Children's Oncology Group
ARST1921
Phase 2 Study of a γ-Secretase Inhibitor, Nirogacestat (PF-03084014), in Children and Adolescents with Progressive, Unresectable Desmoid Tumors

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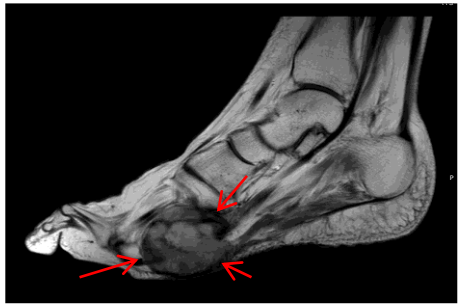
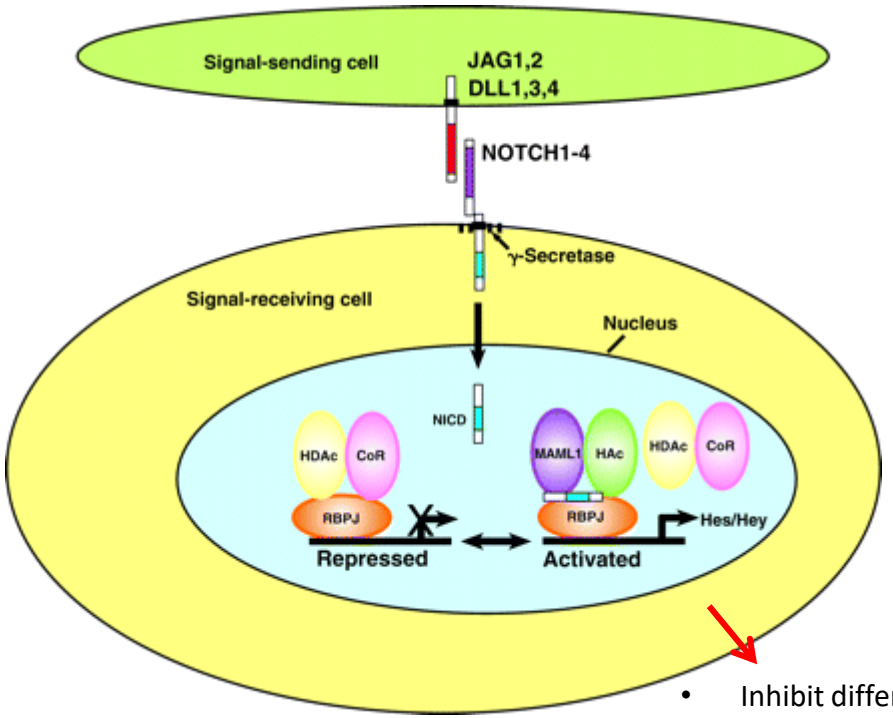
Desmoid Tumors

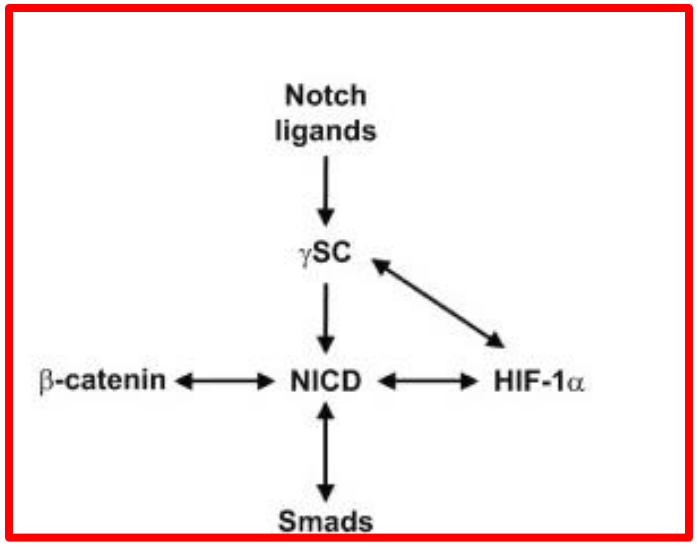
- Wide range of behaviors
  - Spontaneous regression, stable to rapidly growing
  - Low potential to metastasize, but can be locally aggressive
- Most have mutation in β-catenin and less commonly in APC gene (regulator of β-catenin)
- Treatment
  - Surgery (first line, if feasible)
  - Radiation
  - Ablation techniques
  - Systemic therapy: cytotoxic chemotherapy, anti-estrogen, NSAIDS, hydroxyurea, tyrosine kinase inhibitors (e.g. sorafenib), and recently **γ-secretase inhibitor**



Notch Signaling



- Inhibit differentiation
- Promote survival
- Accelerate proliferation



Borggrefe et al. Biochimica et Biophysica Acta 2016

Nirogacestat (PF-03084014)

- Potent, selective, reversible inhibitor of γ-secretase at IC50 < 10 nM
  - Initially developed for Alzheimer's Disease
    - Development stopped due to poor CNS penetration
- Growth inhibition in xenograft models of T-ALL, pancreatic CA, breast CA, CRC
- Initially developed by Pfizer/Pfizer Cures, now Springworks Therapeutics

Adult Phase I Study with Dose Expansion Cohort

- Relapsed solid tumors, including desmoid tumors
- 64 patients enrolled
  - 41 patients in dose-finding
- Tested doses range of 20-330 mg PO BID in 21 day cycles
- 3+3 design

Messersmith et al. CCR 2014

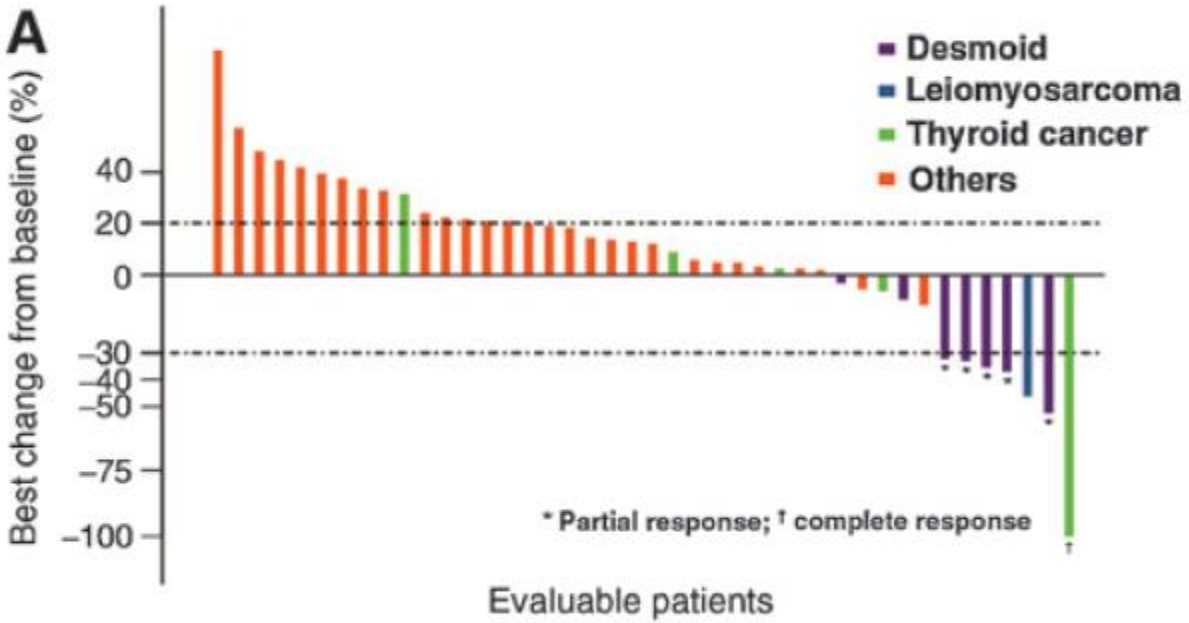
DLTs by Dose Level
Adult Phase I

Dose (mg BID for 21d)	No. Patients Evaluable for DLT	DLTs
20	3	-
40	3	-
80	3	-
100	6	Grd 4 analphylaxis
130	3	-
150	6	Grd 3 diarrhea
RP2D → 220	6	Grd 3 diarrhea
MTD → 330	2	Grd 3 rash(1); Unable to complete 80% dose due to palpitations (grd 1) and mouth pain (grd 1)

Treatment-related AE in ≥5% Patients
Adult Phase I

Adverse Event	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Diarrhea	35 (54.7)	6 (9.4)	0
Nausea	24 (37.5)	1 (1.6)	0
Fatigue	19 (29.7)	0	0
↓ PO4	17 (26.6)	15 (23.4)	0
Vomiting	15 (23.4)	1 (1.6)	0
Rash	13 (20.3)	2 (3.1)	0
Anorexia	11 (17.2)	0	0
Mucosal inflammation	6 (9.4)	0	0
Dry mouth	5 (7.8)	0	0
Headache	5 (7.8)	0	0
↓ Potassium	4 (6.3)	1 (1.6)	0
Pruritus	4 (6.3)	0	0
Dyspepsia	4 (6.3)	0	0

Best Response



Desmoid Tumors:
5 of 7 with PR; 2 SD
Median time to response = 11.9 mo (range, 2.5- 21.4)
Duration of Response = 48 and 73+ months

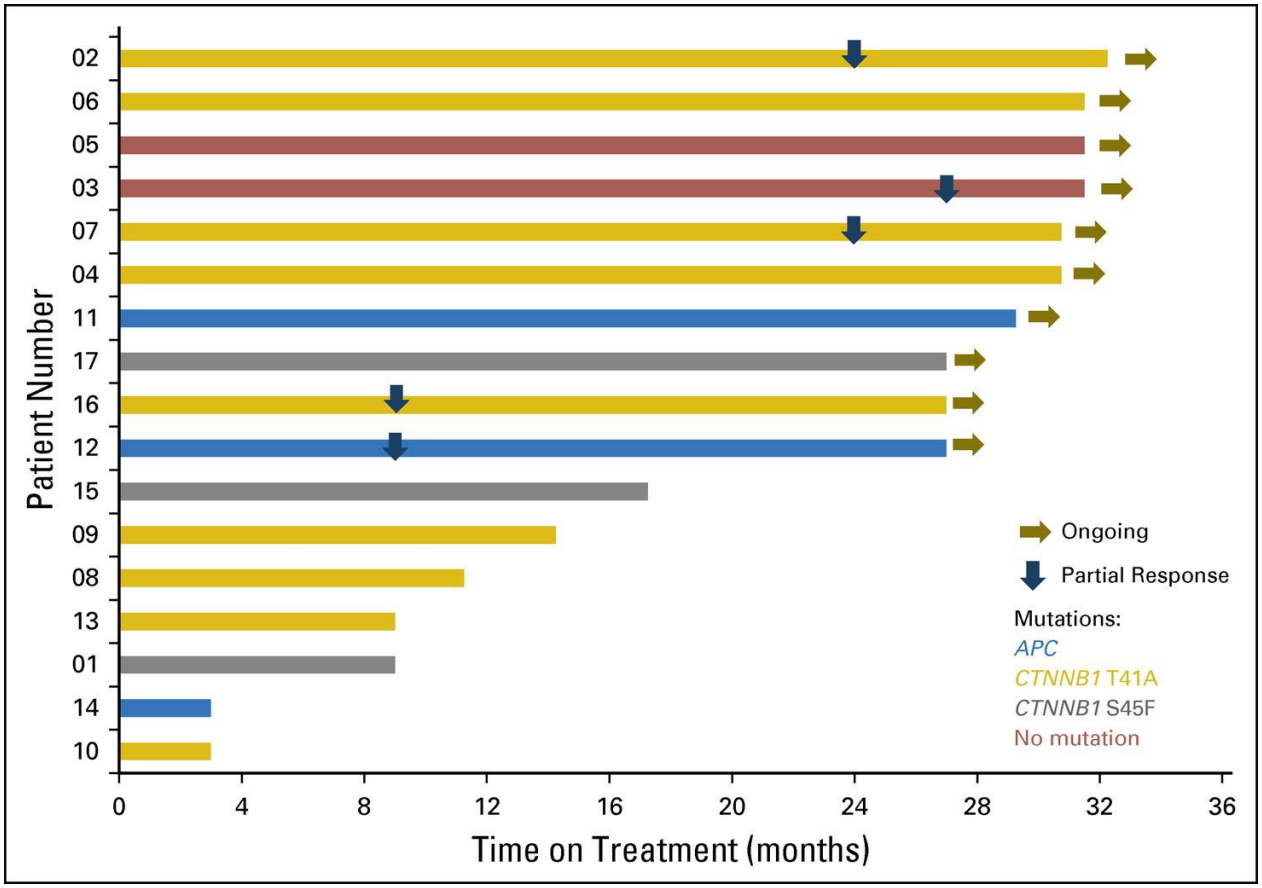
Messersmith et al. CCR 2014
Villalobos et al. Ann Surg Oncol 2017

Nirogacestat: Adult Phase II

- Single institution (NCI)
- Inclusion:
  - Age ≥ 18 years
  - Desmoid tumor not amenable to surgery or RT and PD with at least one line of standard therapy
- 17 patients enrolled (16 evaluable for response)
  - Median age 34 years (range 34 – 69)
- 150 mg BID in 21 day cycles
- Response by RECIST after 3 weeks then every 18 weeks

Kummar et al. JCO 2017

Tumor Response and Mutation Status



5 PR (29%)
11 SD (5 prolonged)

Future Development

- Adult randomized phase 3 study
  - Age ≥ 18 years
- Phase 2 pediatric study through the Children's Oncology Group

Pediatric Clinical Trials in Desmoid Tumors

	POG 9650 Skapek et al. JCO 2007	COG ARST0321 Skapek et al. PBC 2013
Treatment	VBL/MTX (52 weeks)	Tamoxifen/Sulindac (12 mo)
Duration of study (period of accrual)	8/1997-2/2001 (35 mo)	2004-2009 (63 mo)
No. of patients enrolled	28 (27 eligible)	70 (59 eligible)
Median age in years (range)	11.5 (0.6-20.5) (at enrollment)	13 (<1-18) (at diagnosis)
2-yr PFS (range)	46 % (25-65)	36% (23-48)
Tumor response (%) (WHO criteria)	26 evaluable	59 evaluable
CR+PR	19 % (CI: 6.6 – 43.7)	8%

Primary Objectives

- To determine the objective tumor response rate of Nirogacestat in children with progressive, surgically unresectable desmoid tumors

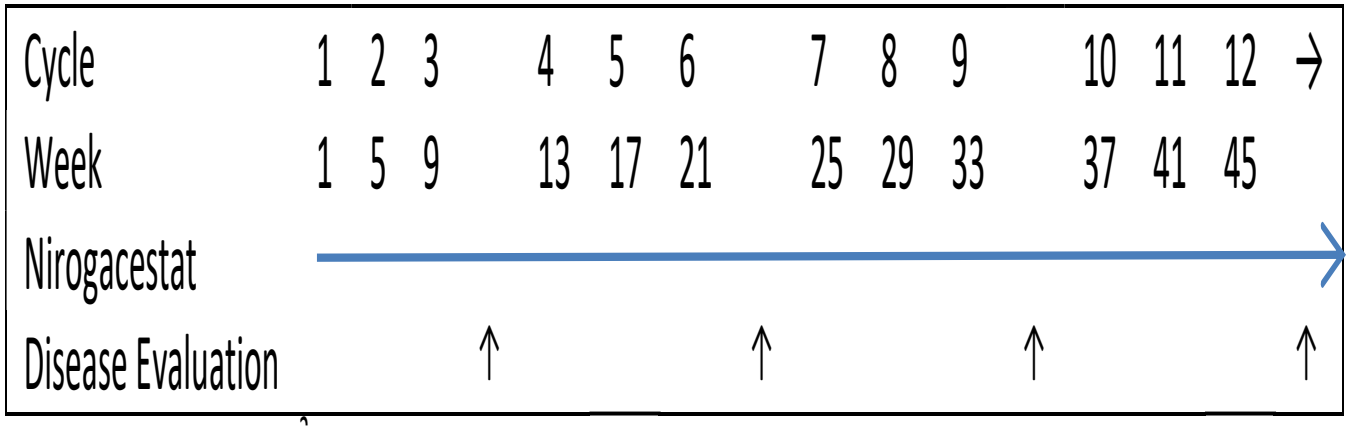
Secondary Objective

- To estimate the 2-year PFS rate
- To describe the toxicities of Nirogacestat in children and adolescents
- To characterize the PK of Nirogacestat in children and adolescents

Inclusion Criteria

- Age at enrollment 12 month to < 18 years
- Primary or recurrent desmoid tumor not amenable to surgery without significant morbidity and demonstrating progression in the past 12 months
- Measureable disease by WHO criteria
- Able to swallow tablets
- No prior γ-secretase inhibitor or anti-NOTCH receptor antibody

Treatment Plan



- Nirogacestat 90 mg/m^2/dose PO BID daily (Adult RP2D, assuming adult BSA 1.7 m^2)
- One cycle = 28 days
- Disease evaluation at baseline then following every 3 cycles
- Therapy will continue until evidence of disease progression or unacceptable toxicity

Statistical Considerations

- Primary Endpoint: Overall Response Rate
  - Target response rate (CR+PR) by WHO criteria of 30%; no worse than 10%
- Estimated sample size: 28 evaluable patients
- Estimated duration of study: 3.5 years

Exploratory Objectives

- To explore the relationship between patient reported outcomes (PROs) and tumor response and PFS
- To compare assessment of tumor response using WHO criteria with RECIST 1.1 and T2 and volumetric changes using MRI
- Correlative biology studies

Correlative biology studies

- Mutational analysis for CTNNB1 and APC genes
- Genetic profiling of archival tumor samples
- Assess changes in NOTCH and WNT pathway-related signaling genes in peripheral blood cells at baseline, during treatment and at the time of progression
- Assess effect of nirogacestat on immune cells, chemokines and cytokines

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Thank you
Questions/Comments