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The Tissue-Agnostic Development of Larotrectinib / Vitrakvi

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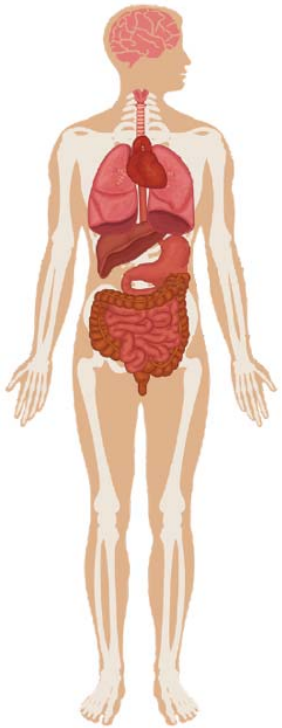
Tissue-Agnostic DD: Philosophical Underpinnings

- The molecular classification of cancer is valid
- Context-independent drug activity
- Biology >> statistical purity
- Intellectual flexibility in the service of patient access

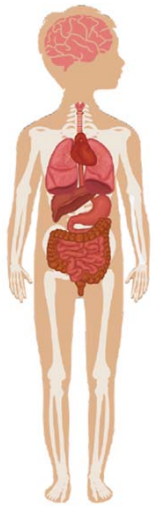
A Development Plan Born Out of Necessity: Rarity and Diversity of NTRK Fusions

Adult



- Brain cancers (0.4–3.1%)[1]
- Salivary (MASC; 90–100%)[1]
- Secretory breast cancer (92%)[2*]
- Pancreatic cancer[3]
- Cholangiocarcinoma (3.6%)[1]
- Thyroid cancer (1.5–14.5%)[1]
- Lung cancer (0.2–3.3%)[1]
- GIST (3.2%)[4]
- Colon cancer (1.5%)[1]
- Melanoma (0.3%)[1,5]
- Sarcomas (1%)[5*]

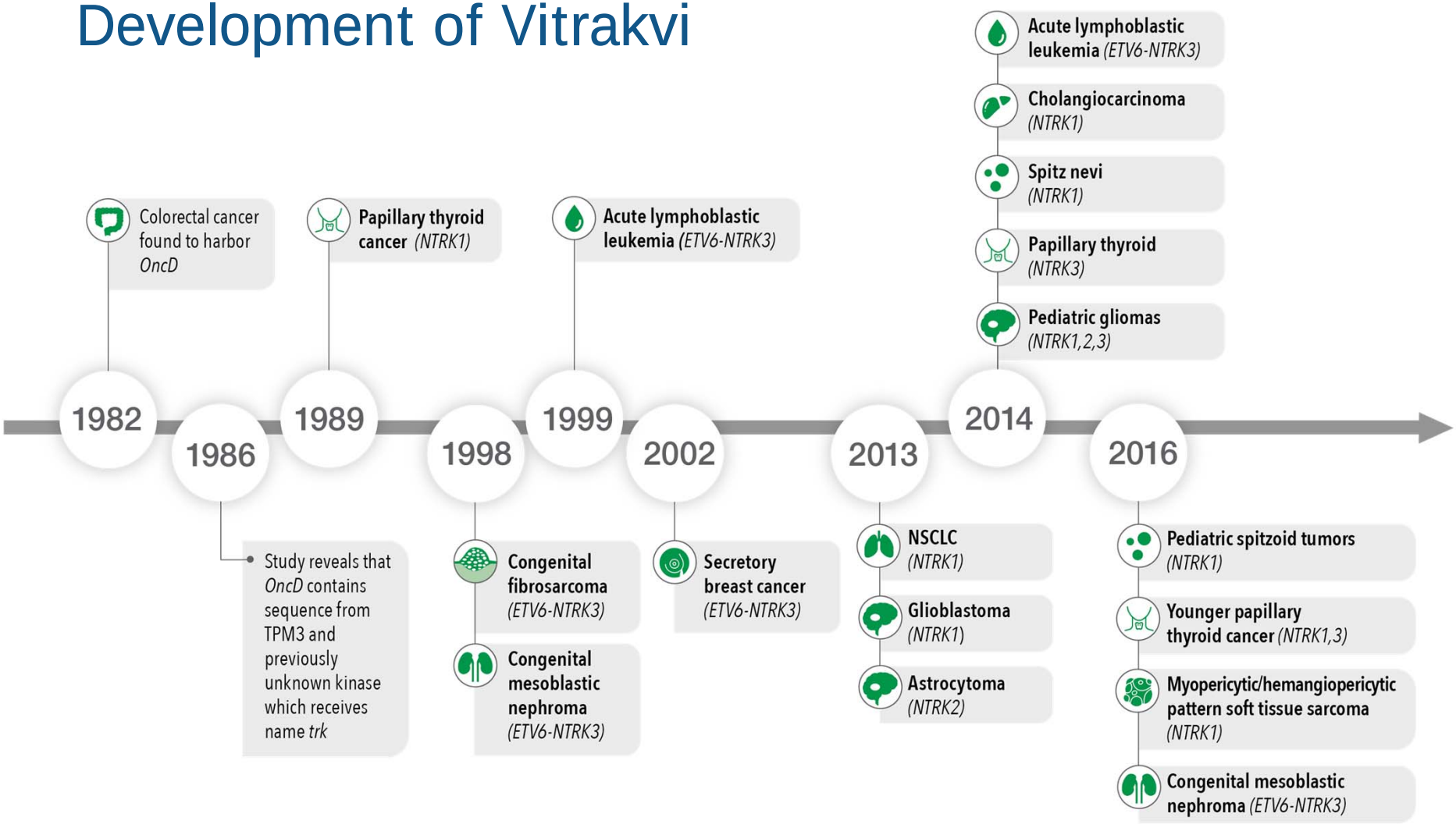
Pediatric



- Spitzoid neoplasms (16.4%)[6]
- Gliomas (7.1%)[1]
- Thyroid (9.4–25.9%)[7,8]
- Infantile fibrosarcoma (91–100%)[9]
- Congenital nephroma (83%)[1]
- Secretory breast cancer (92%)[2*]
- Sarcomas (1%)[5*]

1. Vaishnavi A, Le A, Doebele RC. *Cancer Discov.* 2015;5:25-34. 2. Tognon C, et al. *Cancer Cell*. 2002;2:367-376. 3. Pishvaian MJ, et al. *Journal of Clinical Oncology* 36, no. 4_suppl (February 1 2018) 521-521. 4. Brenca M, et al. *J Pathol* 2016;238:543-549. 5. Stransky N, et al. *Nat Communications* 2014;DOI: 10.1038/ncomms5846. 6. Wiesner T, et al. *Nat Communications* 2014;5:3116. doi:10.1038/ncomms4116. 7. Ricarte_Filho_JC, et al. *J Clin Invest* 2013;123:4935-4944. 8. Prasad ML, et al. *Cancer* 2016; DOI: 10.1002/cncr.29887. 9. Bourgeois JM, et al. Am J Surg Pathol 2000;*24: 937–946.*

Many NTRK Gene Fusions Discovered During the Development of Vitrakvi



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Descriptive ORR Statistics: Lumping vs Splitting

Sensitivity Analysis: Lower Bound of 2-sided 95% CI

Observed ORR	# of Patients: 5	10	20	40	80
20%	0.5%	2%	6%	9%	12%
35%	5%	12%	15%	21%	25%
50%	15%	19%	27%	34%	39%
65%	28%	35%	41%	48%	54%
80%	28%	44%	56%	64%	70%

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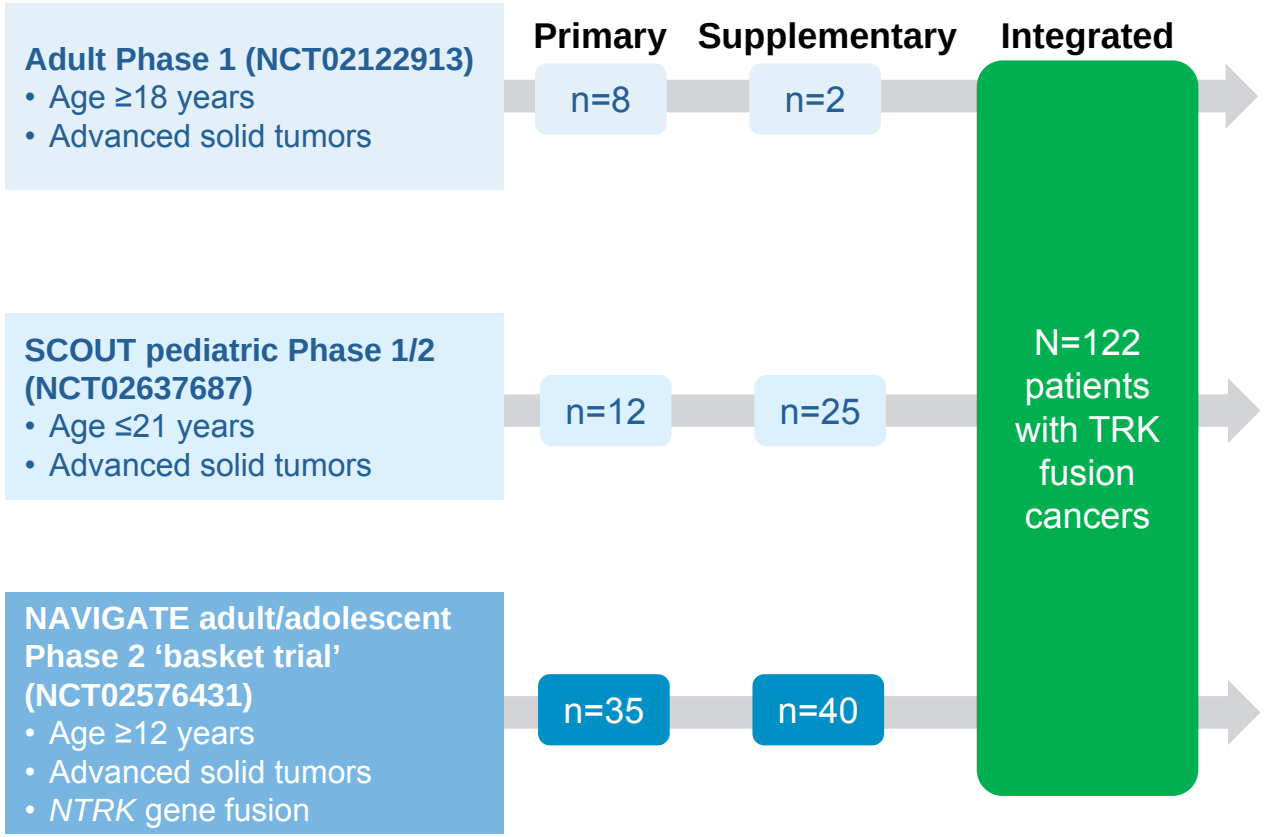
Pooled Analysis of Three Larotrectinib Clinical Trials



TRK fusion status determined by local CLIA

Primary endpoint: ORR

Dosing

- Adults: 100 mg BID
- Children with BSA <1 m^2: 100 mg/m^2 BID

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Vitrakvi Package Insert

Table 5 Efficacy Results by Tumor Type

Tumor Type	Patients (N=55)	ORR		DOR
		%	95% CI	Range (months)
Soft tissue sarcoma	11	91%	(59%, 100%)	3.6, 33.2+
Salivary gland	12	83%	(52%, 98%)	7.7, 27.9+
Infantile fibrosarcoma	7	100%	(59%, 100%)	1.4+, 10.2+
Thyroid	5	100%	(48%, 100%)	3.7, 27.0+
Lung	4	75%	(19%, 99%)	8.2, 20.3+
Melanoma	4	50%	NA	1.9, 17.5+*
Colon	4	25%	NA	5.6*
Gastrointestinal stromal tumor	3	100%	(29%, 100%)	9.5, 17.3
Cholangiocarcinoma	2	SD, NE	NA	NA
Appendix	1	SD	NA	NA
Breast	1	PD	NA	NA
Pancreas	1	SD	NA	NA

Vitrakvi Package Insert (AEs)

Adverse Reaction	VITRAKVI N = 176	
	All Grades* (%)	Grade 3-4** (%)
General		
Fatigue	37	3
Pyrexia	18	1
Edema peripheral	15	0
Gastrointestinal		
Nausea	29	1
Vomiting	26	1
Constipation	23	1
Diarrhea	22	2
Abdominal pain	13	2
Nervous System		
Dizziness	28	1
Headache	14	0
Respiratory, Thoracic and Mediastinal		
Cough	26	0
Dyspnea	18	2
Nasal congestion	10	0

Adverse Reaction	VITRAKVI N = 176	
	All Grades* (%)	Grade 3-4** (%)
Investigations		
Increased weight	15	4
Musculoskeletal and Connective Tissue		
Arthralgia	14	1
Myalgia	14	1
Muscular weakness	13	0
Back pain	12	1
Pain in extremity	12	1
Metabolism and Nutrition		
Decreased appetite	13	2
Vascular		
Hypertension	11	2
Injury, Poisoning and Procedural Complications		
Fall	10	1

* National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v 4.03.
** One Grade 4 adverse reaction of pyrexia.

Vitrakvi PMRs and PMCs

- Increased patient experience for more precise ORR and response duration, especially for certain tumor types (IRC)
- Longer follow-up for response duration for primary analysis set (IRC)
- Long-term effects on growth and development in pediatric patients
- Dosage modification study
- Validation of a companion diagnostic for patient identification
- CYP3A4 inhibitor study

Tissue-Agnostic DD: International Differences

RESEARCH Open Access

Use of biomarkers in the context of orphan medicines designation in the European Union

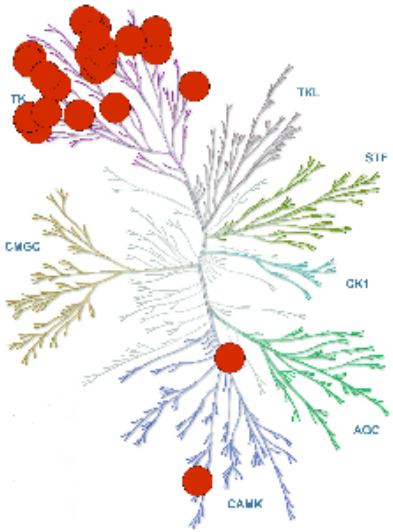
Stelios Tsigkos[1*], Jordi Llinares[1], Segundo Mariz[1], Stiina Aarum[1], Laura Fregonese[1], Bozenna Dembowska-Baginska[2], Rembert Elbers[4], Pauline Evers[2], Tatiana Foltanova[3], Andre Lhoir[2], Ana Corrêa-Nunes[2], Daniel O'Connor[2], Albertha Voordouw[5], Kerstin Westermark[2] and Bruno Sepodes[2,6]

Tsigkos *et al. Orphanet Journal of Rare Diseases* 2014, **9**:13
http://www.ojrd.com/content/9/1/13

European Concerns Around Orphan Subsetting

Limitations based on the
“plausible link to the condition”

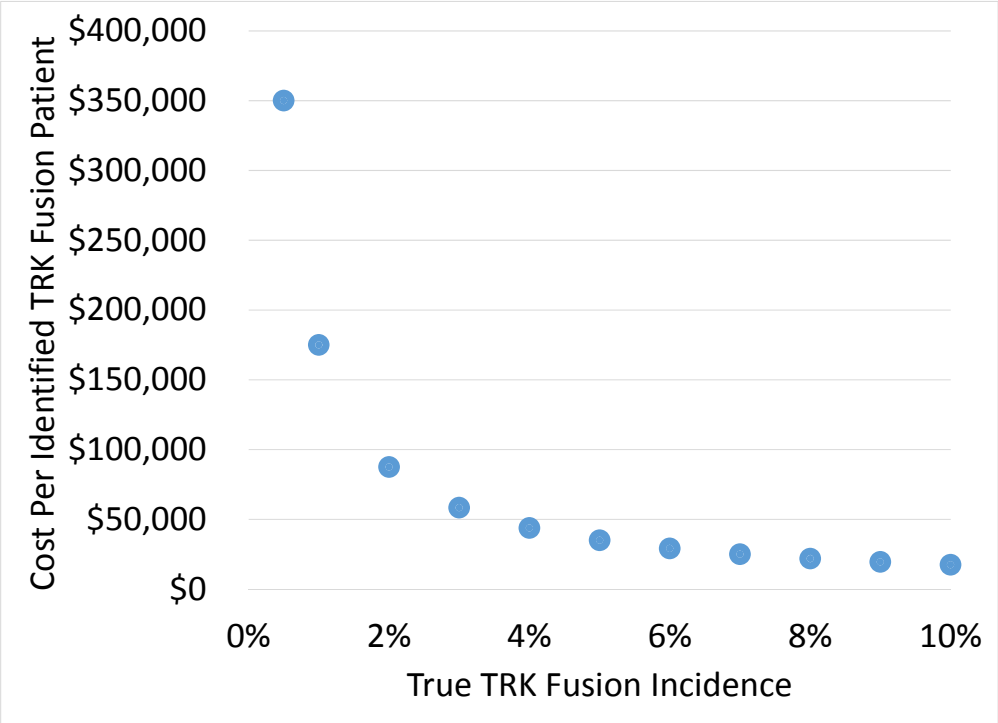
Limitations based on the
“exclusion of effects”



Key Obstacle: Testing

Sponsors Cannot Run an NGS Business On The Side

- Tissue exhaustion
- Logistical complexity
- Regulatory complexity
- Cost
- Prevalence uncertainty



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Instead, We Rely On Other Business Models

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CARIS® LIFE SCIENCES

'T'EMPUS

MSK-IMPACT

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Costs subsidized by:

- Philanthropy
- Perceived ”big data” value
- Pharma collaborations
- Investor aspirations
- Academic commitment
- Self-pay

Hope On the Horizon

But When Will Others Follow CMS?

CMS finalizes coverage of Next Generation Sequencing tests, ensuring enhanced access for cancer patients

Date	2018-03-16
Title	CMS finalizes coverage of Next Generation Sequencing tests, ensuring enhanced access for cancer patients
Contact	press@cms.hhs.gov

CMS finalizes coverage of Next Generation Sequencing tests, ensuring enhanced access for cancer patients

A new opportunity for cancer patients as advanced diagnostic laboratory tests now have expanded Medicare coverage

Democracy Through Affordable, Local Testing

illumina®

ion torrent

by life technologies™

Regulatory issues

- What price perfection? *The test that is never run has zero sensitivity*
- Hard to source tissue for clinical validation
- “Google Ads” problem around clinical claims

Clinical issues

- Onc / pathologist coordination
- Onc / pathologist education
- Financial incentives