Comparison of a highly sensitive, tumor-informed Illumina whole genome sequencing research assay and a tumor-informed bespoke whole exome sequencing assay for molecular residual disease detection in CheckMate 77T (NCT 04025879)

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Jonathan Beer[1], Khai Luong[2], Jeff Tsai[2], Jacob Gibson[2], Jonathan Baden[1], Sven Bilke[2], Kate Broadbent[2], Yuan Ding[2], Christine Eng[2], Yu-Han Hung[1], Artem Movsesyan[2], Jaclyn Neely[1], Mark Stern[1], Weixin Wu[2], David Yu[1], Yunjiao Zhu[2], Traci Pawlowski[2], Li Liu[2]*

[1]Bristol Myers Squibb; [2]Illumina; *corresponding author

Background

- Brief overview of **CheckMate 77T** and clinical context:
  - Phase III trial of **nivolumab (NIVO) vs. placebo (PBO)** as perioperative therapy
  - 461 patients with resectable stage IIA-IIIB NSCLC
  - Clinically meaningful improvements in **event-free survival (EFS)** and **pathologic complete response (pCR)** with NIVO observed[1]
- **Prior ctDNA findings[2-4]:**
  - ctDNA clearance during neoadjuvant period: **66% (NIVO) vs. 38% (PBO)**
  - Reported from 130 patients using a **tumor-informed bespoke panel (TIBP) WES MRD assay**
- **Gap / Rationale:**
  - TIBP WES MRD assays have high operational complexity and long turnaround time (TAT)
  - Hypothesis: A WGS-based MRD assay may offer improved sensitivity and simplified workflow
- **Study Objective:** Compare ctDNA clearance rates and performance metrics between the **Illumina WGS MRD assay** and the **TIBP WES MRD assay** in a subset of CheckMate 77T participants

Methods

- **Study Design / Patient Population:**
  - Substudy of CheckMate 77T
  - 13% (60/461) of total study population, all with TIBP WES MRD data previously reported
  - WGS MRD from residual tumor FFPE tissue or isolated DNA, PBMC germline normal, cfDNA from plasma
- **Illumina WGS MRD Assay Workflow:**
  - Subtracting WGS germline normal from WGS of tumor → tumor-specific genomic fingerprint
  - Bioinformatic monitoring of plasma timepoints via low-pass WGS (lpWGS)
  - Library prep: Illumina WGS Oncology Prep (research use only)
  - Analysis: DRAGEN WGS MRD pipeline
  - Analytical sensitivity and specificity: LoD95 as low as 10 ppm at 99.5% specificity from 5 ng
- **Tumor Informed Bespoke Panel Workflow:**
  - TIBP WES MRD assay (used in prior Provencio et al. analysis)
- **Key Analyses:**
  - ctDNA detection rates at NEO C1D1 (prior to neoadjuvant treatment)
  - ctDNA clearance rates during the neoadjuvant period (NEO C1D1 → NEO END) by treatment arm (NIVO vs. PBO)
  - Concordance metrics: PPA, NPA, OPA (TIBP WES as reference standard)
  - Head-to-head comparison of operational complexity and TAT

Results

Table 1. Comparison of MRD assay characteristics

Parameter	Illumina WGS	TIBP WES
Patient-specific panel design	Not required	Required
cfDNA input requirement	2-5 ng	Typically 10-60 ng
Workflow	Simple streamlined	Complex multi-step
TAT*	1-2 weeks	4-6 weeks
Distributable kit	Yes	No

*TAT (turnaround time) for tumor tissue, PBMC germline, and first plasma timepoint results

Table 2. Samples included in the analysis

ARM	Timepoint	Patient count
NIVO+CHEMO_NIVO	NEO C1D1	27
NIVO+CHEMO_NIVO	NEO END	26
PBO+CHEMO_PBO	NEO C1D1	30
PBO+CHEMO_PBO	NEO END	28

- TAT is 3-4x shorter and cfDNA input requirement is 5-12x lower for Illumina WGS (**Table 1, Figure 1**)
- Only samples that meet the following two criteria were included in this analysis (**Table 2**).
  - Samples collected during neoadjuvant phase (NEO C1D1, NEO END)
  - Samples that have both TIBP WES and Illumina WGS readout
- Filtering yields 111 samples from 60 unique patients

Figure 1. Schematic diagram of MRD workflows

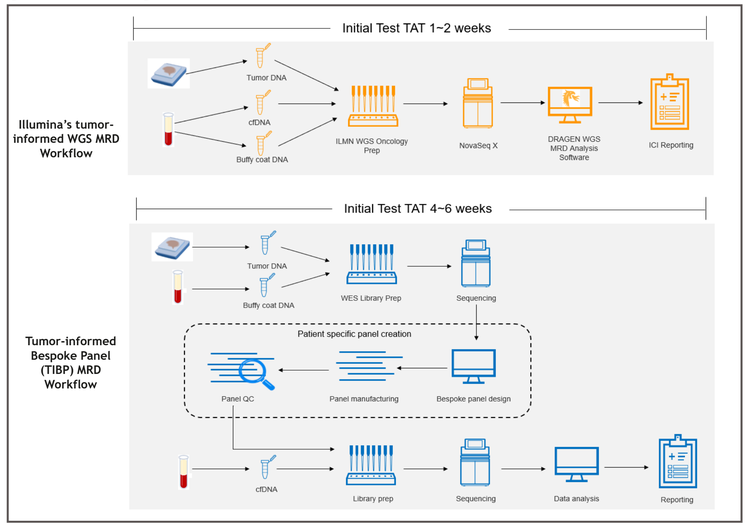


Table 3. ctDNA Detection at NEO C1D1 and NEO END

Assay	NEO C1D1 (n=57)	NEO END (n=42)	Overall (n=111)
Illumina WGS MRD (this study)	91%	48%	70%
TIBP WES MRD (Provencio et al.)	86%	41%	64%

Table 4. Confusion Matrix for TIBP WES (rows) vs Illumina WGS (columns)

	ABSENT	PRESENT	
ABSENT	32	8	40
PRESENT	1	70	71
	33	78	

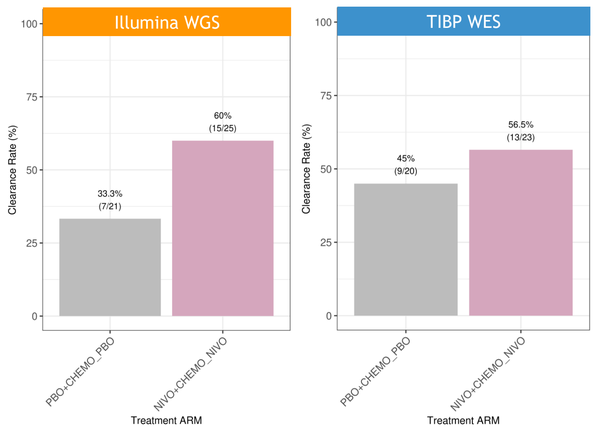
Table 5. Concordance with TIBP WES (reference) at NEO C1D1 and NEO END

	NEO C1D1	NEO END	Overall
PPA	100%	95%	99%
NPA	63%	84%	80%
OPA	95%	89%	92%

PPA: positive percent agreement; NPA: negative percent agreement; OPA: overall percent agreement

- ctDNA detection rates prior to neoadjuvant treatment (NEO C1D1) were greater in this study than previously reported, 91% for Illumina WGS vs 86% for TIBP WES (**Table 3**)
- 8 out of 9 disagreement cases (3 at NEO C1D1 and 6 at NEO END) were samples classified as "ctDNA present" by Illumina WGS but "ctDNA absent" by TIBP WES (**Table 4**)
- A high overall concordance rate (92% OPA) was observed between the TIBP WES and Illumina WGS platforms. The concordance rate prior to neoadjuvant treatment was 95% and 89% at the end of neoadjuvant treatment (**Table 5**)

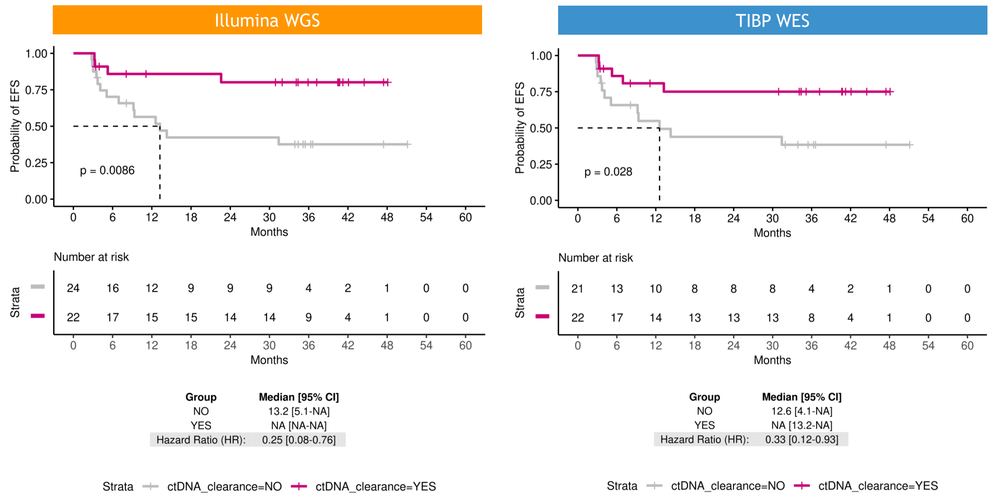
Figure 2. Rate of ctDNA clearance* (CL) during neoadjuvant phase



*Definition of ctDNA CL event: ctDNA status change from "present" (at NEO C1D1) to "absent" (at NEO END). Patients who had ctDNA status "absent" at NEO C1D1 were excluded from this assessment.

- Rate of ctDNA clearance during neoadjuvant phase (ctDNA change from "present" to "absent") by arm. Both platforms showed higher ctDNA clearance rate in NIVO compared to PBO arm. Directional consistency with previously published findings (**Figure 2**)

Figure 3. EFS by ctDNA clearance during neoadjuvant phase



- Both platforms showed that ctDNA clearance is associated with better EFS. Hazard Ratio between clearance and non-clearance outcomes is 0.25 with Illumina WGS MRD vs 0.33 with TIBP WES (**Figure 3**)

Conclusions

- The Illumina WGS MRD assay demonstrated high concordance with tumor-informed WES MRD for MRD-positive detection (PPA = 99%)
- Illumina WGS MRD demonstrated improved analytical sensitivity at baseline (91% vs. 86% detection)
- Lower Hazard Ratio between clearance and non-clearance outcomes with Illumina WGS MRD (0.25 vs. 0.33)
- Significantly reduced TAT with Illumina WGS MRD (1-2 weeks vs. 4-6 weeks)
- Lower cfDNA input requirements with Illumina WGS MRD (2-5 ng vs. 10-60 ng)
- Decreased operational complexity of Illumina WGS MRD — eliminates need for patient-specific panel design, manufacturing, and validation
- Illumina's WGS-based MRD may represent a distributable, clinically scalable and operationally practical approach for ctDNA monitoring in resectable NSCLC

References

1. Cascone et al. Perioperative Nivolumab in Resectable Lung Cancer. NEJM, 2024
2. Provencio et al. LBA50, ESMO 2024
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- Illumina WGS Oncology Prep is for research use only

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Contact: Li Liu Email: lliu3@illumina.com