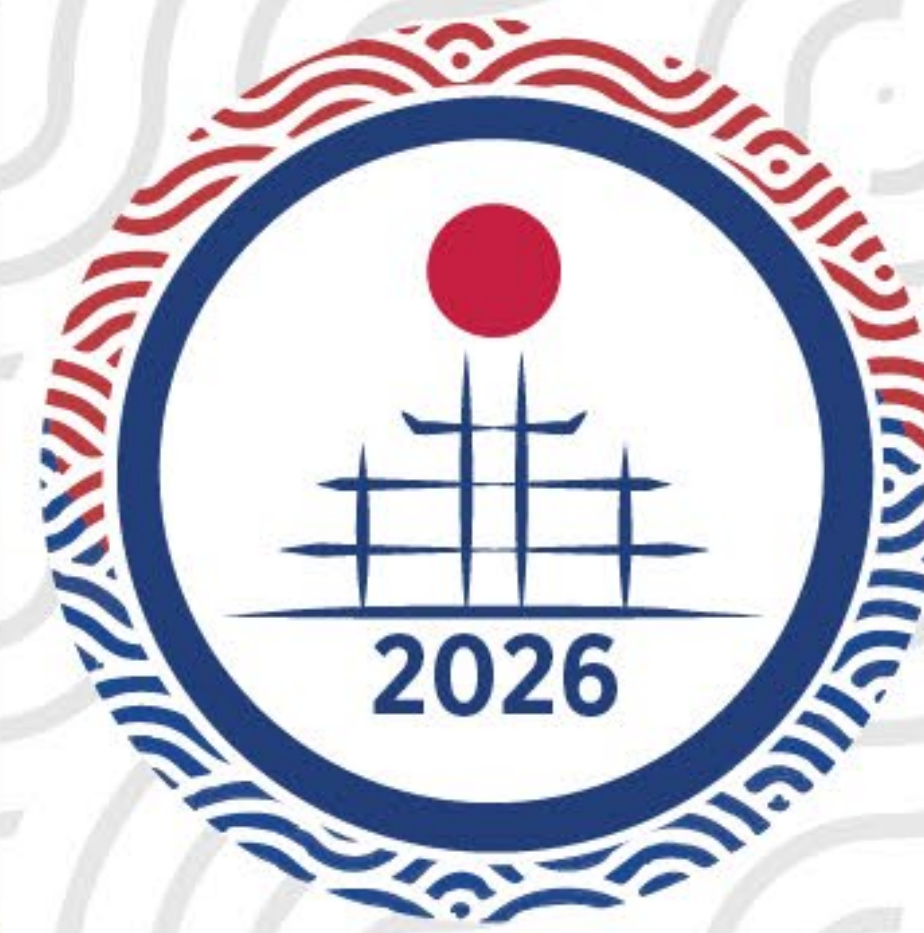


IASLC



2026 World Conference on Lung Cancer

SEPTEMBER 12 – 15, 2026 | SEOUL, REPUBLIC OF KOREA

IASLC PRECENT: Trial-Level Validation of Pathologic Complete Response (pCR) After Neoadjuvant Therapies as an Early Clinical Endpoint in NSCLC

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USA



P1.133: IASLC PRECENT: Trial-Level Validation of Pathologic Complete Response (pCR) After Neoadjuvant Therapies as an Early Clinical Endpoint in NSCLC

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INTRODUCTION

IASLC has a long history of leading neoadjuvant initiatives.¹⁻⁵ Neoadjuvant chemimmunotherapy has improved event-free and overall survival (EFS and OS) in multiple phase III trials in patients with resectable Stage IB to IIIA non-small cell lung cancer without oncogenic drivers. However, endpoints like EFS and OS mature slowly, delaying access to effective therapies. Pathologic complete response (pCR) in resection specimens following neoadjuvant therapies determined in just months, is an attractive early endpoint. Regulatory guidance to establish early clinical endpoints² emphasizes two distinct requirements: individual-level association (I-association; patients with pCR have better outcomes) and trial-level association (T-association; treatments that improve pCR also improve EFS/OS across trials).

Our Goal: Prove pathologic complete response (pCR) is an early clinical endpoint by creating a database containing the data elements from neoadjuvant treatment trials and performing the necessary statistical analyses

METHODS

PRECENT (Pathologic Response as an Early Clinical Endpoint in Neoadjuvant Therapy) is an IASLC-led effort to assemble an integrated database of individual-level data phase II/III studies testing multiple immune checkpoint inhibitors in the neoadjuvant setting. We are following FDA guidance⁶ and working with the FDA to maximize the opportunity for regulatory approval as an early clinical endpoint.

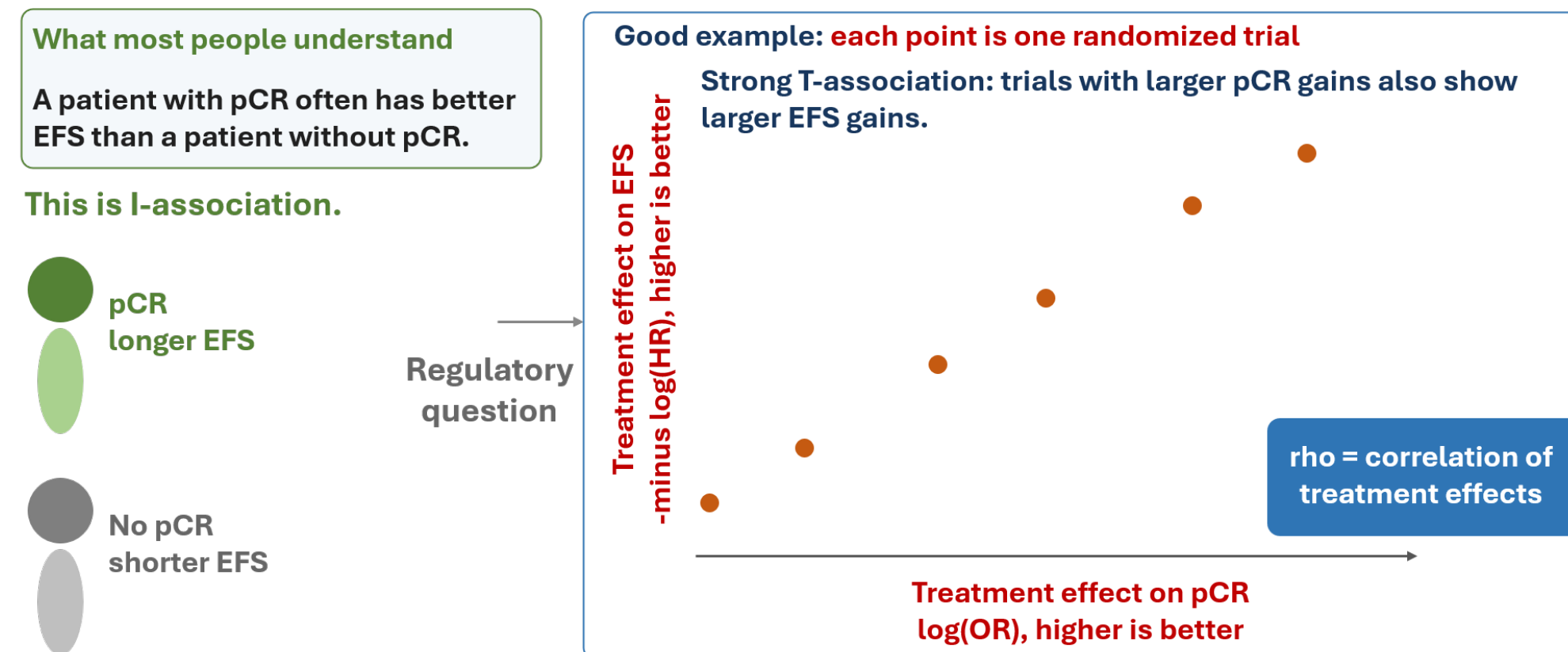
To achieve our goal, we must prove both:

I-Association: The association between the surrogate end point (e.g., pCR) and the true end point (e.g., EFS).

T-Association: The association between the effect of treatment on the surrogate end point (e.g., odds ratio for pCR), and the effect of treatment on the true end point (e.g., hazard ratio for EFS).

I-Association is routinely assessed, but T-Association is frequently overlooked.⁷

T-Association in Plain Language



Why T-Association Matters

Bone density illustrates why a prognostic marker is not automatically a valid surrogate

Classic Cautionary Example		PRECENT Question	
Surrogate endpoint	Bone mineral density	Surrogate endpoint	Pathologic complete response
True endpoint	Fracture rate	True endpoint	Event-free survival
Treatment example	Sodium fluoride increased bone density.	Treatment question	Do therapies that improve pCR also improve EFS?
What happened	Fractures did not improve as expected, and some remained high.	What we must show	Randomized trials with larger OR of pCR gains should also show larger HR EFS gains.
Lesson	A marker can improve without creating true clinical benefit.	Lesson	Strong I-association alone is not enough for surrogate validation.

DISCUSSION AND CONCLUSION

Actionable Take Away Message:

- IASLC PRECENT combines the individual level data from a sufficient number of trials with the capability to deliver trial level evidence for pCR as an approvable endpoint by explicitly addressing both the I- and T-association.

Future Direction for Research:

- We plan to close the biggest evidentiary gap in surrogate validation. This data can support the qualification of pCR as an early clinical endpoint for trials of neoadjuvant therapies for resectable lung cancers and provide a scalable template for early-endpoint validation in oncology.

ACKNOWLEDGEMENTS & REFERENCES

PRECENT is a project of the IASLC with funding and data support from AstraZeneca, BeOne Medicines, Bristol Myers Squibb, Genentech/Roche, MSD, and Junshi/TopAlliance. Thank you to our additional collaborators from Columbia, Cornell, Duke, IASLC, MD Anderson, and the U.S. Food and Drug Administration.

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RESULTS

Global Neoadjuvant Clinical Trials Working With PRECENT

PRECENT has been a collaborative effort between the IASLC and investigators and advisors from industry, academia, and regulatory bodies. The following sponsors and investigators are involved in PRECENT and all clinical trials in **bold maroon font** already have signed data use agreements (Tables 1 and 2).

Table 1: Phase III and Randomized Phase II Studies

Sponsor	Trial	Checkpoint Inhibitor (s)	Patients
AstraZeneca	AEGEAN ⁸	Durvalumab	802
BeOne	RATIONALE-315⁹	Tislelizumab	453
BMS	CheckMate 816¹⁰	Nivolumab	358
BMS	CheckMate 816¹¹	Nivolumab / Ipilimumab	221
BMS	CheckMate 77T¹²	Nivolumab	461
Genentech/ Roche	IMpower030 ¹³	Atezolizumab	453
MSD	KEYNOTE - 671¹⁴	Pembrolizumab	797
GECP	NADIM II¹⁵	Nivolumab	86
Junshi/ TopAlliance	Neotorch¹⁶	Toripalimab	404
			4121

Table 2: Phase II Single Arm Studies

Sponsor/Trial	PI	Checkpoint Inhibitor(s)	Patients
Columbia ¹⁷	Shu	Atezolizumab	39
Cornell ¹⁸	Altorki	Durvalumab	60
Duke TOP1501 ¹⁹	Reddy	Pembrolizumab	35
Genentech/ Roche ²⁰	LCMC3	Atezolizumab	181
GECP NADIM I²²	Provencio	Nivolumab	46
			361

How Do You Evaluate T-Association? Development of a New Method

We will analyze the I-association using both single arm and randomized studies. This has been previously done in other cancers, but T-association has remained a significant challenge.

We propose a method to evaluate T-association:²²

- Assume that the treatment effects on both endpoints follow **a bivariate normal distribution**.
- Use **the correlation coefficient** between the two endpoints as the key evaluation metric.

This method will facilitate future FDA accelerated approvals for new drugs.

Proposed Method for Evaluating T-Association

- Estimate treatment effects on pCR and EFS within each randomized trial.
- Jointly model both treatment effects across trials using a bivariate normal random-effects framework, with their correlation as the primary measure of T-association.
- Apply maximum likelihood (ML) and restricted maximum likelihood (REML), with confidence intervals to quantify uncertainty (Table 3).
- Apply Bayesian estimation to obtain the posterior distribution and credible intervals for T-association (Table 4).
- Accommodate unavailable within-study correlations, an important advantage for completed or published trials.

Data Collection & Next Steps

The PRECENT Database, housed securely at the University of Memphis, was completed in early 2026 and data collection has begun.

As of August 2026, data from three clinical trials has been entered representing 536 individual patient-level cases (Figure 1) and two distinct immune checkpoint inhibitors. Data collection continues with initial analyses planned for 2027.

Artificial Intelligence (AI) Use Disclaimer: AI was not used in the development of this content.

Table 3: Frequentist Simulation Results

n	Method	Bias	SE (empirical)	SE (theoretical)	Coverage Probability
n=15	ML	-0.0141	0.1546	0.1415	87.4
	REML	-0.0141	0.1546	0.1451	88.1
n=8	ML	-0.0153	0.2553	0.2102	82.2
	REML	-0.0155	0.2552	0.2246	83.6
n=6	ML	-0.0049	0.2953	0.2299	76.9
	REML	-0.0050	0.2949	0.2515	78.5

Table 4: Bayesian Simulation Results – ρ

n	Bias	SE (empirical)	SE (posterior)	Empirical Coverage
n=15	-0.0211	0.0634	0.0666	91.6
n=8	-0.0439	0.0925	0.0982	83.9
n=6	-0.1053	0.1433	0.1684	80.3

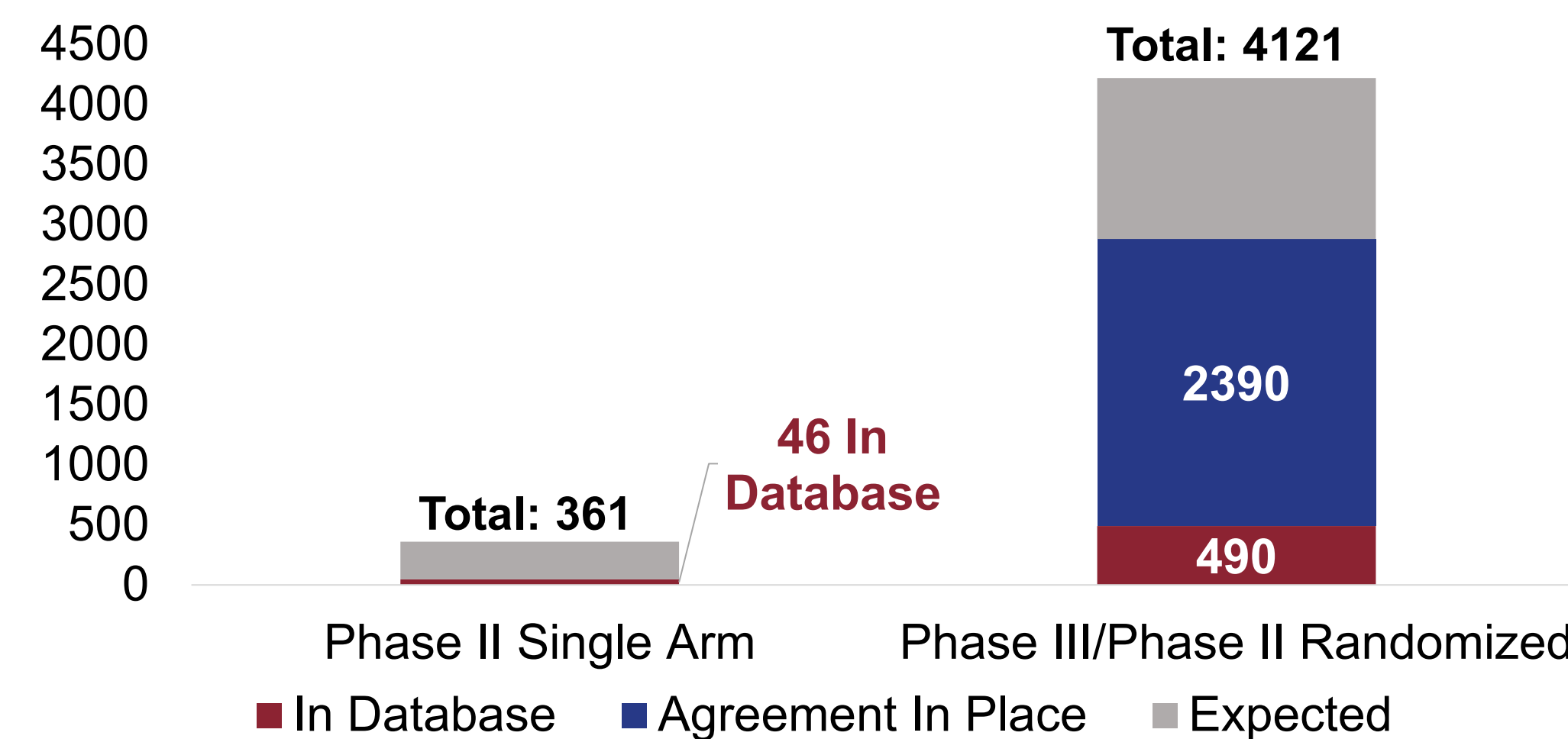


Figure 1: Enrollment in PRECENT Database

Background

- IASLC has a long history of leading neoadjuvant initiatives.¹⁻⁵
- Neoadjuvant chemoimmunotherapy has improved event-free and overall survival (EFS and OS) in multiple phase III trials in patients with resectable Stage IB to IIIA non-small cell lung cancer without oncogenic drivers. However, endpoints like EFS and OS mature slowly, delaying access to effective therapies. Pathologic complete response (pCR) in resection specimens following neoadjuvant therapies determined in just months, is an attractive early endpoint.
- **Our Goal:** Prove pathologic complete response (pCR) is an early clinical endpoint by creating a database containing the data elements from neoadjuvant treatment trials and performing the necessary statistical analyses

Methods

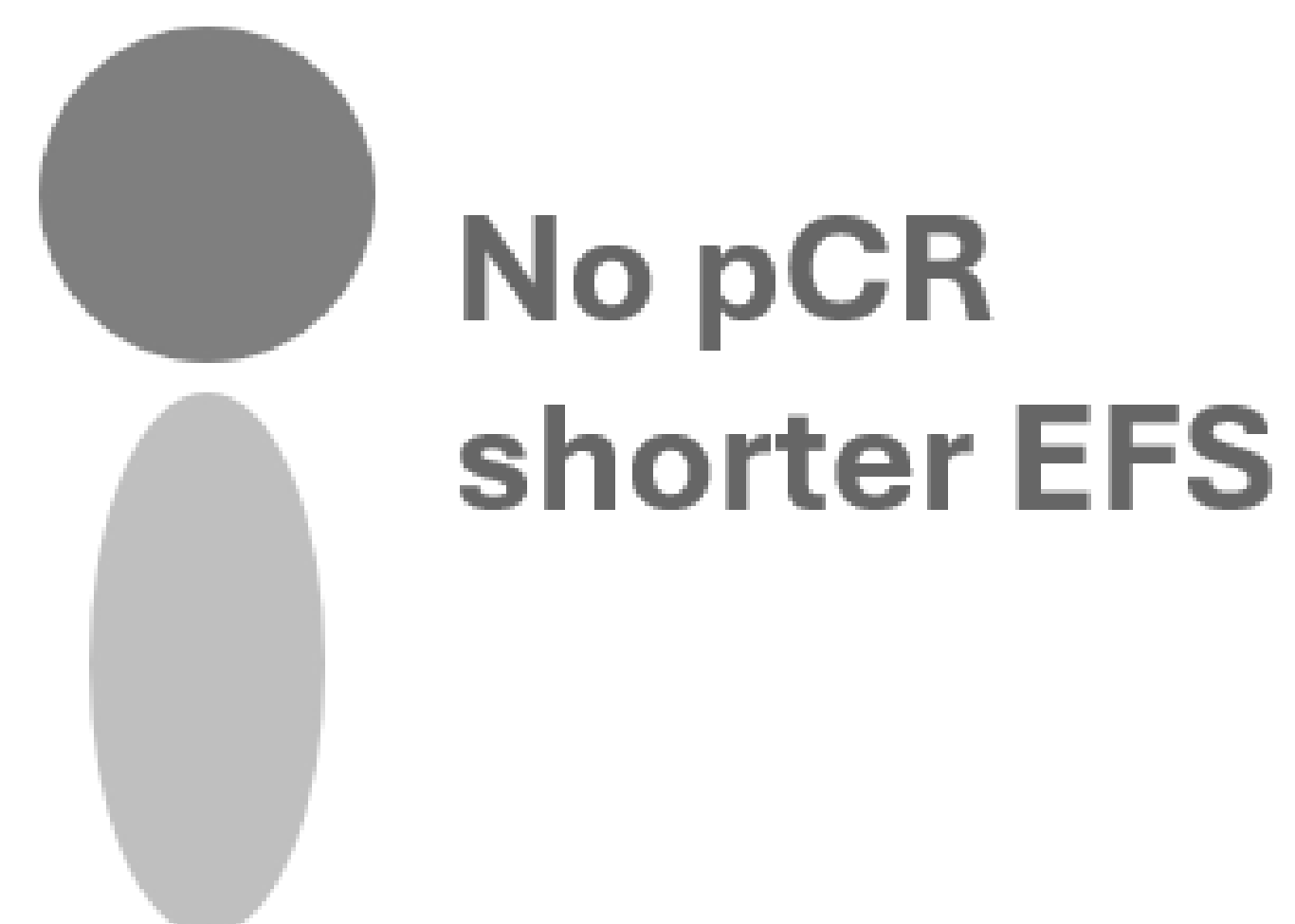
- PRECENT (Pathologic Response as an Early Clinical Endpoint in Neoadjuvant Therapy) is an IASLC-led effort to assemble an integrated database of individual-level data phase II/III studies testing multiple immune checkpoint inhibitors in the neoadjuvant setting. We are following FDA guidance⁶ and working with the FDA to maximize the opportunity for regulatory approval as an early clinical endpoint.
- **To achieve our goal, we must prove both:**
 - **I-Association:** The association between the surrogate end point (e.g., pCR) and the true end point (e.g., EFS).
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- I-Association is routinely assessed, but T-Association is frequently overlooked.⁷

T Association in Plain Language

What most people understand

A patient with pCR often has better EFS than a patient without pCR.

This is I-association.

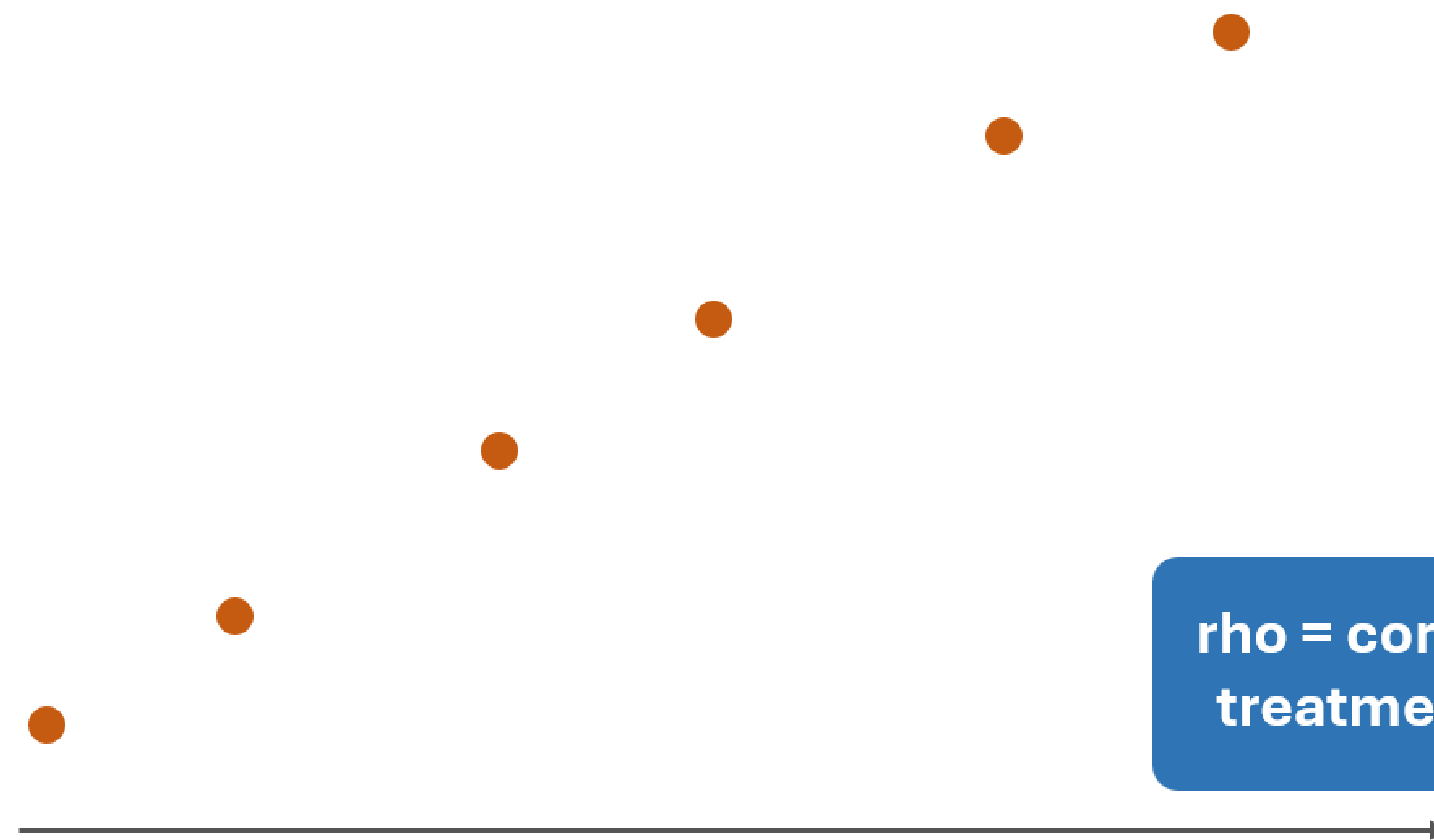


Regulatory
question

Good example: **each point is one randomized trial**

Strong T-association: trials with larger pCR gains also show larger EFS gains.

Treatment effect on EFS
-minus log(HR), higher is better



rho = correlation of
treatment effects

Treatment effect on pCR
log(OR), higher is better

Why T Association Matters

Bone density illustrates why a prognostic marker is not automatically a valid surrogate

Classic Cautionary Example

Surrogate endpoint	Bone mineral density
True endpoint	Fracture rate
Treatment example	Sodium fluoride increased bone density.
What happened	Fractures did not improve as expected, and some remained high.
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PRECENT Question

Surrogate endpoint	Pathologic complete response
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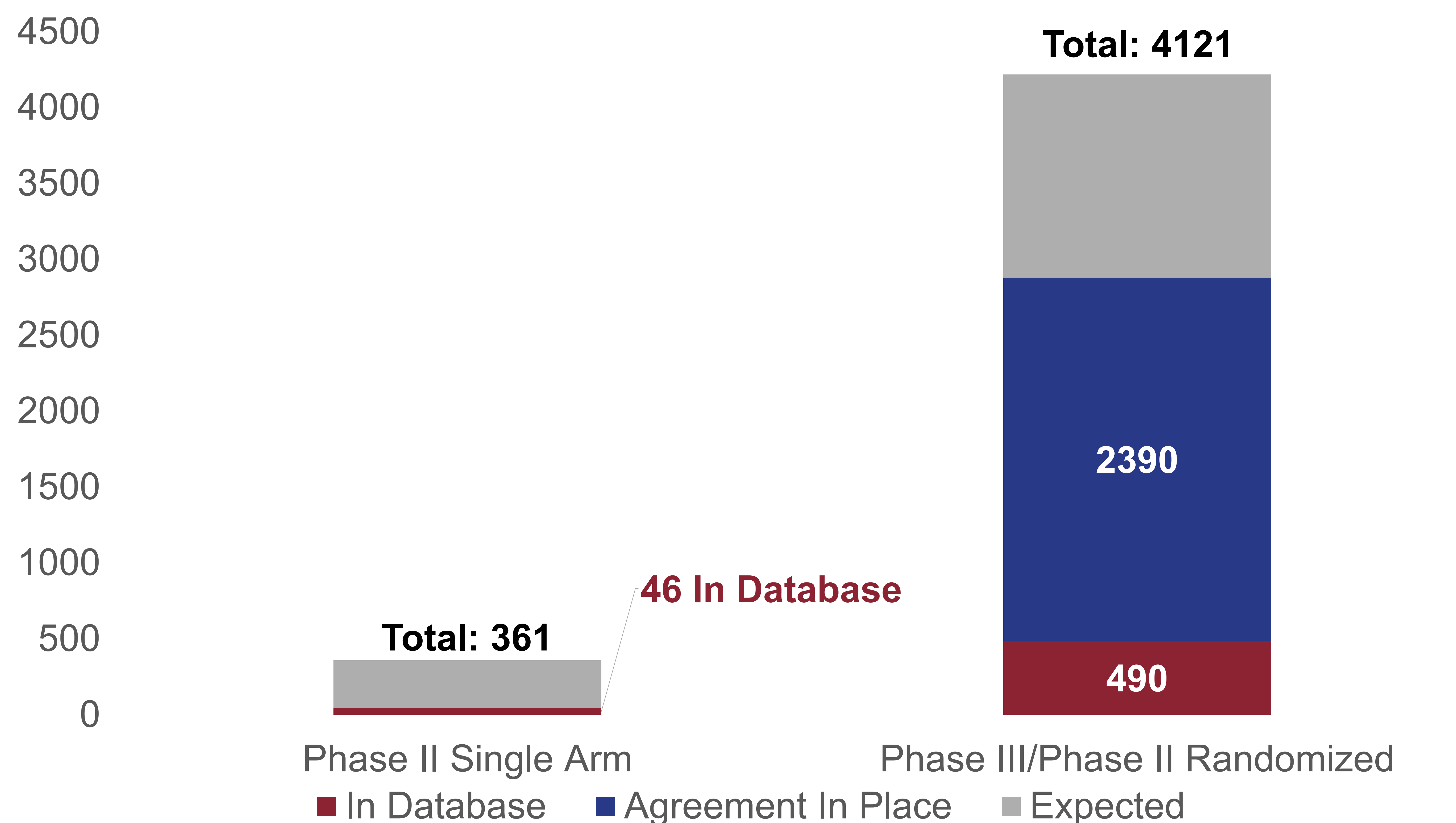
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