BRIGHTSTAR: Local Consolidative Therapy with Brigatinib in Tyrosine Kinase Inhibitor-Naïve ALK-Rearranged Metastatic NSCLC

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Background

- ALK tyrosine kinase inhibitors (TKIs) are now the standard of care for patients with ALK-rearranged metastatic NSCLC with impressive response rates in the first line setting.
- Approximately 95% of patients who have an initial response to ALK-TKIs exhibit an incomplete response resulting in residual disease that may enable the emergence of acquired resistance[1].
- Minimizing or eliminating residual disease with local consolidation therapy (LCT) may delay the development of resistance and improve clinical outcomes.

[1] Biovona and Doebele Nat Med 2016
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Local Consolidative Therapy and Brigatinib in Treating Patients With Stage IV or Recurrent Non-small Cell Lung Cancer

TKI-naïve ALK+ advanced NSCLC

Key inclusion criteria:

- ≥ 18 years
- Documented ALK rearrangement (tissue or liquid biopsy)
- TKI naïve or first-line Brigatinib within ≤ 8 weeks of enrollment
- At least one site of residual disease for LCT
- ECOG PS ≤2

Enrollment Window
Brigatinib x8 weeks

CT/PET
Brain MRI

non-PD →

Brigatinib
Until PD

Local Consolidative Therapy

- If < 3 active sites of disease then LCT to all sites
- If > 3 active sites of disease then LCT to sites at physician discretion

- Brigatinib until disease progression or unacceptable toxicity.
- Primary objective is safety and tolerability of Brigatinib with LCT.
- Secondary objectives include PFS, OS and TTP on non-LCT lesions. PFS calculated from brigatinib initiation.
- Exploratory objectives include utility of pre-treatment, pre-LCT and post-LCT liquid biopsy assessment as a prognostic and predictive biomarker

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PATIENT CHARACTERISTICS (N=34)

PATIENT CHARACTERISTICS (N=34)	N (%)
Median age, (range)	55 (33-73)
GENDER	
Male	14 (41%)
Female	20 (59%)
HISTOLOGY	
Adenocarcinoma	33 (97%)
Squamous	1 (3%)
EML4-ALK VARIANTS	
Variant 1	10 (29%)
Variant 2	2 (6%)
Variant 3a/b	18 (53%)
E6a:A19	1 (3%)
Unknown	3 (9%)

NUMBER OF METASTASES AT BASELINE	
≤3	6 (18%)
>3	28 (82%)

OBJECTIVE RESPONSE TO BRIGATINIB

RESPONSE TO BRIGATINIB AT 8 WEEKS	
Partial response	27 (79%)
Stable disease	7 (21%)

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LCT DETAILS

LCT MODALITY	N (%)
Radiation	27 (79%)
Surgery	3 (9%)
Surgery and radiation	2 (6%)
No LCT amenable residual disease	1 (3%)
Withdrew consent	1 (3%)
EXTENT OF LCT	**N (%)**
Complete	20 (62%)
Partial	12 (48%)

32/34 patients successfully completed planned LCT

RADIATION AND SURGERY DETAILS

RADIATION	N*
SBRT	8
IMRT/VMAT	20
2D/3D conformal radiation	8
Proton beam therapy	1
BRIGATINIB HELD DURING RADIATION?	**(TOTAL N=29)**
Yes	19
Partial	10
SURGICAL PROCEDURES**	**(TOTAL N=5)**
Pulmonary lobectomy	3
Sublobar pulmonary resection	1
Adrenalectomy	1

* Nine patients received two modalities of radiation
** Two patients had complete pathological response and 1 patient had complete pathological response at the primary tumor

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Safety of Brigatinib and LCT

GRADE (G) ≥3 LCT RELATED ADVERSE EVENTS

ADVERSE EVENT	N
G4 bronchopulmonary hemorrhage	1
G3 anemia	1
G3 pneumonitis	1
G3 esophagitis	1
G3 vomiting	1
G3 nausea	1

There were no grade 5 events related to LCT

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Progression Free Survival

PFS RATE	BRIGHTSTAR	ALTA 1L* (FIRST LINE SINGLE AGENT BRIGATINIB)
1-yr	94%	80%
3-yr	76%	56%
3-yr	66%	47%

*Includes only patients who did not progress at 12-week on ALTA 1L. PFS calculated from randomization

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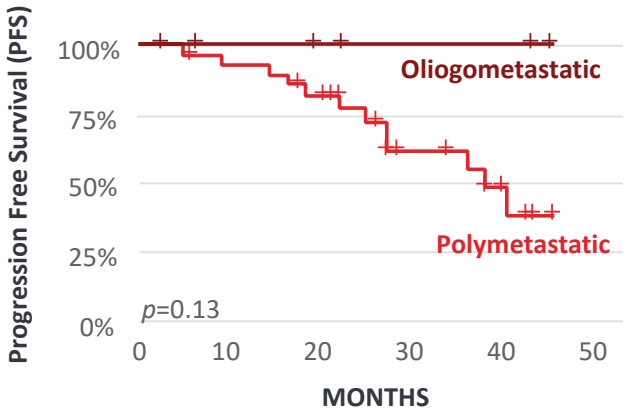
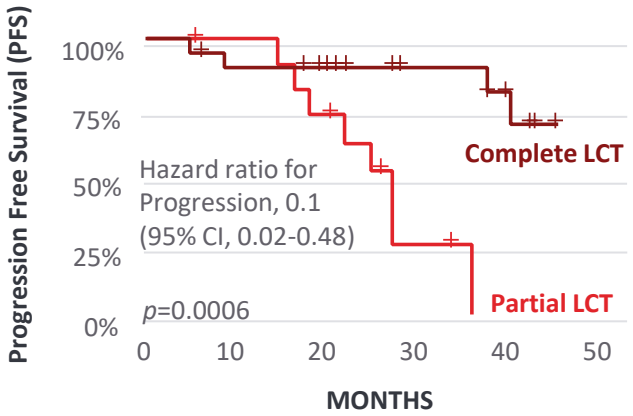
Predictors of outcome

No. of mets at baseline



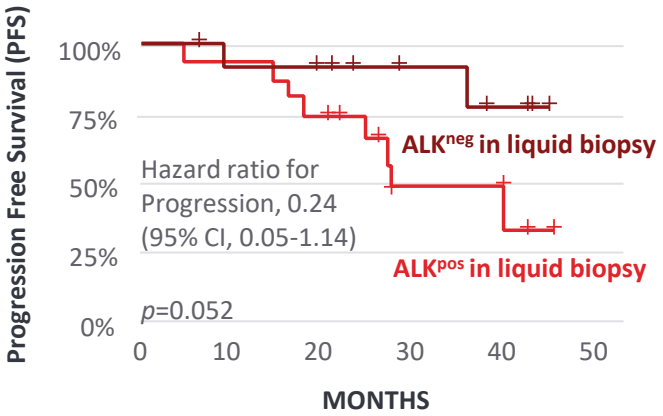
No. at risk						
Oliogometastatic	6	4	3	2	2	0
Polymetastatic	28	25	21	10	6	0

Extent of LCT



No. at risk						
Complete LCT	20	17	15	10	8	0
Partial LCT	12	11	8	2	0	0

ALK status in plasma at baseline



No. at risk						
ALK^{neg}	13	11	10	7	4	0
ALK^{pos}	15	14	11	4	4	0

LCT to all sites of residual disease and negative ALK status in plasma at baseline were associated with better outcomes

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Preliminary Univariate Analysis of 3D tumor volume and Patient Progression-free Survival

VARIABLE	HR	95% CI	P-VALUE
Disease Burden at Baseline (per cc)	1.006	1.002-1.01	0.007
Disease Burden after induction (per cc)	1.009	1.001-1.017	0.029
Delta volume (per cc)	0.995	0.99-0.9997	0.036

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Conclusion

Brigatinib with LCT is safe in patients with ALK-rearranged advanced NSCLC.

Brigatinib with LCT yielded promising outcomes when compared to historical outcomes: 3-year PFS rate was 66% in Brightstar compared to 47% in the Brigatinib arm of ALTA-1L.

Complete LCT, baseline ALK plasma negativity, and lower post-induction volume, but not number of metastases at baseline (oligo vs poly) were associated with increased benefit for LCT.

A randomized trial (BrightStar-2) is planned to compare two intensifications strategies, LCT and chemotherapy, with Brigatinib alone as first line therapy for ALK+ NSCLC.

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