Patologie del pathway RAS-MAPK:

l'importanza della rete multidisciplinare

Salerno, 19-20 Maggio 2023

Grand Hotel Salerno
Lungomare Clemente Tafuri, 1

RASopatie: Overview sulla terapia

Salerno, 20 maggio 2023

Alessandro Mussa – alessandro.mussa@unito.it
Ospedale Infantile Regina Margherita -Università di Torino

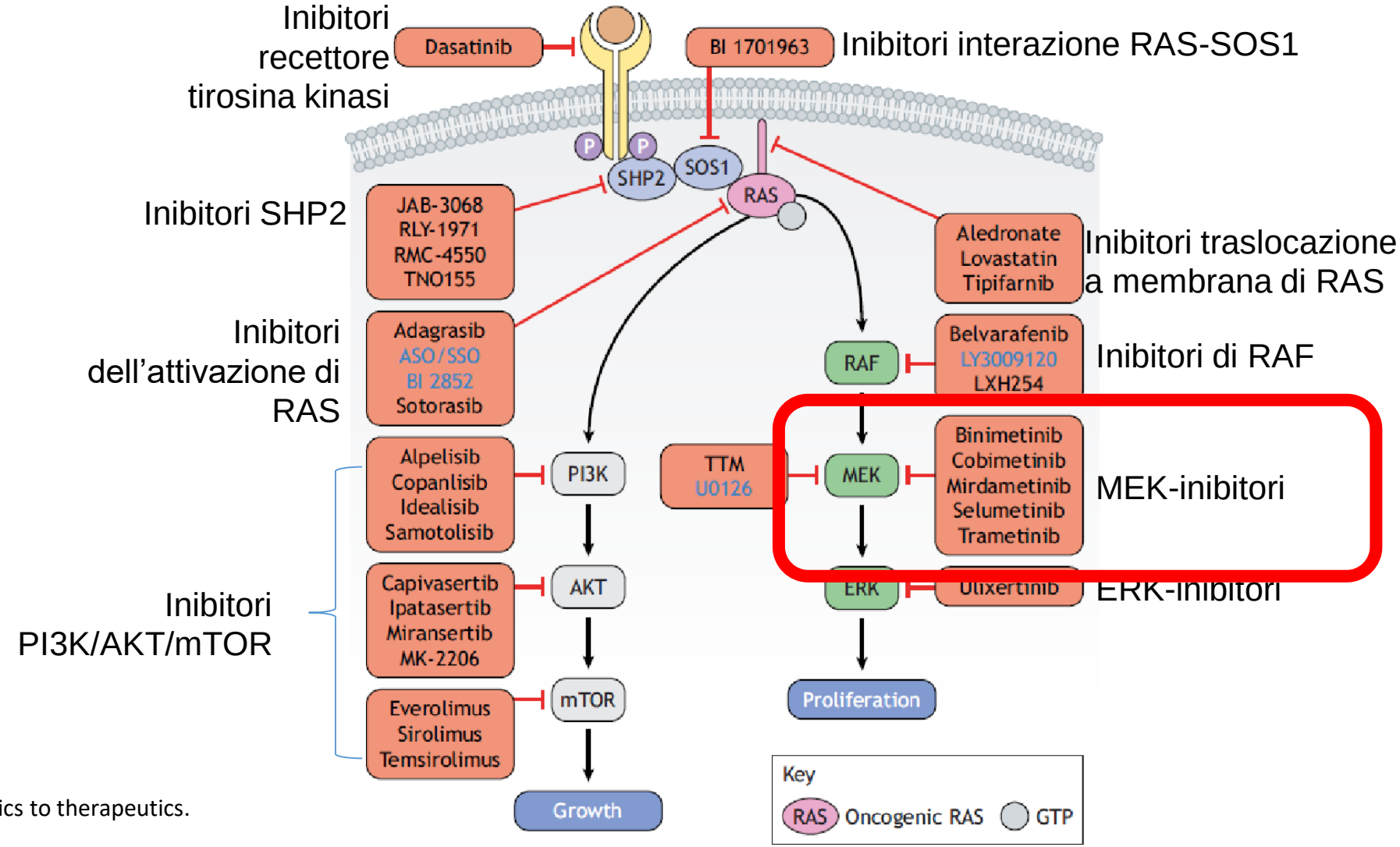
UNIVERSITÀ DI TORINO

Strategie per il trattamento delle RASopatie

Inibitori/modulatori della RAS/MAPK pathway

Studiati per applicazione oncologica, riposizionabili teoricamente nel trattamento delle RASopatie complicate

Una serie di altre opzioni terapeutiche



Hebron KE et al. The RASopathies: from pathogenetics to therapeutics. Disease Models & Mechanisms (2022) 15

Modelli murini – inibizione RAS/MAPK

Activation of multiple signaling pathways causes developmental defects in mice w
Noonan syndrome–associated *Sos1* mut

Peng-Chieh Chen,[1,2] Hiroko Wakimoto,[1,3] David Conner,[1] Toshiyuki Araki,[4] Tao Yu
Amy Roberts,[5] Christine E. Seidman,[1,6] Roderick Bronson,[7] Benjamin G. Neel,
Jonathan G. Seidman,[1] and Raju Kucherlapati[1,2]

Circulation Research

ORIGINAL RESEARCH

The Noonan Synd
Cardiovascular Fu
Vesicular Traffickir

Raj Nayan Sewduth, Silvia Pandolfi, Mikhail Ste
Benoit Lechat, Rozeen Quarck, Francis Impens,

epoca prenatale Lztr1

Mechanisms underlying cognitive deficits in a mouse model for Costello Syndrome are distinct from other RASopathy mouse

Vaart[1,2],
shner[3,3], Dick

Related Commentary, page 844 Research a

MEK-ERK pathway modulation ameliorates disease phenotypes in a mouse model of Noonan syndrome associated with the *Raf1*^{L613V} mutation

Xue Wu,[1,2] Jeremy Simpson,[3,4] Jenny H. Hong,[1,2] Kyoung-Han Kim,[3]
Nirusha K. Thavarajah,[2] Peter H. Backx,[3] Benjamin G. Neel,[1,2] and Toshiyuki Araki[2]

RESEARCH Open Access

MEK inhibition ameliorates social behavior phenotypes in a Spred1 knockout mouse model for RASopathy disorders

Sarah C. Borrie[1], Ellen Plasschaert[1], Zsuzsanna Callaerts-Vegh[2], Akihiko Yoshimura[3], Rudi D'Hooge[2], Ype Elgersma[4,5], Steven A. Kushner[4,6], Eric Legius[1] and Hilde Brems[1*]

Spred1, risposta parziale fenotipo neuro

New *BRAF* knockin mice provide a pathogenetic mechanism of developmental defects and a therapeutic approach in cardio-facio-cutaneous syndrome

Shin-ichi Inoue[1], Mitsuji Moriya[1], Yusuke Watanabe[4], Sachiko Miyagawa-Tomita[5,6], Tetsuya Niihori[1], Daiju Oba[1], Masao Ono[2], Shigeo Kure[3], Toshihiko Ogura[4], Yoichi Matsubara and Yoko Aoki[1,*]

Original article

Chronic treatment with a MEK inhibitor reverses enhanced excitatory field potentials in *Syngap1*$^{+/-}$ mice

Maksym V. Kopanitsa[a,*], Gemma Gou[b,c], Nurudeen O. Afinowi[a,1], Àlex Bayés[b,c], Seth G.N. Grant[d], Noboru H. Komiyama[d]

[a] Synome Ltd, Babraham Research Campus, Cambridge, UK
[b] Biomedical Research Institute Sant Pau, Barcelona, Spain

knockout eterozigote SYNGAP1

K-Ras^{V14I} recapitulates Noonan syndrome in mice

Isabel Hernández-Porras[a], Salvatore Fabbiano[b], Alberto J. Schuhmacher[a,1], Alexandra Aicher[c], Marta Cañamero[d,2], Juan Antonio Cámara[d], Lorena Cussó[e,f,g], Manuel Desco[e,f,g], Christopher Heeschen[c], Francisca Mulero[d], Xosé R. Bustelo[b], Carmen Guerra[a,3], and Mariano Barbacid[a,3]

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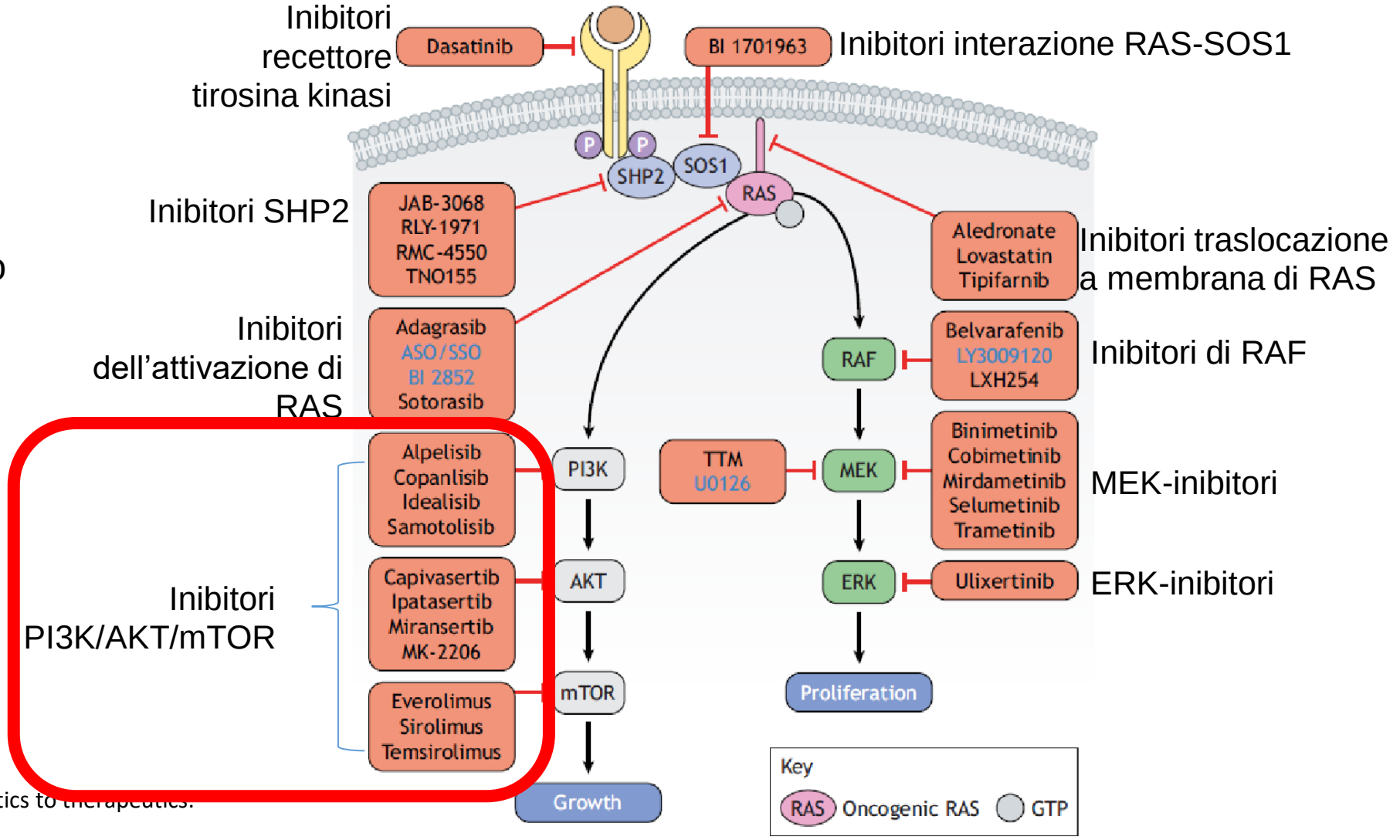

Hebron KE et al. The RASopathies: from pathogenetics to therapeutics. Disease Models & Mechanisms (2022) 15

Modelli murini

Inibizione del pathway collaterale PI3K/mTOR o del recettore potrebbero essere vantaggiose rispetto all'inibizione del RAS/MAPK pathway in alcune RASopatie

PI3K/mTOR/AKT Pathway inhibitors

tyrosine kinase inhibitor dasatinib

Cardiovascular Drugs and Therapy (2022) 36:589–604
https://doi.org/10.1007/s10557-021-07169-z

ORIGINAL ARTICLE

Low-dose Dasatinib Ameliorates Hypertrophic Cardiomyopathy in Noonan Syndrome with Multiple Lentigines

Jae-Sung Yi[1] · Sravan Perla[1] · Yan Huang[2] · Kana Mizuno[3] · Frank J. Giordano[2] · Alexander A. Vinks[3,4] · Anton M. Bennett[1,5]

PLOS ONE

RESEARCH ARTICLE

In vivo efficacy of the AKT inhibitor ARQ 092 in Noonan Syndrome with multiple lentigines-associated hypertrophic cardiomyopathy

Jianxun Wang[1☯], Vasanth Chandrasekhar[1☯], Giovanni Abbadessa[2], Yi Yu[2], Brian Schwartz[2], Maria I. Kontaridis[1,3]*

Low-dose dasatinib rescues cardiac function in Noonan syndrome

Jae-Sung Yi,[1] Yan Huang,[2] Andrea T. Kwaczala,[3] Ivana Y. Kuo,[1] Barbara E. Ehrlich,[1] Stuart G. Campbell,[3] Frank J. Giordano,[2] and Anton M. Bennett[1,4]

Rapamycin reverses hypertrophic cardiomyopathy in a mouse model of LEOPARD syndrome–associated *PTPN11* mutation

Talita M. Marin,[1,2] Kimberly Keith,[1] Benjamin Davies,[1] David A. Conner,[3] Prajna Guha,[1] Demetrios Kalaitzidis,[4] Xue Wu,[5,6] Jessica Lauriol,[1] Bo Wang,[1] Michael Bauer,[7] Roderick Bronson,[8] Kleber G. Franchini,[2] Benjamin G. Neel,[5,6] and Maria I. Kontaridis[1,9]

Tyrosyl phosphorylation of PZR promotes hypertrophic cardiomyopathy in *PTPN11*-associated Noonan syndrome with multiple lentigines

Jae-Sung Yi,[1] Sravan Perla,[1] Liz Enyenihi,[2] and Anton M. Bennett[1,3]

[1]Department of Pharmacology, Yale School of Medicine, Yale University, New Haven, Connecticut, USA. [2]Department of Chemistry, Emory University, Atlanta, Georgia, USA. [3]Program in Integrative Cell Signaling and Neurobiology of Metabolism, Department of Comparative Medicine, Yale School of Medicine, Yale University, New Haven, Connecticut, USA.

Strategie per il trattamento delle RASopatie

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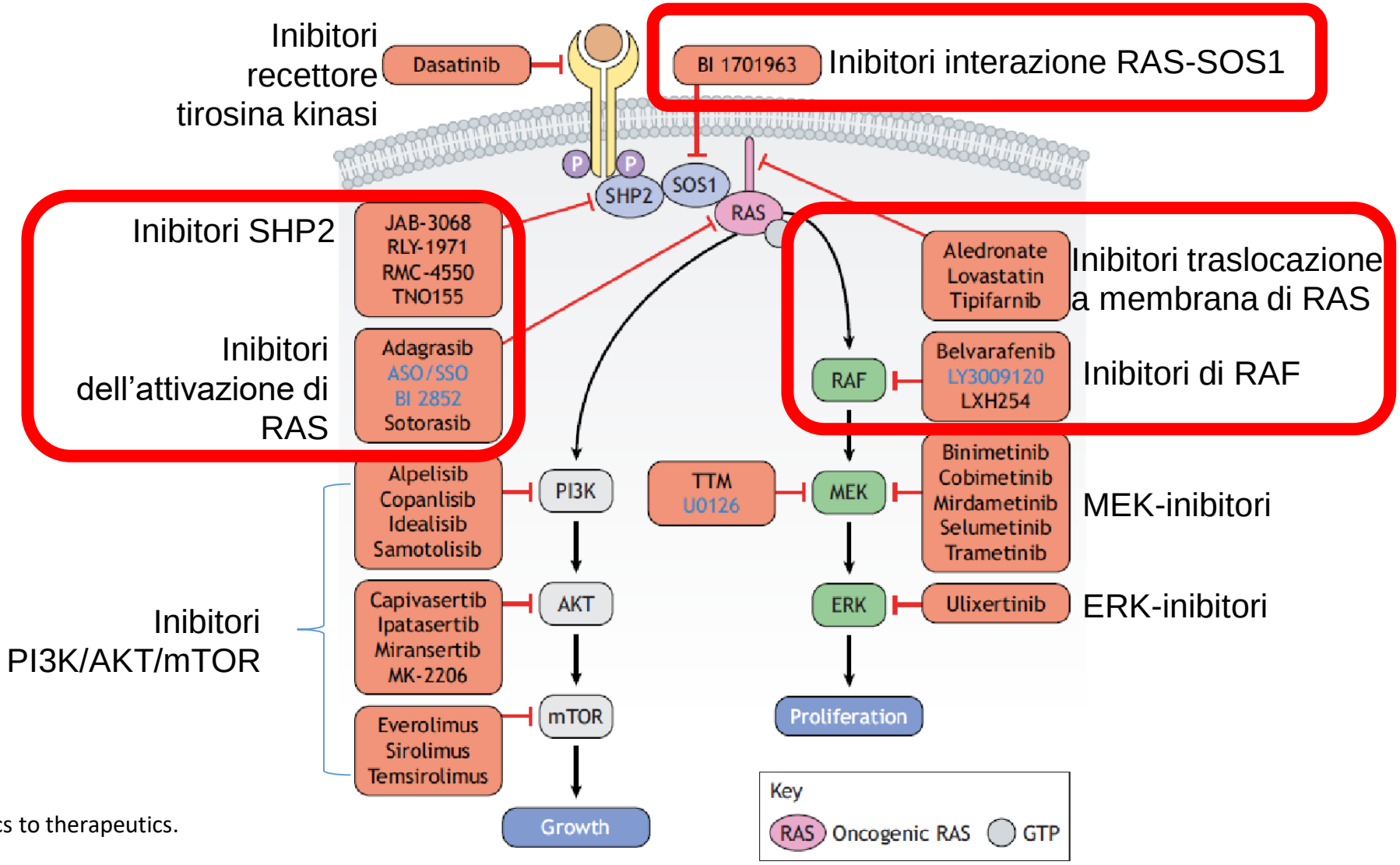


Hebron KE et al. The RASopathies: from pathogenetics to therapeutics. Disease Models & Mechanisms (2022) 15

Stra tie

Inibitori/mo RAS-SOS1
RAS/MAPK

Studiati per
oncologica, ibitori traslocazione
teoricamen membrana di RAS
delle RASo

Una serie di ibitori di RAF
terapeutiche

MEK-inibitori

RK-inibitori

Hebron KE et al. The RA
Disease Models & Mecl

NF1 *vs* RASopatie (con complicanze)

Lo studio di fase 2 di selumetinib nel **neurofibroma plessiforme inoperabile** (SPRINT) ha comportato una riduzione >20% delle dimensioni basali in ¾ dei bambini NF1 con miglioramenti clinicamente significativi.

Sulla base dei risultati di questo studio, **selumetinib** ha ricevuto l'approvazione della FDA ed è stato approvato nel **2020** per bambini >2 anni con questa indicazione

Table 2. Ongoing trials of MEK inhibitors in neurofibromatosis 1

MEK inhibitor	Identifier	Title	Studied conditions	Phase	Age of studied population
Selumetinib	NCT01362803	AZD6244 Hydrogen Sulfate or Children With Nervous System Tumors (SPRINT)	Plexiform Neurofibroma	Phase 1 Phase 2	2–18 years
Selumetinib	NCT03326388	Intermittent Dosing Of Selumetinib In Childhood NF1 Associated Tumours (INSPECT)	Plexiform Neurofibroma Optic nerve glioma	Phase 1 Phase 2	3– 18 years
Selumetinib	NCT02839720	Selumetinib in Treating Patients With Neurofibromatosis Type 1 and Cutaneous Neurofibroma	Cutaneous Neurofibroma Optic Nerve Glioma	Phase 2	18 years and older
Selumetinib	NCT02407405	MEK 1/2 Inhibitor Selumetinib (AZD6244 Hydrogen Sulfate) in Adults With Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas	Plexiform Neurofibroma	Phase 2	18 years and older
Selumetinib + Sirolimus	NCT03433183	SARC031: MEK Inhibitor Selumetinib (AZD6244) in Combination With the mTOR Inhibitor Sirolimus for Patients With Malignant Peripheral Nerve Sheath Tumors	Malignant Peripheral Nerve Sheath Tumours	Phase 2	12 years and older
Selumetinib	NCT01089101	Selumetinib in Treating Young Patients With Recurrent or Refractory Low Grade Glioma	Recurrent or Refractory Pediatric Low Grade Glioma	Phase 1 Phase 2	3–21 years
Selumetinib vs. Carboplatin/ Vincristine	NCT03871257	A Phase 3 Randomized Study of Selumetinib Versus Carboplatin/Vincristine in Newly Diagnosed or Previously Untreated Neurofibromatosis Type 1 (NF1) Associated Low-Grade Glioma (LGG)	Low Grade Glioma	Phase 3	2–21 years
Selumetinib vs. Carboplatin and Vincristine	NCT04166409	A Study of the Drugs Selumetinib vs. Carboplatin and Vincristine in Patients With Low-Grade Glioma	Low Grade Glioma	Phase 3	2–21 years
Mirdametinib	NCT03962543	MEK Inhibitor Mirdametinib (PD-0325901) in Patients With Neurofibromatosis Type 1 Associated Plexiform Neurofibromas (RENEU)	Plexiform Neurofibroma	Phase 2	2 years and older
Trametinib	NCT03741101	Treatment of NF1-related Plexiform Neurofibroma With Trametinib (plexifpc)	Plexiform Neurofibroma	Phase 2	1–17 years
Trametinib	NCT03363217	Trametinib for Pediatric Neuro-oncology Patients With Refractory Tumor and Activation of the MAPK/ERK Pathway.	Low-grade Glioma Plexiform Neurofibroma Central Nervous System Glioma	Phase 1 Phase 2	1 month to 25 years
Trametinib with or without Dabrafenib	NCT02124772	Study to Investigate Safety, Pharmacokinetic (PK), Pharmacodynamic (PD) and Clinical Activity of Trametinib in Subjects With Cancer or Plexiform Neurofibromas and Trametinib in Combination With Dabrafenib in Subjects With Cancers Harboring V600 Mutations	For patients with NF1: Plexiform Neurofibromas	Phase 1 Phase 2	1 month to 17 years
Trametinib with Hydroxychloroquine	NCT04201457	A Trial of Dabrafenib, Trametinib and Hydroxychloroquine for Patients With Recurrent LGG or HGG With a BRAF Aberration	For patients with NF1: Low-grade Glioma	Phase 1 Phase 2	1–30 years
Trametinib	NCT03190915	Trametinib in Treating Patients With Relapsed or Refractory Juvenile Myelomonocytic Leukemia	Juvenile Myelomonocytic Leukaemia	Phase 2	1 month to 21 years
Binimetinib	NCT03231306	Phase II Study of Binimetinib in Children and Adults With NF1 Plexiform Neurofibromas (NF108-BINI)	Plexiform Neurofibroma	Phase 2	1 year and older

Bergqvist C et al, MEK inhibitors in RASopathies Curr Opin Oncol

Criticità per clinical trial nelle RASopatie

- Terapie limitate ai **casi gravi**, life-threatening
- **Rarità** delle singole condizione
- Variabilità **fenotipica** interindividuale
- Eterogeneità **genotipica** e plausibilmente di risposta
- Scarsa conoscenza della **storia naturale** della malattia
- Esistenza di **terapie convenzionali di supporto**
- **Molteplicità dei farmaci** a disposizione

Obiettivi di un clinical trial:

- Efficacia per la condizione in oggetto
- Tollerabilità farmaci sulla lunga distanza
- Dose ottimale
- Scelta del farmaco in maniera **genotipo-specifica**

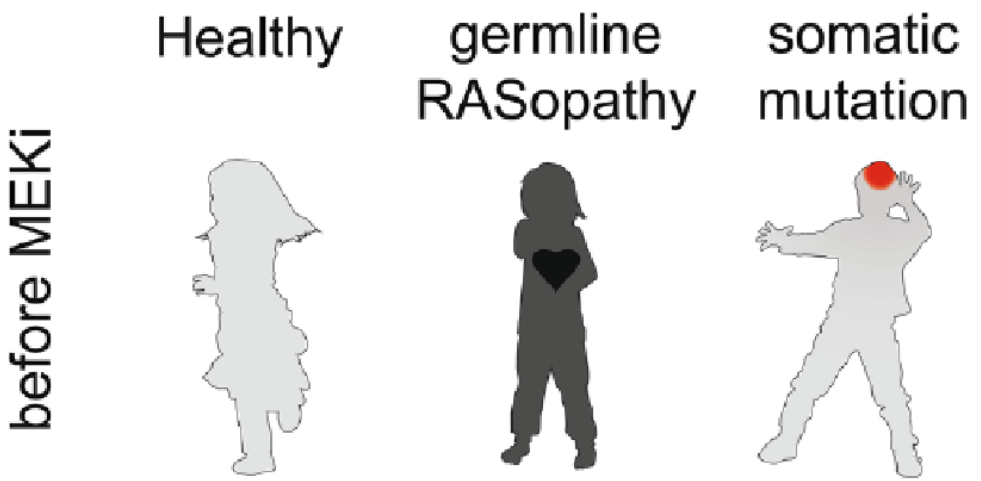
Campi di indicazione **attuali: chi curare**

Manifestazioni delle RASopatie che le rendono **complicate** o **life-threatening (o che possiamo presupporre lo diventeranno)** in assenza/esaurite le **alternative** terapeutiche

- Chilotorace/discrasie linfatiche gravi
- Cardiomiopatia progressiva
- Aritmia cardiaca
- Diascrasie ematiche e diatesi emorragica

- Epilessia?
- Mieloproliferazione?

a



maggiore **tollerabilità a lungo termine** nei modelli di RASopatie.

Possono essere selezionati in modo specifico per il **genotipo** del paziente

Trattamento precoce, prima della cardiopatia irreversibile rimodellamento, può essere la chiave per ottenere il massimo beneficio da questa strategia terapeutica

Gelb BD. New prospectives on treatment opportunities in the RASopathies. 2021

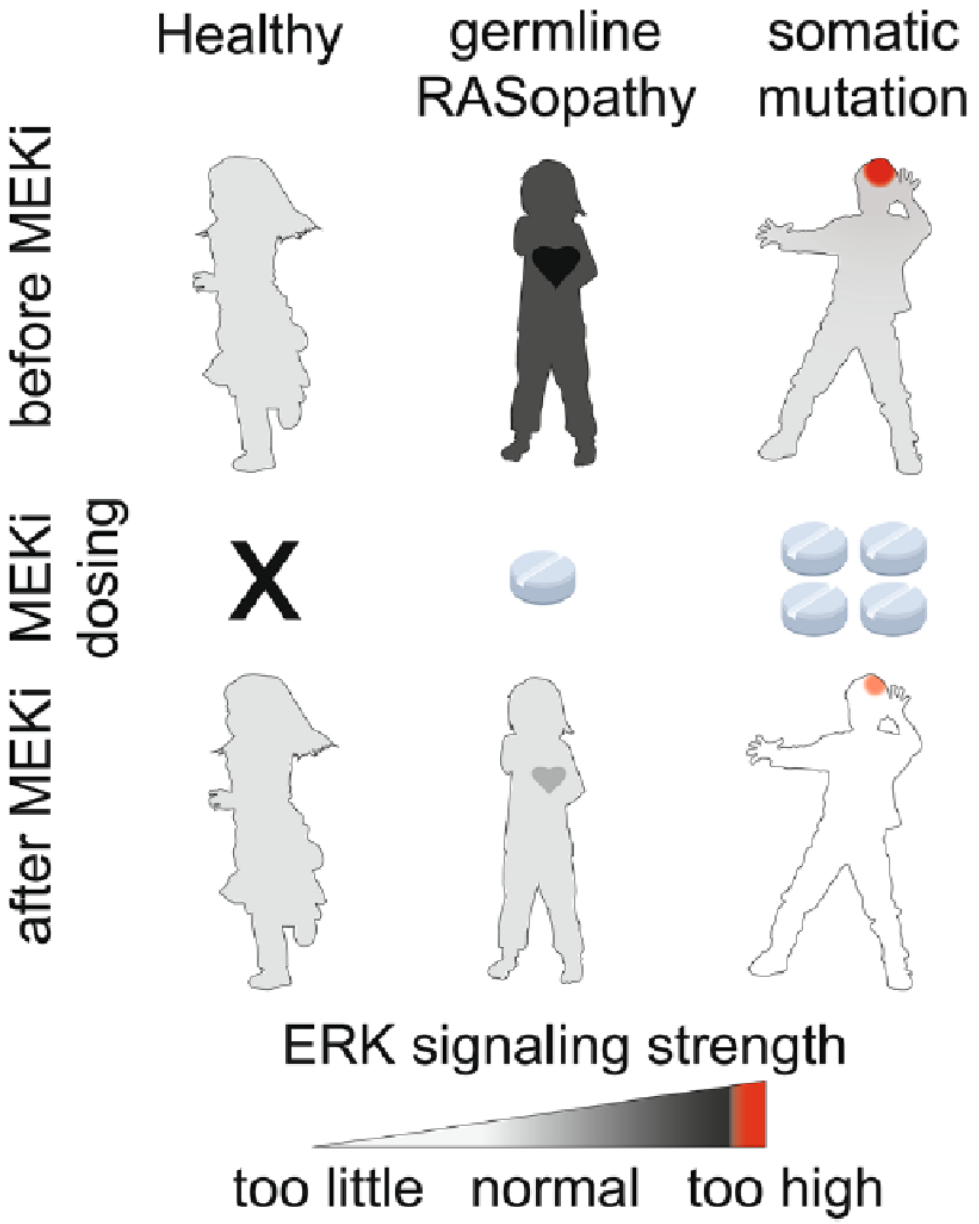
Dosi e inibizione della via

Biochimicamente, varianti osservate nel cancro sono spesso «**fortemente attivanti**», rispetto alle varianti responsabili delle RASopatie.

L'efficacia è osservata a **dosi inferiori** alla dose raccomandata in oncolgia (Jousma et al., 2015).

Dosi inferiori […] possono essere efficaci e avere maggiore **tollerabilità a lungo termine** nei modelli di RASopatie.

Possono essere selezionati in modo specifico per il **genotipo** del paziente



Trattamento precoce, prima della cardiopatia irreversibile rimodellamento, può essere la chiave per ottenere il massimo beneficio da questa strategia terapeutica

Gelb BD. New prospectives on treatment opportunities in the RASopathies. 2021

Scelta del farmaco

Short Presentations
E-Posters DGPK

MEK-Inhibition Treatment with Trametinib in a 7.7-Year-Old Girl with Noonan's Syndrome and Life-Threatening Lymphangiopathy

M. Hofbeck, A. Hanser, G. Wiegand, R. Kaulitz, M. Kumpf, L. Sieverding, M. Zenker, S. Waldmüller, G. Andelfinger

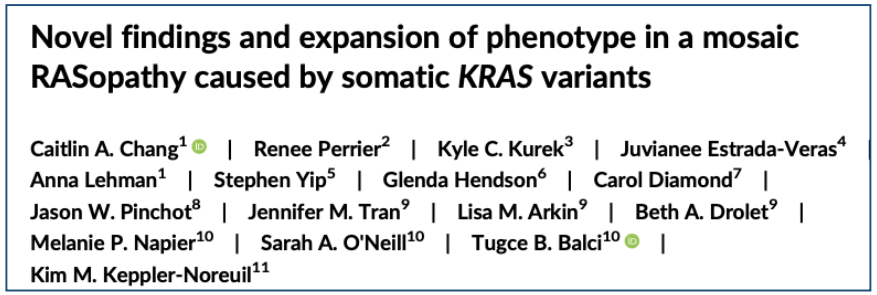
Thorac Cardiovasc Surg 2021 *PTPN11* germline

CLINICAL LETTER

Molecular Management of Multifocal Atrial Tachycardia in Noonan's Syndrome With MEK1/2 Inhibitor Trametinib

Joshua K. Meisner, MD, PhD; David J. Bradley, MD; Mark W. Russell, MD

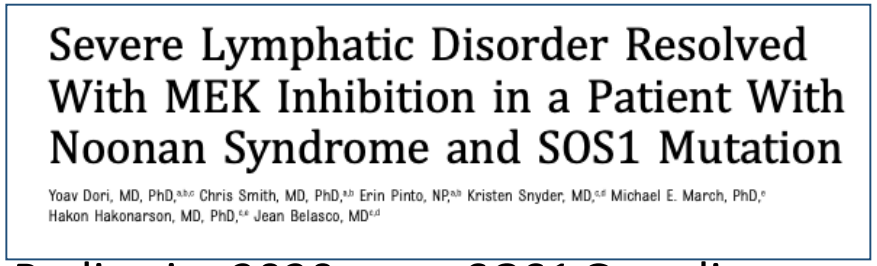
Circ Genom Precis Med 2021 *RAF1* Germline



Novel findings and expansion of phenotype in a mosaic RASopathy caused by somatic *KRAS* variants

Caitlin A. Chang[1] | Renee Perrier[2] | Kyle C. Kurek[3] | Juvianee Estrada-Veras[4] | Anna Lehman[1] | Stephen Yip[5] | Glenda Hendson[6] | Carol Diamond[7] | Jason W. Pinchot[8] | Jennifer M. Tran[9] | Lisa M. Arkin[9] | Beth A. Drolet[9] | Melanie P. Napier[10] | Sarah A. O'Neill[10] | Tugce B. Balci[10] | Kim M. Keppler-Noreuil[11]

Am J Medical Genet A 2021 *KRAS* somatic



Severe Lymphatic Disorder Resolved With MEK Inhibition in a Patient With Noonan Syndrome and SOS1 Mutation

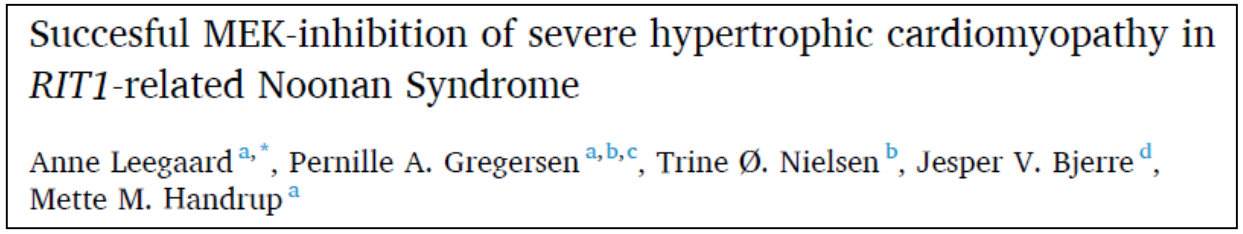
Yoav Dori, MD, PhD,[a,b,c] Chris Smith, MD, PhD,[a,b] Erin Pinto, NP,[a,b] Kristen Snyder, MD,[c,e] Michael E. March, PhD,[e] Hakon Hakonarson, MD, PhD,[c,e] Jean Belasco, MD[c,d]

Pediatrics 2020 *SOS1* Germline

Case Report: Progressive central conducting lymphatic abnormalities in the RASopathies. Two case reports, including successful treatment by MEK inhibition

Kristiana Gordon[1,2], Matthew Moore[3], Malou Van Zanten[1], Julian Pearce[2], Maxim Itkin[4], Brendan Madden[3], Lakshmi Ratnam[5], Peter S. Mortimer[1,2], Rani Nagaraja[6] and Sahar Mansour[1,7]*

Frontiers in Genetics 2022 *BRAF* Germline



Succesful MEK-inhibition of severe hypertrophic cardiomyopathy in *RIT1*-related Noonan Syndrome

Anne Leegaard[a,*], Pernille A. Gregersen[a,b,c], Trine Ø. Nielsen[b], Jesper V. Bjerre[d], Mette M. Handrup[a]

Eu J Medical Genet A 2022 *RIT1* germline

Severe Lymphatic Disorder and Multifocal Atrial Tachycardia Treated with Trametinib in a Patient with Noonan Syndrome and SOS1 Mutation

Michele Lioncino[1,†], Adelaide Fusco[1,†], Emanuele Monda[1], Diego Colonna[2], Michelina Sibilio[3], Martina Caiazza[1], Daniela Magri[4], Angela Carla Borrelli[4], Barbara D'Onofrio[1], Maria Luisa Mazzella[1], Rossella Colantuono[4], Maria Rosaria Arienzo[4], Berardo Sarubbi[2], Maria Giovanna Russo[5], Giovanni Chello[4] and Giuseppe Limongelli[1,6,*]

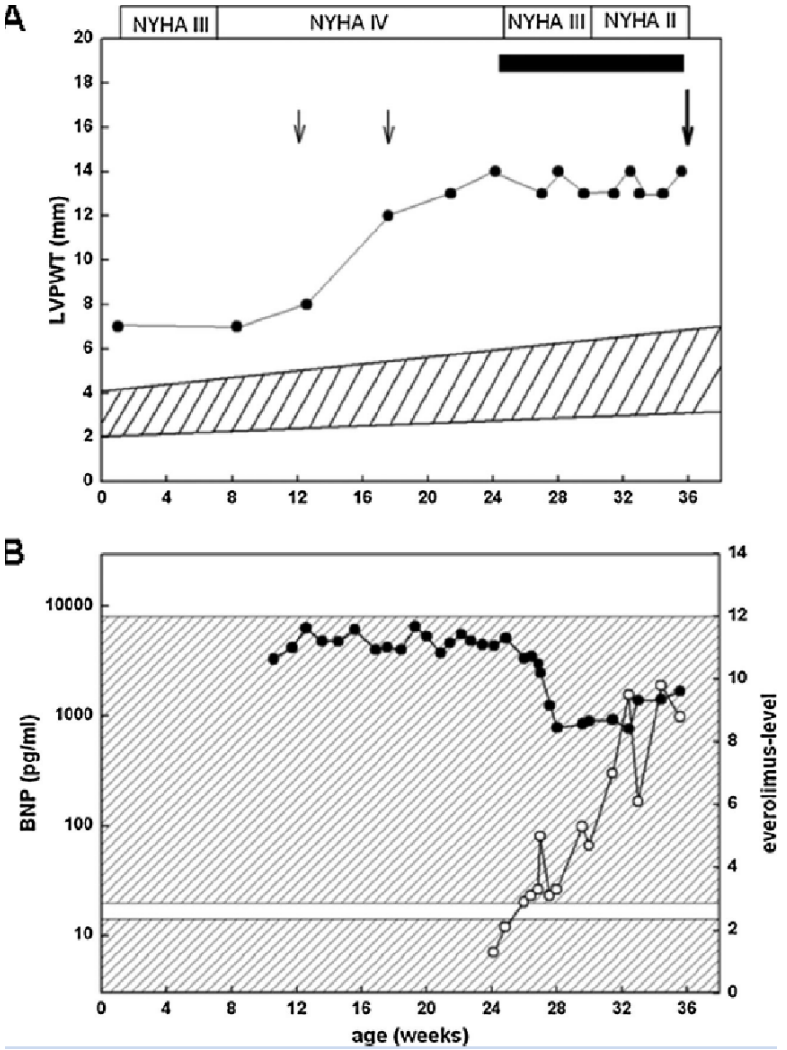
Genes 2022 *SOS1* Germline

Metting an unmet need: uso **compassionevole** delle «small molecules therapies»

Prima estrapolazione degli studi sui topi alla patologia umana con la somministrazione dell'inibitore mTOR (mTORi) everolimus in un bambino con NS-multiple lentigines e HCM biventricolare grave, rapidamente progressiva con esordio neonatale o prenatale con conseguente scompenso cardiaco (Hahn et al., 2015).

Da HCM progressiva a significativo miglioramento clinico in attesa del trapianto di cuore (+3 mesi)

PTPN11 (c.1528C>G; p.Q510E)



Hahn et al (2015). Rapidly progressive hypertrophic cardiomyopathy in an infant with Noonan syndrome with multiple lentigines: Palliative treatment with a rapamycin analog. American Journal of Medical Genetics Part A, 167A(4), 744–751.

Table 1. Comparison of Dosing, Pharmacologic Characteristics, and Clinical Trial Experience of Five MEK Inhibitors

Agent	Available Formulations	Dosage in NF1	Adult Cancer Dosage	Available Literature and Use in NF1	Dosage Forms	CNS Penetration	Grade 3/4 AEs (>5%)	Half-life	Metabolism	Excretion	Distinguishing Features	Availability and Approval
Binimetinib (MEK162, ARRY-162)	Tablet; pharmacy-prepared suspension	32 mg/m^2/dose BID continuous (max dose 45 mg PO BID) (For adults with PN, max dose 30 mg PO BID[6])	45 mg PO BID (melanoma)	Adult trials in colorectal cancer (>200 pts treated with binimetinib in combination)[7] Pediatric phase 1 (19 pts, 17 with LGG)[8]	15 mg	Diffuse penetration (brain and tumor) in rodent model[8]	Anemia, fatigue, dyspnea[9]	3.5 hours[10]	UGT1A1 glucuronidation. Active metabolite produced by CYP1A2 and CYP2C19.[10]	Feces and urine[10]	Transient muscle weakness may be a common drug-specific and pediatric-specific toxicity	FDA and EMA approved in combination with encorafenib for BRAF-mutant melanoma
Cobimetinib (GDC-0973, XL-518)	Tablet	60 mg PO QD (21 days on, 7 days off)	60 mg PO QD (21 days on, 7 days off) (melanoma)	Adult trials in melanoma (>200 pts received cobimetinib in combination)[11,12]	20 mg	Brain to plasma ratio (Kp) at 6-hour postdose was 0.3 in WT mice[13]	Diarrhea, rash, fatigue[14]	43.6 hours[15]	CYP3A4, also by direct glucuronidation via UGT2B7[15]	Feces via biliary excretion[15]		FDA and EMA approved in combination with vemurafenib for metastatic melanoma
Mirdametinib (PD-0325901)	Capsule and liquid formulations available	2 mg/m^2/dose bid (max 4 mg) 3 weeks on, 1 week off	15 mg BID, 5 days on/2 days off, 3 weeks on, 1 week off (NSCLC)	Phase 2 (19 with NF1-PN)[16]	1 mg	Excellent penetration at clinically relevant doses[17]	Lymphopenia, dehydration, fatigue, diarrhea, rash, confusion, dyspnea, hallucination, alkaline phosphatase abnormality, hyponatremia, hypocalcemia[18]	8.6 hours[19]	Glucuronidation and oxidation[19]	Feces via biliary excretion[19]	Can be administered with food, excellent CNS penetration	Not FDA or EMA approved
Selumetinib (AZD6244, ARRY-142886)	Capsule	25 mg/m^2 PO BID continuous (max dose 50 mg PO BID)	75 mg PO BID (melanoma)	Phase 1 (38 with LGG, 24 with NF1-PN)[20,21] Phase 2 (50 LGG [25 with NF1] and 50 NF1-PN)[22,23] Ongoing studies in NF1-LGG, non-NF1 LGG, and NF1-PN	10 mg 25 mg	Poor CSF penetration in primate model; effective in clinical trials of low-grade glioma[24]	CK increase, rash, neutropenia, paronychia, diarrhea, weight gain[22,23]	5.3-7.2 hours[25]	CYP3A4, also by direct glucuronidation via UGT1A1 and -1A3[25]	Feces and urine[25]	Extensively studied in NF1	FDA and EMA approved for children with symptomatic, inoperable NF1 plexiform neurofibroma
Trametinib (GSK1120212)	Tablet; suspension as compassionate use	0.032 mg/kg (<6 years old) 0.025 mg/kg (>6 years old) (max 2 mg) various schedules	2 mg PO QD (melanoma)	Adult studies in melanoma (in combination)[26] Phase 1 in children (78 pts including at least 26 with NF1)[27,28]	0.5 mg 1 mg 2 mg	Brain to plasma ratio (Kp) in WT mice = 0.15[29]	Hypertension, rash[30]	4-5 days[30]	Deacetylation alone or in combination with hydroxylation[30]	Feces and urine[30]	Suspension available as compassionate use	FDA and EMA approved for BRAF-mutant melanoma, and (in combination with dabrafenib) for BRAF-mutant NSCLC

de Blank PMK et al. MEK inhibitors for neurofibromatosis type 1 manifestations: Clinical evidence and consensus Neuro Oncol . 2022.

Primo impiego di MEK-inibitore: **Trametinib**

RIT1 c.104G>C; p.Ser35Thr
RIT1 c.246T>G, p.Phe82Leu

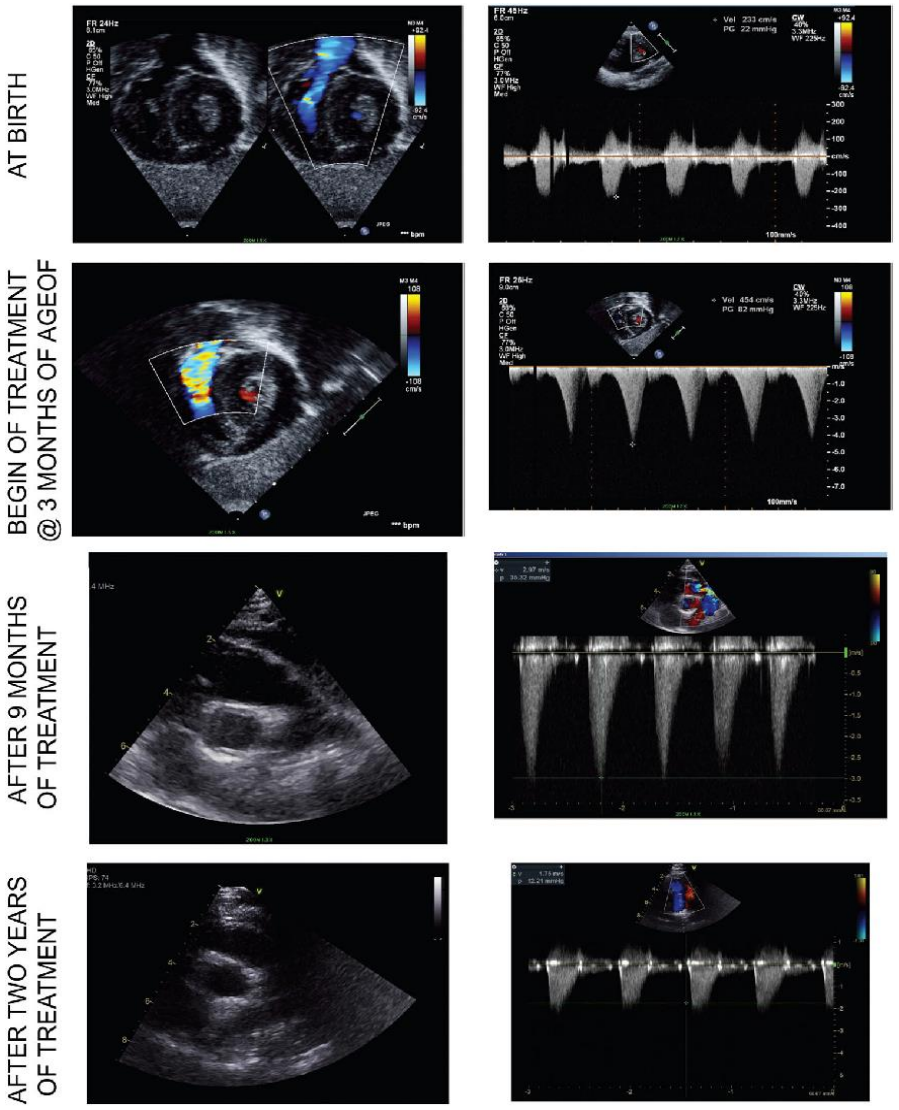
3 mesi di trattamento

Miglioramento rapido dello **scompenso**
Riduzione del **NT-pro-BNP**
Riduzione **gradiente** transvalvolare e ostruzione all'efflusso
Riduzione dello **spessore** settale e trasmurale ventricoli ipertrofici
Risoluzione aritmia e versamento chiloso

Ripresa dello scompenso dopo cessazione

TABLE 1 Evolution of Clinical and Echocardiographic Parameters at Birth, at Start of Therapy and at 3.5- and 17-Month Follow-Up

	Patient 1				Patient 2			
	At Birth (38 Weeks)	At Start of Therapy	After 3.5 Months of Therapy	After 17 Months of Therapy	At Birth (36 Weeks)	At Start of Therapy	After 3.5 Months of Therapy	After 17 Months of Therapy
Length, cm (percentile)	51.5 (P90)	62 (P78)	66 (P69)	86 (P99)	49 (P46)	53 (<P3)	62 (P72)	79 (P54)
Weight, kg (percentile)	4.2 (P99)	6.18 (P65)	8 (P86)	16 (>P99)	3.05 (P35)	4.49 (<P3)	5.95 (P46)	10.8 (P81)
Weight/length ratio, percentile	P90	P75	P75	>P97	P50	P75	P25	P50
Left ventricular mass index, g/height$^{2.7}$ by echo (percentile) (4)	114.5 (>>P99)	135.7 (>>P99)	103.5 (>>P99)	61.6 (P90-95)	54.9 (P50)	111.0 (>>P99)	65.4 (P90)	54.0 (P75-90)
Left ventricular mass, g/m^2 by CMR	N/A	75	59	N/A	N/A	119	65.4	N/A
NT-proBNP	N/A	N/A	2,470	37	N/A	127,560	8,217	172
Left ventricular outflow tract gradient	12	49	73	40	20	40	21	Normal
Right ventricular outflow tract gradient	24	62	45	8	20	45	45	21
Infundibular right ventricular outflow tract gradient	0	49	0	0	0	36	16	0
Concomitant medications	N/A	Propranolol Trametinib	Propranolol Trametinib	Propranolol Trametinib	N/A	Propranolol Trametinib	Propranolol Trametinib	Propranolol Trametinib

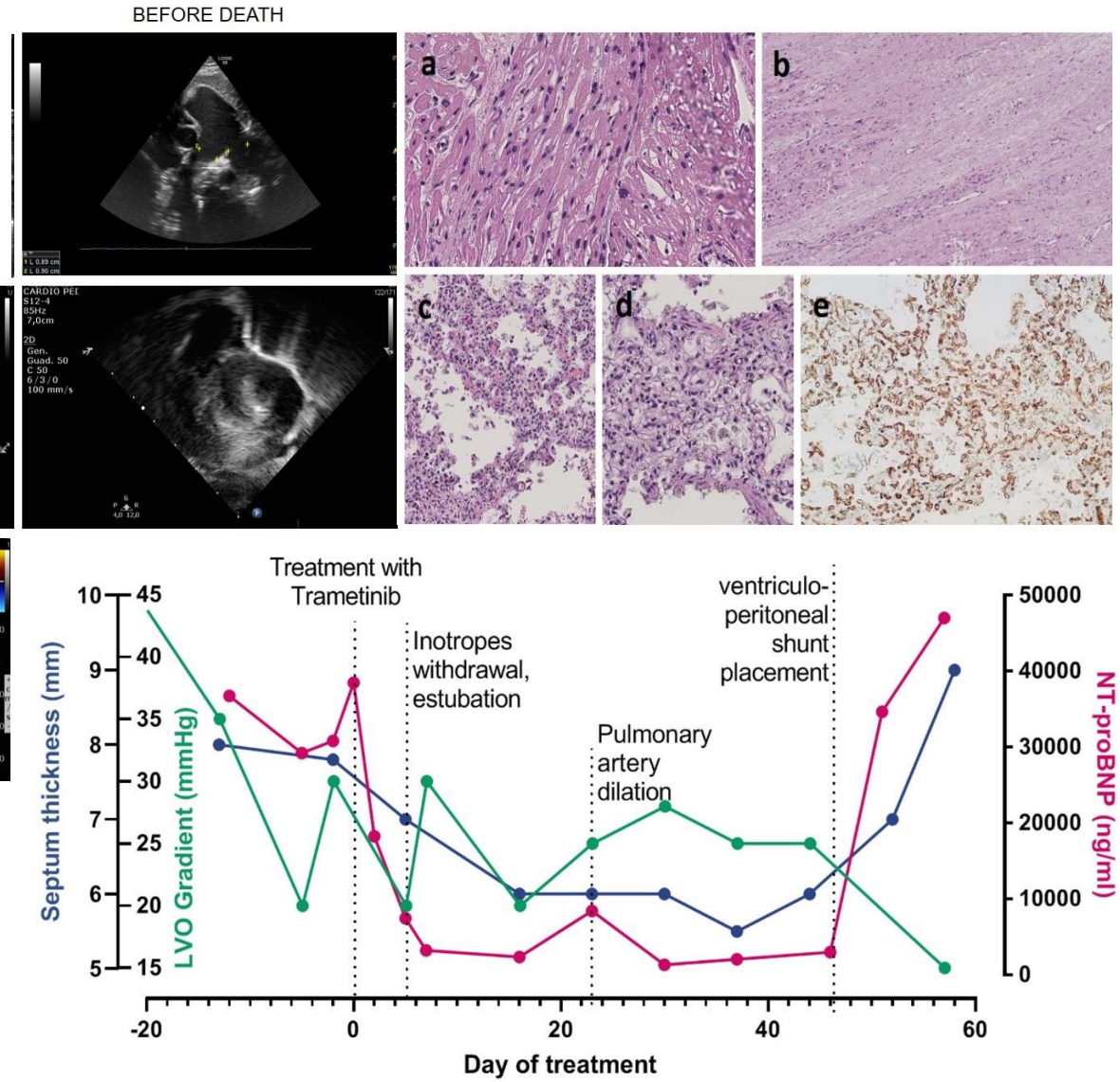


Andelfingeret al Hypertrophic cardiomyopathy in Noonan syndrome treated by MEK-inhibition. Journal of the American College of Cardiology, 73

Article

MEK inhibition in a newborn with *RAF1*-associated Noonan syndrome ameliorates hypertrophic cardiomyopathy but is insufficient to revert pulmonary vascular disease

Alessandro Mussa[1], Diana Carli[1], Elisa Giorgio[2], Anna Maria Villar[3], Simona Cardaropoli[1], Caterina Carbonara[4], Maria Francesca Campagnoli[4], Paolo Galletto[4], Martina Palumbo[5], Simone Olivieri[1], Claudio Isella[5,6], Gregor Andelfinger[7], Marco Tartaglia[8], Giovanni Botta[9], Alfredo Brusco[10], Enzo Medico[5,6], and Giovanni Battista Ferrero[1,11,*]



La nostra esperienza nelle CMP

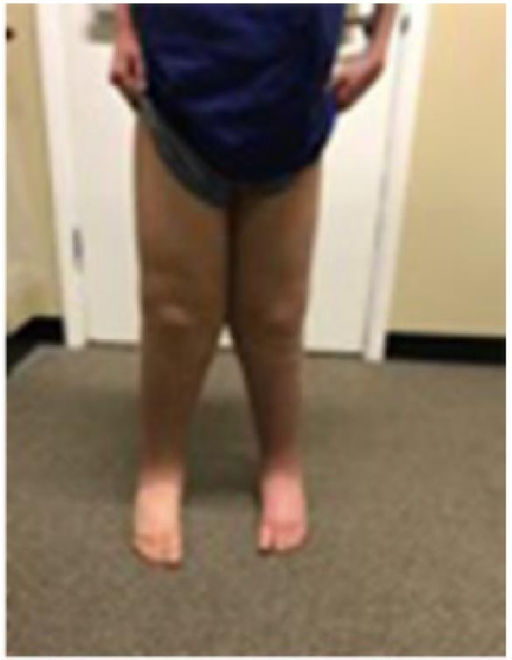
Trametinib in 4 casi RAF1:c.770C>T

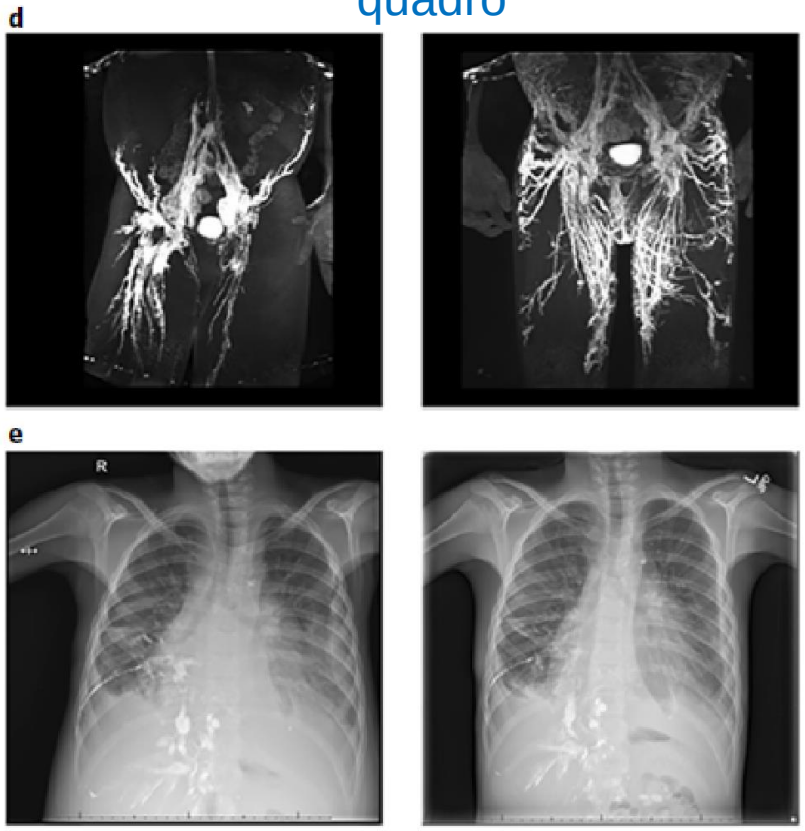
Buona risposta, ottima in 2 casi «giovani»
2 casi con effetti collaterali cutanei, alopecia, iniziale imbibizione del disco ottico

Disordini/effusioni linfatiche

***ARAF* mutation (c.640T>C:p.S214P)**
12-year-old boy
Grave anomalia linfatica toracica e corporea
Non responsivo a sirolimus

Trametinib 0.025 mg/kg per day
Efficace e rapida risoluzione del quadro





6 pazienti con NS e grave malattia linfovascolare sono (Dori et al., 2020; D. Li et al., 2019; Lioncino et al., 2022; Nakano et al., 2022).

In tutti questi pazienti, miglioramento significativo o risoluzione della malattia linfovascolare

con iniziale risposta a partire da circa 2 giorni a 1 mese dopo l'inizio del trattamento alla risposta sostenuta a 12 mesi dopo l'inizio del trattamento

Li, D., March, M. E., Gutierrez-Uzquiza, A., Kao, C., Seiler, C., Pinto, E., … Hakonarson, H. (2019). ARAF recurrent mutation causes central conducting lymphatic anomaly treatable with a MEK inhibitor. Nature Medicine, 25(7), 1116–1122.

Chilotorace refrattario

SOS1 c.2536G.A: p.[E846K]

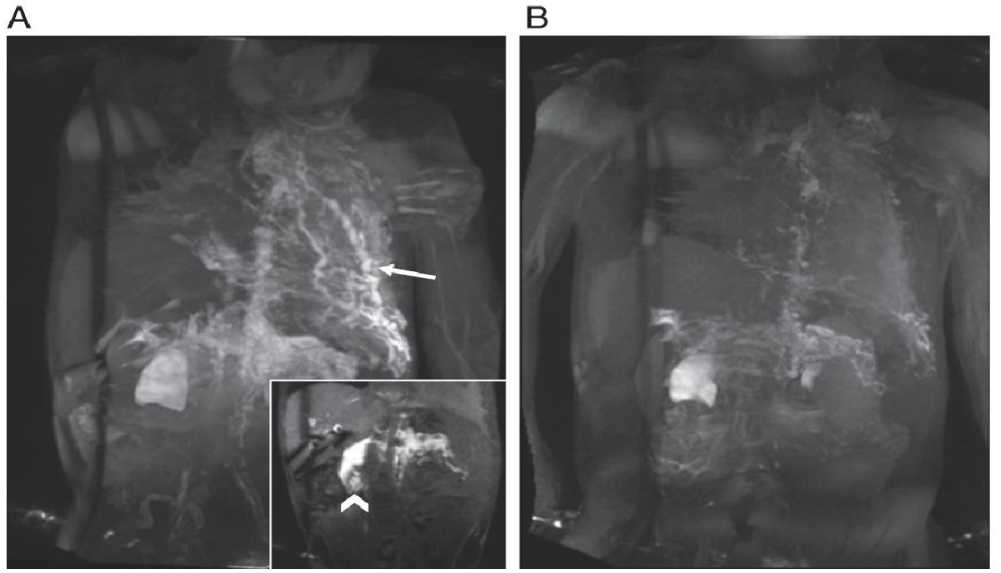
5 anni, chilotorace persistente ed ingravescente

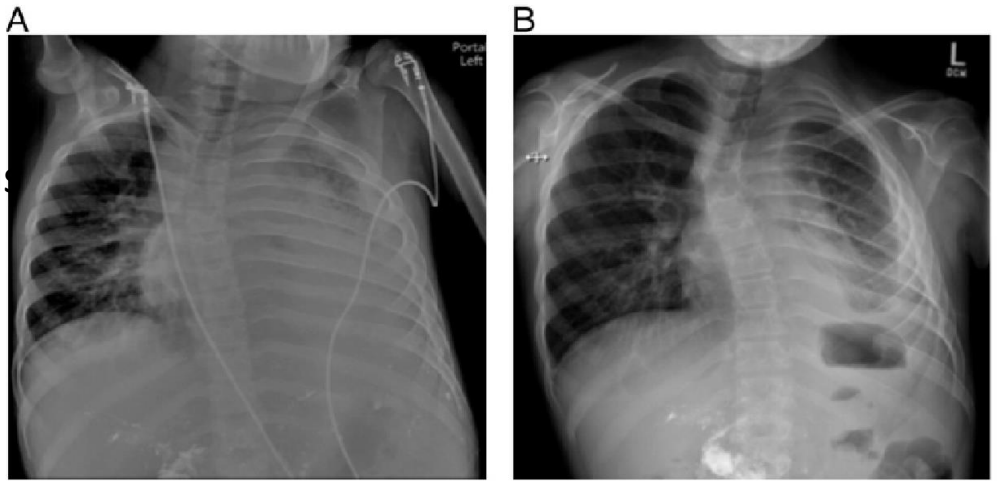
Trametinib «low-dose» 0.01 mg/kg
Riassorbimento chilotorace
Normalizzazione Albumina e Hb
(non più trasfusione-dipendente)

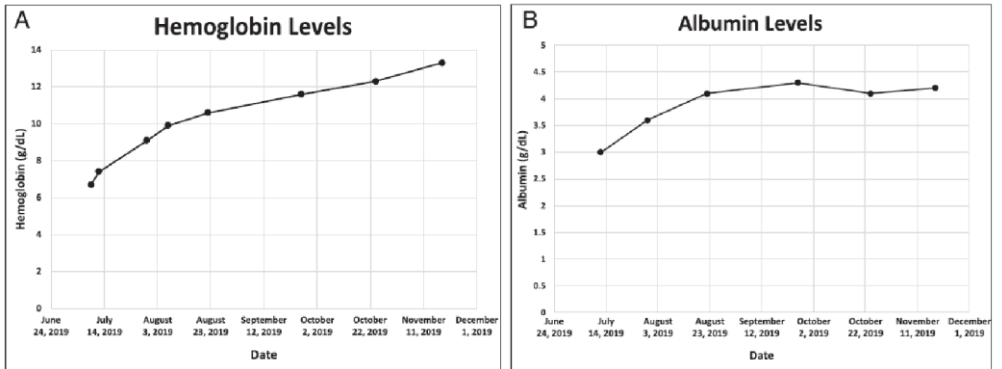
RIT1 gene (NM_006912.6 c.246T>G, p.Phe82Leu)
HCM + chilotorace refrattario a dieta, diuretici, ocrtreotide e sirolimus
Trametinib 0.018 mg/kg/day.
Riassorbimento e normalizzazione albumina serica

PTPN11 (c.854T>C; p.Phe285Ser)
SOS1 gene (c.1322G>A; p.Cys441Tyr)

Risoluzione del disordine mieloproliferativo







Nakano, (2022). Trametinib for refractory chylous effusions and systemic complications in children with Noonan syndrome. The Journal of Pediatrics, 248, 81–88.e1.

Dori, (2020). Severe lymphatic disorder resolved with MEK inhibition in a patient with Noonan syndrome and SOS1 mutation. Pediatrics, 146(6), 1–5.

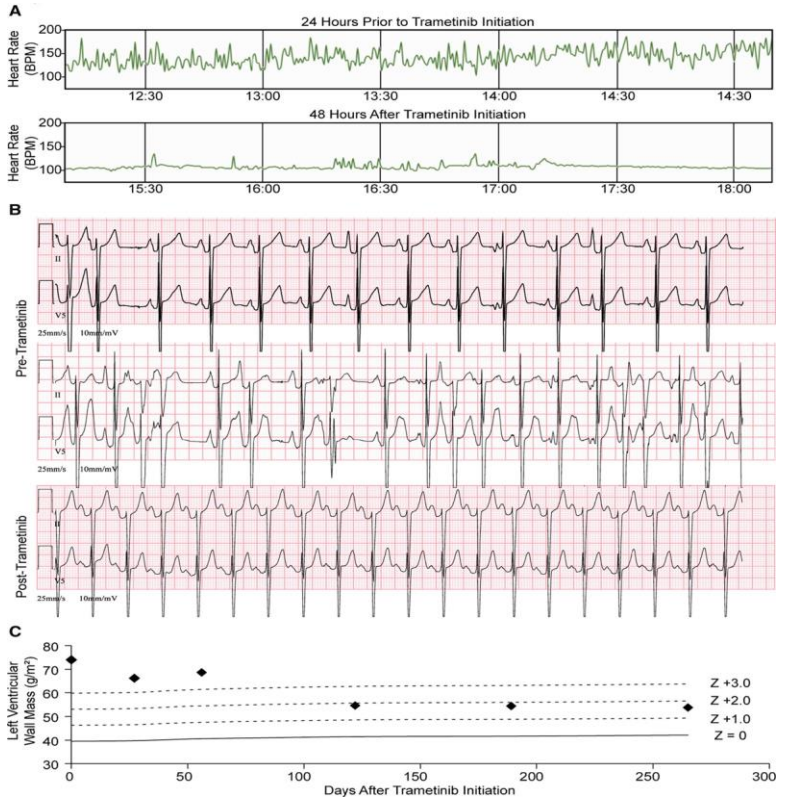
Tachiaritmie atriali

RAF1 c.770C>T, p.S257L

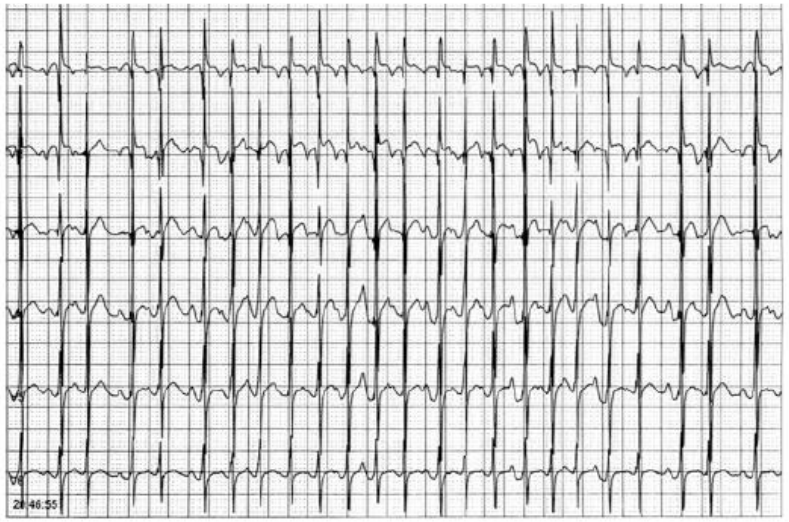
Ectopie atriali ad alta frequenza, HCM
Peggioramento con Insufficienza respiratoria e cardiaca
Cardioversioni, terapia massimale con antiaritmici
Chilotorace recidivamente

Trametinib 0.025 mg/kg per day

Risposta con ritorno a ritmo gestibile
migliorata HCM e scompenso rispetto ai 6 mesi iniziali



Meisner, et al (2021). Molecular management of multifocal atrial tachycardia in Noonan's syndrome with MEK1/2 inhibitor trametinib. Circulation: Genomic and Precision Medicine



SOS1 c.1655G>C, p.Arg552Thr

Chilotorace + Aritmia atriale multifocale + Scompenso + DIV+SP
Propranololo, flecainide, amiodarone: scarsa efficacia
Trametinib 0,02 mg/kg/day → risoluzione chilotorace e aritmia in 4 giorni!

Case Report

Severe Lymphatic Disorder and Multifocal Atrial Tachycardia Treated with Trametinib in a Patient with Noonan Syndrome and SOS1 Mutation

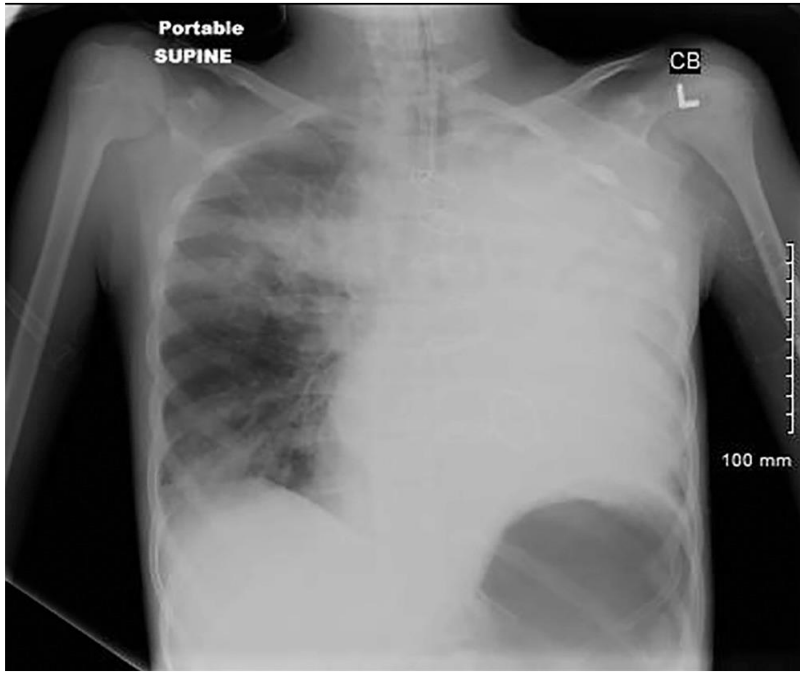
Michele Lioncino [1,†], Adelaide Fusco [1,†], Emanuele Monda [1], Diego Colonna [2], Michelina Sibilio [3], Martina Caiazza [1], Daniela Magri [4], Angela Carla Borrelli [4], Barbara D'Onofrio [1], Maria Luisa Mazzella [1], Rossella Colantuono [4], Maria Rosaria Arienzo [4], Berardo Sarubbi [2], Maria Giovanna Russo [5], Giovanni Chello [4] and Giuseppe Limongelli [1,6,*]

Selumetinib e bleeding

PTPN11 Q510E

extracorporeal membrane
oxygenation (ECMO) e complicanze d'intervento
cardiologico per displasia valvolare

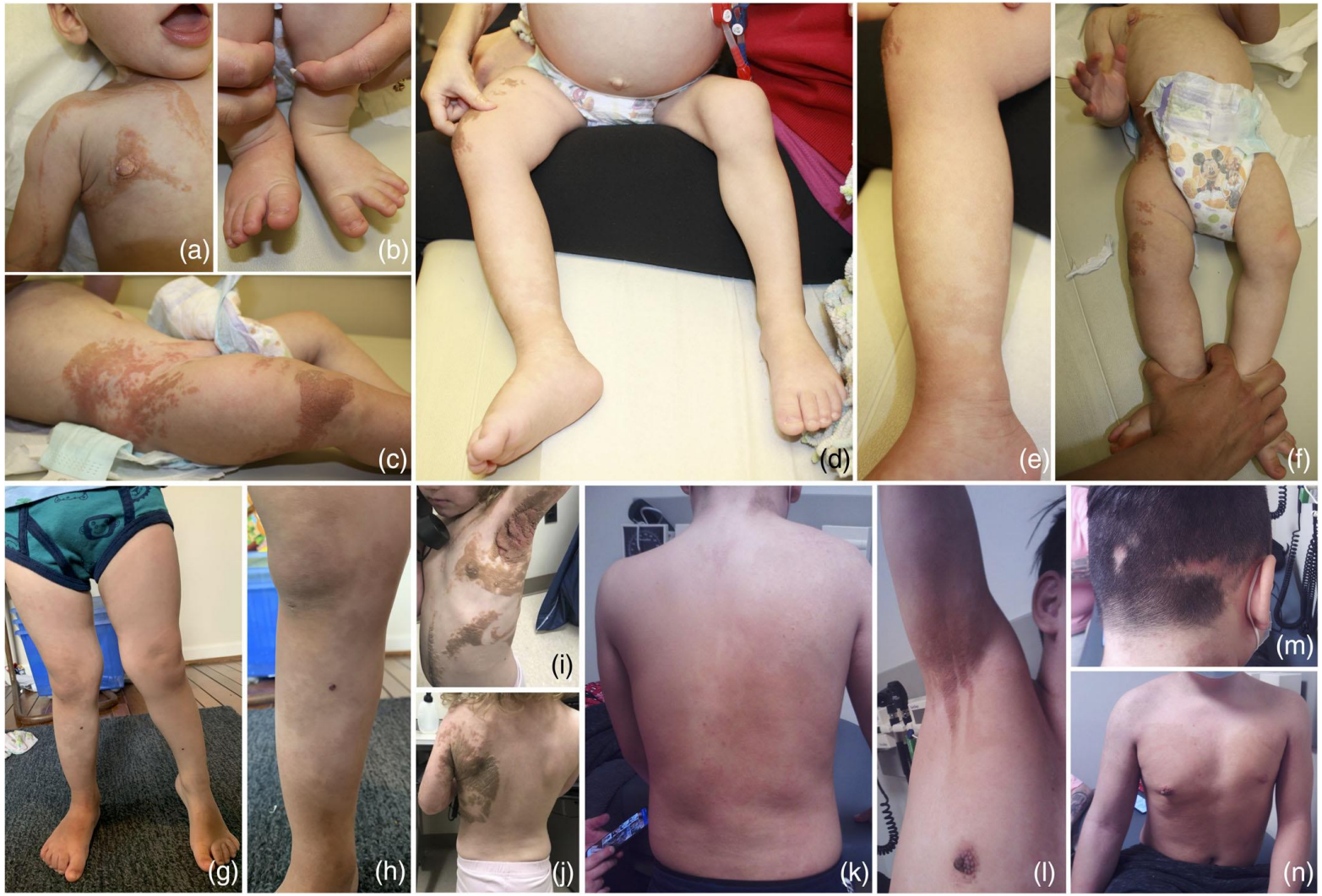
Emorragia polmonare diffusa e massiva
neo-angiogenesi polmonare con vasi collaterali
Sanguinamenti ricorrenti e non controllabili



Selumetinib for Refractory Pulmonary and Gastrointestinal Bleeding in Noonan Syndrome

Abhishek Chakraborty, MBBS, MD,[a] Gary Beasley, MD,[a] Hugo Martinez, MD,[a] Rohith Jesudas, MD,[b] Pilar Anton-Martin, MD,[a] Georgios Christakopoulos, MD,[b] Jennifer Kramer, MD[a]

Iperaccrescimento a mosaico (KRAS)



KRAS p.Gln61His
15 anni, F

Fistola AV nasale
Epistassi multiple ingravescenti
Anemizzazione e complicazioni locali
Vari interventi infruttuosi
Effetti collaterali da sirolimus

Successo terapeutico con Tametinib con effetti collaterali cutanei limitati nel tempo e contenuti

Novel findings and expansion of phenotype in a mosaic RASopathy caused by somatic *KRAS* variants

Caitlin A. Chang[1] | Renee Perrier[2] | Kyle C. Kurek[3] | Juvianee Estrada-Veras[4] | Anna Lehman[1] | Stephen Yip[5] | Glenda Hendson[6] | Carol Diamond[7] | Jason W. Pinchot[8] | Jennifer M. Tran[9] | Lisa M. Arkin[9] | Beth A. Drolet[9] | Melanie P. Napier[10] | Sarah A. O'Neill[10] | Tugce B. Balci[10] | Kim M. Keppler-Noreuil[11]

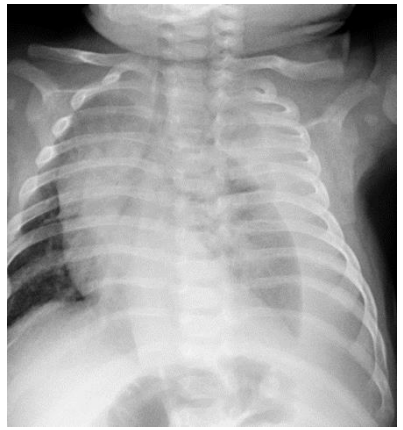
Cutaneous skeletal hypophosphatemia syndrome

NRAS: c.182A > G;p.(Gln61Arg)

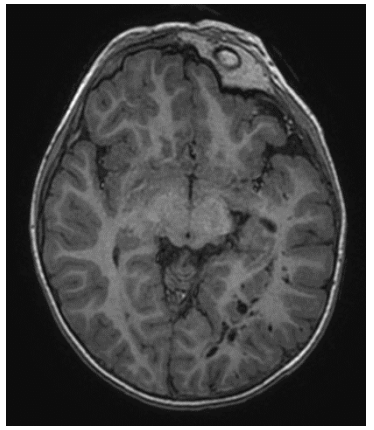
Amartomi cutanei

Nevo serorroico e menocitario

Chilotorace

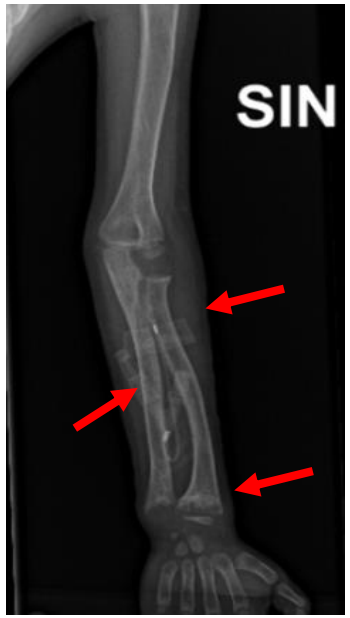


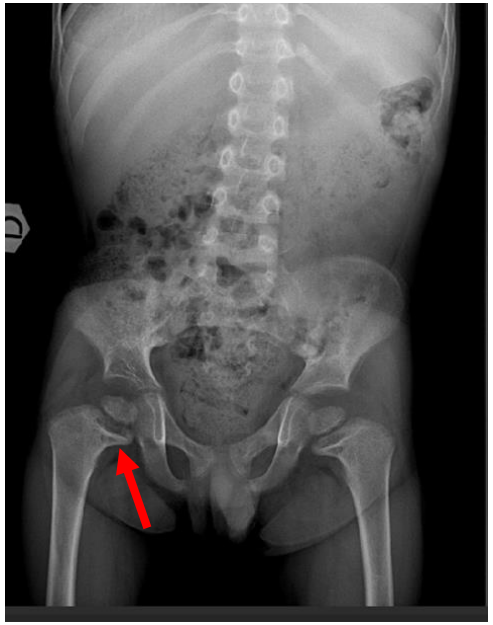
Atrofia e lipoma cerebrale

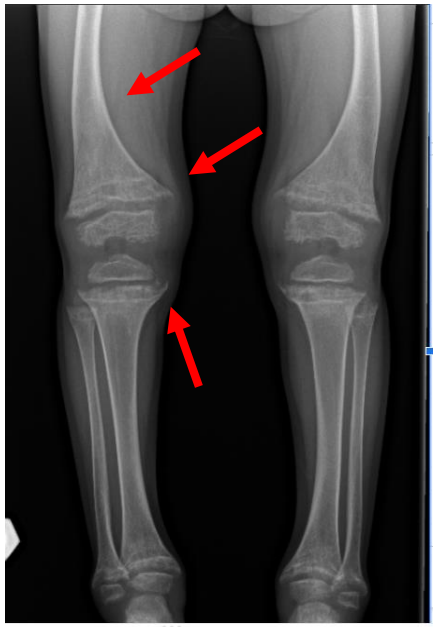


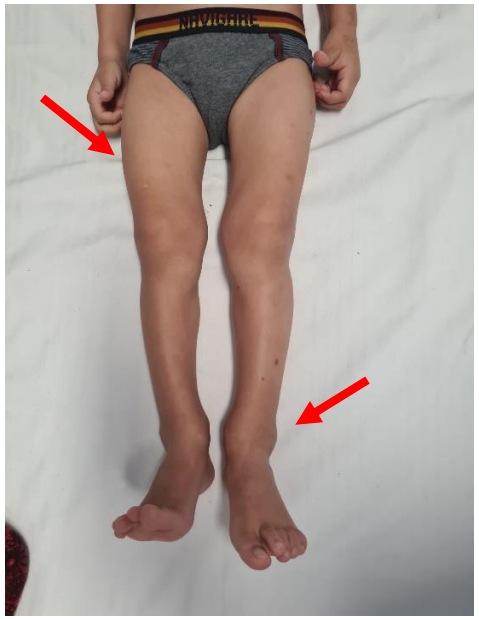
Rachitismo ipofosfatemico severo (life-threatening)

Scarsi risultati con **sirolimus, nessuna risposta a fosfati-vitD**





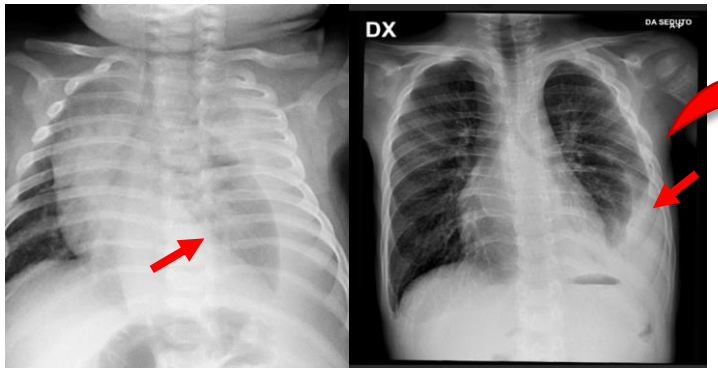


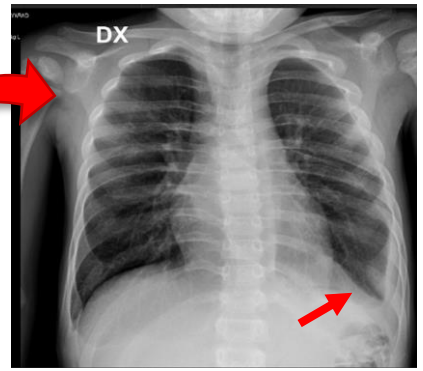


Trametinib 0,025 mg/kg/day

Normalizzazione densità ossea

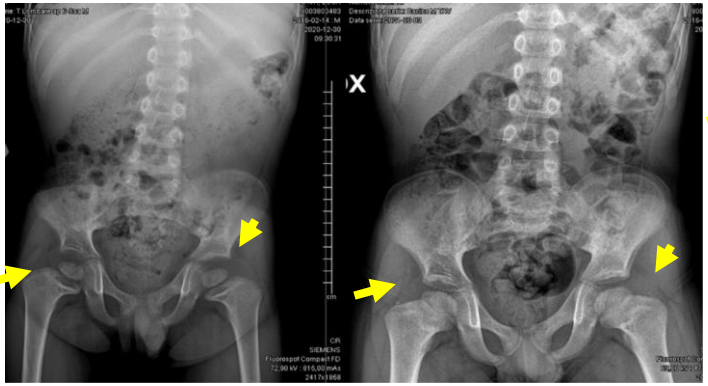
	Baseline (t0)	18 months of treatment
Rickets Severity Score	10/10	6/10
DXA (bone density)	-2,3 SDS	+1,1 SDS

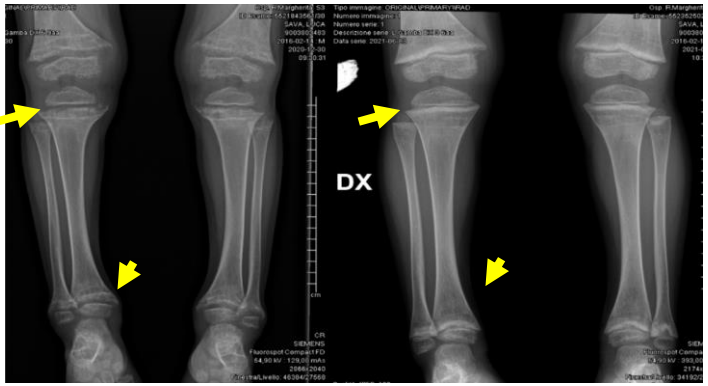




Riassorbito versamento pleurico/ chilotorace

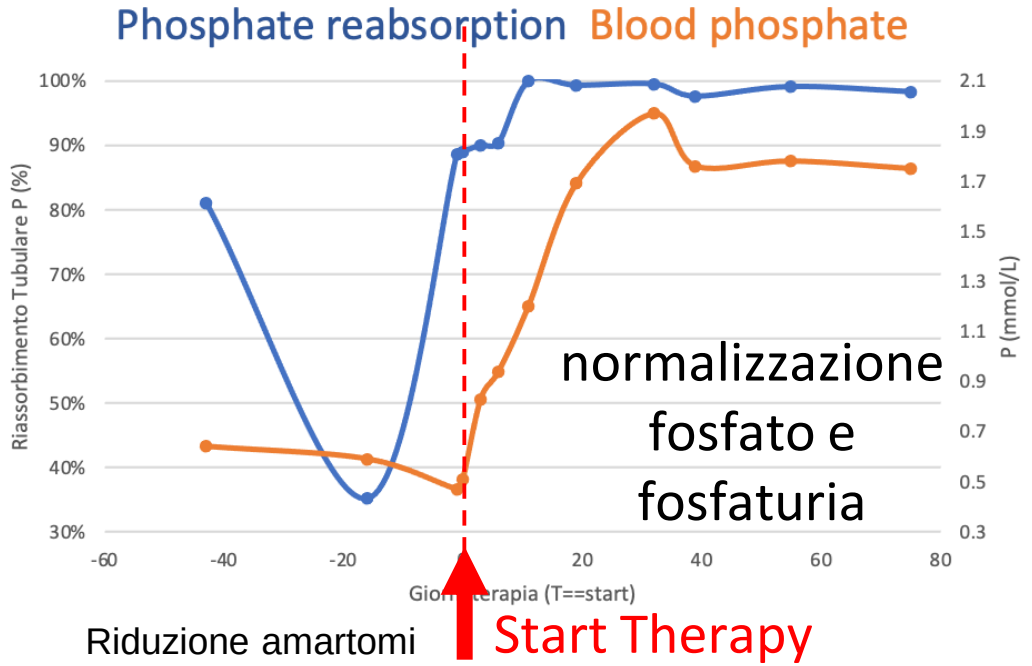
BEFORE **AFTER 6 MONTHS**



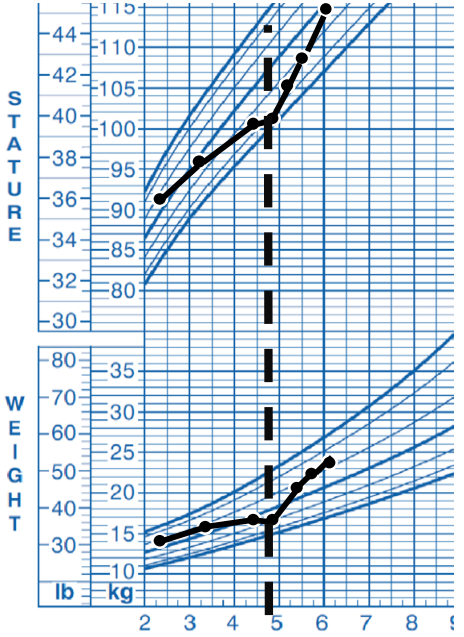


BEFORE **AFTER 6 MONTHS** **BEFORE** **AFTER 6 MONTHS**

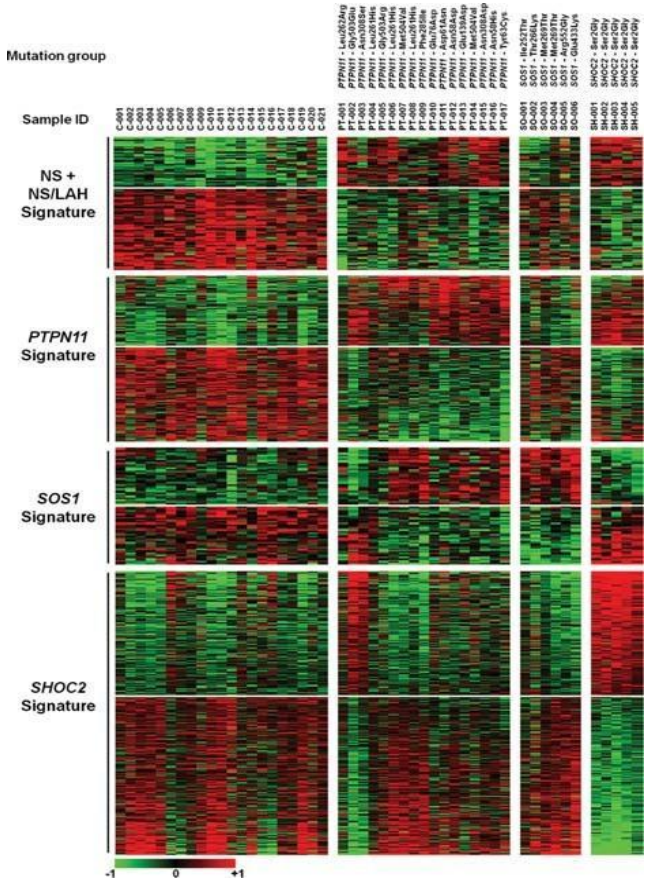
Riduzione dello score per rachitismo



Catch-up growth

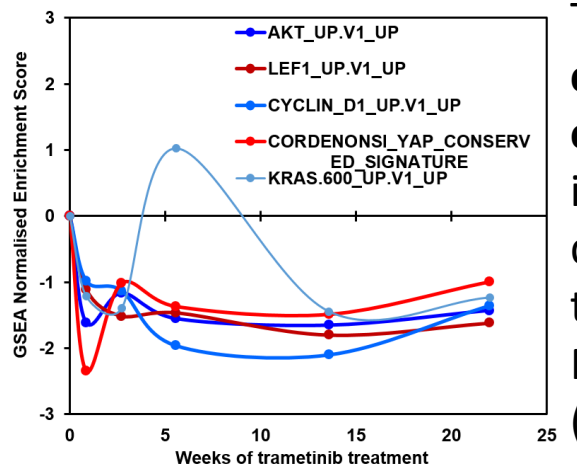


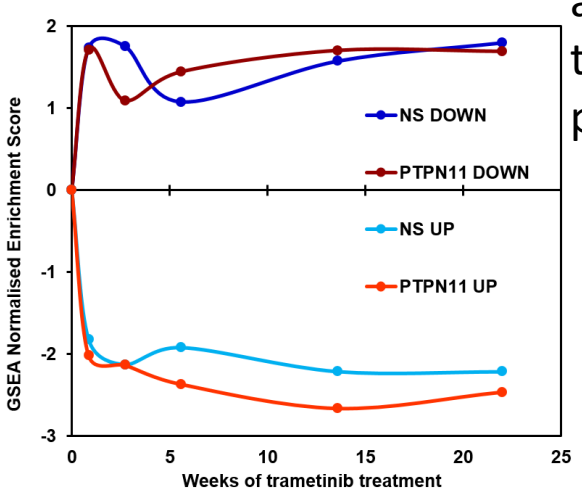
RASopathy RNA signatures on blood under MEK-inhibitor treatment



RNA seq on PBMCs before treatment and at different times during treatment highlights treatment-induced expression changes in previously described blood signatures upregulated in the RASopathies

Ferrero et al, Hum Mut 2012





Trametinib-induced **changes in the expression of signatures** previously identified as downmodulated by trametinib in PBMCs of a Noonan Syndrome patient (Mussa et al, Genes, 2021), at various times of trametinib treatment vs. pretreatment.

Expression of NS signatures is completely reverted by trametinib

Mussa et al, Genes 2021

RNAseq signature potenzialmente utile per definire e quantiticare la risposta alla terapia e monitorarla nel tempo

Conclusioni

1. Abbiamo curato più topi che umani
2. Necessitiamo di trial, non saremo in grado di farne di perfetti
3. L'esperienze **in vivo** in contesti **critici** con **MEK-inibitori** e PI3K-inibitori sono tutte **positive** e con effetti collaterali limitati

Questioni aperte

Risposta diversa in diverse varianti
Durata del trattamento e tempistica
Effetti collaterali a distanza
Rebound, recidive, tachifilassi, finestre critiche?
Dosaggio ottimale?

Approccio pragmatico ed etico ai casi di RASopatia senza alternativa terapeutica