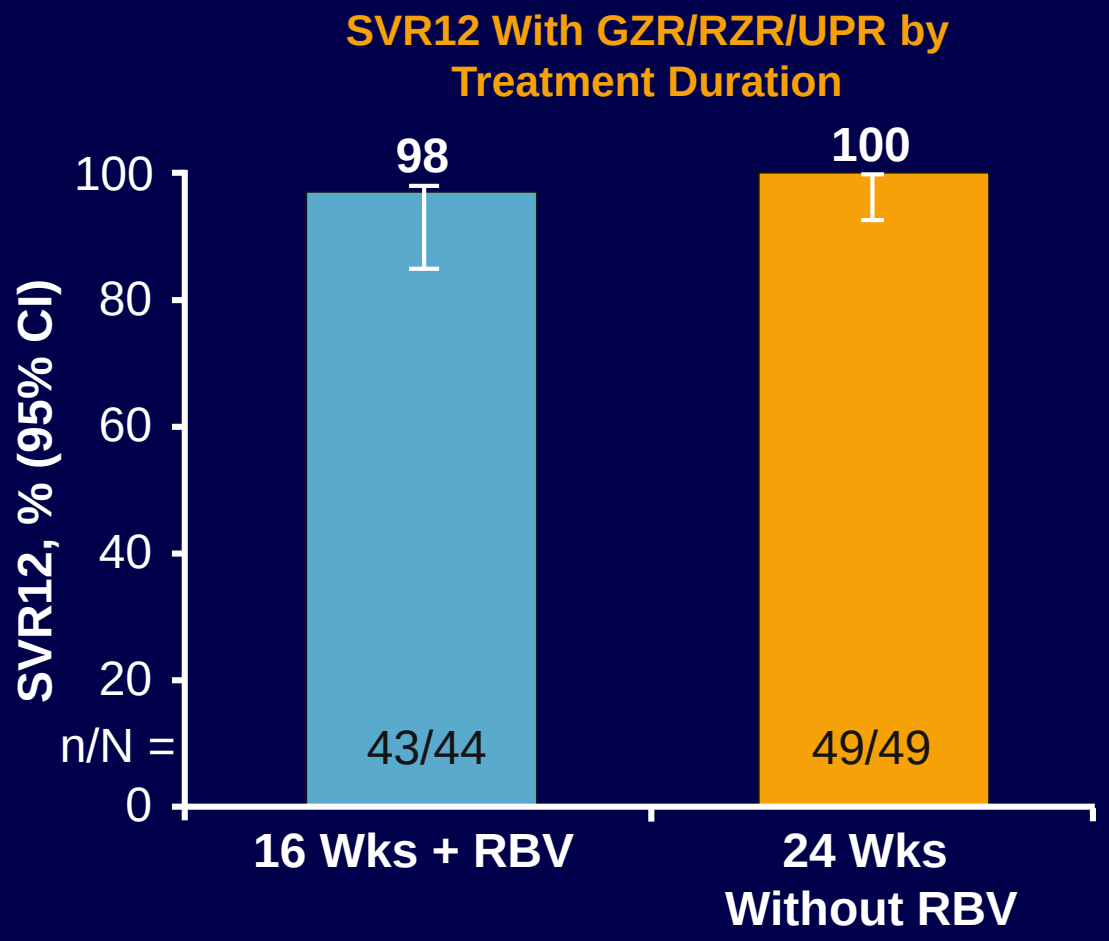


- Baseline characteristics:
  - Noncirrhotic, 56%; compensated cirrhosis, 43%; unknown, 1%
  - NS5A RASs, 84%; NS3 RASs, 65%; dual NS5A and NS3 RASs, 55%
- Primary endpoints: SVR12 (HCV RNA < 15 IU/mL), safety

Wedemeyer H, et al. EASL 2017. Abstract PS-159.

Slide credit: clinicaloptions.com

C-SURGE: Efficacy and Safety Outcomes



- SVR12 achieved independent of presence of BL NS5A/NS3 RASs (including Y93)
- GZR/RZR/UPR + RBV arm had greater frequency of fatigue, pruritus, rash, decreased hemoglobin

Safety Outcome, n (%)	16 Wks + RBV (n = 44)	24 Wks Without RBV (n = 49)
≥ 1 AE	40 (91)	39 (80)
▪ Drug-related AE	32 (73)	23 (47)
Any serious AE*	1 (2)	4 (8)
AEs occurring in ≥ 10% of pts		
▪ Fatigue	21 (48)	12 (24)
▪ Headache	6 (14)	6 (12)
▪ Diarrhea	3 (7)	5 (10)
▪ Pruritus	5 (11)	0
▪ Rash	6 (14)	2 (4)
Hemoglobin < 10 g/dL	4 (9)	0

*All serious AEs deemed unrelated to study treatment.

Wedemeyer H, et al. EASL 2017. Abstract PS-159. Reproduced with permission.

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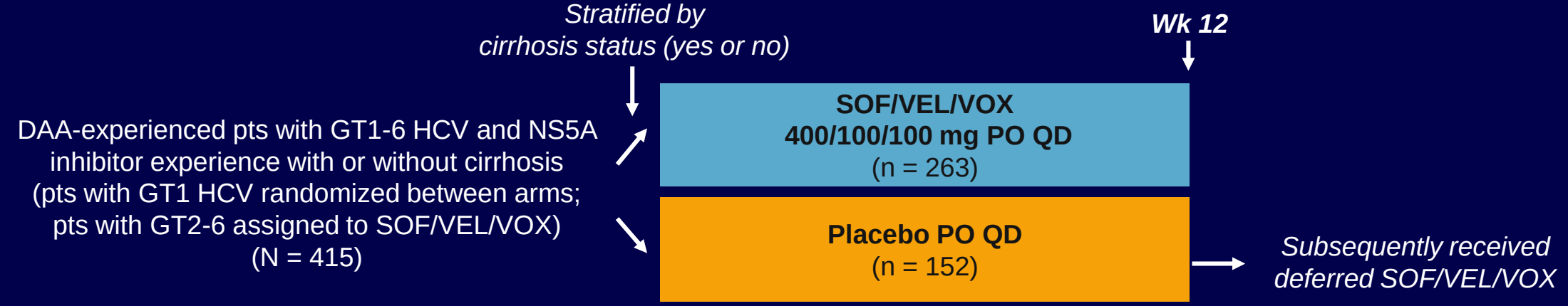
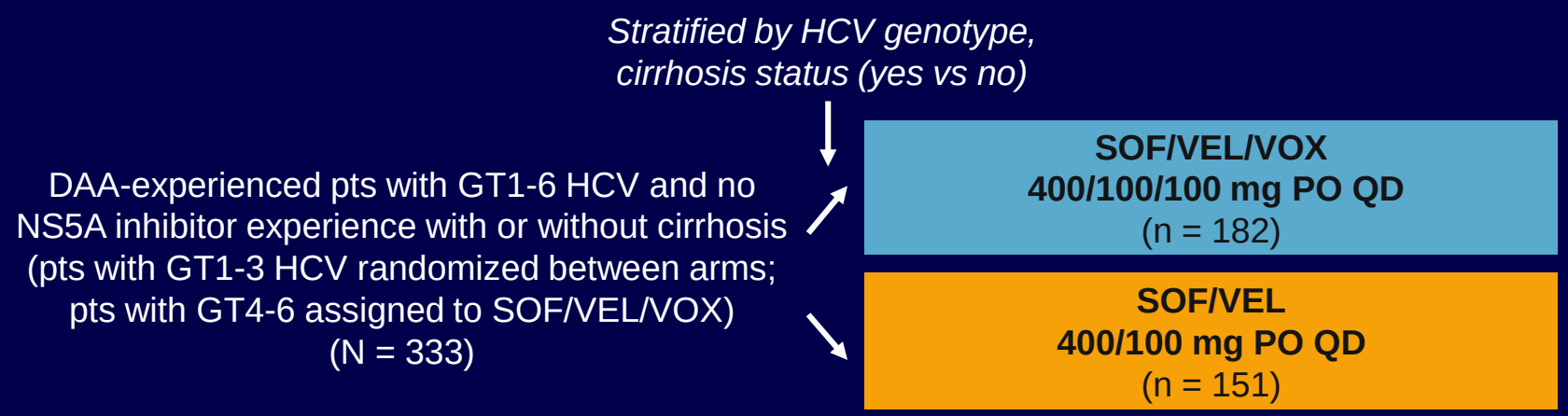
POLARIS-1 and -4: SOF/VEL/VOX in DAA-Experienced Pts

POLARIS-1: randomized, double-blind, placebo-controlled phase III trial[1,2]



POLARIS-4: randomized, open-label, active-controlled phase III trial[1,3]



References in slidenotes.

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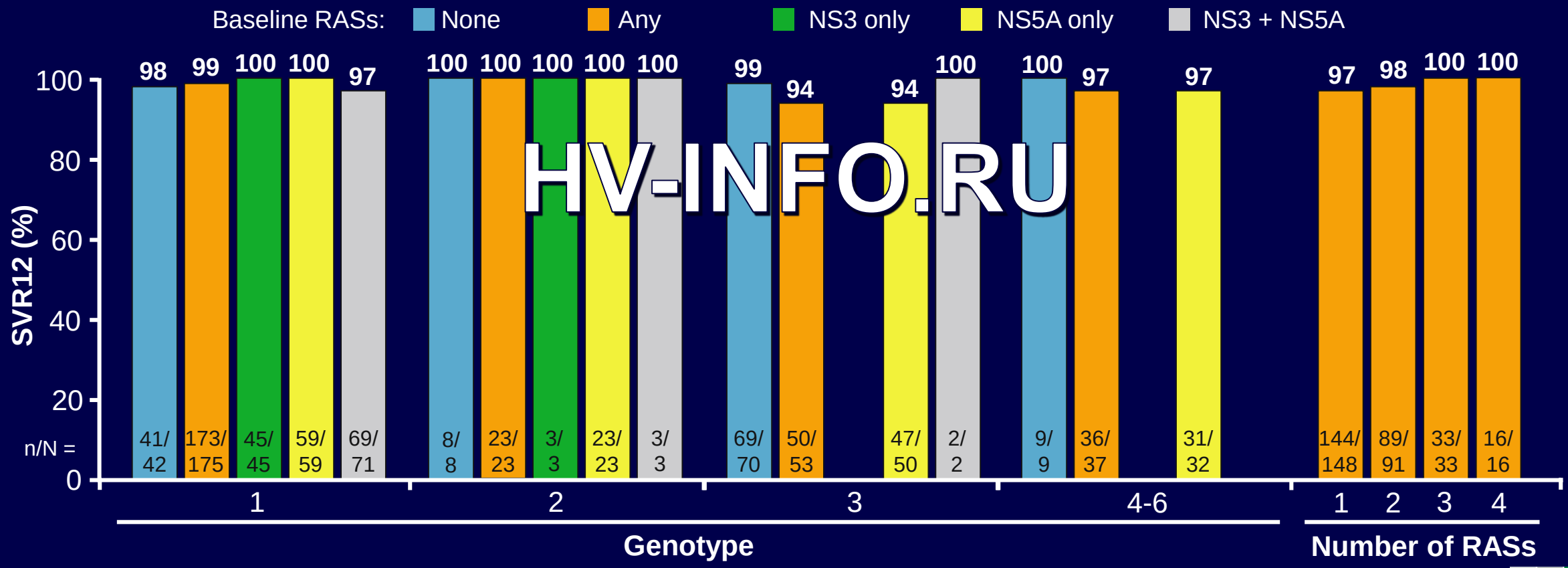
POLARIS-1 and -4: Impact of Baseline RASs on 12-Wk SOF/VEL/VOX in DAA-experienced Pts

- Integrated analysis of data from SOF/VEL/VOX arms of 2 phase III trials of DAA-experienced pts with (n = 263) and without (n = 182) previous NS5A inhibitors, 46% with cirrhosis



Sarrazin C, et al. EASL 2017. Abstract THU-248. Reproduced with permission.

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Investigational NASH Treatments

Histologic Predictors of Progression in NASH

- In pts with bridging fibrosis (Metavir F3), 21.5% progressed to cirrhosis after median follow-up of 24.9 mos
  - No difference in progression between Ishak 3 vs 4 (*P* = .39)
  - BL ballooning score 2 vs 0 associated with progression (aHR: 7.30; 95% CI: 1.72-30.91; *P* = .007)
- Risk of progression increased with greater ELF and hepatic collagen

Parameter	HR (95% CI)	*P* Value
Hepatic collagen, per 5%		
▪ BL	3.28 (2.31-4.85)	< .001
▪ Change from BL	2.99 (2.36-3.78)	< .001
ELF		
▪ BL	3.13 (2.31-4.22)	< .001
▪ Change from BL	1.59 (1.18-2.13)	.002

- In pts with cirrhosis (Metavir F4), 19.0% had a liver-related clinical event after median follow-up of 26.7 mos
  - No difference for Ishak 5 vs 6 (*P* = .50)
- Increased risk of liver-related clinical events with higher BL hepatic collagen and ELF, worsening of fibrosis

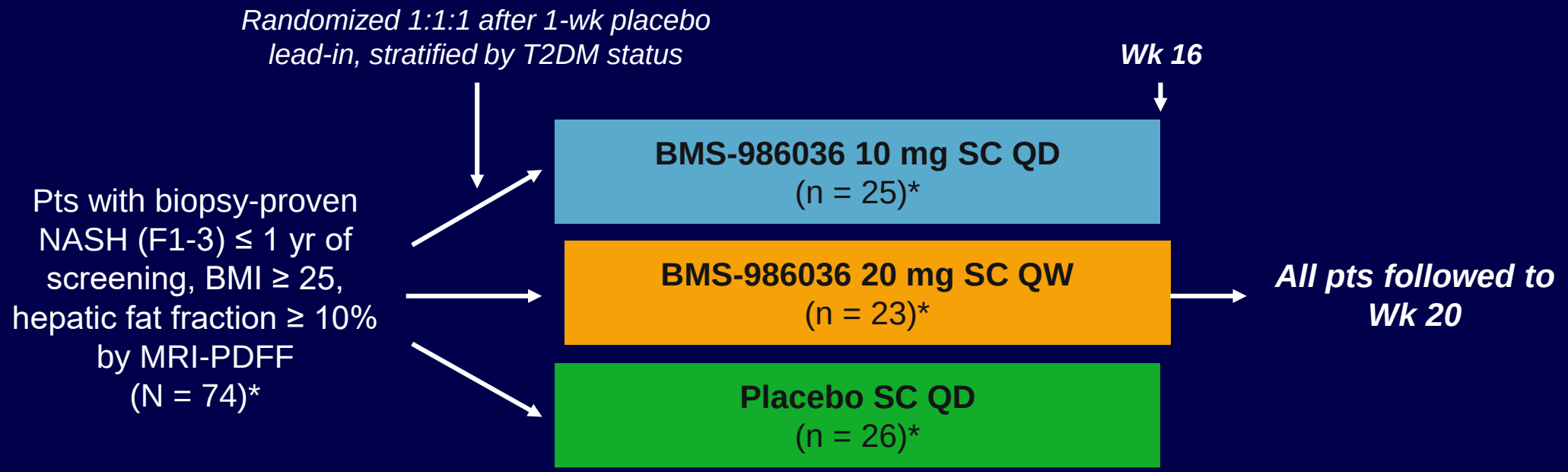
Parameter	HR (95% CI)	*P* Value
BL Ishak stage 5 vs 6	1.25 (0.68-2.29)	.48
No improvement vs improvement	9.63 (1.33-69.81)	.025
Hepatic collagen, per 5%		
▪ BL	1.38 (1.15-1.69)	< .001
▪ Change from BL	1.20 (1.03-1.39)	.017
ELF		
▪ BL	2.37 (1.69-3.31)	< .001
▪ Change from BL	1.54 (1.10-2.15)	.002

Sanyal AJ, et al. EASL 2017. Abstract GS-004.

Slide credit: clinicaloptions.com

Pegylated FGF21 Analogue BMS-986036 in Pts With NASH After 16 Wks

- Multicenter, randomized, double-blind, placebo-controlled phase II trial



*Enrollment stopped before planned 30 pts per arm due to significant effect on primary endpoint in preplanned interim analysis at Wk 8.

- Primary endpoint: change in hepatic fat fraction from BL to Wk 16 (not a histological endpoint)
- Exploratory endpoints: adiponectin, lipids, ALT, AST, MRE, serum Pro-C3
- Safety endpoints: AEs, laboratory parameters, vital signs

Sanyal A, et al. EASL 2017. Abstract LBO-02.

Slide credit: clinicaloptions.com

BMS-986036 in Pts With NASH After 16 Wks: Efficacy and Safety

- Significant reduction in hepatic fat fraction with BMS-986036 QD and QW vs placebo

Change in Liver MRI-PDFF, %	BMS-986036		Placebo (n = 24)
	10 mg QD (n = 23)	20 mg QW (n = 21)	
Mean absolute change	-6.8*	-5.2*	-1.3
≥ 30% relative reduction	57*	52	25
≥ 20% relative reduction	65	71	42
≥ 10% relative reduction	83	76	54

*P < .05 vs placebo arm (not adjusted for multiple comparisons).

- Significantly greater increase from BL in adiponectin with BMS-986036 QD and QW vs placebo (+15.3% vs +15.9% vs -2.3%, respectively; all P < .01)

- Triglycerides and HDL levels improved from BL with BMS-986036 QD and QW vs no meaningful changes from BL with placebo

- No deaths, treatment-related serious AEs, or AE-related discontinuations

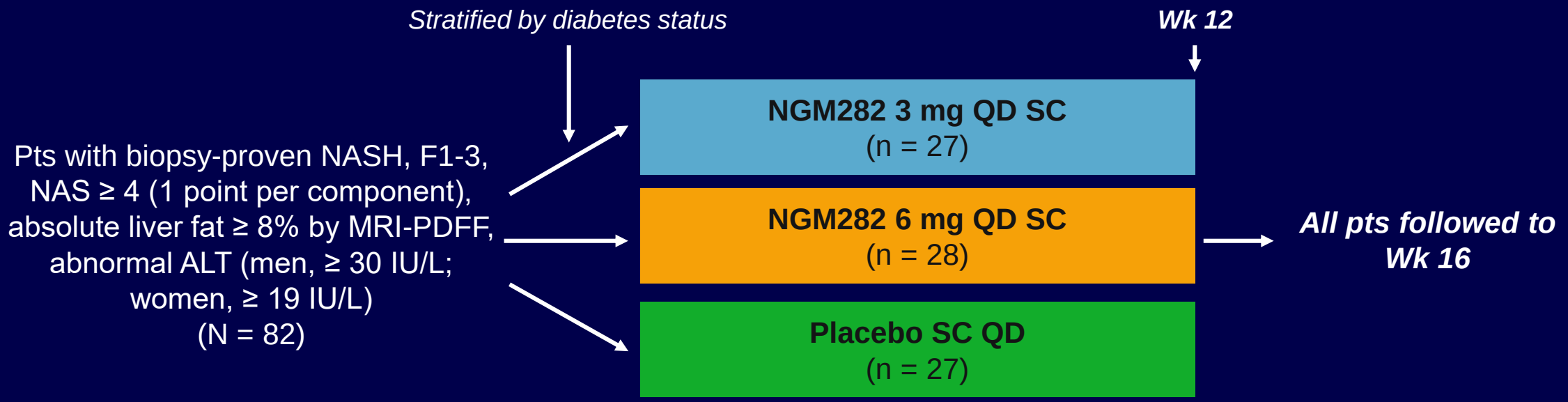
Event, n (%)	BMS-986036		Placebo (n = 26)
	10 mg QD (n = 25)	20 mg QW (n = 23)	
Serious AEs	1 (4)	0	1 (4)
AEs in ≥ 10% of pts			
▪ Diarrhea	3 (13)	5 (22)	2(8)
▪ Nausea	4 (16)	3 (13)	2(8)
▪ Frequent bowel movements	5 (20)	0	0
Treatment-emergent grade 3/4 lab abnormalities	1 (4)	2 (9)	2 (8)

Sanyal A, et al. EASL 2017. Abstract LBO-02.

Slide credit: clinicaloptions.com

FGF19 Variant NGM282 in Pts With NASH After 12 Wks

- International, randomized, double-blind, placebo-controlled phase II trial



- Primary endpoint: decrease ≥ 5% in absolute liver fat content (not a histological endpoint)
- Other endpoints: Absolute liver fat content normalization to < 5%, ALT, C4 levels, triglycerides, LDL, antifibrotic markers, safety

Harrison SA, et al. EASL 2017. Abstract LBO-07.

Slide credit: clinicaloptions.com

NGM282 in Pts With NASH After 12 Wks: Efficacy and Safety

- 79% of NGM282-treated pts had absolute decrease in LFC > 5% (decrease greatest in pts with most active disease)
  - ALT normalized in 36% of NGM282-treated pts

Outcome at Wk 12	NGM282		Placebo (n = 27)
	3 mg (n = 27)	6 mg (n = 26)	
Response*, %	74	85	7
Normalization†, n (%)	7 (25.9)	11 (42.3)	0

*Decrease in liver fat content of ≥ 5%
†Decrease in liver fat content to < 5%

- NGM282 CYP7A1 inhibition reflected by significant C4 decreases and LDL increases
- NGM282 antifibrotic activity suggested by significant decreases in PIINP, TIMP-1

Tx-Emergent AE in > 10% Pts, %*	NGM282		Placebo (n = 27)
	3 mg (n = 27)	6 mg (n = 28)	
Injection-site rxn	40.7	53.6	7.4
Diarrhea	40.7	35.7	22.2
Abdominal pain	29.6	17.9	7.4
Nausea	33.3	14.3	3.7
Headache	11.1	17.9	18.5

*Also included: abdominal distension, vomiting, frequent bowel movements, increased appetite, constipation, injection-site bruising, and decreased weight.

- 1 serious AE (acute pancreatitis)

Harrison SA, et al. EASL 2017. Abstract LBO-07.

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