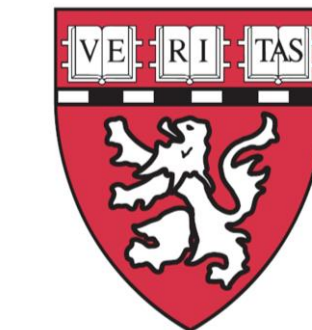


SPARK: An International Study of Acquired Resistance to KRAS Inhibitors in KRAS-Driven NSCLC Using Remote Plasma ctDNA and Tissue Profiling

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Introduction

Large-scale efforts to systematically characterize the landscape of acquired resistance mechanisms to KRAS inhibitors in non-smallcell lung cancer (NSCLC) remain lacking. We report the initial results from the NSCLC cohort of SPARK, a non-interventional, decentralized biospecimen collection study enrolling patients with KRAS-mutant cancers who experienced disease progression on KRAS G12C inhibitors or other KRAS-targeted therapies. SPARK (NCT05272423) was a single-coordinating center, non-interventional study conducted at the Dana-Farber Cancer Institute that enrolled patients with any cancer type who experienced disease progression on KRAS G12C inhibitors or other KRAS-targeted therapies. The study enabled remote participation through complimentary circulating tumor DNA (ctDNA) collection and tumor DNA sequencing obtained at the time of acquired resistance. Mechanisms of acquired resistance were characterized and compared across drugs, tumor types, and treatment regimens.

Study objectives

Primary objective

1. To elucidate genomic mechanisms of acquired resistance to FDA-approved KRAS G12C inhibitors through next generation sequencing of circulating tumor DNA.
2. To elucidate the landscape of acquired resistance to novel KRAS G12C inhibitors alone or in combination with other therapies using next generation sequencing of circulating tumor DNA.
3. To elucidate the landscape of acquired resistance to novel KRAS non-G12C inhibitors alone or in combination with other therapies using next generation sequencing of circulating tumor DNA.

Exploratory objectives

1. To compare FoundationOne® Liquid Biopsy results to other sequencing results when available (e.g. tissue sequencing, other plasma assays)

Secondary objectives

1. To study differences in resistance mutation spectrum across different KRAS drugs (e.g., adagrasib vs sotorasib).
2. To study differences in resistance mutation spectrum across different tumor types (e.g., NSCLC vs colorectal cancer).
3. To calculate PFS, time to treatment discontinuation, and OS for patients treated with KRAS inhibitors depending on the resistance mechanism (e.g., on-target vs off-target) and the number of resistance mechanisms (e.g. single identified mechanism vs multiple mechanisms).
4. To study subsequent treatment outcomes after the development of acquired resistance to determine if ctDNA testing leads to effective next lines of therapy.

Key eligibility criteria and study cohorts

Cohort 1: Liquid biopsy

Cohort 1A- Liquid Biopsy - KRAS G12C

1. Age ≥ 18.
2. Advanced KRAS G12C positive cancer.
3. Systemic progression within the past 30 days on a KRAS G12C inhibitor.
4. Patient must not have started a new line of therapy before signing the informed consent form.

Cohort 1B- Liquid Biopsy – other KRAS mutations

1. Age ≥ 18.
2. Advanced KRAS non-G12C positive cancer.
3. Systemic progression within the past 30 days on a KRAS inhibitor.
4. Patient must not have started a new line of therapy before signing.

Cohort 2: Data sharing

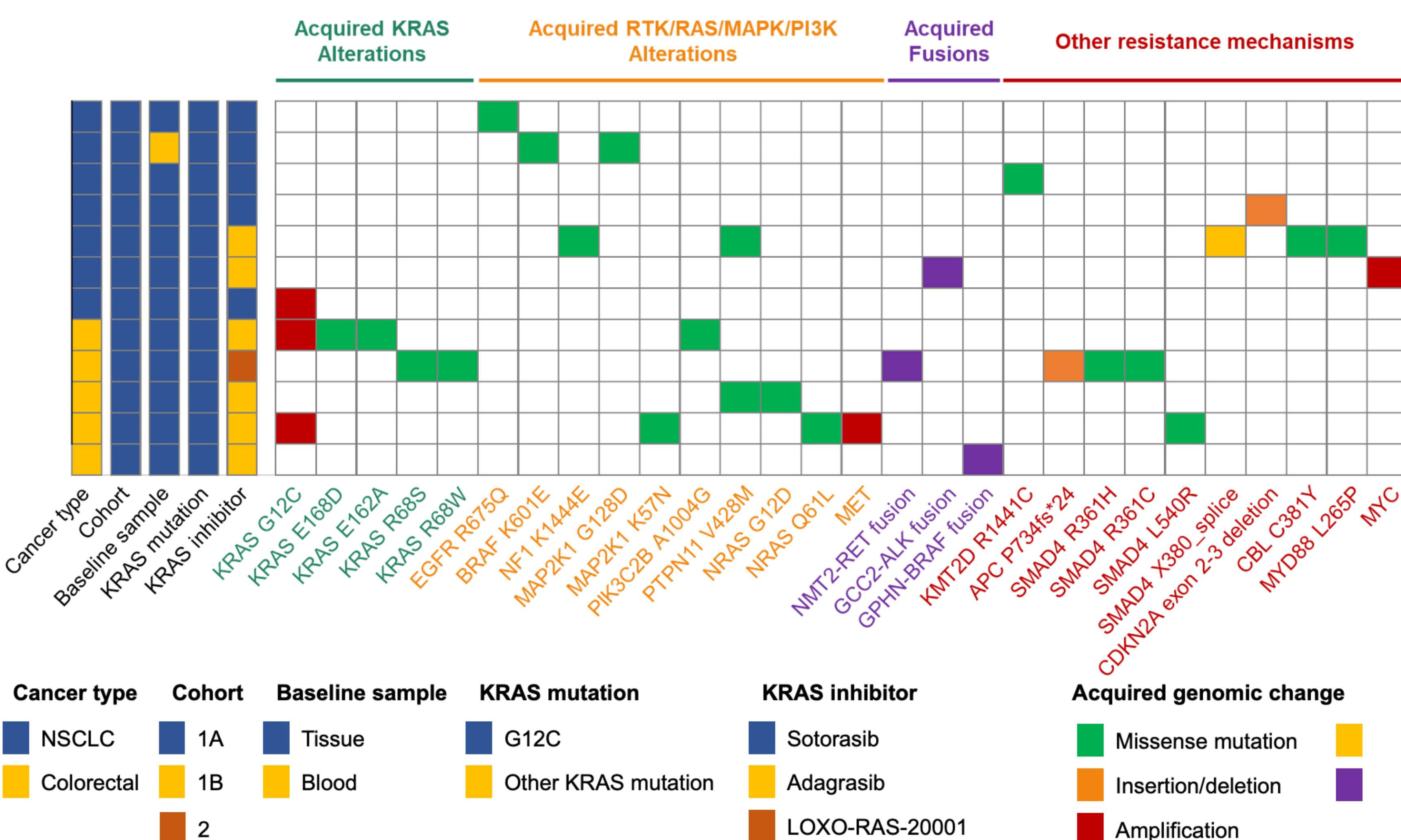
Cohort 2: Data Sharing

1. Age ≥ 18.
2. Advanced KRAS positive cancer.
3. Systemic progression on any KRAS inhibitor.
4. Patient must have prior tumor genotyping available (tissue or plasma) after progression on therapeutic targeting the specific KRAS mutation.

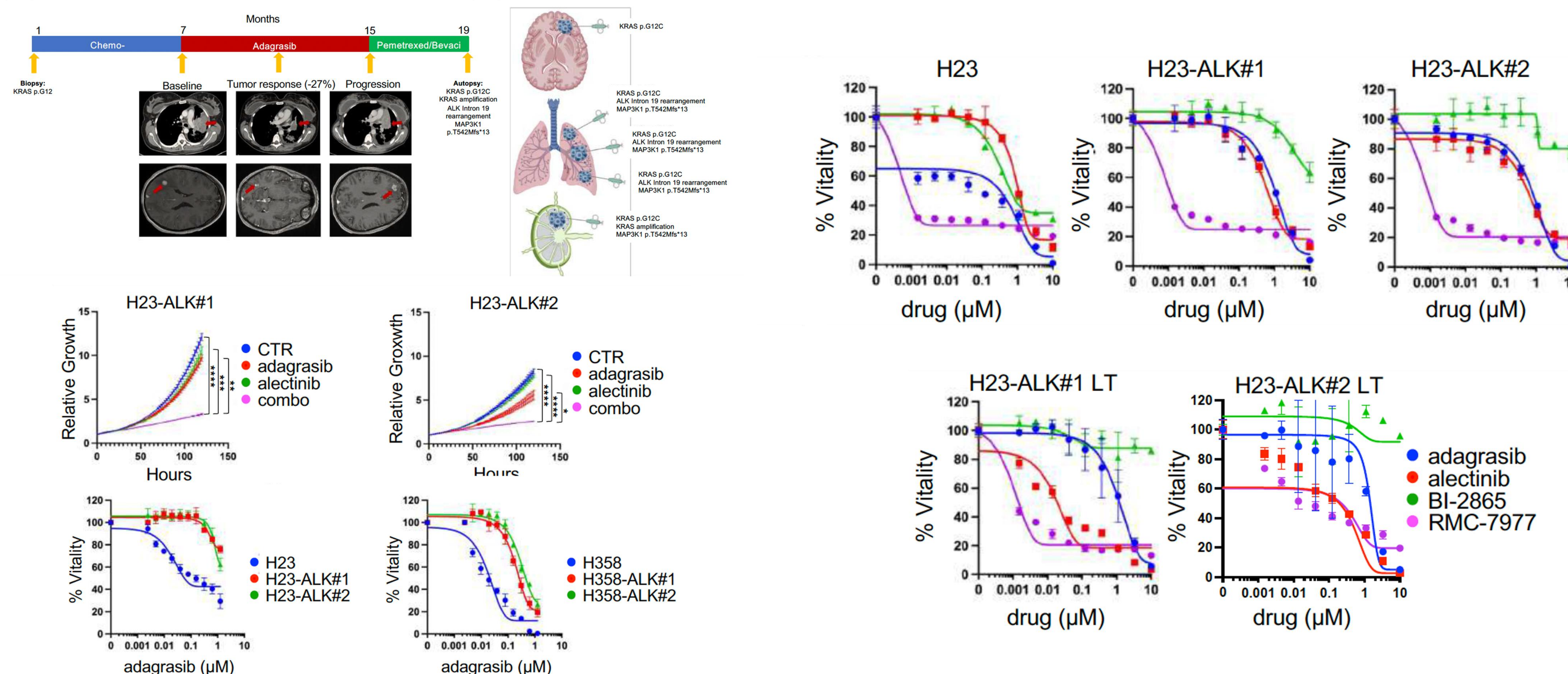
Exclusion criteria

1. Unable to comply with the study procedures.
2. Known existence of an uncontrolled intercurrent illness including, but not limited to, psychiatric illness or social situations that would impair compliance with study requirements.
3. Participants who have previously enrolled to the study.

Acquired resistance mechanisms after KRAS inhibition



Targeting EML4—ALK in KRAS G12C mutant NSCLC with ALK TKI + KRAS G12Ci or panRASI



Conclusion

This first analysis of SPARK demonstrates that acquired resistance to KRAS inhibitors in KRAS-driven NSCLC is molecularly heterogeneous but frequently actionable, involving on-target KRAS alterations and bypass pathway activation affecting key MAPK signaling nodes. These findings highlight the value of repeat molecular profiling at progression to identify targetable resistance mechanisms and inform rational combination or next-generation KRAS-directed therapies.

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