CRESTONE

CLINICAL STUDY OF **RE**SPONSE TO
SERIBANTUMAB IN **T**UM**O**RS WITH
NEUREGULIN-1 (NRG1) FUSIONS

CLINICALTRIALS.GOV IDENTIFIER: NCT04383210

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Thank you for your interest in the CRESTONE study!

The information presented in this document is introductory and is not intended for presentation.

For additional data and resources for both seribantumab and the CRESTONE study, please contact our team at medicalaffairs@elevationoncology.com or +1 (716) 371 – 1125.

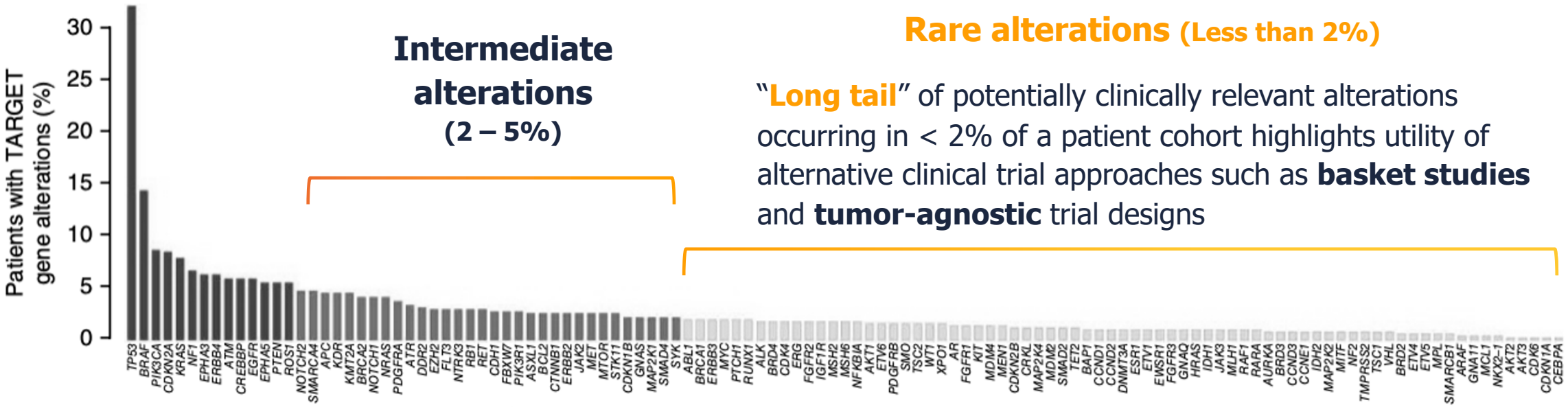
Novel clinical trial approaches are needed for **rare but actionable** driver alterations

Common alterations
(5% or greater)

Intermediate alterations
(2 – 5%)

Rare alterations (Less than 2%)

"**Long tail**" of potentially clinically relevant alterations occurring in < 2% of a patient cohort highlights utility of alternative clinical trial approaches such as **basket studies** and **tumor-agnostic** trial designs



Source: Van Allen EM et al., Nature Med 2014 May(20):682-688
Retrospective whole exome analysis of Tumor Alterations Relevant for GEnomics-driven Therapy (TARGET) gene alterations in a cohort of 511 patients

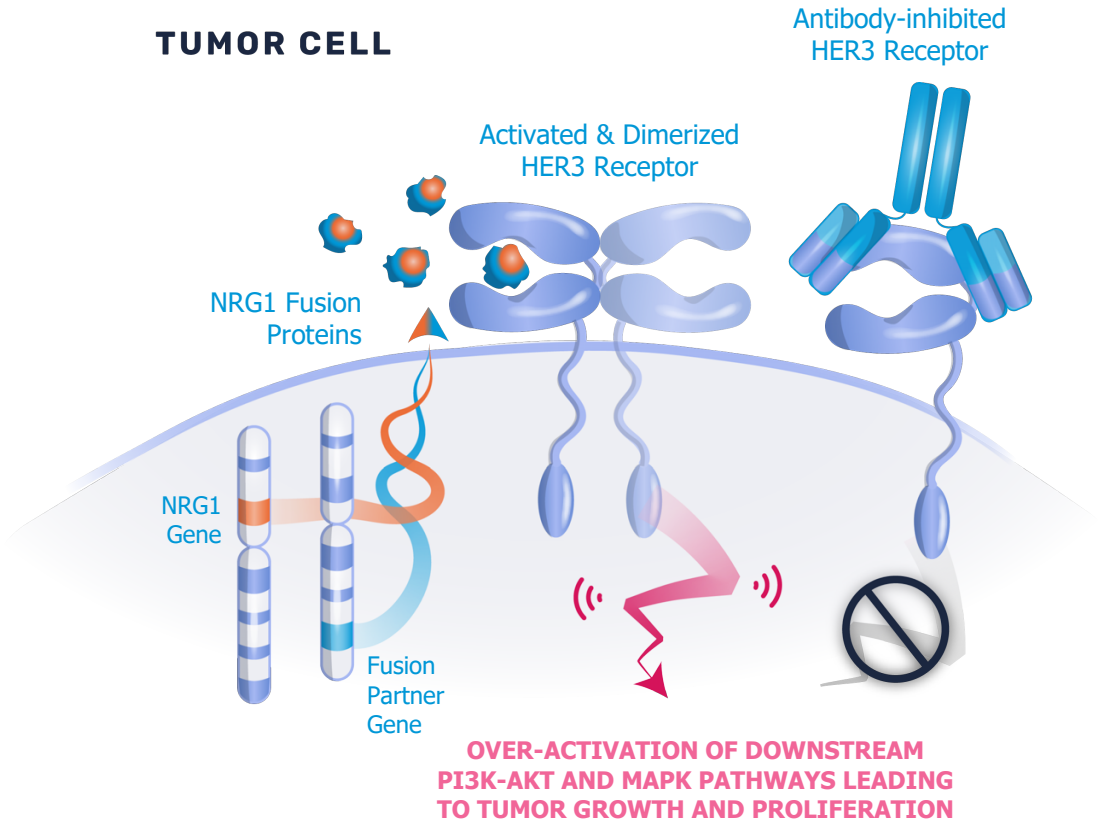
Gene fusions are **proven therapeutic targets** and candidates for a **tumor-agnostic** approach to development

GENE FUSION	DRUG	DISEASE	YEAR OF APPROVAL
ALK fusions	Crizotinib	NSCLC	2011
	Ceritinib	NSCLC	2014*
	Alectinib	NSCLC	2015*; 2017 (full)
	Brigatinib	NSCLC	2017
	Lorlatinib	NSCLC	2018
BCR-ABL1	Imatinib	CML and ALL	2001
	Dasatinib	CML and ALL	2006
	Nilotinib	CML	2007
	Bosutinib	CML	2012
	Ponatinib	CML and ALL	2012
COL1A1-PDGFRB	Imatinib	DFSP	2006
FIP1L1-PDGFRA	Imatinib	HES/CEL	2006
NTRK fusions	Larotrectinib	**Any solid tumor**	2018*
	Entrectinib	**Any solid tumor**	2019*
PDGFR fusions	Imatinib	MDS/MPN	2006
RET fusions	Selpercatinib	NSCLC	2020*
	Selpercatinib	Thyroid cancer	2020*
ROS1 fusions	Entrectinib	NSCLC	2019*

Source: Drugs@FDA: FDA-Approved Drugs (www.accessdata.fda.gov); * Accelerated, conditional approval

NRG1 gene fusions are emerging as a rare but potentially actionable driver alteration

- NRG1 gene fusions result from the combination of the NRG1 gene with a partner gene (i.e., CD74, SLC3A4, ATP1B1 etc.) and are found in 0.2% of solid tumors
- NRG1 fusion proteins can bind and activate HER3, allowing it to dimerize with HER2 and activate downstream pathways leading to unregulated growth and proliferation
- Tumor cells with NRG1 fusions are unlikely to carry other known driver mutations (such as KRAS, EGFR, ALK, ROS1, and RET), making NRG1 fusions a critical therapeutic target
- HER3 inhibition in a tumor with an NRG1 fusion may directly address the driving cause of the tumor's growth



Sources: Fernandez-Cuesta L et al., *Clin Cancer Res* 2014.; Jonna S et al., *Clin Cancer Res* 2019.; Drilon A et al. *Cancer Discov* 2018.; Jones et al., *Clinical Cancer Research* 2019.

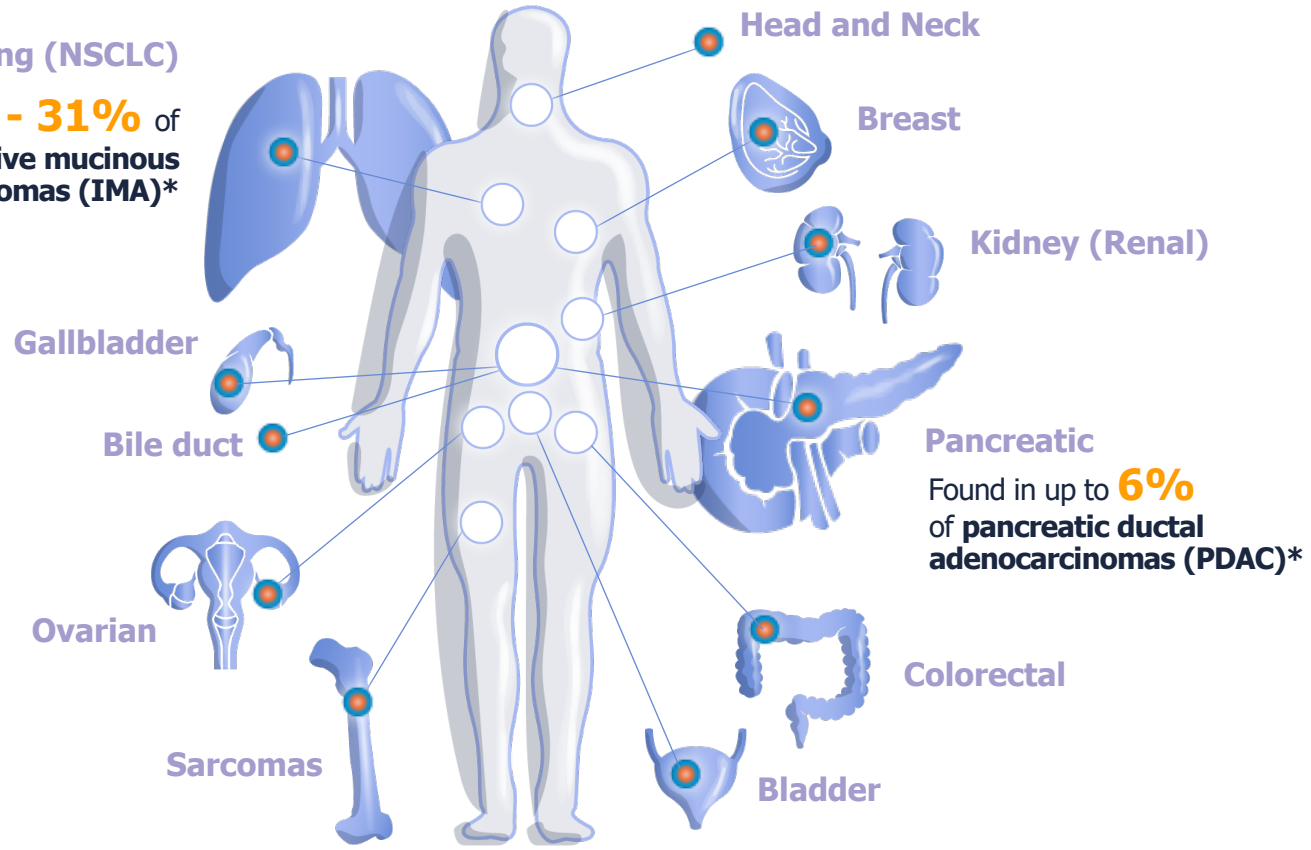
Identification of NRG1 fusions across multiple tumor types supports pursuit of a **tumor-agnostic approach**

0.2%

Percent of solid tumors with an NRG1 fusion*

10+

Unique solid tumor types where an NRG1 fusion has been found



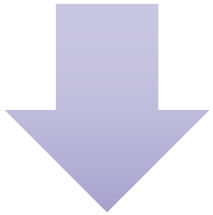
* Emerging research suggests that NRG1 fusions may be more common in some subtypes of cancer such as IMA (est. 0.2% of lung cancers) and PDAC (est. 90% of pancreatic cancers).As testing methodologies improve and more patients are tested, the identification of NRG1 fusions is expected to increase.

Sources: Jonna S et al., *Clin Cancer Res* 2019.; Drilon A et al. *Cancer Discov* 2018.; Jones et al., *Clinical Cancer Research* 2019.; Moon SW et al., J Thorac Dis. 2018.; Adamska A et al., Int J Mol Sci. 2017.

New targeted therapies are needed for tumors with an NRG1 fusion

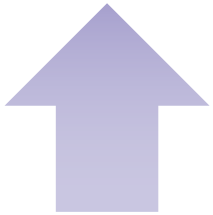
Standard of Care

Patients with NRG1 fusions do not normally respond well to treatment with standard chemotherapy, chemoimmunotherapy or novel checkpoint inhibitors such as anti-PD-1/anti-PD-L1 therapies.



OS & DFS

Presence of an NRG1 fusion has been correlated with worse overall and disease-free survival when treated with current therapies.



Therapy resistance

NRG1 fusions can also emerge at the time of progression and may be the driving cause of acquired resistance to a previous targeted therapy, such as an ALK, EGFR, or HER2 inhibitor.

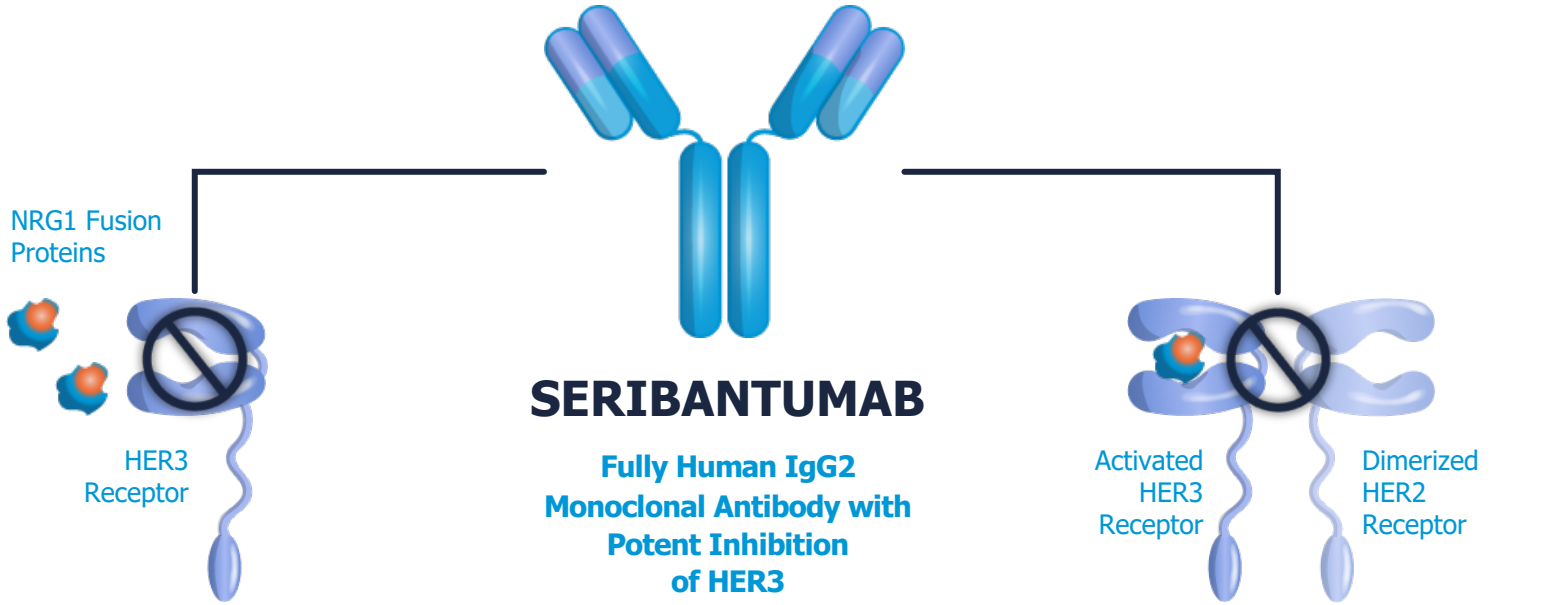
"WHILE THESE FUSIONS ARE UNCOMMON EVENTS, **IF WE DETECT JUST ONE, IT CHANGES EVERYTHING.**"

DR. ROBERT DOEBELE, MD, PHD
Targeted Oncology, January 2020

Sources: Duruisseaux M et al., ASCO 2019, Abstract 9081.; Shin DH et al., Oncotarget 2016.; Drilon A et al. *Cancer Discov* 2018.; Fernandez-Cuesta L and Thomas RK, Clin Cancer Res 2015; Dimou A and Camidge DR, Clin Cancer Res 2019.; Kaplan DA., Targeted Oncology 2020.

Seribantumab (anti-HER3 mAb)

Previous clinical experience in more than 800 patients has confirmed the ability of seribantumab to inhibit HER3 in patients with a well-tolerated safety profile as a monotherapy



Sources: Seribantumab Investigator's Brochure, 2020; Elevation Oncology data on file.

Clinical research goals

1

Describe the anti-tumor activity and toxicity of seribantumab as a precision therapy for solid tumors with an NRG1 gene fusion

2

Continue to build clinical experience in support of a tumor-agnostic approach to oncology drug development

3

Explore diagnostic collaborations in support of clinical trial enrollment for patients with rare genomic alterations

Eligibility | Pivotal Cohort 1 (n = 55)

- Advanced solid tumor with an NRG1 fusion that has an active EGF-like domain*
- No longer benefiting from standard treatment, or no standard treatment available
- Healthy enough to participate (ECOG Performance Status 0 or 1)
- No prior treatment with anti-ERBB3 (HER3) directed therapy (distinct from pan-ERBB directed therapy)*
- At least one measurable extra-cranial lesion as defined by RECIST v1.1
- Availability of fresh or archived FFPE tumor biopsy or liquid biopsy sample for central review*

* Patients who do not fully meet this criteria may be eligible for one of two exploratory cohorts:

Exploratory Cohort 2 (n = 10):
Patients who are relapsed/refractory following treatment with a Pan-ERBB, HER2, or HER3 targeted therapy

Exploratory Cohort 3 (n = 10):
Patients whose NRG1 fusion does not have an active EGF-like domain or with insufficient tissue for central confirmatory testing

Investigational dosing regimen

All patients in all cohorts will receive investigational therapy, seribantumab (IV)

The investigational dosing regimen is divided into 3 phases to rapidly achieve steady state levels, optimize exposure, and deliver maximal NRG1 inhibition.

Investigational Therapy: Seribantumab (IV)		
Phase 1: Induction*	**Phase 2: Consolidation**	**Phase 3: Maintenance**
Weeks 1 – 4: 3,000 mg weekly	**Weeks 5 – 16:** 3,000 mg biweekly (6 cycles)	**Until PD or toxicity:** 3,000 mg every 3 weeks

1 2 3 4 5 7 9 11 13 15 17 20 +

* Induction for the first 6 patients will follow an Initial Regimen (3/2) of 3g at week 1 and 2g weekly at weeks 2 – 4. An assessment of DLTs by the Safety Review Committee will either allow escalation to the Target Regimen (3/3), maintain the Initial Regimen (3/2), or recommend de-escalation to a Modified Regimen (3/1.5) for subsequently enrolled patients.

Endpoints & analysis

Pre-planned interim analysis

Futility analysis to be conducted following enrollment and initial induction treatment of 20 patients with centrally confirmed NRG1 status in pivotal Cohort 1

Primary endpoint (Cohort 1 only)

Objective response rate (ORR)
per RECIST v1.1 by independent/ central radiologic review

<u>Secondary endpoints</u>

- Duration of response (DoR)
- Safety
- Progression free survival (PFS)
- Overall survival (OS)
- Clinical Benefit Rate (CR, PD, SD > 24 weeks)

Genomic testing for NRG1 fusions

Study enrollment:

NRG1 fusion status determined by local testing in a CLIA/CAP-certified or similarly accredited lab

Molecular assays able to detect known NRG1 fusions include RT-PCR, NGS (RNA or DNA-based), and FISH

Central confirmation:

Commercially available RNA-based NGS test

Benefits of RNA-based NGS:

The CRESTONE study provides a research opportunity to advance understanding of the clinical implications of oncogenic gene fusion structure, including exon involvement and partner gene relevance.

RNA-based NGS has been chosen to confirm fusion protein expression and overcome read-length limitations seen with DNA sequencing.

Whole transcriptome analysis may be utilized to ensure that each NRG1 fusion is fully characterized and novel NRG1 fusions can be identified.

Collaborations for patient identification

Efficient development of new therapies for rare genomic alterations will require new approaches to patient identification and enrollment.

The CRESTONE study is exploring collaborations with diagnostic partners that enhance patient enrollment through real-time patient identification and site initiation:

NGS-Focused Lab Services
Next Generation Sequencing experts delivering premier personalized medicine services and patient referrals

"Just-In-Time" Network
Site activation and patient enrollment in as little as 10 days following patient identification at 340 research centers

Precision Oncology Network
Oncology network of 25 healthcare systems offering NGS testing and patient referrals with a focus on precision medicine

TIME Trial™ Network
Intelligent identification of eligible patients treated by >1,800 oncologists across 40 provider networks

Key milestones

July 2020	Study launch – First site initiated
2H 2020	Preclinical publication
Mid-2021	Planned interim analysis

CRESTONE

Science Patients Physicians Researchers Contact

CRESTONE

CLINICAL STUDY OF RESPONSE TO SERIBANTUMAB IN TUMORS WITH NEUREGULIN-1 (NRG1) FUSIONS

The **CRESTONE** study is open and enrolling today for patients whose solid tumor has tested positive for an NRG1 gene fusion. If you or your patient have already had their tumor genomically tested, you may be eligible for our study.

FIND OUT IF OUR TRIAL IS RIGHT FOR YOU:

FOR PATIENTS | FOR PHYSICIANS

LEARN MORE:

www.nrg1fusion.com | ClinicalTrials.gov ID: NCT04383210

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ELEVATION ONCOLOGY

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