5th Congress of the European Academy of Neurology

Oslo, Norway, June 29 - July 2, 2019

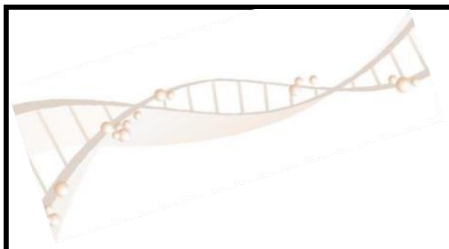
Teaching Course 11

Current treatment in neurology (Level 1)

Examples of successful gene treatment - FAP

Laura Obici
Pavia, Italy

Email: L.Obici@smatteo.pv.i



ean congress Oslo 2019
5th Congress of the European Academy of Neurology
June 29 – July 2

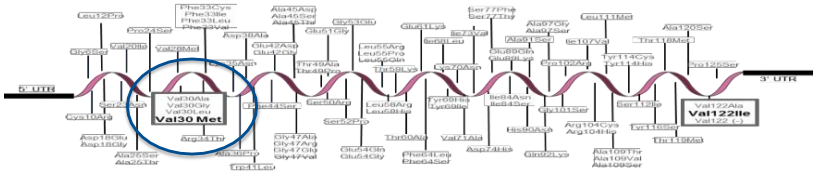
Examples of successful gene treatment: Familial Amyloid Polyneuropathy (ATTR-FAP)

Laura Obici, MD
Amyloidosis Research and Treatment Centre
Fondazione Policlinico San Matteo, Pavia, Italy
l.obici@smatteo.pv.it

Disclosure

Acknowledges speaker honoraria from Pfizer, Akcea and Alnylam Pharmaceuticals

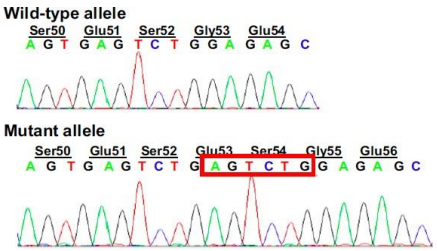
Mutations in the *TTR* gene cause hereditary systemic amyloidosis



Worldwide distribution of Val30Met ATTR-FAP

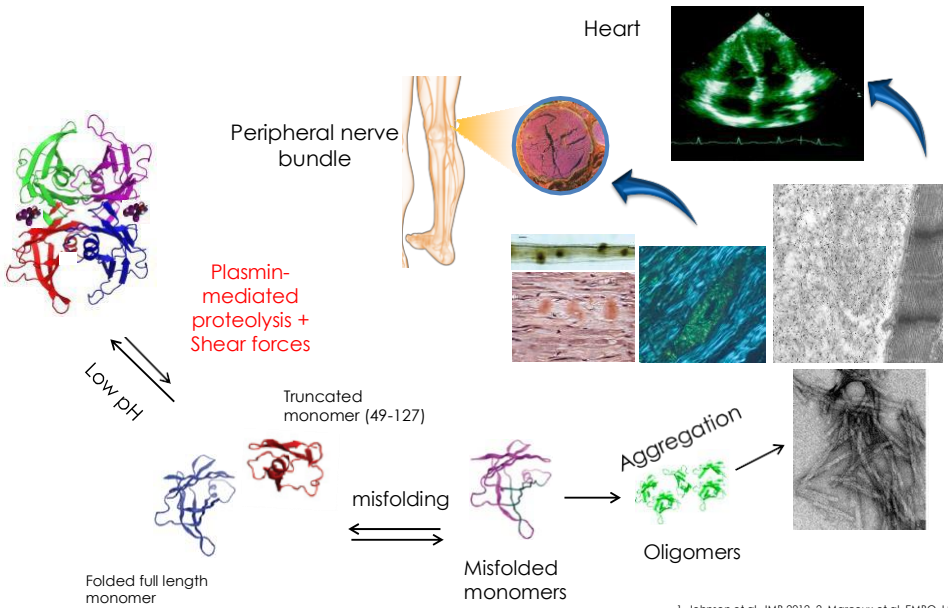
Unusual duplication mutation in a surface loop of human transthyretin leads to an aggressive drug-resistant amyloid disease

Elena S. Klimtchuk[a], Tatiana Prokaeva[a,1], Nicholas M. Frame[b,1], Hassan A. Abdullahi[a], Brian Spencer[a], Surendra Dasari[c], Haili Cui[a,d], John L. Berk[a], Paul J. Kurtin[e], Lawreen H. Connors[a,d,2], and Olga Gursky[a,b,2]



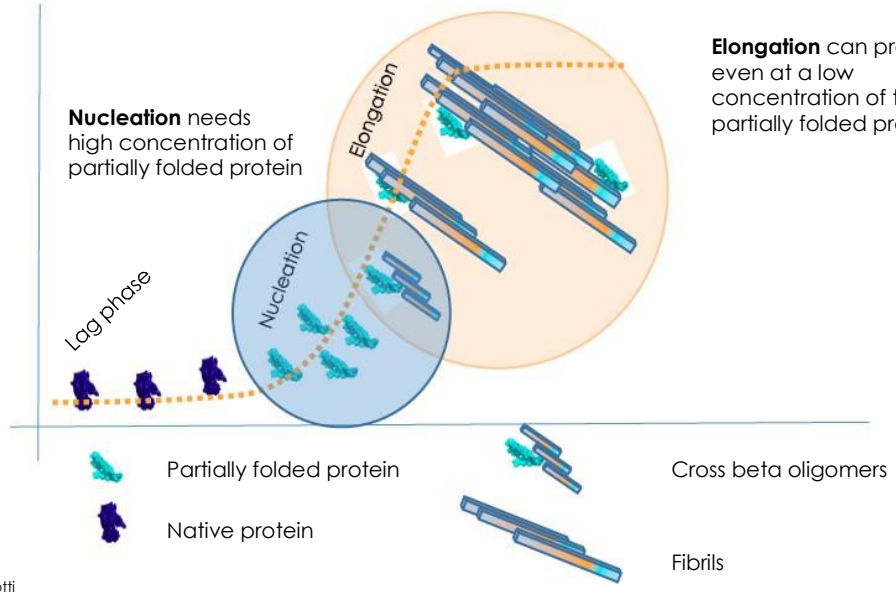
Klimtchuk et al. *PNAS* 2018.

Molecular mechanisms of transthyretin amyloid formation



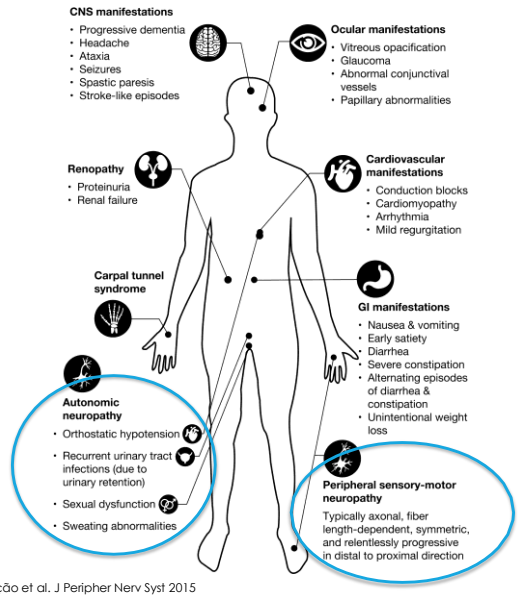
1. Johnson et al. JMB 2012. 2. Marcoux et al. EMBO J 2015. 3. Mangione et al. JBC 2018

The kinetics of amyloid formation



Courtesy of Prof. V Bellotti

Hereditary transthyretin amyloidosis (ATTR) is a heterogeneous multisystem degenerative disease



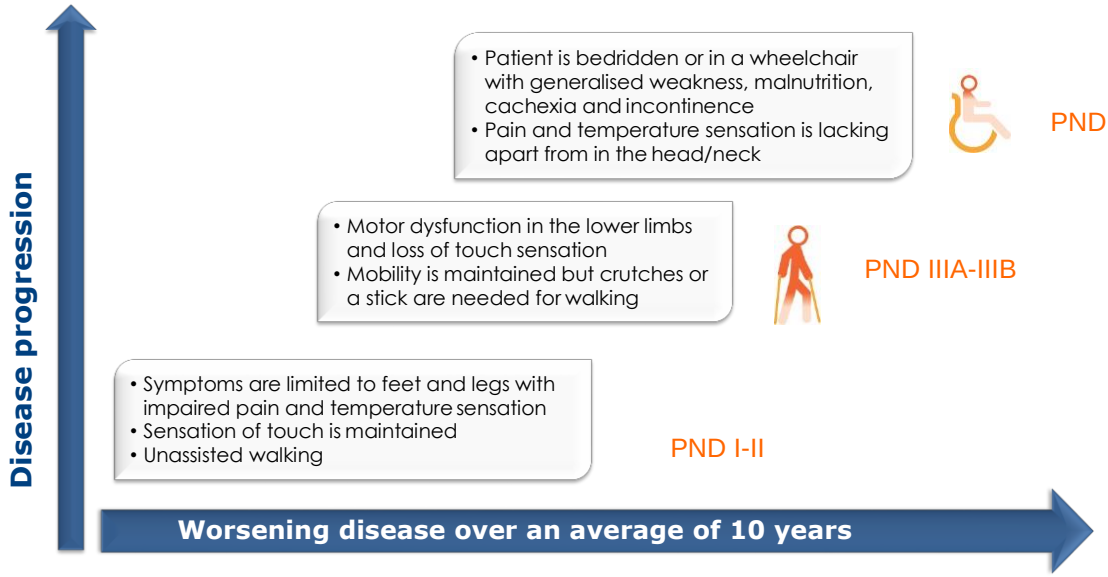
Conceição et al. J Peripher Nerv Syst 2015

High phenotypic variability is observed with regard to:

- Clinical presentation
- Age at onset
- Disease penetrance
- Rate of progression
- Response to therapy

Such a significantly diverse clinical presentation negatively impacts on early disease recognition, resulting in **diagnostic delays**

A relentlessly progressive sensory-motor polyneuropathy according to FAP stage



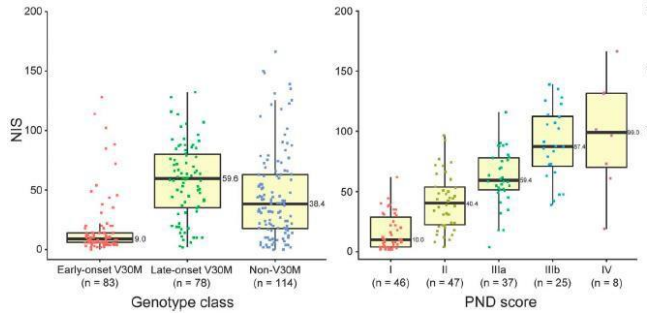
Hou X *et al. FEBS J* 2007; Coutinho P. In: Glenner GG *et al*, eds. *Amyloid and amyloidosis* 1980; Benson MD *et al. Amyloid*

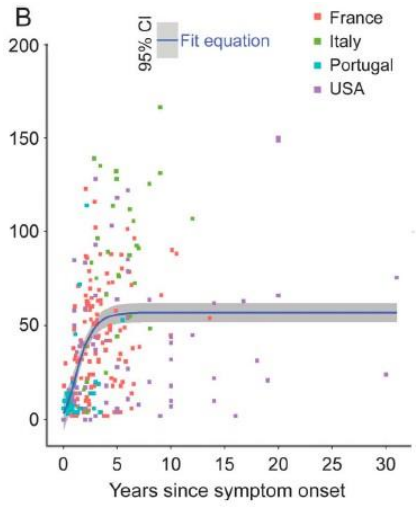
Rapid progression of familial amyloidotic polyneuropathy

A multinational natural history study

Adams et al. *Neurology 2015*

Retrospective study of 283 patients with different genotypes and a range of neurologic impairment, representative of real-world population

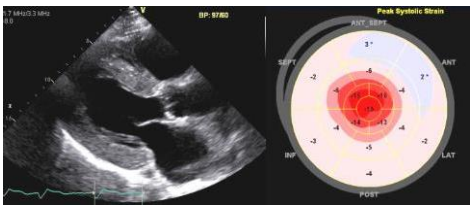




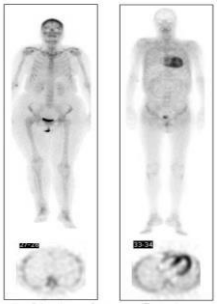
- Loess fit and Gompertz fit models show a rapid neuropathy progression rate over the initial 3–5 years
- Estimated ΔNIS score 14.3 points/year

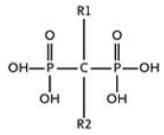
Imaging TTR cardiac amyloidosis

Echocardiography: wall thickness-GLS



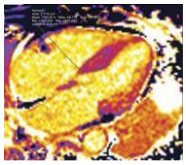
Bone scintigraphy

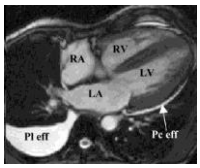


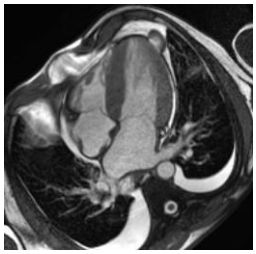


Rapezzi et al JACC Imaging 2011

Cardiac MRI: T1 mapping - LGE



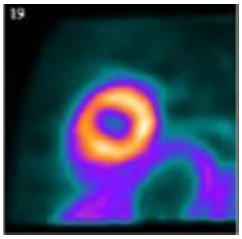




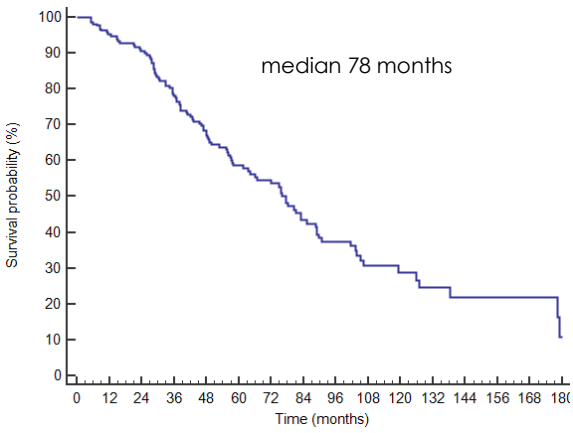
Maceira et al, *Circulation 2005*
Banypersad et al, *Circ Cardiovasc Img. 2013*
Fontana et al, *JACC Cardiovasc Img. 2017*
Martinez-Naharro et al, *ISA 2018 PA060*
Cibeira et al, *ISA 2018 PB095*

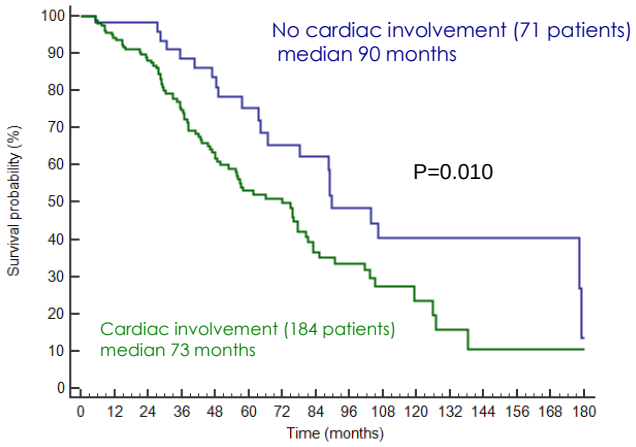
^{18}F-florbetapir
^{18}F-florbetaben
^{11}C-Pittsburgh compound B

Dorbala et al, *EJNMMI 2014*
Park et al, *Circ Cardiov Img. 2015*
Law et al, *J Nucl Med 2016*
Pilebro et al, *J Nucl Cardiol. 2017*
Manwani et al, *ISA 2018 PB054*

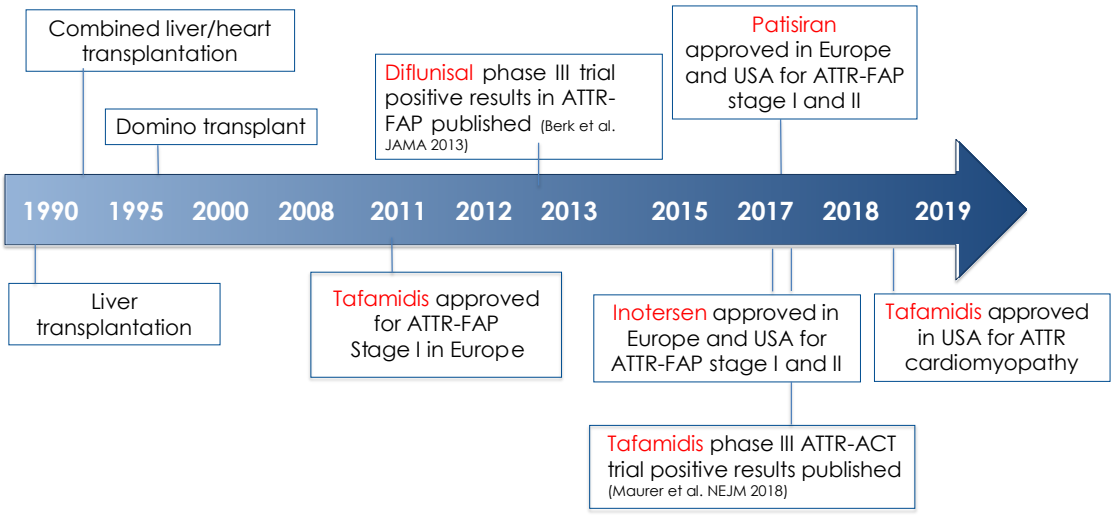


Survival of 255 patients with hereditary ATTR amyloidosis

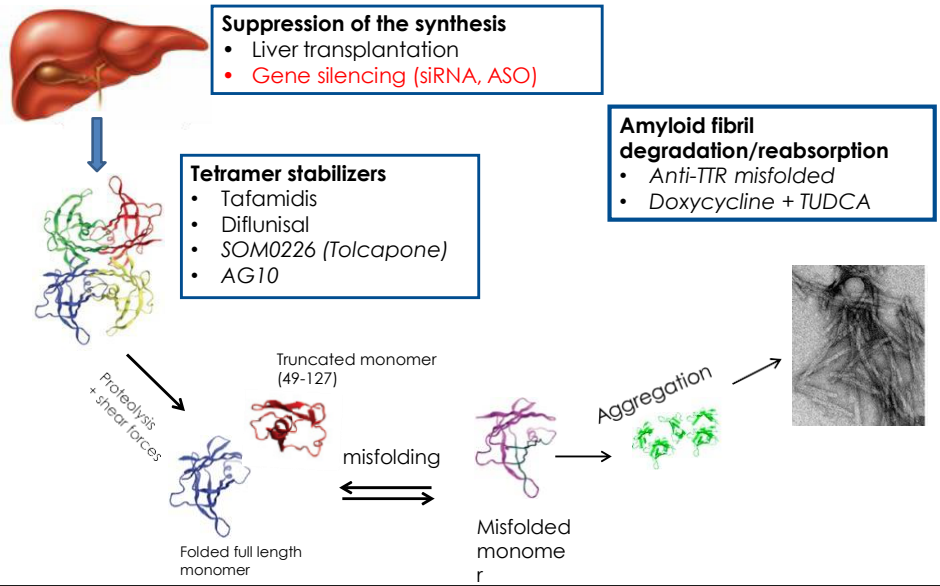




Treatment for hereditary ATTR is now rapidly evolving

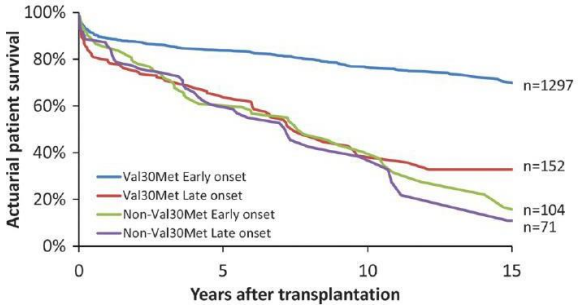


Therapeutic targets for hereditary TTR amyloidosis



Liver transplantation: long-term survival benefit

20-year survival rate 55,3% in 1940 patients from 19 countries (www.fapwtr.org)



80% survival at 10 years in early-onset Met30

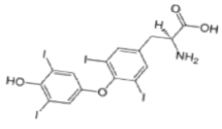
Combined liver-heart or liver-kidney transplantation

Careful patient selection

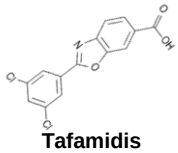
- Val30Met
- Early-onset of disease
- Short disease duration
- High mBMI

Ericzon BG et al, *Transplantation* 2015
Yamashita et al, *Neurology* 2012
Calvalho et al, *Liver Transplantation* 2015

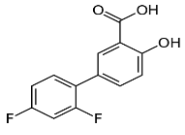
TTR stabilizers



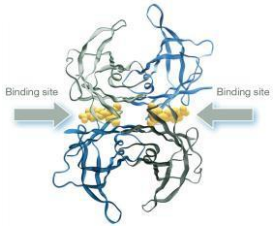
Thyroxine



Tafamidis



Diflunisal

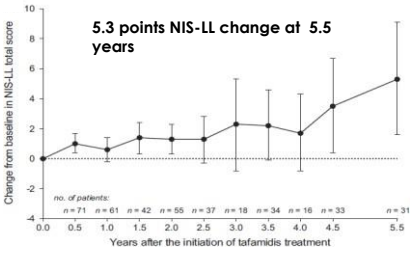


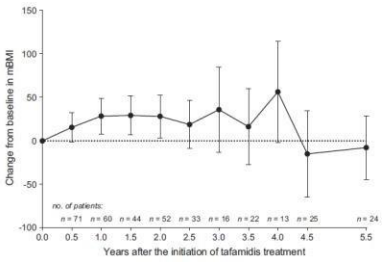
- Tafamidis is approved in Europe for ATTR-FAP stage I
- It is also approved in Mexico, Brasil, Argentina, Japan and Israel
- Approved in the USA of ATTR cardiomyopathy

- Diflunisal is a non-steroidal anti-inflammatory drug repositioned for hereditary ATTR (Berk et al, JAMA 2013)
- Not approved for this indication
- Available as a galenic product in Italy

Early intervention with tafamidis provides long-term (5.5-year) delay of neurologic progression in transthyretin hereditary amyloid polyneuropathy

Márcia Waddington Cruz[1], Leslie Amass[2], Denis Keohane[2], Jeffrey Schwartz[2], Huihua Li[2], and Balarama Gundapaneni[3]





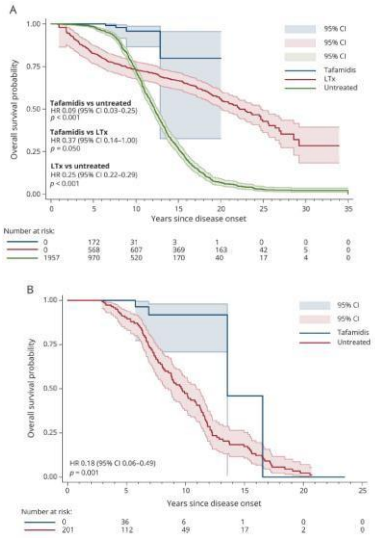
ARTICLE CLASS OF EVIDENCE

Natural history and survival in stage 1 Val30Met transthyretin familial amyloid polyneuropathy

Teresa Coelho, MD,* Mónica Inês, MSc,* Isabel Conceição, MD, Marta Soares, MSc, PhD, Mamede de Carvalho, MD, PhD, and João Costa, MD, PhD

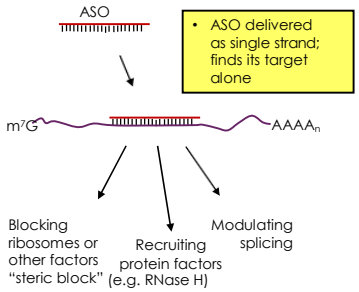
Correspondence
Dr. Costa
jncosta@medicina.ulisboa.pt

Neurology® 2018;91:e1999-e2009. doi:10.1212/WNL.0000000000006543



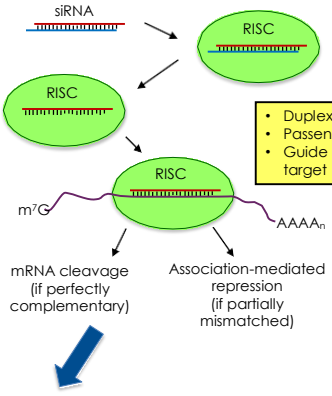
Innovative Disease-Modifying Therapeutics: TTR-lowering Agents

Antisense oligonucleotides (ASOs)



- ASO delivered as single strand; finds its target alone

RNA interference (RNAi)



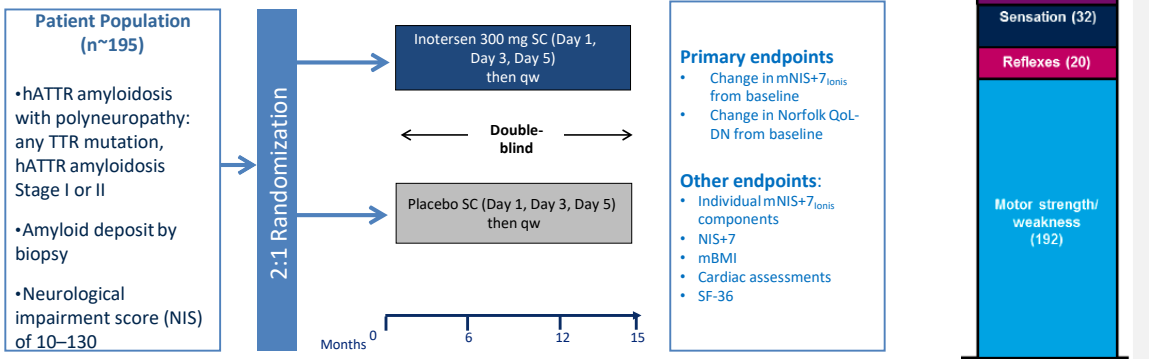
- Duplex associates with RISC
- Passenger strand is removed
- Guide strand leads RISC to target

Suppression of hepatic production of wild-type and mutant TTR

siRNA, small Interfering RNA; RISC, RNA–induced silencing complex–responsible for the silencing phenomenon known as RNA interference
Watts & Corey. *J Pathol* 2012;226:365–79

Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis

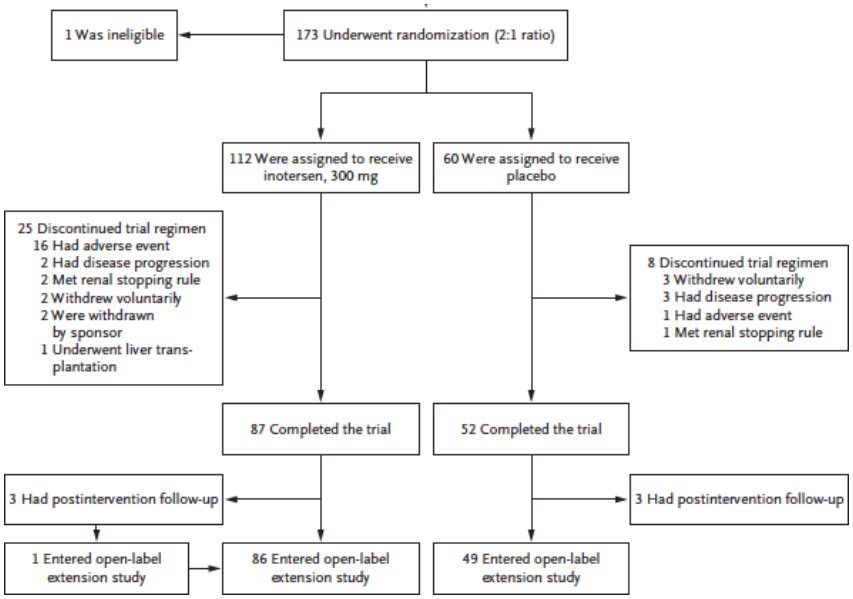
M.D. Benson, M. Waddington-Cruz, J.L. Berk, M. Polydefkis, P.J. Dyck, A.K. Wang, V. Planté-Bordeneuve, F.A. Barroso, G. Merlini, L. Obici, M. Scheinberg, T.H. Brannagan III, W.J. Litchy, C. Whelan, B.M. Drachman, D. Adams, S.B. Heitner, I. Conceição, H.H. Schmidt, G. Vita, J.M. Campistol, J. Gamez, P.D. Gorevic, E. Gane, A.M. Shah, S.D. Solomon, B.P. Monia, S.G. Hughes, T.J. Kwoh, B.W. McEvoy, S.W. Jung, B.F. Baker, E.J. Ackermann, M.A. Gertz, and T. Coelho



*Patients who complete the study may be eligible for inotersen treatment on Phase 3 OLE study (NCT02175004)

Benson et al, *NEJM 2018*

Enrollment and disposition of patients



Benson et al, *NEJM 2018*

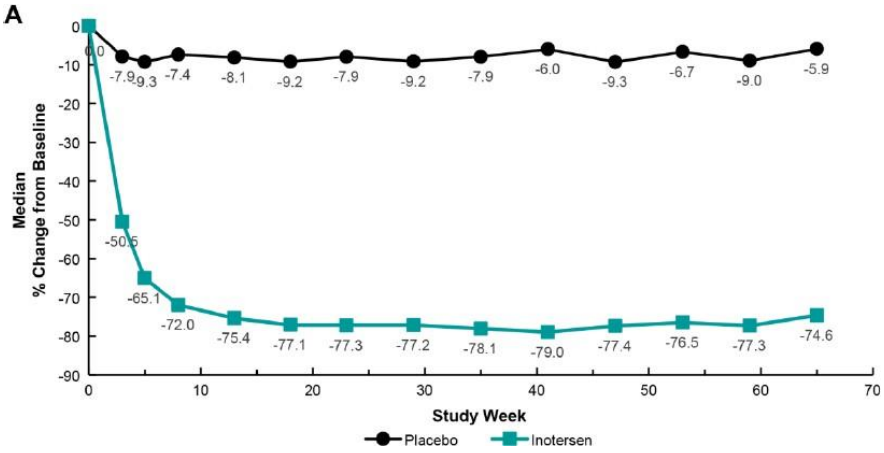
Baseline demographics and disease characteristics were well balanced between treatment groups

Characteristic	Placebo (N=60)	Inotersen (N=112)	Total (N=172)
Age — yr	59.5±14.0	59.0±12.5	59.2±13.0
Male sex — no. (%)	41 (68)	77 (69)	118 (69)
Modified BMI§	105.0±22.8	101.1±22.8	102.5±22.8
Val30Met *TTR* mutation — no. (%)¶‖	33 (55)	56 (50)	89 (52)
Disease stage — no. (%)‖**			
1: patient is ambulatory	42 (70)	74 (66)	116 (67)
2: patient is ambulatory with assistance	18 (30)	38 (34)	56 (33)
Previous treatment with tafamidis or diflunisal — no. (%)‖	36 (60)	63 (56)	99 (58)
Duration of disease from diagnosis of hATTR-PN — mo††	39.3±40.3	42.4±51.2	41.3±47.6
Duration of disease from onset of hATTR-PN symptoms — mo††	64.0±52.3	63.9±53.2	63.9±52.7
Presence of cardiomyopathy — no. (%)‡‡	33 (55)	75 (67)	108 (63)
mNIS+7 composite score§§	74.8±39.0	79.2±37.0	77.6±37.6
Norfolk QOL-DN total score¶¶	48.7±26.7	48.2±27.5	48.4±27.2

Benson et al, *NEJM 2018*

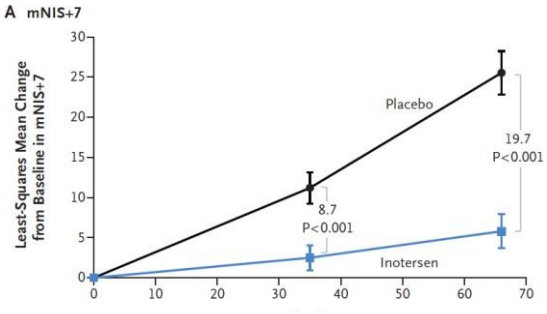
Sustained reduction in circulating TTR over 15 months

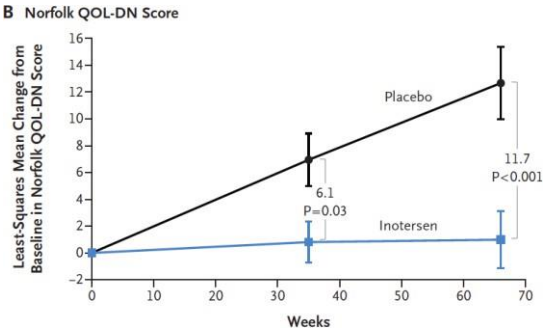
Median reduction of serum TTR level was 79%

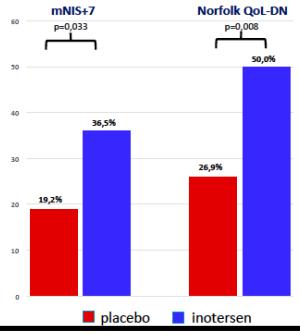


Benson et al, *NEJM 2018*

Primary efficacy end points: change in mNIS+7 and Norfolk QOL-DN from baseline at week 66





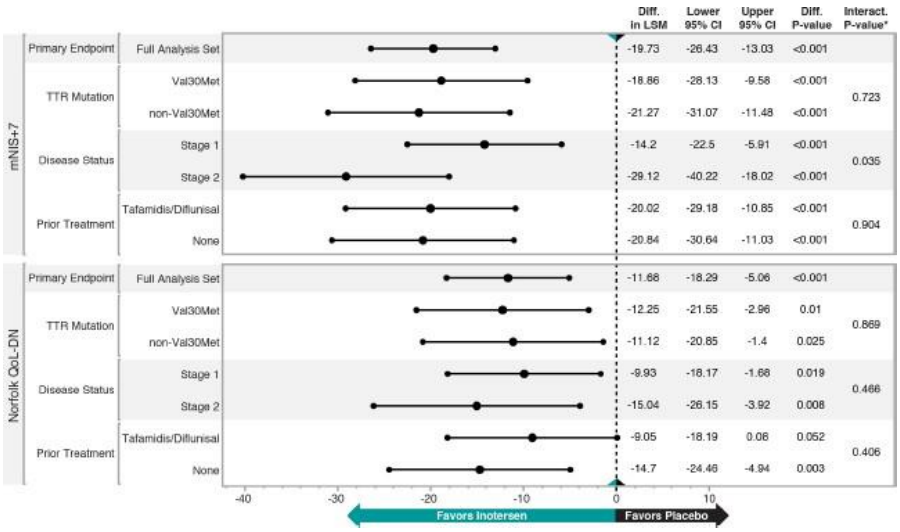


Patients with ≤ 0-point change from baseline at week 66

Approved by FDA and EMA for hereditary ATTR polyneuropathy FAP stages I and II

Benson et al, *NEJM 2018*

Significant benefit of inotersen compared with placebo across all subgroup analyses



Benson et al, *NEJM 2018*

Safety and tolerability

Table 2. Summary of Adverse Events.*

Event	Placebo (N=60)	Inotersen (N=112)
	no. of patients (%)	
Any adverse event	60 (100)	111 (99)
Event related to trial regimen†	23 (38)	87 (78)
Any serious adverse event	13 (22)	36 (32)
Event related to trial regimen†	1 (2)	8 (7)
Glomerulonephritis	0	3 (3)‡
Thrombocytopenia	0	2 (2)
Deep-vein thrombosis	1 (2)	1 (<1)
Intracranial hemorrhage	0	1 (<1)§
Tubulointerstitial nephritis	0	1 (<1)¶
Pulmonary embolism	0	1 (<1)
Embolic stroke	0	1 (<1)
Myelopathy	0	1 (<1)
Death	0	5 (4)

TEAEs more common with inotersen vs placebo: low platelet count, nausea, chills, fever, vomiting, anemia, thrombocytopenia

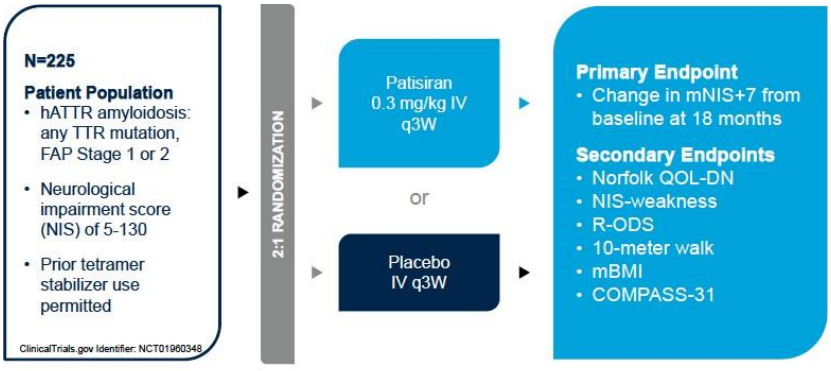
Enhanced safety monitoring implemented for thrombocytopenia and renal parameters, no additional issues

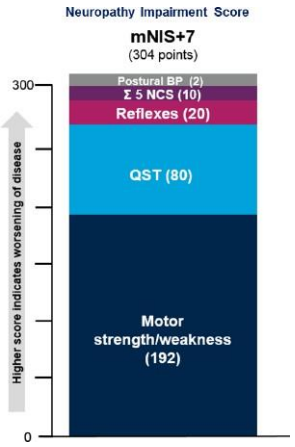
Patients receiving inotersen should take oral supplementation of vitamin A per day to reduce potential risk of ocular toxicity

Benson et al, *NEJM 2018*

Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis

D. Adams, A. Gonzalez-Duarte, W.D. O'Riordan, C.-C. Yang, M. Ueda, A.V. Kristen, I. Tournev, H.H. Schmidt, T. Coelho, J.L. Berk, K.-P. Lin, G. Vita, S. Attarian, V. Planté-Bordeneuve, M.M. Mezei, J.M. Campistol, J. Buades, T.H. Brannagan III, B.J. Kim, J. Oh, Y. Parman, Y. Sekijima, P.N. Hawkins, S.D. Solomon, M. Polydefkis, P.J. Dyck, P.J. Gandhi, S. Goyal, J. Chen, A.L. Strahs, S.V. Nochur, M.T. Sweetser, P.P. Garg, A.K. Vaishnaw, J.A. Gollob, and O.B. Suhr

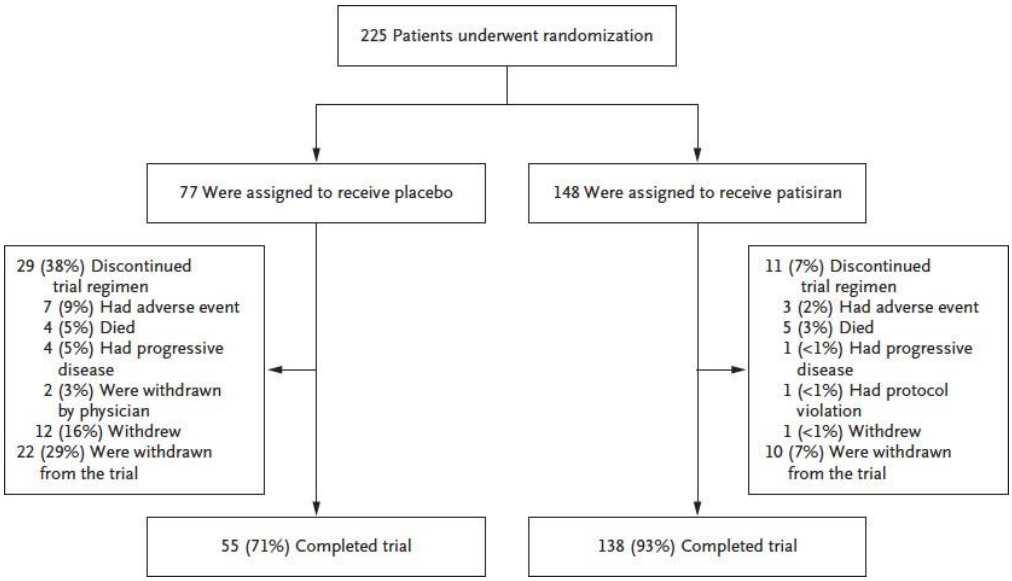




Patients who complete the study may be eligible for patisiran treatment on Phase 3 OLE study (APOLLO-OLE), ClinicalTrials.gov Identifier: NCT02510261

Adams et al, *NEJM 2018*

Enrollment and disposition of patients



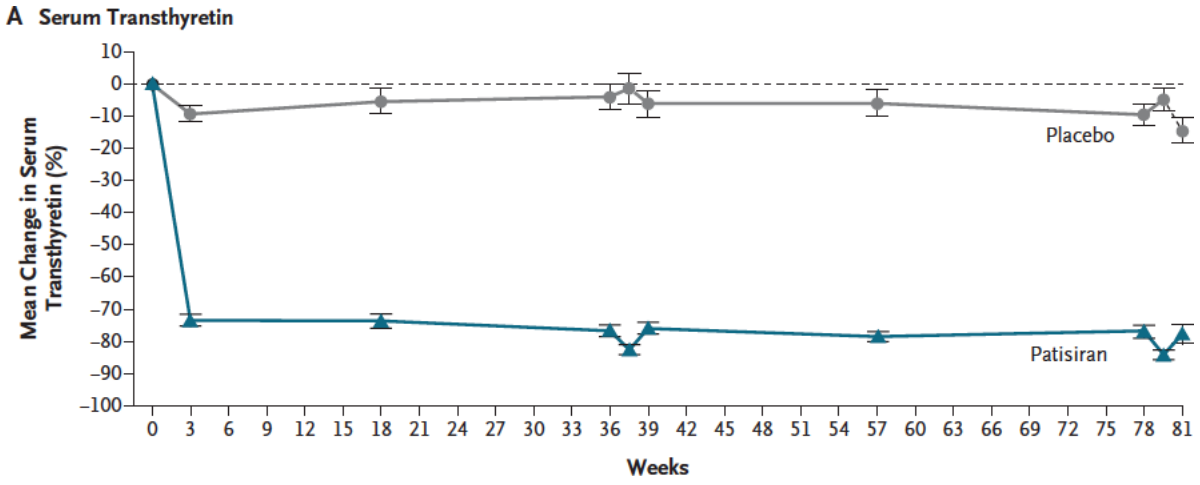
Adams et al, *NEJM 2018*

Baseline demographic and clinical characteristics of the patients

Characteristic	Placebo (N=77)	Patisiran (N=148)	Total (N=225)
Median age (range) — yr	63 (34–80)	62 (24–83)	62 (24–83)
Male sex — no. (%)	58 (75)	109 (74)	167 (74)
Median time since diagnosis of hereditary transthyretin amyloidosis (range) — yr	1.4 (0.0–16.5)	1.3 (0.0–21.0)	1.4 (0.0–21.0)
TTR genotype — no. (%)			
V30M	40 (52)	56 (38)	96 (43)
With onset of disease before 50 yr of age	10 (13)	13 (9)	23 (10)
Non-V30M§	37 (48)	92 (62)	129 (57)
Previous use of tetramer stabilizer — no. (%)	41 (53)	78 (53)	119 (53)
FAP stage — no. (%)			
1: unimpaired ambulation	37 (48)	67 (45)	104 (46)
2: assistance with ambulation	39 (51)	81 (55)	120 (53)
3: wheelchair-bound or bedridden	1 (1)	0	1 (<1)
New York Heart Association class — no. (%)			
I	40 (52)	70 (47)	110 (49)
II	36 (47)	77 (52)	113 (50)

Adams et al, *NEJM 2018*

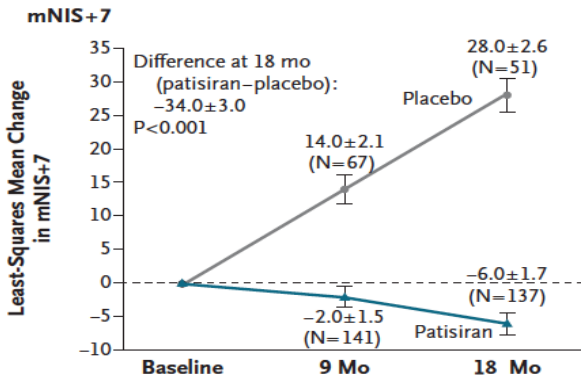
Reduction in Serum TTR Levels Was Rapid and Sustained over 18 Months in the APOLLO Study

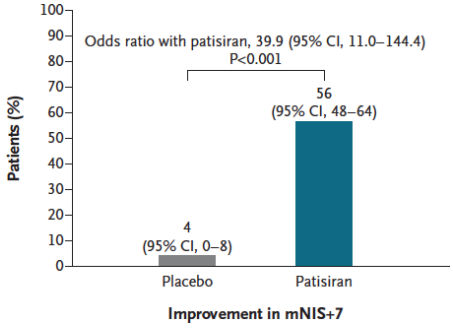


Mean reduction of serum TTR level after 18 months' patisiran treatment was 84 %

Adams et al, *NEJM 2018*

Patisiran Treatment Improved the Primary Endpoint mNIS+7 from Baseline to Month 18



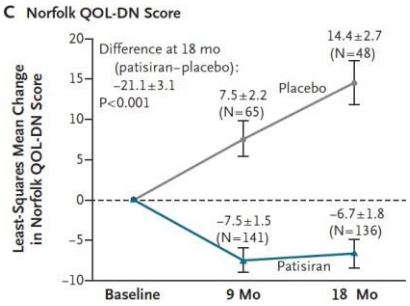


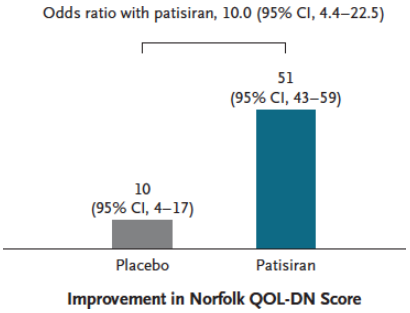
Improvement in mNIS+7 score at 18 months was consistent across all subgroups, significantly favoring patisiran

Approved by FDA and EMA for hereditary ATTR polyneuropathy FAP stages I and II

Adams et al, *NEJM 2018*

All secondary endpoints were significantly improved with patisiran compared with placebo



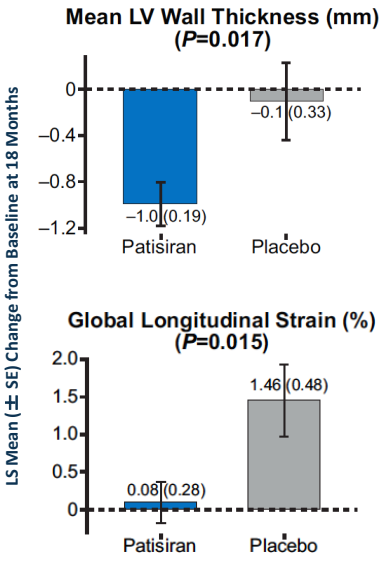


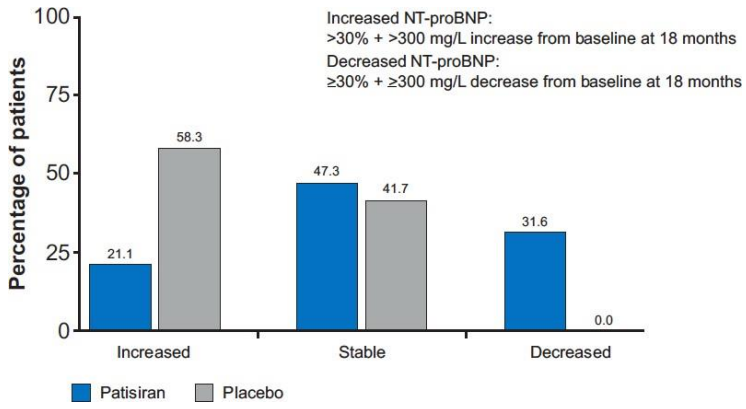
End Point	Placebo	Patisiran	Least-Squares Mean Difference (Patisiran – Placebo)	P Value
Secondary end points in the modified ITT population*				
No. of patients	77	148		
Modified BMI¶				
Mean (±SD) baseline value	989.9±214.2	969.7±210.5		
Least-squares mean (±SE) change from baseline at 18 mo	−119.4±14.5	−3.7±9.6	115.7±16.9	<0.001
Composite Autonomic Symptom Score 31‖				
Mean (±SD) baseline score	30.3±16.4	30.6±17.6		
Least-squares mean (±SE) change from baseline at 18 mo	2.2±1.9	−5.3±1.3	−7.5±2.2	<0.001

Adams et al, *NEJM 2018*

Effects of Patisiran, an RNA Interference Therapeutic, on Cardiac Parameters in Patients With Hereditary Transthyretin-Mediated Amyloidosis

Analysis of the APOLLO Study





Solomon et al, *Circulation 2018*

Table 3. Safety and Side Effects.

Event	Placebo (N=77)	Patisiran (N=148)
	no. of patients (%)	
Any adverse event	75 (97)	143 (97)
Adverse events occurring in ≥10% of patients in either group		
Diarrhea	29 (38)	55 (37)
Edema, peripheral	17 (22)	44 (30)
Fall	22 (29)	25 (17)
Nausea	16 (21)	22 (15)
Infusion-related reaction	7 (9)	28 (19)
Constipation	13 (17)	22 (15)
Urinary tract infection	14 (18)	19 (13)
Dizziness	11 (14)	19 (13)
Fatigue	8 (10)	18 (12)
Headache	9 (12)	16 (11)
Cough	9 (12)	15 (10)
Vomiting	8 (10)	15 (10)
Asthenia	9 (12)	14 (9)
Insomnia	7 (9)	15 (10)
Nasopharyngitis	6 (8)	15 (10)
Pain in extremity	8 (10)	10 (7)
Muscular weakness	11 (14)	5 (3)
Anemia	8 (10)	3 (2)
Syncope	8 (10)	3 (2)
Adverse event leading to discontinuation of the trial regimen	11 (14)	7 (5)
Adverse event leading to withdrawal from the trial	9 (12)	7 (5)
Death	6 (8)	7 (5)
Any serious adverse event	31 (40)	54 (36)
Any severe adverse event	28 (36)	42 (28)

Adams et al, *NEJM 2018*

Safety and tolerability

Majority of AEs were mild or moderate in severity

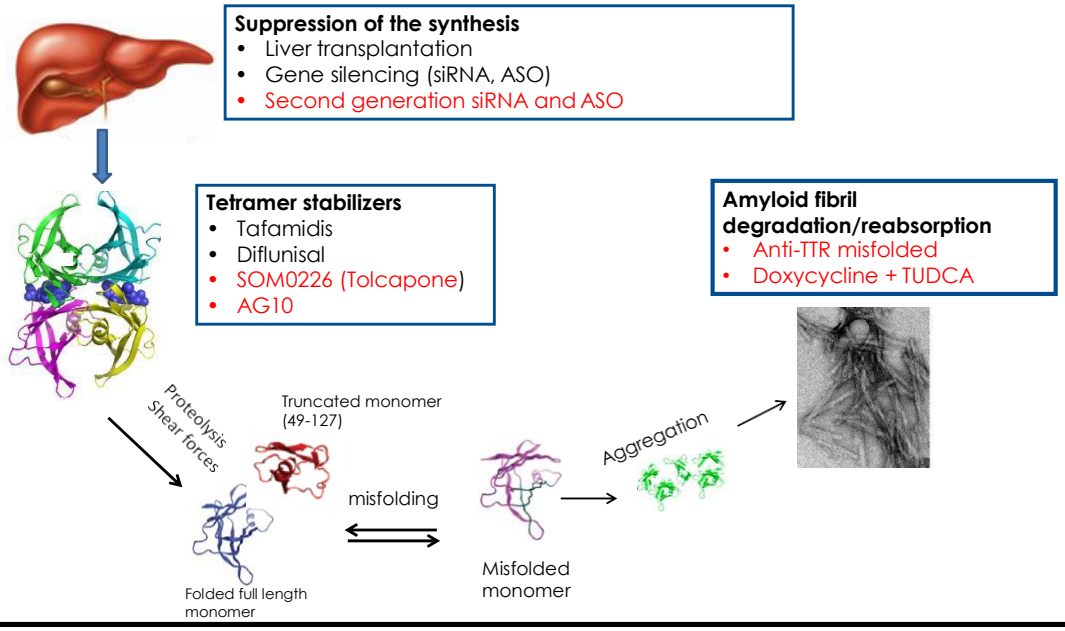
- Most frequent AEs in patisiran-treated patients were peripheral edema (29.7%) and IRRs (18.9%); an IRR led to discontinuation of 1 patient (0.7%)

In patients experiencing an IRR, the majority experienced the first IRR within the first two infusions

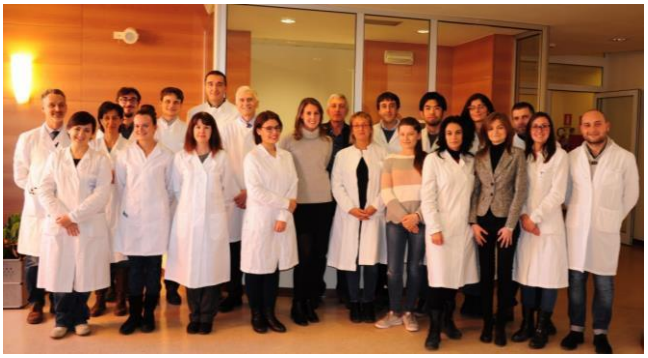
To reduce the risk of IRRs, patients should receive premedications on the day of patisiran infusion, at least 60 minutes prior to start of infusion

Patients receiving patisiran should take oral supplementation vitamin A per day to reduce potential risk of ocular toxicity

Present and future investigational drugs



Acknowledgements



Department of Molecular Medicine Univ. Pavia & NAC at UCL, London
Vittorio Bellotti and collaborators

Neurological Institute IRCCS C. Mondino University of Pavia
A. Cortese, E Alfonsi, I. Callegari, E. Vegezzi, R. Currò

Giampaolo Merlini
Giovanni Palladini
Andrea Foli
Paolo Milani
Alessandro Lozza
Francesca Lavatelli
Roberta Mussinelli
Marco Basset

Stefano Perlini
Paola Rognoni
Simona Casarini
Giovanni Ferraro
Pasquale Cascino
Margherita Bozzola
Jessica Ripepi
Alice Nevone

Anna Carnevale Baraglia
Claudia Sforzini
Elona Luka
Eleonora Di Buduo
Mario Nuvolone