PLUS™ THERAPEUTICS

CSF Tumor Cell (CSF-TC) **Detection, Quantification and Biomarker assessment helps in clinical management of breast cancer and Non-Small Cell Lung cancer patients having Leptomeningeal Disease** (FORESEE Study, NCT05414123)

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Summary

FORESEE was a clinical utility study assessing the impact of the CSF diagnostic platform CNSide on disease management of patients with Leptomeningeal Disease

Preliminary analysis shows that CNSide:

+ Contributed to making a clinical decision in 91% (50/55) of decisions
+ Confirmed a positive LM diagnosis on 18% (7/39) of patients
+ Confirmed a negative LM diagnosis in 8% (3/39) of patients
+ Informed a specific drug selection in 26% (10/39) patients

*Immature data

Timeline of the FORESEE Study

Biocept

March 2023	Sept. 2023	Oct. 2023
Enrollment started	Enrollment completed	Study prematurely ended

Nov.'23-March '24
Study closed and trial data not accessible

Plus Therapeutics

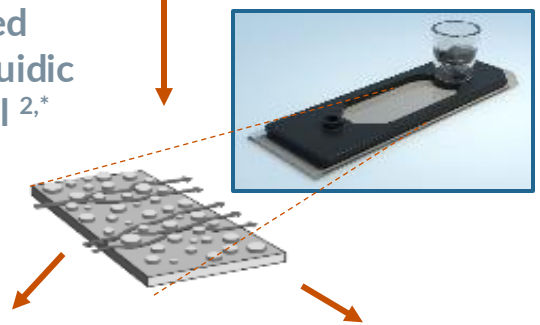
May 2024	June-July	Near Future
Plus Therapeutics acquired FORESEE data	Analysis of preliminary data (not locked)	Working with sites to monitor and lock data

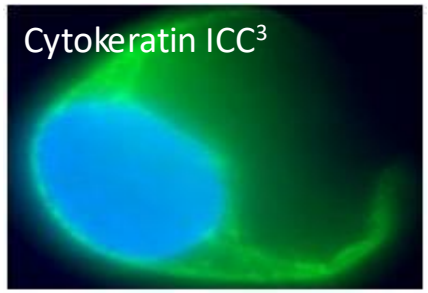
CNSide CSF Diagnostic Platform

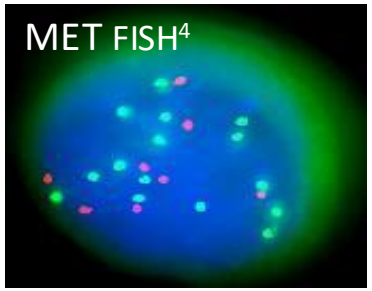
Tumor Cell Detection Workflow

Antibody Cocktail Tumor Cell Isolation[1, *]

Patented Microfluidic Channel [2,*]





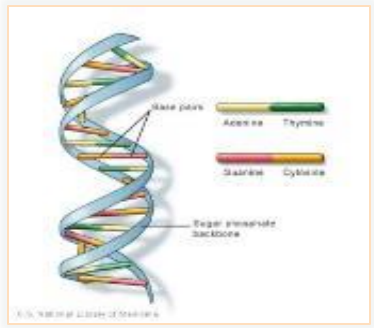


Collection tube forambient shipping up to 4 days

*Unique cell capture technology for FISH and protein expression assays

cfDNA Detection Workflow

CSF cfDNA Isolation



NGS on CSF cfDNA

[1] Mikolajzyk et al. JCO (2011), [2] Dickson et al. Microfluidics (2011)
[3] Pecot et al. Cancer Discovery (2011), [4] Mayer et al. Cancer Genetics (2011)

Retrospective analyses showing utility

(but no prospective study to date)

No prospective data in controlled setting to confirm clinical utility observed from retrospective analysis

Need to understand clinical performance of tumor cell detection of CNSide compared to current gold standard, CSF cytology

CNSide helps to diagnose LMD

CNSide helps to determine response to LMD directed therapy

CNSide helps to inform specific LMD therapy selection

Puri et al (Neuro-Oncology Advances, 2023), Kumthekar et al (Frontiers in Oncology 2024)

FORESEE Study:

Trial Schema

At each visit clinical decision made based on:

+ Cytology
+ MRI Image Evaluation
+ Clinical Evaluation
+ CNSide results

+ At each visit, CNSide's contribution to a clinical decision was evaluated via a Questionnaire
+ Treatment decisions were at Physician discretion
+ Enrollment goal: 20 patients with breast cancer, 20 with NSCLC

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FORESEE Study:

Study End Points

Primary End Point

Evaluate if CNSide contributes to a clinical decision (Target: 20% of decisions)

Secondary End Point

Evaluate tumor cell detection by CNSide as a therapy response monitoring tool
Sensitivity, Specificity, NPV and PPV of CNSide compared to CSF cytology

FORESEE Study:

Inclusion and Exclusion criteria

Inclusion Criteria

+ Positive breast cancer or NSCLC diagnosis
+ Suspected or confirmed LMD diagnosis
+ Willingness to sign informed consent
+ Positive or negative for Parenchymal brain metastasis

Exclusion criteria

+ Patients with any other cancer than breast cancer or NSCLC cancer
+ Patients with a primary brain tumor

Precedence for Clinical Utility Trial Design

Title	NCT#	Primary End Point	Type of Test
BESPOKE Study of ctDNA Guided Immunotherapy	04761783	Percent of Melanoma, - NSCLC and Colorectal patients who have their immunotherapy treatment regimen changed due to the SIGNATERA ctDNA test result	Patient tailored gene panel to detect cfDNA from the blood
Treatment Decision Impact of OncotypeDx in HR+, N- Breast Cancer Patients (SWITCH)	01446185	Impact of OncotypeDx Recurrent Score on treatment decisions	21-gene test that predicts recurrence of early-stage breast cancer
Study of the Clinical Utility of PSMA Imaging in the Evaluation of Men With Prostate Cancer	02825875	Changes to clinical management of patients with prostate cancer after Physician reviews a PET/CT scan of PSMA	PSMA Imaging by PET/CT
Prospective Clinical Utility Study to Assess the Impact of Decipher on Treatment Decisions after Surgery (PRO-IMPACT)	02080689	Number of participants for which the Urologist changed the patient's treatment plan based on Decipher test results	Next Generation Sequencing of tumor tissue
Decision Impact Study of PreciseDx Breast (PDxBRUTILITY)	06309615	Proportion of Physicians who utilized PBxBR results in their management of patients with invasive breast cancer (target: 20%)	Combination of Artificial Intelligent grading of histology and clinical data that predicts recurrence in early-stage breast cancer patients

FORESEE Study:

Physician Questionnaire

Baseline:

- Was the patient diagnosed with LM prior to Baseline visit (yes, no)
  - If no, is the patient diagnosed with LM at the Baseline visit (yes, no)
  - If yes, what is the status of the LM tumor at this visit (No Change, Progression, Resolution)
- Did CNSide contribute to this assessment? (yes, no)
- Did CNSide inform the specific drug selected for treatment? (yes, no)

Subsequent visits:

- What is the status of the LM tumor (No Change, Progression, Resolution)
- Did CNSide contribute to this assessment? (yes, no)
- Did CNSide inform the specific drug selected for treatment? (yes, no)

Patient Demographics

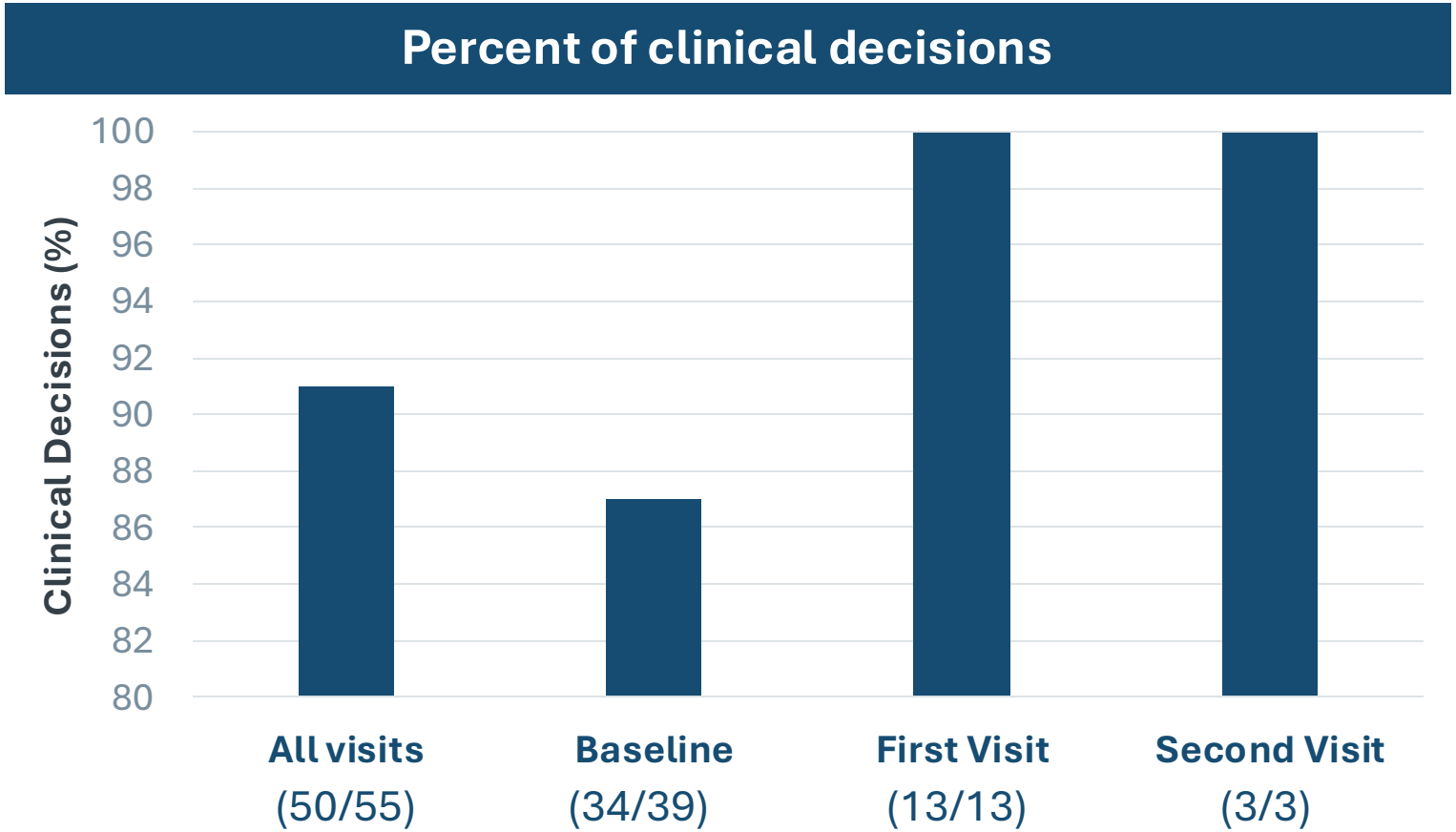
(n=39 pts*, n=55 decision points)

	Breast Cancer (N=21)	**NSCLC** (N=18)
Age range	58 years	58 years
Gender	F (N=21)	F (N=9), M (N=9)
Parenchymal brain metastasis diagnosed prior to enrollment	52% (11/21) Positive, 43% (9/21) Negative , 5% (1/21) Unknown	56% (10/18) Positive, 44% (8/18)) Negative
LMD Diagnosed prior to trial enrollment (by investigator assessment)	81% (17/21) Positive, 14% (3/21) Negative, 5% (1/21) Unknown	61% (11/18) Positive, 39% (7/18) Negative
Primary HER2 status	19% (4/21) Positive, 76% (16/21) Negative, 5% (1/21) Unknown	Not Applicable
Primary HER2-/ER-/PR-	9% (2/21)	Not Applicable
Primary ER+	76% (16/21) Positive, 19% (4/21) Negative, 5% (1/21) Unknown	Not Applicable
Primary PR+	67% (14/21) Positive, 24% (5/21) Negative, 10% (2/21) Unknown	Not Applicable
Number of Questionnaires completed (N=55 total; 29 BC and 26 NSCLC)	72% (21/29) Baseline, 24% (7/29) First Visit, 3% (1/29) Second Visit	69% (18/26) Baseline, 33% (6/26) First Visit, 8% (2/26) Second Visit
Number of patients with Baseline Visit	21	18
Number of patients with Baseline + First Visit	7	6
Number of patients with Baseline + First Visit + Second Visit	1	2

*N=40 patients enrolled; data was entered for N=39 patients (N=21 breast cancer, N=18 NSCLC)

Take Home #1:

CNSide helped make clinical decisions in LMD patients



Take Home #2:

CNSide helped to diagnose LMD

N=10 patients not diagnosed with LMD prior to trial enrollment

- These patients were deemed LMD positive or negative after the Baseline visit based on Investigator assessment

LMD Positive Patients (N=7)

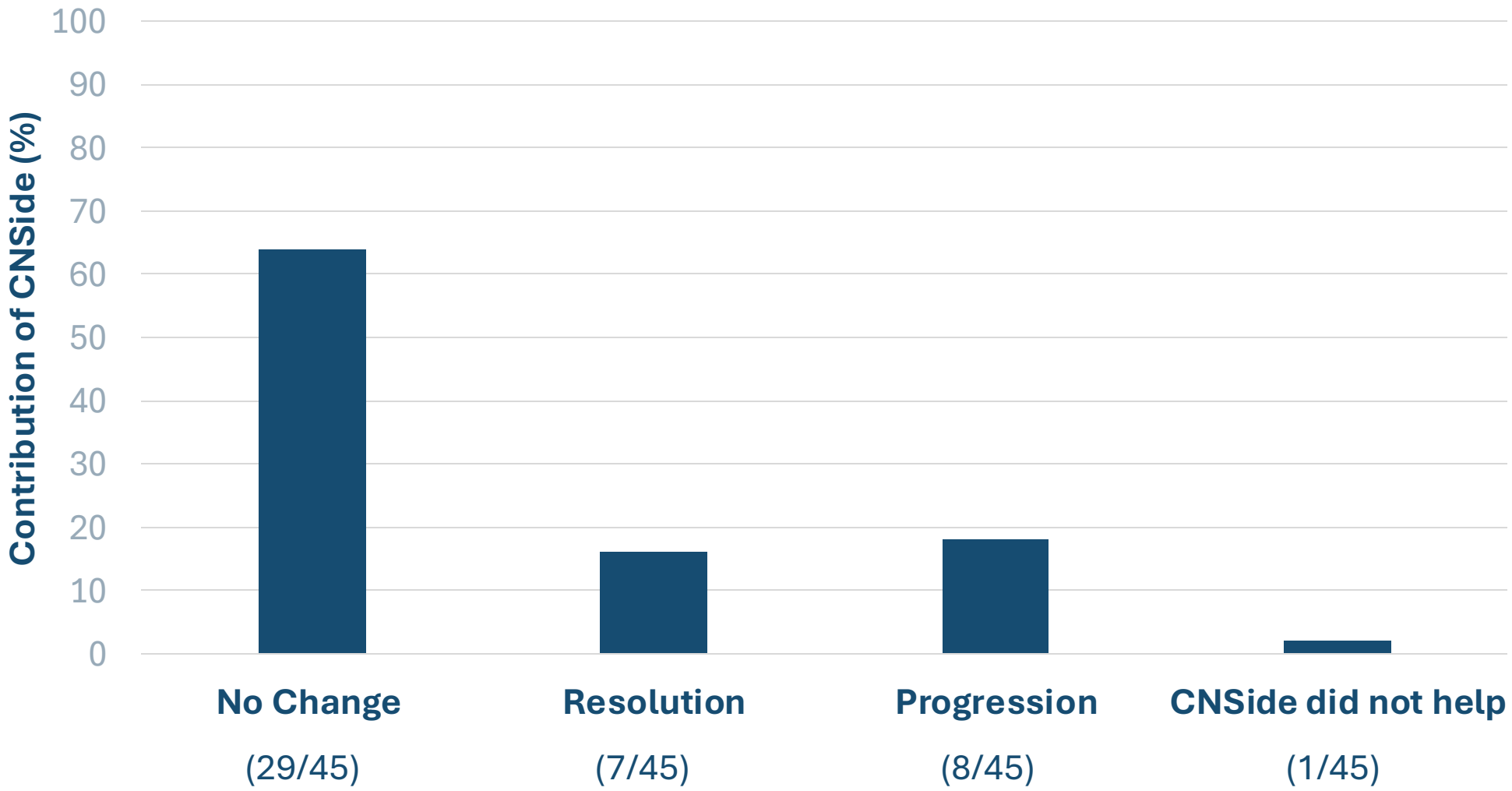
- Cytology Positive, CNSide Positive: N=2
- Cytology Negative, CNSide Positive: N=5

LMD Negative Patients (N=3)

- All three patients were Cytology Negative and CNSide Negative
- Investigators noted on the questionnaire that CNSide helped to rule out LMD

Take Home #3:

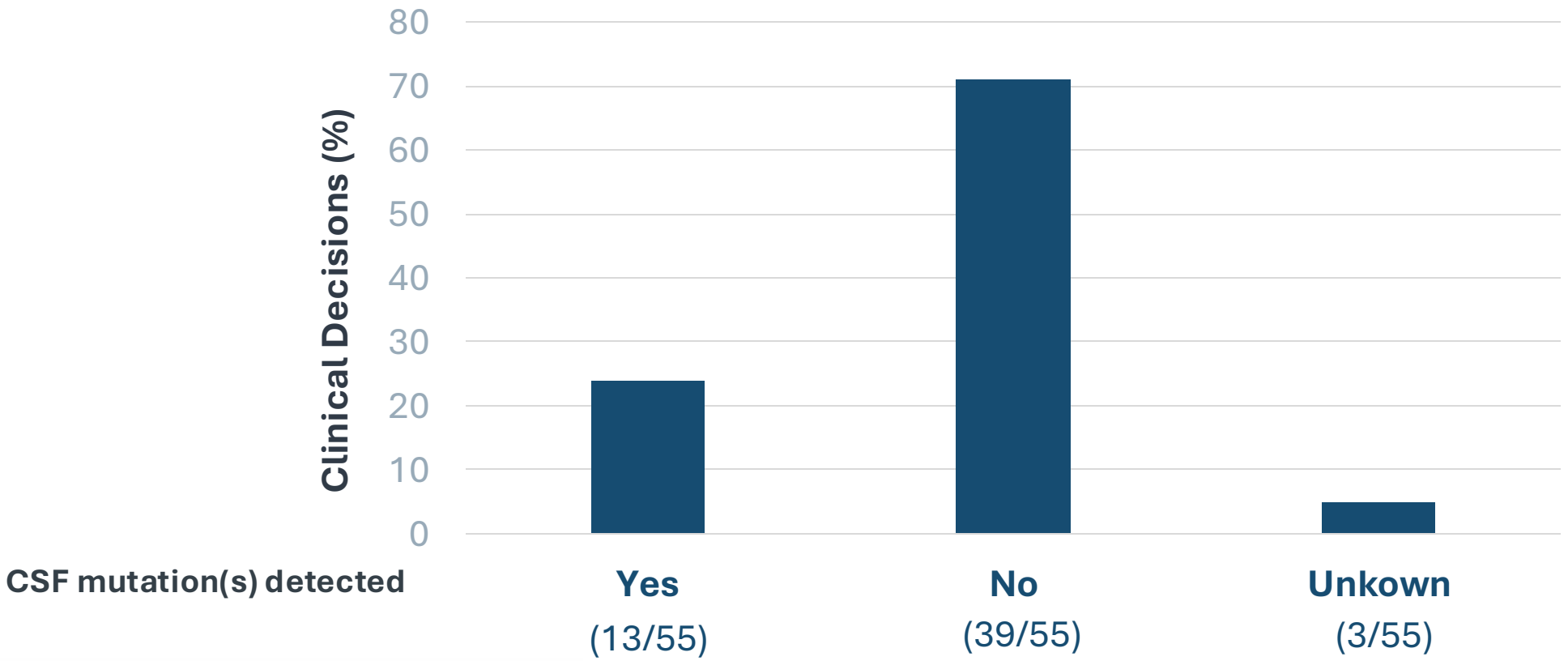
CNSide helped to evaluate the status of the LMD tumor (45 questionnaires)*



*N=35 pts

Take Home #4:

CNSide identified mutations used to make a specific drug selection



Improved sensitivity of tumor cell detection in LMD patients*with CNSide vs cytology** in matched samples

Cytology

Cytology (positive or negative)	LMD Status: Positive	LMD Status: Negative	LMD Status: Total
Positive	13	0	13
Negative	27	3	30
Total	40	3	43

Cytology

+ Sensitivity: 33%
+ Specificity: 100%
+ PPV: 100%
+ NPV: 10%

CNSide

CNSide (positive or negative)	LMD Status: Positive	LMD Status: Negative	LMD Status: Total
Positive	31	0	31
Negative	9	3	12
Total	**40**	**3**	**43**

CNSide

+ Sensitivity: 78%
+ Specificity: 100%
+ PPV: 100%
+ NPV: 25%

*LMD based on investigator assessment
** Only cytology Positive and Negative results included

Improved sensitivity of tumor cell detection in LMD patients* of CNSide compared to cytology

Matched CSF samples (N=45, of N=39 unique patients)

Patients with an LMD positive diagnosis (all visits)

- Cytology detected cells in 29% (13/45) samples
- Cytology did not detect cells in 60% (27/45) samples
- Cytology was Atypical in 9% (4/45) samples
- Cytology was Suspicious in 2% (1/45) samples

CNSide detected cells in 80% (36/45) samples

CNSide did not detect cells in 20% (9/45) samples

*LMD based on investigator assessment

Improved tumor cell detection in LMD patients* of CNSide compared to Cytology** in matched samples (N=45)

CNSide	Cytology
+ Detected cells in 80% (36/45) samples of LMD Positive Patients (N=36)	+ Detected cells in 29% (13/45) samples of LMD Positive Patients (N=36)
+ Did not detect cells in LMD Negative Patients (N=3)	+ Detected Atypical or Suspicious cells in (4/45) samples of LMD Positive Patients
	+ Did not detect cells in LMD Negative Patients (N=3)

*LMD based on investigator assessment

**Cytology Atypical and Suspicious for Malignant cells included

Conclusions and Next Steps

Preliminary Conclusions

+ FORESEE study met primary end point
+ CNSide helped to make a clinical decision in 91% (50/55) of decisions
+ CNSide helped to inform therapy selection in 24% (13/55) of decisions
+ Compared to cytology in matched samples, CNSide more than doubled the sensitivity of tumor cell detection in the CSF

Next steps

+ Working with the sites to obtain mature data to be presented/published in near future

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