Retrospective clinical analysis of circulating tumor DNA (ctDNA)–based molecular response (MR) and baseline blood-based tumor mutational burden (bTMB) for monitoring response in Phase 3 trial of bintrafusp alfa vs pembrolizumab treatment of non-small cell lung cancer (NSCLC) (NCT03631706)

Zheng Feng[1*], Andreas Machl[1*], Danyi Wang[1], Brooke Overstreet[2], Arielle Yablonovitch[2], Juergen Scheuenpflug[3#]

[1]EMD Serono, Billerica, MA, USA; [2]Guardant Health Inc. Redwood City, CA [3]the healthcare business of Merck KGaA, Darmstadt, Germany
*Co-first authors # Corresponding author

CONCLUSIONS

- **A molecular response (MR) assessment based on ctDNA analysis from plasma samples in patients treated with immune checkpoint inhibitor (ICI) demonstrated utility as an adjunct to RECIST in monitoring of tumor response.**
- **Blood-based TMB-High combined with defined somatic mutations was associated with ICI treatment benefit.**
- **Analysis of bTMB and MR allowed identification of patients with improved PFS in both treatment arms.**

INTRODUCTION

Bintrafusp alfa, a novel bifunctional fusion protein composed of the extracellular domain of TGF-βRII fused to a human IgG1 monoclonal antibody that blocks PD-L1, has demonstrated promising clinical activity in a Ph1 study in advanced non-small cell lung cancer (NSCLC) patients [1]. The adaptive phase 3 trial, INTR@PID LUNG 037 (NCT03631706), compared the efficacy and safety of bintrafusp alfa to pembrolizumab as a first-line treatment for patients with advanced, PD-L1 high NSCLC. Primary endpoints, including progression-free survival (PFS) and overall survival (OS), were assessed using RECIST 1.1 criteria [2].

Here we report results from exploratory biomarker analyses of this phase 3 study to evaluate the clinical utility of ctDNA-based approaches, such as blood-based tumor mutational burden (bTMB) and molecular response (MR), for monitoring and predicting treatment response during chemo-immunotherapy. A previous clinical utility evaluation offered valuable insights into the potential of employing these methods to guide biomarker-focused precision oncology-driven therapeutic decisions,[3] aiming to improve patient outcomes in advanced NSCLC.

OBJECTIVES

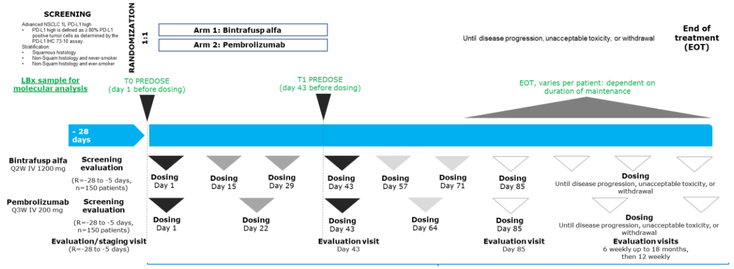
To retrospectively monitor and predict response during immunotherapy and evaluate the clinical utility of ctDNA-based approaches, such as bTMB and MR, using longitudinal cohort samples from Phase 3 trial to assess bintrafusp alfa vs pembrolizumab as first-line treatment of patients with metastatic NSCLC with high PD-L1 expression levels.

METHODS

- ctDNA was collected at baseline (T0 Predose) and day 43 (T1 Predose) after treatment-start with bintrafusp alfa (Q2W, 1200mg) or pembrolizumab (Q3W, 200mg). Pathway inhibition between both compounds is comparable based on full PD-L1 engagement.
- PD-L1 high expression was defined as ≥80% PD-L1–positive tumor cells, as determined by the PD-L1 immunohistochemistry 73-10 assay (Dako North America Inc; Carpinteria, CA).
- The GuardantOMNI liquid biopsy (LBx) assay was used to detect somatic alterations in 497 genes and generate bTMB from baseline, and MR scores from baseline and day 43 (n=424 samples).
- bTMB was calculated as previously described [4].
- MR scores were calculated using the validated Guardant360 Response algorithm [5].
- Associations between ctDNA metrics and PFS were assessed with log-rank analysis and Cox proportional hazards model.

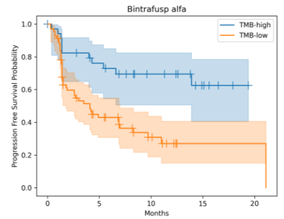
RESULTS

Figure 1. Sample collection regimen of INTR@PID LUNG 037 trial (NCT03631706)

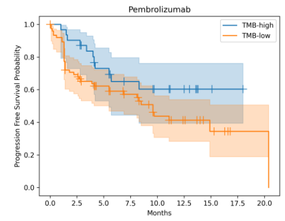


Patients were treated with bintrafusp alfa (Q2W 1200mg IV) or pembrolizumab (Q3W 200mg IV) until confirmed disease progression or unacceptable toxicity. Patients were randomized 1:1 to receive either bintrafusp alfa or pembrolizumab and stratified by histology and smoking history: squamous histology; nonsquamous histology and never smoked; and nonsquamous histology with a smoking history. Tumor evaluation by contrast enhanced computed tomography/magnetic resonance imaging was performed every 6 weeks up to 18 months, then every 12 weeks. Tumor responses were assessed according to RECIST 1.1. ctDNA was collected during patient visits on the day of dosing ~1hr before IV infusion of bintrafusp alfa or pembrolizumab. **BOR**, best overall response; **ctDNA**, circulating tumor DNA; **D**, day; **EOT**, end of therapy; **Q2W**, every 2 weeks; **Q3W**, every 3 weeks; **T**, sample collection time point; **R**, range; **IHC**, immunohistochemistry.

Figure 2. Blood-based TMB-High (≥20mut/Mb) associated with longer Progression Free Survival

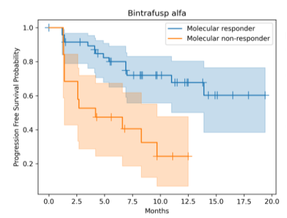


Bintrafusp alfa
- Baseline bTMB was evaluable in 104/116 (90%) patients
- 35 patients had TMB-High, and 69 patients had TMB-Low
- PFS was significantly longer in patients with bTMB-H (median 8.3 months vs 2.7 months, p=0.00086; HR 3.0).



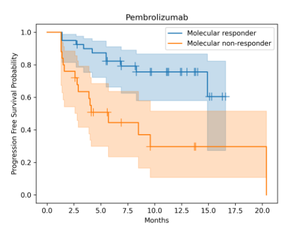
Pembrolizumab
- Baseline bTMB was evaluable in 108/121 (89%) patients
- 32 patients had TMB-High, and 76 patients had TMB-Low
- PFS was longer in patients with bTMB-H (median 5.65 months vs 5.5 months, p=0.0898; HR 1.79).

Figure 3. Bintrafusp Alfa and Pembrolizumab Molecular Responders Are Significantly Associated with Longer Progression Free Survival



Bintrafusp alfa
- Molecular response was evaluable in 67/79 (85%) patients
- 48 patients were molecular responders, and 19 patients were molecular non-responders
- The average time between T0 Predose and T1 Predose was 42.9 days (39-71 days)
- Molecular responders had significantly longer PFS (median 7.9 months vs 4.2 months, p=0.00042; HR 3.74).

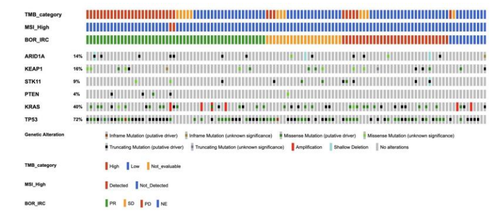
Molecular responders (blue) were defined as patients with ≥50% or greater decrease in ctDNA level and molecular non-responders (orange) as patients with <50% or greater decrease in ctDNA level, or overall increase in ctDNA level.



Pembrolizumab
- Molecular response was evaluable in 65/89 (73%) patients
- 40 patients were molecular responders, and 25 patients were molecular non-responders
- The average time between T0 PREDOSE and T1 PREDOSE was 42.3 days (37-53 days)
- Molecular responders had significantly longer PFS (median 8.95 months vs 4.1 months, p=0.00054; HR 3.79)

Molecular responders (blue) were defined as patients with ≥50% or greater decrease in ctDNA level and molecular non-responders (orange) as patients with <50% or greater decrease in ctDNA level, or overall increase in ctDNA level.

Figure 4A. Oncoprint showing BOR at baseline in patients who received bintrafusp alfa



- Positive predictive biomarkers of response: Mutation (*ARID1A*) was present in 16 of 116 baseline samples. 10 of those patients had a BOR of PR or SD and 6 had non-PD. *ARID1A* mutations were present in 6 of 35 bTMB-High patients.
- Negative predictive biomarkers of response: Mutations (*STK11, KEAP1, PTEN*) were present in 31 of 116 baseline samples. 21 of which had a BOR of PR or SD and 10 had non-PD

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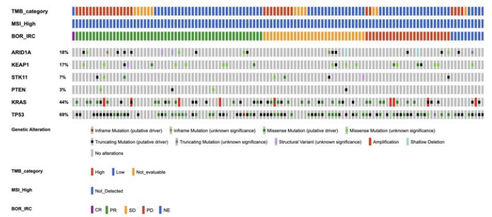
Figure 4B. Oncoprint showing BOR at baseline in patients who received pembrolizumab



- Positive predictive biomarkers of response: Mutation (*ARID1A*) was present in 22 of 121 baseline samples. 16 of those patients had a BOR of PR or SD and 6 had non-PD. *ARID1A* mutations were present in 7 of 32 bTMB-High patients.
- Negative predictive biomarkers of response: Mutations (*STK11, KEAP1, PTEN*) were present in 30 of 121 baseline samples. 22 of which had a BOR of PR or SD and 8 had non-PD

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References: 1. Cho BC, et al. Journal of Clinical Oncology 2020 38:15_suppl, 9558-9558 **2.** M.-J. Ahn, et al. Journal of Thoracic Oncology,Volume 16, Issue 1, Supplement,2021,Pages S27-S28,https://doi.org/10.1016/j.jtho.2020.10.134. **3.** Ciardiello F, et al. Annals of Oncology, 33, Supplement 7, 2022, S1050-S1051, https://doi.org/10.1016/j.annonc.2022.07.1217 **4.** Si H, et al. Clin Cancer Res. 2021 Mar 15;27(6):1631-1640. doi: 10.1158/1078-0432.CCR-20-3771. Epub 2020 Dec 22. **5.** Thompson JC, et al. JCO Precis Oncol 2021 Feb 9:5, 510-524. https://doi.org/10.1200/PO.20.00321

Disclosures: A. Machl is an employee of EMD Serono, Billerica, MA, USA. **Z. Feng** is an employee of EMD Serono, Billerica, MA, USA. **D. Wang** is an employee of EMD Serono, Billerica, MA, USA. **B. Overstreet** is an employee of and has stocks/shares in Guardant Health. **A. Yablonovitch** is an employee of and has stocks/shares in Guardant Health. **J. Scheuenpflug** is an employee of the healthcare business of Merck KGaA, Darmstadt, Germany.

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