HCV Drug Resistance Figure and Table Update PAWG

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Objectives

Compilation of HCV Drug Resistance Data for:
- Compounds approved
- Compounds in Phase 3

1. Figure showing most common HCV DAA resistance associated variants (RAVs)

2. Table containing drug susceptibility data for key HCV resistance mutations
   - Frequent: Observed in ≥ 10 % treatment failure patients
   - Infrequent if observed in less than 10%
   - Published phenotypic drug susceptibility data

Content of Figure

- Resistance associated variants (RAVs):
  - In vivo data
  - In vitro data only IF no in vivo data available (i.e PSI-7977)
  - Quick reference
    - Mutations observed in ≥ 10 % of treatment failure patients
    - Infrequent mutations (<10%) will be noted
    - Subtype (GT1a/1b) specific RAMs will be noted
  - Linked to tabular data and references

Figure: NS5A and Nucleoside RAVs

NS5A Domain I (213 aa)

BMS-790052 — M28T, R30Q, L31F/M/V, P32L, Y93C/H/N
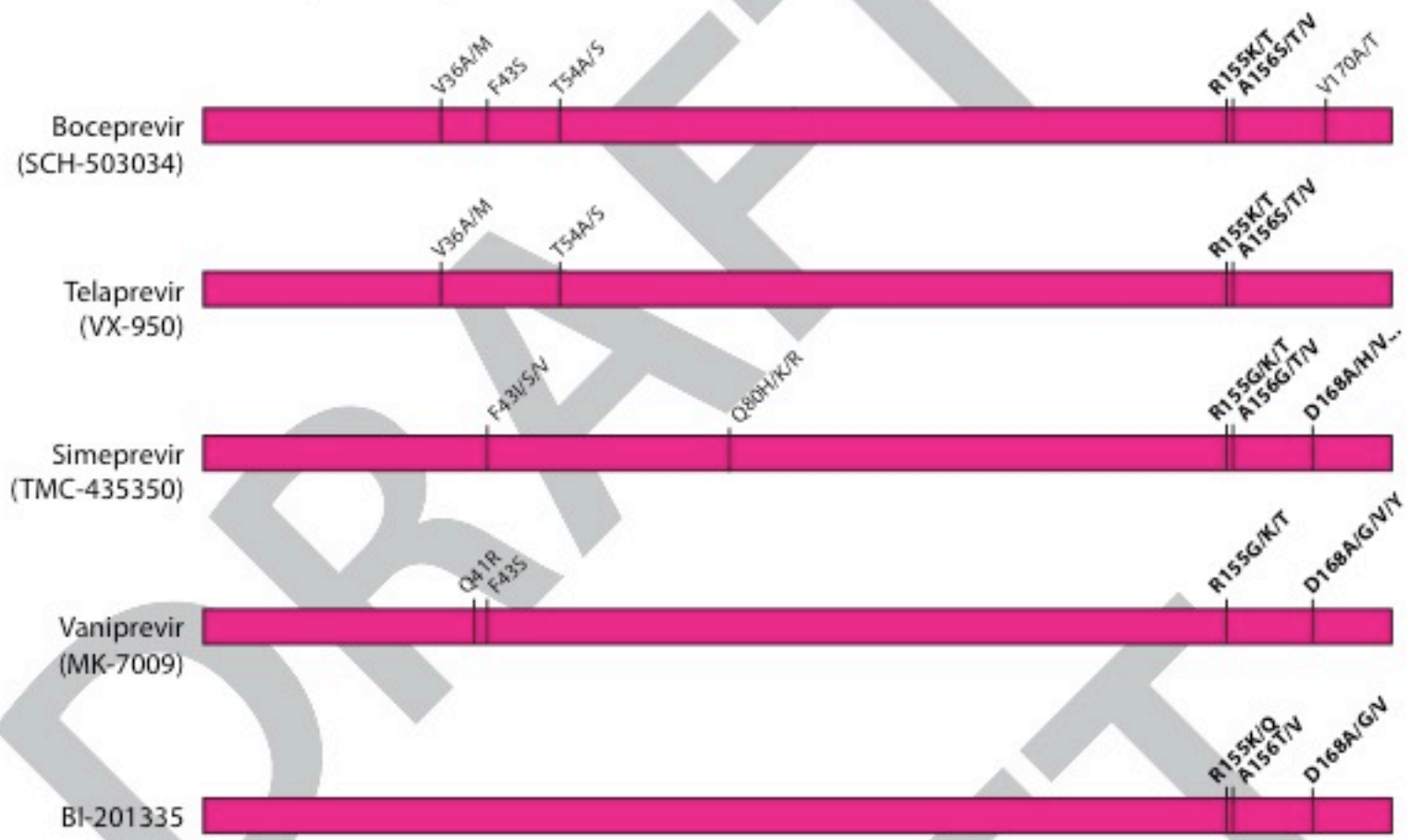
NS5B Polymerase (591 aa)

PSI-7977 — S282T

Footnotes will note:
- subtype specific mutations
- Bold will depict frequent ≥ 10 % TF patients
- Non bold: observed in <10 % or that persist after treatment
- If In vitro only

Figure: Protease Inhibitors RAVs

Content of the Table

- NS3, NS5A and NS5B inhibitor RAVs
  - compounds <u>approved</u> or in <u>Phase 3</u>
- Phenotypic data included:
  - replicon vector (name, subtype)
  - cell type
  - mean EC_{50} +SD
  - mean fold-resistance + SD
  - replicates (N)
  - citation(s)
  - key assay parameters (duration, read out, transient or stable, etc.)

Image of Table

Drug manufacturer	Compound generic name	Compound aka 1	target enzyme	Compound class	resistance mutation	replicon vector	Genotype of replicon vector	cell type	replicates (N)	mean EC50 (µM)	EC50 SD	mean fold-resistance	FR SD
Merck	boceprevir	SCH-503034	NS3	PI	none	modified Bartenschlager Con1 clone	1b	Huh 7		0.18		1.0	
Merck	boceprevir	SCH-503034	NS3	PI	R155K	modified Bartenschlager Con1 clone	1b	Huh 7		0.65		3.6	
Merck	boceprevir	SCH-503034	NS3	PI	A156S	modified Bartenschlager Con1 clone	1b	Huh 7		4.3		24	
Merck	boceprevir	SCH-503034	NS3	PI	A156T	modified Bartenschlager Con1 clone	1b	Huh 7		23		128	
Merck	boceprevir	SCH-503034	NS3	PI	V170A	modified Bartenschlager Con1 clone	1b	Huh 7		3.4		19	
Vertex	telaprevir	VX-950	NS3	PI	none	pBR322-HCV-Neo-mADE	1b	Huh 7	15	0.48	0.12	1.0	0.30
Vertex	telaprevir	VX-950	NS3	PI	R155K	pBR322-HCV-Neo-mADE	1b	Huh 7	3	3.6	0.28	7.4	0.60
Vertex	telaprevir	VX-950	NS3	PI	R155T	pBR322-HCV-Neo-mADE	1b	Huh 7	3	9.6	0.87	20	1.8
Vertex	telaprevir	VX-950	NS3	PI	R155M	pBR322-HCV-Neo-mADE	1b	Huh 7	3	2.7	0.21	5.6	0.40
Vertex	telaprevir	VX-950	NS3	PI	A156S	pBR322-HCV-Neo-mADE	1b	Huh 7	1	4.7	-	9.6	-
Vertex	telaprevir	VX-950	NS3	PI	A156T	pBR322-HCV-Neo-mADE	1b	Huh 7	1	>30	-	>62	-
Vertex	telaprevir	VX-950	NS3	PI	A156V	pBR322-HCV-Neo-mADE	1b	Huh 7	1	>30	-	>62	-
Vertex	telaprevir	VX-950	NS3	PI	V170A	pBR322-HCV-Neo-mADE	1b	Huh 7	3	1.3	0.28	2.6	0.60
Vertex	telaprevir	VX-950	NS3	PI	V36M+R155K	pBR322-HCV-Neo-mADE	1b	Huh 7	3	~31	-	~64	-
BI		BI-201335	NS3	PI	none	129S, H77	1a	Huh 7	7	0.0065	0.0009	1.0	
BI		BI-201335	NS3	PI	D168V	129-S.16	1a	Huh 7	14	8.7	2.5	620	180
BI		BI-201335	NS3	PI	R155K	129-S.16	1a	Huh 7	11	5.0	1.3	360	90
BI		BI-201335	NS3	PI	none	S22.3, Con1	1b	Huh 7	9	0.0031	0.0012	1.0	
BI		BI-201335	NS3	PI	none	pIT2, Con1	1b	Huh 7	79	0.013	0.0042	1.0	
BI		BI-201335	NS3	PI	A156V	pIT2, Con1	1b	Huh 7	3	1.5	0.096	150	10
BI		BI-201335	NS3	PI	R155Q	R3	1b	Huh 7	4	0.30	0.043	60	9
BI		BI-201335	NS3	PI	R155K	716	1b	Huh 7	3	1.8	0.071	350	14
BI		BI-201335	NS3	PI	A156T	R3	1b	Huh 7	9	1.4	0.49	270	98
BI		BI-201335	NS3	PI	D168G	S22.3-7/44	1b	Huh 7	7	0.38	0.13	80	30
BI		BI-201335	NS3	PI	D168A	R3	1b	Huh 7	5	3.5	1.7	690	332
BI		BI-201335	NS3	PI	D168V	716	1b	Huh 7	7	4.9	1.3	970	256
Tibotec	simeprevir	TMC-435350	NS3	PI	WT	Con1 clone ET	1b	Huh7 lunet		0.011		1.0	
Tibotec	simeprevir	TMC-435350	NS3	PI	R155K	Con1 clone ET	1b	Huh7 lunet		0.26		30	
Tibotec	simeprevir	TMC-435350	NS3	PI	A156G	Con1 clone ET	1b	Huh7 lunet		0.21		16	
Tibotec	simeprevir	TMC-435350	NS3	PI	A156T	Con1 clone ET	1b	Huh7 lunet		0.38		44	
Tibotec	simeprevir	TMC-435350	NS3	PI	A156V	Con1 clone ET	1b	Huh7 lunet		2.1		177	
Tibotec	simeprevir	TMC-435350	NS3	PI	D168N	Con1 clone ET	1b	Huh7 lunet		0.079		6.6	
Tibotec	simeprevir	TMC-435350	NS3	PI	D168E	Con1 clone ET	1b	Huh7 lunet		0.30		40	
Tibotec	simeprevir	TMC-435350	NS3	PI	D168T	Con1 clone ET	1b	Huh7 lunet		4.1		308	
Tibotec	simeprevir	TMC-435350	NS3	PI	D168Y	Con1 clone ET	1b	Huh7 lunet		6.2		666	
Tibotec	simeprevir	TMC-435350	NS3	PI	D168H	Con1 clone ET	1b	Huh7 lunet		5.7		368	
Tibotec	simeprevir	TMC-435350	NS3	PI	D168A	Con1 clone ET	1b	Huh7 lunet		6.4		594	
Tibotec	simeprevir	TMC-435350	NS3	PI	D168V	Con1 clone ET	1b	Huh7 lunet		18		2591	
Tibotec	simeprevir	TMC-435350	NS3	PI	D168I	Con1 clone ET	1b	Huh7 lunet		23		1807	
Tibotec	simeprevir	TMC-435350	NS3	PI	F43S+Q80R	Con1 clone ET	1b	Huh7 lunet		1.8		286	
Tibotec	simeprevir	TMC-435350	NS3	PI	F43S+D168E	Con1 clone ET	1b	Huh7 lunet		3.6		694	
Tibotec	simeprevir	TMC-435350	NS3	PI	Q80K+R155K	Con1 clone ET	1b	Huh7 lunet		4.6		364	
Tibotec	simeprevir	TMC-435350	NS3	PI	Q80R+R155K	Con1 clone ET	1b	Huh7 lunet		2.9		270	
Tibotec	simeprevir	TMC-435350	NS3	PI	Q80R+D168E	Con1 clone ET	1b	Huh7 lunet		5.9		412	
Tibotec	simeprevir	TMC-435350	NS3	PI	Q80H+D168E	Con1 clone ET	1b	Huh7 lunet		1.4		163	
Tibotec	simeprevir	TMC-435350	NS3	PI	Q80R+D168A	Con1 clone ET	1b	Huh7 lunet		17		2655	

Publication Plan

- *Annals of the Forum for Collaborative HIV Research* (online publication)
- Forum website: high level overview with the ability to look at the data in greater detail
  - Mutations and drugs linked to details in data table
  - Table can be sorted and filtered by user
  - Links to external sites/databases e.g. LANL, euHCVdb, Japanese HCV db...
- Timelines:
  - Figure and Table to be placed in Basecamp by mid May for final approval of information
  - Publication by mid June
  - Update bi-annually (tentative)

Discussion Points for PAWG 2012

- In the DAA COMBO era:
  - Need to include cross resistance "note" in table/figure?

- How to link resistance data to clinical outcome:
  - Baseline vs On-treatment resistance
    - Need to differentiate?
  - IFN free vs IFN containing regimens
  - Information on persistence of RAVs?