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Real-World Assessment of TROP2 NMR by Quantitative Continuous Scoring (QCS) in Non-Small Cell Lung Carcinoma (NSCLC)

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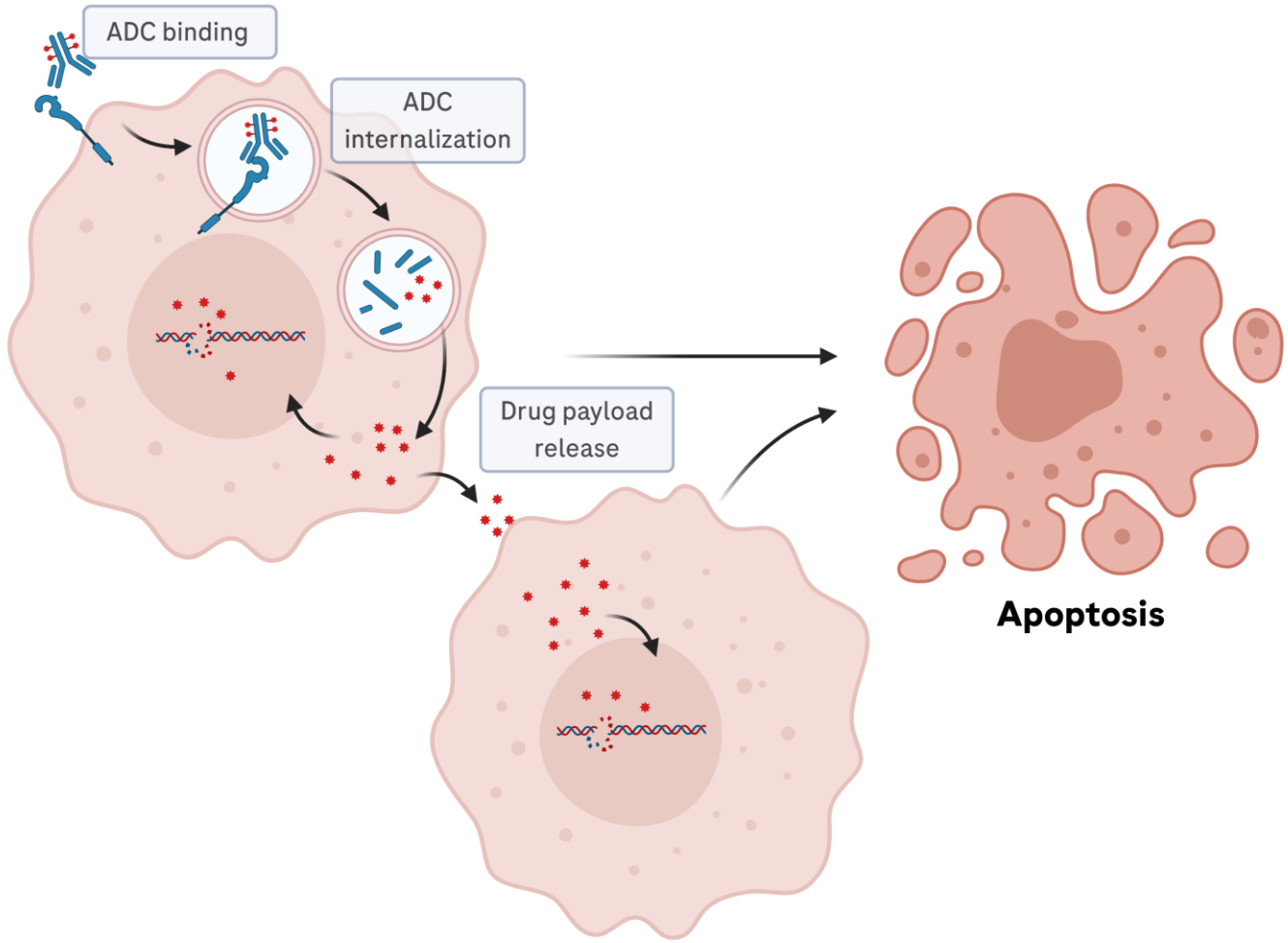
Background

- Trophoblastic antigen 2 (TROP2) is a novel target for antibody drug conjugates (ADCs) in NSCLC[1]
- Conventional IHC manual scoring (H-score) has not shown a relationship between TROP2 expression and response to a TROP2 directed ADC[2]
- A novel computational pathology biomarker, TROP2 NMR [Normalized Membrane Ratio], has shown potential to predict non-AGA NSCLC patient response to a TROP2 directed ADC[3]
- The **aim** of this study is to investigate the **analytical performance** of a RUO TROP2 NMR computational pathology device in real world pathology laboratories

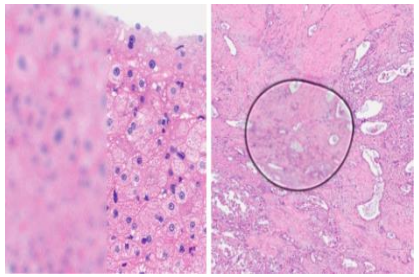


1. Ahmed, Y. et al. The Rise of the TROP2-Targeting Agents in NSCLC: New Options on the Horizon. *Oncology* 99, 673–680 (2021). 2. Shimizu, T. et al. First-in-Human, Phase I Dose-Escalation and Dose-Expansion Study of Trophoblast Cell-Surface Antigen 2–Directed Antibody-Drug Conjugate Datopotamab Deruxtecan in Non–Small-Cell Lung Cancer: TROPION-PanTumor01. *J Clin Oncol.* 41, 4678–4687 (2023). 3. Garassino, MC et al. PL02.11 Normalized Membrane Ratio of TROP2 by Quantitative Continuous Scoring is Predictive of Clinical Outcomes in TROPION-Lung 01. *J Thorac Oncol.* 19, S2–S3 (2024).

TROP2 NMR full device pathologist workflow

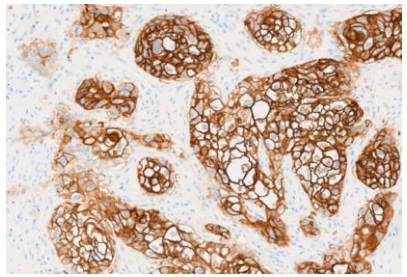
1. WSI acceptability

Confirm WSI are free of significant imaging artifacts (e.g., **out of focus in >20%** of the tumor area, tiles, stitching lines)



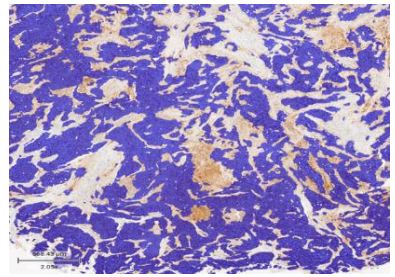
2. IHC acceptability

Confirm the WSI contains at least 100 evaluable NSCLC tumor cells and that there is appropriate staining on the TROP2 WSI and NRC WSI



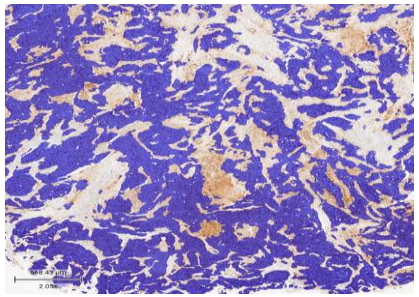
3. Region overlay acceptability:

Confirm that the Tumor Region Overlay has detected sufficient evaluable tumor



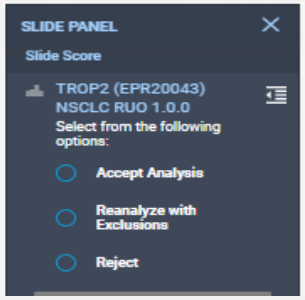
4. Tumour overlay acceptability

Confirm the Tumor Region Overlay covers definitive tumor. Non-analyzable areas (if needed) are excluded from analysis by drawing annotations



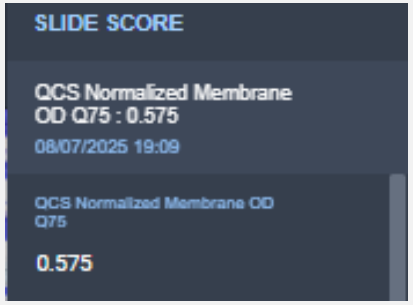
5. Accept or reject analysis

After review of the overlay, the pathologist can either accept the TROP2 (EPR20043) RUO algorithm's analysis, re-analyze the WSI with exclusions or reject the case if steps 1-4 are not met



6. Results display

The algorithm (not the pathologist) quantifies and computes the NMR for all identified tumor cells. The algorithm then organizes the NMR dataset to determine the 75th quantile



Digital Analysis

IHC, immunohistochemistry; NMR, normalized membrane ratio; NRC, negative reagent control; NSCLC, non-small cell lung cancer; TROP2, trophoblastic antigen 2, WSI, whole slide image

Methodology

Sample characteristics

- NSCLC samples from commercial source
- Histologies included AdenoCa, SCC & others
- FFPE
- Primary and metastatic tissue samples

Case set	Total number of cases	Positive** cases ≤ 0.563 NMR	Negative** cases > 0.563 NMR
Digital analysis only	64	32	32
Full Device*	36	18	18

Pathologist characteristics

- 3 pathologists from each of 9 academic and large reference sites in USA, EU and Canada and 3 pathologist from the internal Roche clinical lab (n=30) performed both digital and full device analysis, with a 2-week interval between ('wash out')
- Pathologist were a mixture of thoracic and non-thoracic specialists

100 cases → Serially sectioned → QC & exclusion criteria applied

Requirements for sample acceptance
- Sufficient tissue to provide serial sections(62 total) for all sites
- NMR range between 3 stained bracketed serial sections is ≤ 0.01
- Consistent case level NMR status across serial sections

'Wash out' period of 2 weeks

Digital analysis only

64 NSCLC cases stained (NRC & TROP2 IHC) at **central site** with staining platform*

Stained slides scanned at **central site** with digital platform*; WSI uploaded to nDP

Access to 64 cases was provided to each reader at each site for blinded assessment; this resulted in a total of 1920 unique reads

Full device

36 NSCLC cases stained (NRC & TROP2 IHC) at **each site** with staining platform*

Stained slides scanned at **each site** with digital platform*; WSI uploaded to nDP

36 cases created for each pathologist at each site for blinded assessment; this will result in 108 unique reads per site (interim data presented here)

Assess concordance between sites and between readers (OPA, PPA, NPA)
For OPA, PPA and NPA analyses, case-level mode status (status most frequently assigned by readers, also referred to as the majority status) was used as the reference status

*Full device= Staining platform [primary TROP2 RUO antibody, detection kit, staining instrument]+ Digital platform [scanner]+ image management system (nDP) and TROP2 NMR RUO algorithm (Roche)
**Determined during case QC. Status was not used for concordance analysis.

CLIA, Clinical Laboratory Improvement Amendments; NMR, normalized membrane ratio; NPA, negative percent agreement; NRC, negative reagent control,; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; OPA, overall percent agreement; PPA, positive percent agreement; RUO, research use only; FFPE, formalin fixed paraffin embedded; nDP, Navify Digital Pathology, WSI, whole slide image, RUO, Research Use Only, SCC, Squamous Cell Carcinoma; QC, quality check

Results: Concordance between sites (digital analysis only cases)

Based on case-level mode status from Roche CLIA laboratory as reference

		Reference TROP2 status (case-level mode status from Roche CLIA lab)					
	Assigned TROP2 Status	**Positive**	**Negative**	**Total****	**Measure***	**% (n/N)**	**95% CI**
External Sites (n=9)***	**Positive**	859	0	859	PPA	99.9 (859/860)	(99.6, 100.0)
	Negative	1	860	861	NPA	100.0 (860/860)	(99.6, 100.0)
	Total**	860	860	1720	OPA	99.9 (1719/1720)	(99.8, 100.0)

*Overall Percent Agreement (OPA)=(Number of concordant algorithm scores/Total number of algorithm scores) X 100%
Positive Percent Agreement PPA=(Number of concordant algorithm scores from NMR positive cases/Total number of algorithm scores from NMR positive cases) X 100%
Negative Percent Agreement NPA=(Number of concordant algorithm scores from NMR negative cases/Total number of algorithm scores from NMR negative cases) X 100%

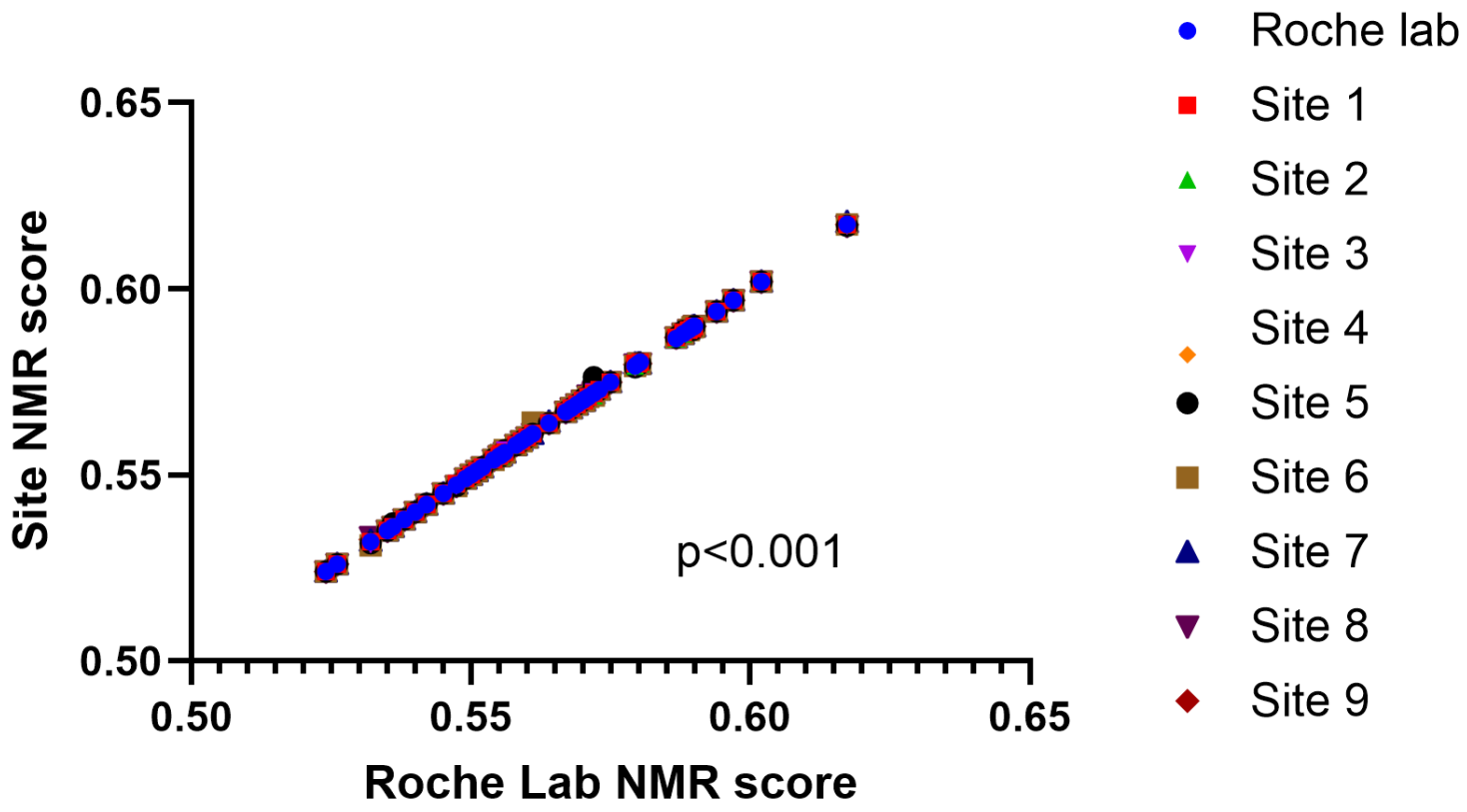
**Total number of TROP2 statuses = # cases X # sites X # pathologists per site - # of cases rejected at QC step; 64 cases x 9 sites X 3 pathologists per site – 8 cases rejected at QC step =1720 total

***Case algorithm scores (positive [≤ 0.563 NMR] or negative [> 0.563 NMR]) for each site were compared to the case-level mode (most common status or majority status) status for each case generated by the 3 pathologists at the Roche lab. Aggregated results from individual site to Roche lab comparisons are presented.

CI, confidence interval; CLIA, Clinical Laboratory Improvement Amendments; NPA, negative percent agreement; OPA, overall percent agreement; PPA, positive percent agreement; QC, quality control; TROP2, trophoblastic antigen 2.

Correlation of site NMR scores* to Roche CLIA lab

Digital analysis only cases



*Median NMR (Q75) score from 3 readers for each case (n=64)

CLIA, Clinical Laboratory Improvement Amendments; NMR, normalized membrane ratio.

Concordance between sites (digital analysis only cases)

Based on case-level mode [most common status] status from all sites as reference

		Reference TROP2 status (case-level mode status from all sites)					
	Assigned TROP2 Status	**Positive**	**Negative**	**Total****	**Measure***	**% (n/N)**	**95% CI**
All sites (n=10)***	**Positive**	955	0	955	PPA	99.9 (955/956)	(99.7, 100.0)
	Negative	1	956	957	NPA	100.0 (956/956)	(99.6, 100.0)
	Total**	956	956	1912	OPA	99.9 (1911/1912)	(99.8, 100.0)

*Overall Percent Agreement (OPA)=(Number of concordant algorithm scores/Total number of algorithm scores) X 100%
Positive Percent Agreement PPA=(Number of concordant algorithm scores from NMR positive cases/Total number of algorithm scores from NMR positive cases) X 100%
Negative Percent Agreement NPA=(Number of concordant algorithm scores from NMR negative cases/Total number of algorithm scores from NMR negative cases) X 100%

**Total number of TROP2 statuses = # cases X # sites X # pathologists per site - # of cases rejected at QC step; 64 cases x 10 sites X 3 pathologists per site – 8 cases rejected at QC step =1912 total

*** Case algorithm status (positive [≤ 0.563 NMR] or negative [> 0.563 NMR]) for each site were compared to the case-level mode [most common or majority status] status for each case generated by all sites (n=10). Aggregated results from individual site to case-level mode comparisons are presented.

CI, confidence interval; NPA, negative percent agreement; OPA, overall percent agreement; PPA, positive percent agreement; TROP2, trophoblastic antigen 2.

Concordance between pathologists (digital analysis only cases)

Based on case-level mode [most common status] status from all pathologists as reference

		Reference TROP2 status (case-level mode status from all pathologists)					
	Assigned TROP2 Status	**Positive**	**Negative**	**Total****	**Measure***	**% (n/N)**	**95% CI**
All pathologists (n=30)***	**Positive**	955	0	955	PPA	99.9 (955/956)	(99.7, 100.0)
	Negative	1	956	957	NPA	100.0 (956/956)	(99.6, 100.0)
	Total**	956	956	1912	OPA	99.9 (1911/1912)	(99.8, 100.0)

*Overall Percent Agreement (OPA)=(Number of concordant algorithm scores/Total number of algorithm scores) X 100%
Positive Percent Agreement PPA=(Number of concordant algorithm scores from NMR positive cases/Total number of algorithm scores from NMR positive cases) X 100%
Negative Percent Agreement NPA=(Number of concordant algorithm scores from NMR negative cases/Total number of algorithm scores from NMR negative cases) X 100%

**Total number of TROP2 statuses = # cases X # sites X # pathologists per site - # of cases rejected at QC step; 64 cases x 10 sites X 3 pathologists per site – 8 cases rejected at QC step =1912 total

*** Case algorithm status (positive [≤ 0.563 NMR] or negative [>0.563 NMR]) for each reader were compared to the case-level mode [most common status or majority status] status for each case generated by all readers (n=30). Aggregated results from individual reader comparisons to case-level mode are presented.

CI, confidence interval; NPA, negative percent agreement; OPA, overall percent agreement; PPA, positive percent agreement; TROP2, trophoblastic antigen 2.

Interim results on concordance between sites (full device*)

Based on Case-Level Mode [most common status] Status as reference

		Reference TROP2 status (case-level mode status from all sites)					
	Assigned TROP2 Status	**Positive**	**Negative**	**Total*** **	**Measure****	**% (n/N)**	**95% CI**
All sites (n=4)******	**Positive**	160	12	172	PPA	88.9 (160/180)	(84.6, 95.5)
	Negative	20	240	260	NPA	95.2 (240/252)	(90.6, 98.9)
	Total**	180	252	432	OPA	92.6 (400/432)	(88.7, 96.1)

*Interim data from 4 sites, 12 pathologists
**Overall Percent Agreement (OPA)=(Number of concordant algorithm scores/Total number of algorithm scores) X 100%
Positive Percent Agreement PPA=(Number of concordant algorithm scores from NMR positive cases/Total number of algorithm scores from NMR positive cases) X 100%
Negative Percent Agreement NPA=(Number of concordant algorithm scores from NMR negative cases/Total number of algorithm scores from NMR negative cases) X 100%

***Total number of TROP2 statuses = # cases X # sites X # pathologists per site - # of cases rejected at QC step; 36 cases x 4 sites X 3 pathologists per site – 0 cases rejected at QC step =432 total

****Case algorithm status (positive [≤ 0.563 NMR] or negative [> 0.563 NMR]) for each site were compared to the case-level mode [most frequent or majority status] status for each case generated by all sites (n=4). Aggregated results from individual site to case-level mode comparisons are presented.

CI, confidence interval; NPA, negative percent agreement; OPA, overall percent agreement; PPA, positive percent agreement; TROP2, trophoblastic antigen 2.

Conclusions

- **Reproducibility of TROP2 NMR assessment using the TROP2 (EPR20043) NSCLC NMR RUO algorithm was high across both sites and readers**
  - When compared to the Roche CLIA lab, the nine external sites showed a PPA of 99.9%, NPA of 100.0%, and OPA of 99.9%
  - Across all 10 sites, the algorithm demonstrated a PPA of 99.9% and an NPA of 100.0%, resulting in an OPA of 99.9%
  - Agreement between 30 participating pathologists remained consistently high, with a PPA of 99.9%, NPA of 100.0%, and OPA of 99.9%

These results confirm the robustness of TROP2 (EPR20043) NSCLC NMR RUO algorithm in the real world

CLIA, Clinical Laboratory Improvement Amendments; NMR, normalized membrane ratio; NPA, negative percent agreement; OPA, overall percent agreement; PPA, positive percent agreement; RUO, research use only; TROP2, trophoblastic antigen 2.

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