SUPPLEMENTAL MATERIAL

Supplementary Table 1: Therapies and Outcomes for Newly Diagnosed AL Patients

Therapy	Trial or Series	N	Deaths within 100 days (%)	CR + VGPR (%)	PFS (yrs)	OS (yrs)	Cardiac/Renal Responses (%)
SCT[1]	Series	421	11.4	CR = 34	2.6	6.3	NR
SCT+ BorDex[2]	Trial (NCT00458822)	41	10	CR = 58	NR		52/53
CyBorD[3]	Series	230	13	43	1.1	> 5	17/23
CTD [4]	Series	69	NR	46	1.2	NR	19/39
Oral Melphalan/Dex[5]	Trial	46	0	CR = 33	3.8	5.1	19/48

Bor = bortezomib; CR = complete hematologic response; Cy = oral cyclophosphamide; D or Dex = dexamethasone; NR = not reported; OS = overall survival; PFS = progression-free survival; SCT = stem cell transplant

Supplementary Table 2: Clinical Trials for TTR Amyloidosis

Agent	Patient Population	Citation/ NCT #	Phase	Design	Enrollment (N)	Exposure	Primary Outcome	Efficacy	Safety
Diflunisal	ATTRm with peripheral neuropathy (~50% had cardiac involvement)	[6,7]	Phase III	Multicenter, Randomized Double Blind Placebo Controlled	130	Diflunisal 250 mg PO BID (n=64) vs. Placebo (n=66) for 24 months	NIS+7 at 24 months	Mean NIS+7 difference between diflunisal and placebo of 16.3 points, P<0.001 Mean SF-36 physical and mental scores improved with diflunisal but deteriorated with placebo No significant reduction in LV wall thickness or longitudinal strain in patients with cardiac involvement compared with placebo.	Similar SAEs in both groups. Did not observe a significant rate of GI bleed or volume overload.
	ATTRwt and ATTRmt cardiac amyloidosis	[8]	Phase II	Single Center Open label Non-randomized	13	Diflunisal 250 mg PO BID	Changes in LVEF, MCF and LV Mass. Changes in hemoglobin, creatinine, mBMI	No change in LVEF, LV mass or Myocardial contraction fraction.	Stable hemoglobin and platelet counts Decline in eGFR of 6% (non-significant) which was related to duration of diflunisal exposure.
Tafamidis	Val30Met, Stage I, ATTR-FAP	[9]	Phase II/III	Multicenter, Randomized, Double Blind, Placebo controlled	128	1:1 allocation to tafamidis 20 mg (n=65) or placebo (n=63) for 18 months	Co-primary: NIS-LL response and Total QOL by the Norfolk Quality of Life-Diabetic Neuropathy total score	Intention to treat: NIS-LL responders with Tafamidis (45.3%) vs. placebo (25.9%): p=0.068) Efficacy Evaluable: Tafamidis (60.0%) vs. placebo (38.1%), p=0.041. Intention to treat TQoL change Tafamidis 2.0 vs. placebo 7.2, p=0.116), Efficacy Evaluable: Tafamidis 0.1 vs placebo 8.9, p=0.045)	SAEs (8-9%) and AEs did not differ Higher rate of UTI, vaginal infections and diarrhea in tafamidis arm

	Same as above	[10]	Phase III/IV-OLE	Open label extension for 12 months	86	Tafamidis 20 mg	NIS-LL, QOL, neurologic function and mBMI	Stable NIS-LL and TQOL in those that continued on tafamidis. Decline in NIS-LL (from 0.34 to 0.16/month; p = 0.01) and TQOL score (from 0.61 to -0.16; p < 0.001) in those that switched to tafamidis from placebo. Early treatment with tafamidis was associated with 55.9 % greater preservation of neurologic function than later treatment.	No new safety signal during longer term use
	Non-Val30Met and Non-Val122Ile Mutations	[11]	Phase II	Multicenter, Open label Non randomized	21	Tafamidis 20 mg for 12 months	TTR stabilization at 6 weeks compared to baseline	TTR stabilization in 94.7% at 6 weeks. NIS score worsened at month 12 No change in QoL or mBMI at month 12	SAE in 4 subjects Most common AE were falls, diarrhea and extremity pain
	ATTRwt (n=31) and Val122Ile (n=4)	[12]	Phase II	Multicenter Open label Non-randomized	35	Tafamidis 20 mg for 12 months	TTR stabilization at 6 weeks compared to baseline	TTR stabilization in 97.1% at week 6 48.4% had clinical progression NT-pro-BNP levels did not increase significantly, troponin I and troponin T increased moderately No consistent clinically relevant changes were seen in echocardiographic cardiac assessments	Tafamidis treatment was generally well tolerated although 7 of 31 patients had bouts of diarrhea.
	Same as above	[13]	Phase II-OLE	Multicenter Open label Non-randomized	31	Tafamidis 20 mg	Clinical events, biomarkers and	Survival of 49% at five years. Stable biomarkers and echocardiographic measures till	No new safety signals, well tolerated.

								36 months	
	ATTRm with Stage ≥ 2 FAP	[14]	Phase II	Single Center Open label Non-randomized	37	Tafamidis 20 mg for 12 months	NIS-LL and NIS-UL scores and disability scores.	93% of patients deteriorated on disability or NIS parameters	AEs included febrile UTIs, diarrhea and fecal incontinence
	ATTRm and ATTRwt Cardiac amyloid	NCT 01994889	Phase III	Multicenter, International, Double-Blind, Placebo-Controlled, Randomized	441	Tafamidis 20mg or 80mg for 30 months Placebo PO QD x 30 months	All-cause mortality and frequency of cardiovascular-related hospitalization	Discontinued development of drug	N/A
Patisiran	Healthy Volunteers	[15]	Phase 1	Dose Escalation study Placebo controlled	17	Patisiran 0.01 – 0.5 mg/kg or placebo	Safety, Pharmacokinetics Pharmacodynamics	Dose-dependent reductions in serum TTR with patisiran Maximal TTR mean knockdown of ~ 90% with single dose of patisiran0.3 – 0.5 mg/kg	No SAEs reported Skin erythema was most common AE but did not differ between patisiran 46% and placebo 50%.
	ATTRm FAP Stage I or II	[16]	Phase II	Dose Escalation	29	Patisiran at 0.01 – 0.3 mg/kg every 4 weeks and 0.3 mg/kg every 3 weeks	Safety, Pharmacokinetics Pharmacodynamics	Dose-dependent reductions in serum TTR following 2 doses of Patisiran. Mean maximal TTR knockdown of ~85% with two doses of Patisiran 0.3 mg/kg. TTR knockdown not affected by concurrent use of Diflunisal or Tafamidis	SAE observed in 1 patient at 0.3 mg/kg dose No significant lab abnormalities. Most common AEs were infusion-related reactions (10% overall)
	ATTRm FAP Stage I or II	[17]	Phase II	OLE	28	Patisiran at 0.3mg/kg every 2 weeks for 2 years	Safety and tolerability. mNIS+7, NIS, cardiac involvement, autonomic symptoms, QoL (EQ-5D) and serum TTR levels	TTR mean knockdown at 87% and sustained over 18 months Decrease in mNIS+7 of 0.8 points at 18 months Those with associated cardiomyopathy (N=11) showed stability in their echocardiographic, biomarker, and functional measures,	Infusion-related reactions in 18.5% of patients SAEs in 3 patients but not related to study drug) No significant lab abnormalities

								including 10-meter-walk speed.	
	ATTRm FAP NIS ranging from 5-130	NCT 01960348	Phase 3	Multicenter, Multinational, Randomized, Double-blind, Placebo-controlled	225	ALN-TTR02 IV infusion vs Normal Saline IV infusion 2:1 allocation to patisiran	Difference between ALN-TTR02 and placebo in the change from baseline of mNIS+7	Anticipated 2017	N/A
Reuvsiran *Discontinued development of drug*	Healthy Volunteers	[18]	Phase 1	Dose escalation	41	Reuvsiran 1.25–10 mg/kg SQ as single or multiple doses	Safety, Pharmacokinetics Pharmacodynamics	Dose-dependent TTR knockdown Mean maximal TTR knockdown of ~90% with multiple dosing of Reuvsiran 7.5-or 10 mg/kg	No SAEs and no significant laboratory abnormalities Mild to moderate infusion-related reactions were most common AEs.
	ATTRm and ATTRwt Cardiac amyloid	[19]	Phase 2	Open label	26	Reuvsiran at 500 mg x 5 days SQ, then every week for 5 weeks	Pharmacodynamics Echo, 6MWT, NYHA, CMR, NT-proBNP, KCCQ, EQ-5D	Knockdown of serum TTR levels by ~ 90% with multiple dosing, which was similar in ATTRwt and ATTRm. Echo, MRI, biomarkers and 6MWD stable to day 90	All treatment related AEs of mild intensity No significant laboratory abnormalities observed Transient injection-site reactions in 23% of patients
	ATTRm and ATTRwt Cardiac amyloid		Phase 2	Open label extension	25	Reuvsiran at 500 mg/week Apply to dose reduce to 250 mg/week	Safety and tolerability of long term dosing with revusiran	Effect on serum TTR and on mortality, hospitalization and 6-minute walk distance (6-MWD) Pharmacokinetics and effects on cardiac biomarkers, cardiac imaging, NYHA class, KCCQ, and Quality of Life (EQ-5D	New or worsening peripheral neuropathy in 13 subjects typically after 10 or more months on therapy. Lactic acidosis observed in five subjects. 14 stopped study drug most commonly due to disease progression (n=3) or death (n=5) . 15(56%) had SAE but only 1 possibly related to study drug. Mean knockdown of 88%

	ATTRm Cardiac Amyloid	NCT 02319005	Phase 3	Randomized, Double Blind Placebo Controlled	200	Reuvsiran at 500 mg x 5 days, then every week for 5 weeks vs. placebo. 2:1 allocation to revusiran	Change in 6MWT and serum TTR levels	Discontinued development of drug	Imbalance of mortality in the revusiran arm as compared to placebo
Ionis TTR Rx	Healthy volunteers	[20]	Phase I	Dose ranging Study	NR	Ionis-TTR_{Rx} 50 – 400 mg or Placebo as single or multiple doses	Safety, Pharmacokinetics Pharmacodynamics	Dose-dependent reductions in serum TTR with Ionis-TTR_{Rx} Mean reduction of ~80% with Ionis-TTR_{Rx} at 300 and and 400 mg dosing.	No SAEs reported and no significant lab abnormalities. Most common AEs were injection-site pain
	ATTRm with FAP	NCT 01737398	Phase II/III	Randomized, Double-Blind, Placebo-Controlled Multicenter	195	Ionis TTR_{Rx} 300mg SQ TID x1 week, then every week x 16 months vs. placebo. 2:1 allocation to Ionis-TTR_{Rx}	Change from baseline in mNIS+7 and Norfolk QOL Diabetic Neuropathy questionnaire Exploratory of echo and NT-pro-BNP	Anticipated 2018	Severe thrombocytopenia with life threatening bleeding reported.
	ATTRm and ATTRwt cardiac amyloid	[21]	II	Open-Label, Non-randomized	20	Ionis TTR_{Rx} 300mg SQ qweek	Echo and cardiac MRI measures in comparison to historical controls	6 subjects completed 12 months, 15 subject completed 6 months, 1 heart transplant No progression of strain and LV mass decline of ~5%	Well tolerated with no major SAEs.
	ATTRm and ATTRwt cardiac amyloid	NCT 02627820	II	Open Label Non-randomized	50	ISIS TTR Rx 300mg SQ TID x1 week, then every week x 18 months	Systolic strain imaging by echo speckle tracking	On hold	N/A
	ATTRm and ATTRwt cardiac amyloid	NCT	Phase III	Randomized, Double blind, Placebo-controlled Multicenter	490	ISIS TTR Rx 300mg SQ TID x1 wk, then qweek x 16 months Placebo SQ TID x 1wk, then qweek for 24 months 2:1 allocation to	Death, cardiac transplant or cardiovascular (CV) hospitalization	On hold	N/A

						ISIS-TTRrx			
Doxycycline + TUDCA	ATTRmt and ATTRwt	NCT 01171859	Phase II	Open-label, Non-randomized Prospective Study	40	Doxycycline 100mg BID + TUDCA 250mg TID for 12 months	Response if: mBMI reduction <10% and change in NIS-LL<2 in subjects with neuropathy and mBMI reduction <10% and increase in NT-pro BNP concentration <30% or <300 pg/mL in subjects with isolated cardiomyopathy	Stable cardiac disease was observed in 75% and stable neuropathy in 46% of patients.	Generally well tolerated, Mild persistent skin redness 4 patients discontinued by 12 months due to gastrointestinal events.
	TTR Cardiac Amyloid	NCT 01855360	Phase II	Open Label Non-randomized Prospective Study Historical Controls	40	Doxycycline 100mg BID + TUDCA 250mg TID for 18 months	Changes in longitudinal strain echo assessed every 6 months compared with historical controls	30 patients (all but 3 with ATTRwt) enrolled > 12 months Controls had greater % decline in strain that treated, p=0.006 NT-proBNP increased in treated.	3 died, 2 technically inadequate follow-up echocardiograms, 1 had pacemaker inserted and 2 unable to tolerate therapy.
	Amyloid both AL, ATTm and ATTwt	NCT 01677286	Phase II	Open Label Non-randomized Prospective study	60	Doxycycline 100 mg PO bid x 12 months	Composite measures specific to the organ system affected. For cardiomyopathy: cardiac biomarkers (BNP, Troponin I), echo parameters (IVSd, longitudinal strain, diastolic indices [e/e']), ECG	Data from 25 patients(10 AL, 6 ATTRwt, 3 ATTRm and 6 others) showed increases in BNP after 12 months, no change in troponin I; No change in IVSd, LVEF nor VO2 max	60% experienced dermatologic complications. Sun hypersensitivity and GI complaints limited administration in over 30% of cohort.
EGCG	ATTR-CM	[22]	Phase II	Open label Non-randomized Prospective	19	500–700 mg EGCG	Blood tests, echo and cardiac MRI (n = 9)	No increase of LV wall thickness and mass by echo. In the subgroup of patients evaluated by cardiac MRI LV mass decreased by 12.5%	2 subjects discontinued GT/GTE consumption No SAEs

	ATTRwt	[23]	Phase II	Open label Non-randomized Prospective	25	600 mg EGCG for 12 months	Blood tests, echo and cardiac MRI (n=14)	Decrease in LV mass by 6% p=0.03 by cMRI. LVEF, LV wall thickness and MAPSE by echocardiography remained unchanged	

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