CRITERIA TO ASSESS CANCER IMMUNOTHERAPY COMBINATIONS IN EARLY-PHASE CLINICAL TRIALS: An NCI Perspective on Novel Trial Designs for Immunotherapy Resistance

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Disclosure Slide:

- Nothing to disclose

An Ideal Design for 2 Active Agents

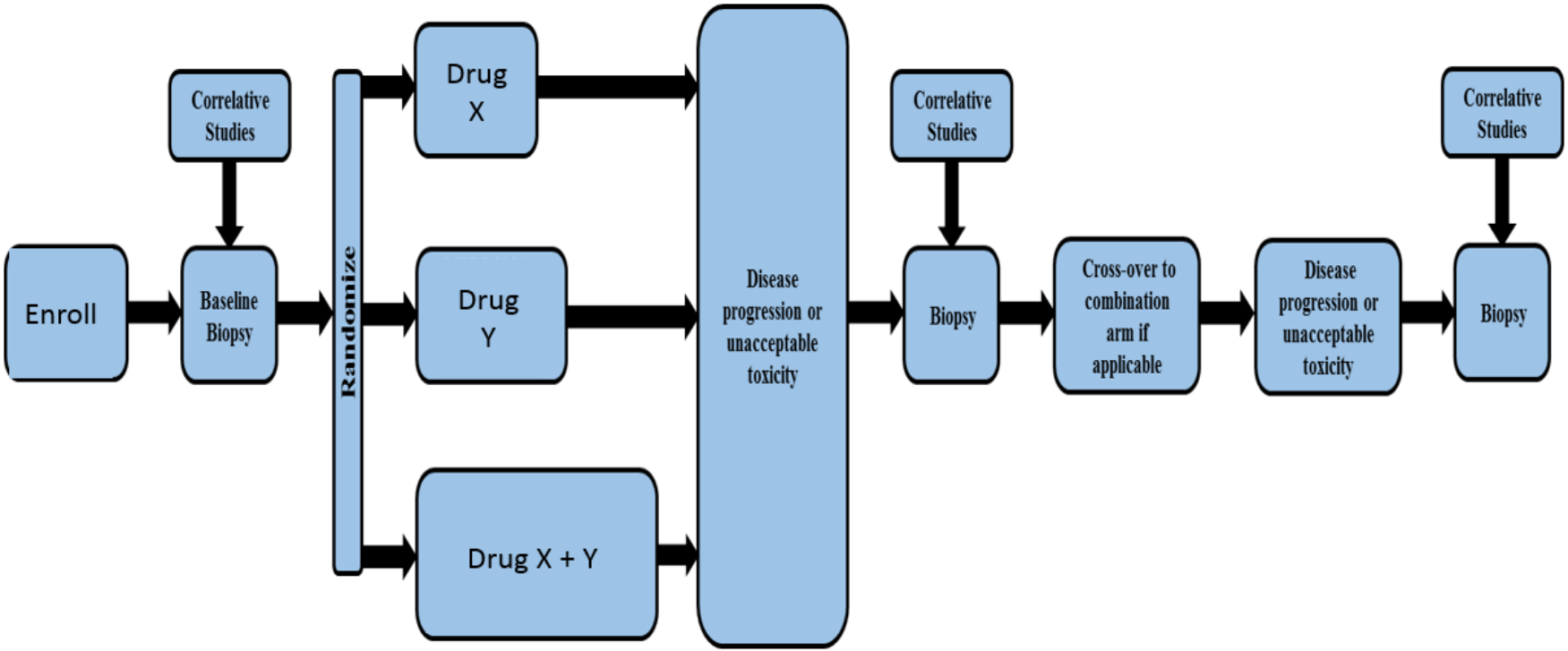
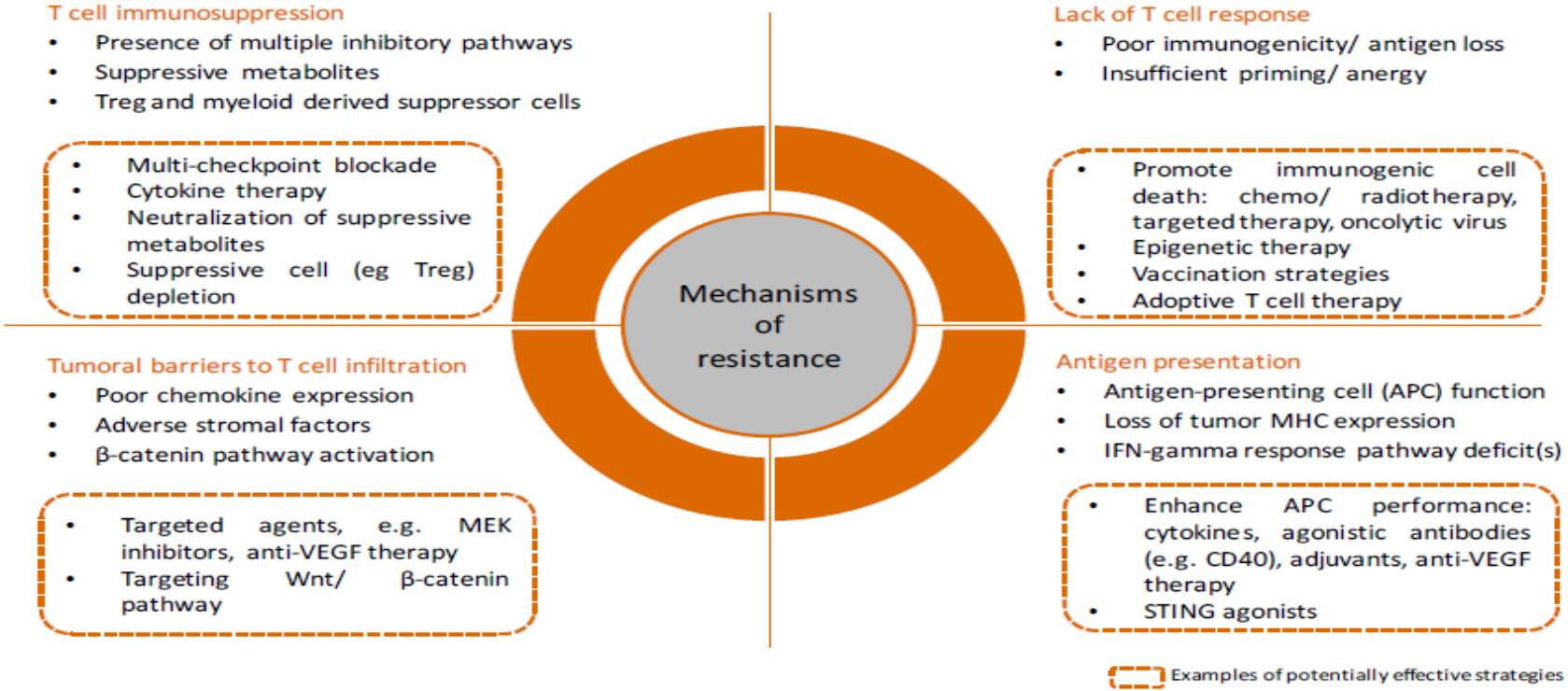


Figure 1. Potential mechanisms of resistance to immunotherapy and examples of therapeutic strategies



Treg, regulatory T cells; MEK, mitogen-activated protein kinase kinase; VEGF, vascular endothelial growth factor; MHC, major histocompatibility complex; IFN, interferon; STING, stimulator of interferon genes.

Day, Monjazeb, Sharon, Ivy, Rubin, Rosner, Butler. *CCR Focus* 2017.

Challenges caused by I-O success

- Benefits and gains of our current era of precision oncology and immunotherapy have emerged as a boon to patients with cancer as well as a conundrum to our efforts to further drug development
- Patients with specific mutations or sensitivity to a particular immunotherapy regimen have some benefit from a new medication, these clinical advances often fail to represent cures
- In this new era, many immunotherapy and targeted therapy regimens are being developed as combination regimens
- In some instances, the combinations being pursued consist only of experimental agents

Proper Trial Design: When is a Single-Arm Trial Appropriate?

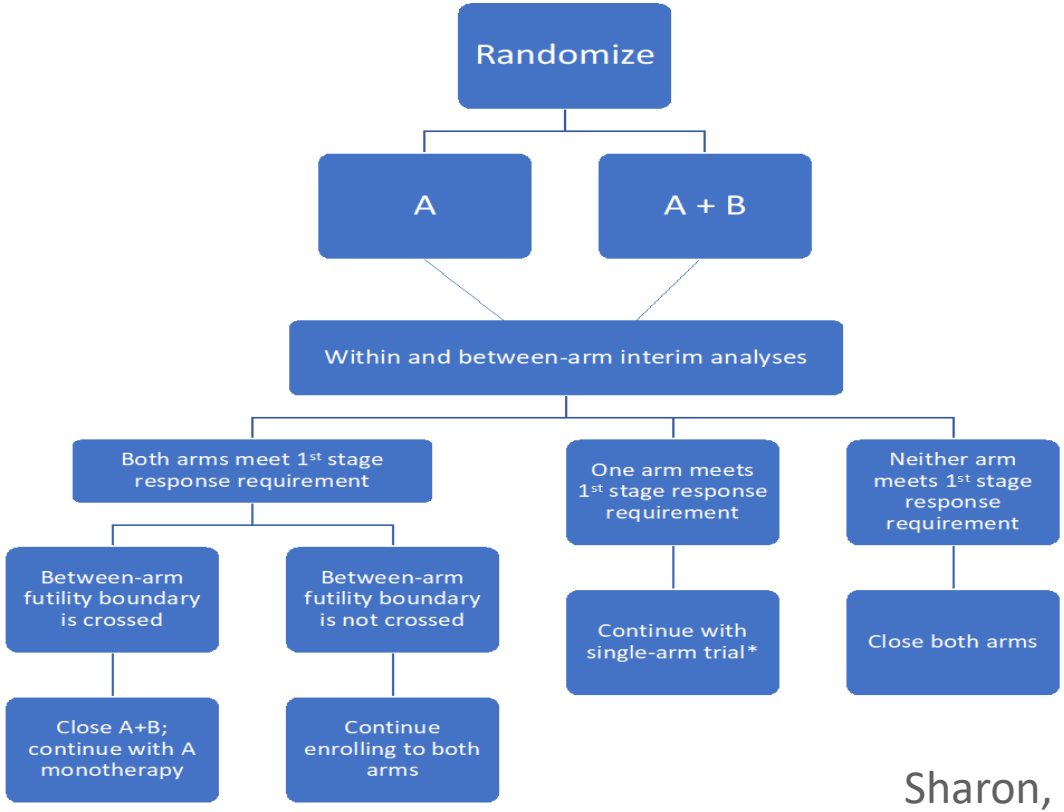
- One common scenario illustrating this phenomenon of this type arises when none of the agents making up the experimental combination have demonstrated single-agent activity in the clinical setting of interest
- Single-arm trials of combination therapies typically cannot answer the question of whether the combination is better than its component agents
- As a result, these trials frequently produce ambiguous results (Foster, *et al*., *JNCI.* 2020)

Appropriate designs for historical data scenarios with two-drug combinations

Drug A \ Drug B	Demonstrated single-agent activity	Demonstrated lack of single-agent activity	Insufficient historical data to determine single-agent activity
Demonstrated single-agent activity	Randomized	Randomized	Randomized
Demonstrated lack of single-agent activity	Randomized	Single arm (with response endpoint)	Randomized
Insufficient historical data to determine single-agent activity	Randomized	Randomized	Randomized

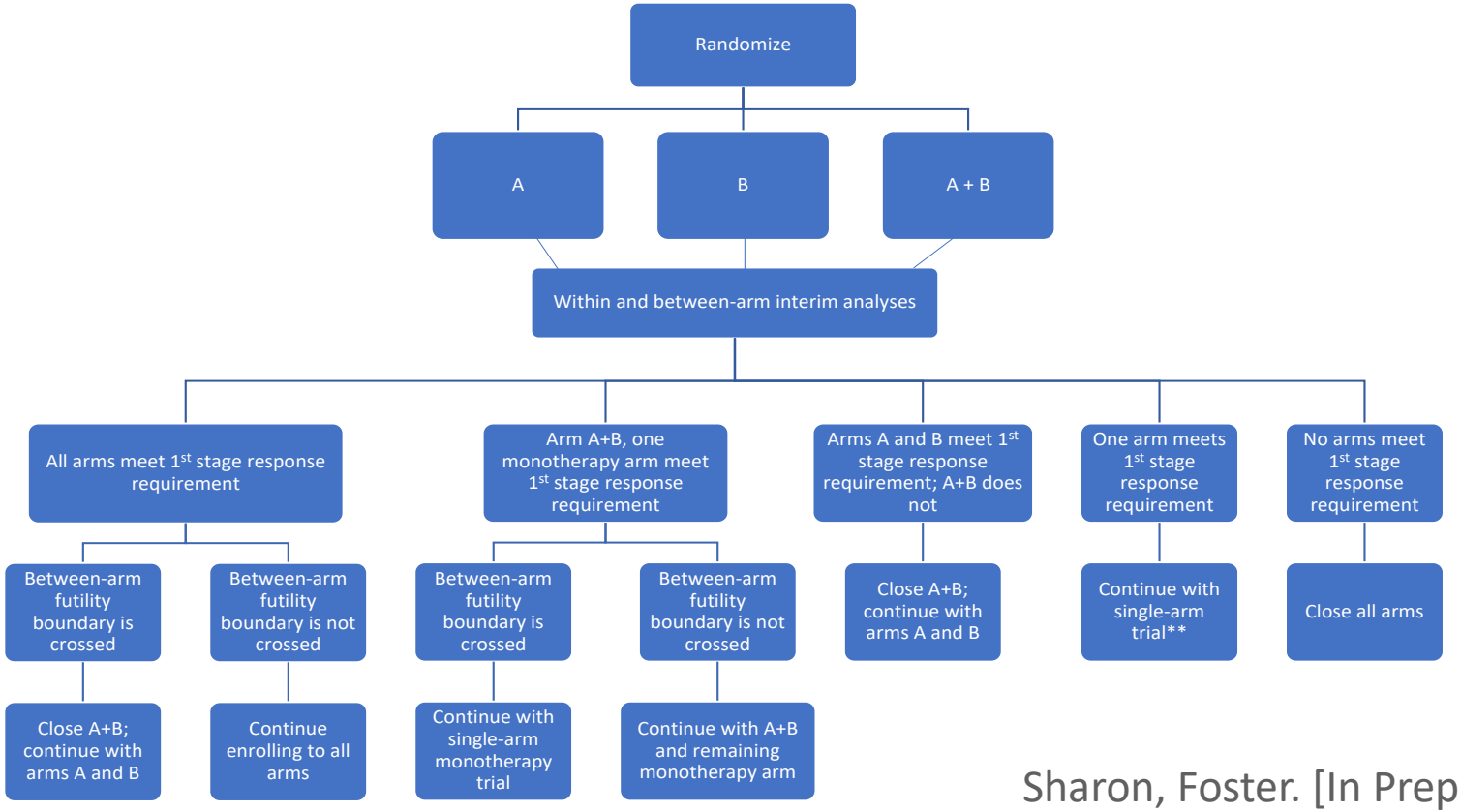
Sharon, Foster. [In Preparation]

Two-arm randomized comparative trial with only experimental arms



Sharon, Foster. [In Preparation]

Three-arm randomized comparative trial with only experimental arms



Sharon, Foster. [In Preparation]

Biomarkers are critical to further development of I-O drugs

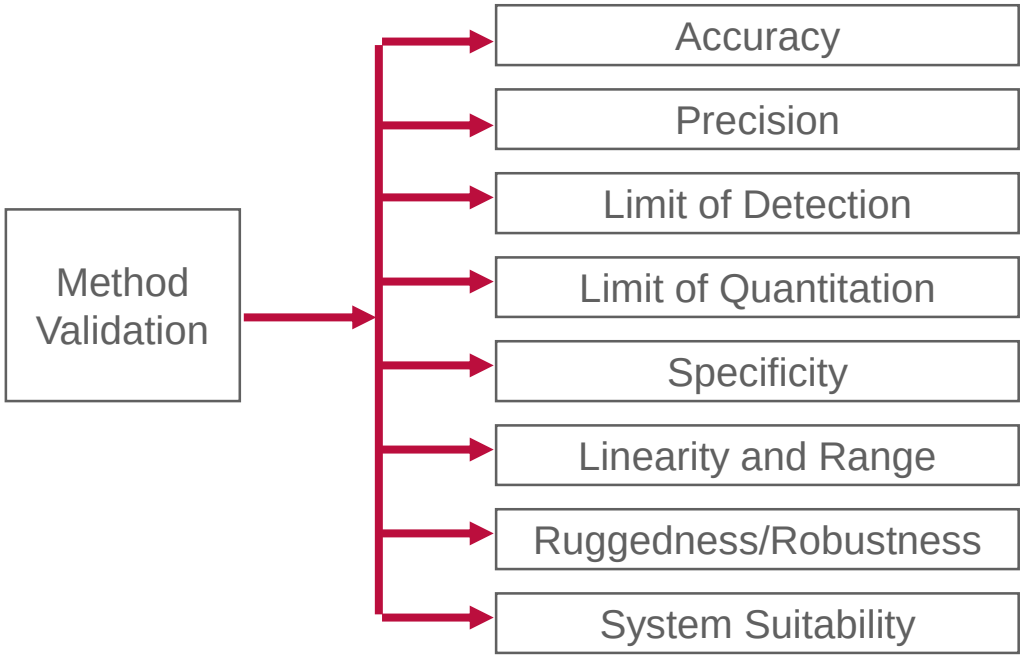
- Immunotherapy has shown remarkable activity in a variety of cancers, but only a minority of patients receive benefit
- Strategies to optimize patients' outcomes will rely on:
  - Use of biomarkers to characterize the tumor/immune interphase at the cellular and molecular levels
  - Rational combination therapies to overcome intrinsic or acquired resistance

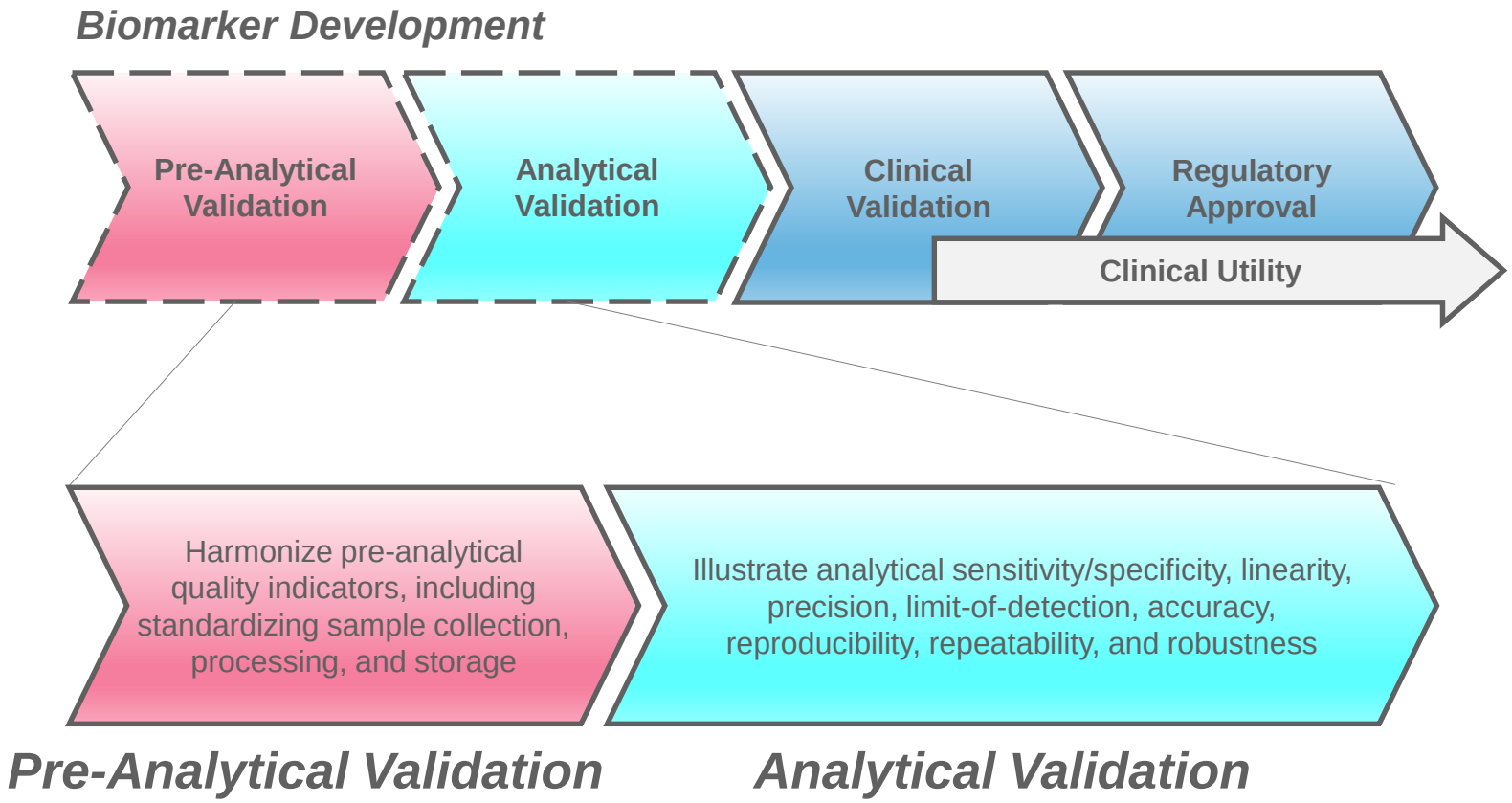
- Categories of biomarkers to inform immunotherapy:
  - Predictive biomarkers that inform about the likelihood of benefit or adverse events from various therapies
  - Mechanism-based resistance biomarkers that are potentially actionable
  - Biomarkers for designing rational clinical combination strategies
  - Biomarkers for monitoring treatment response and recurrence
  - Pharmacodynamic biomarkers for dose selection and sequencing of therapies

Unique Challenges of I-O Biomarker Development

- Biomarkers that predict response, resistance, or toxicity are of paramount importance to effectively develop immunotherapy
- Immunotherapy involves a systems approach to tumor cell killing
  - There is an inherent dynamism to the tumor microenvironment and the interplay of immune cells within the TME
  - Difficulties with specimen quality and tumor heterogeneity are compounded by the differential and time-dependent variable response of components of the immune system to the TME

What are the performance characteristics of the assay?




Biomarker Development
Pre-Analytical Validation
Analytical Validation
Clinical Validation
Regulatory Approval
Clinical Utility
Harmonize pre-analytical quality indicators, including standardizing sample collection, processing, and storage
Illustrate analytical sensitivity/specificity, linearity, precision, limit-of-detection, accuracy, reproducibility, repeatability, and robustness
Pre-Analytical Validation
Analytical Validation

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