Local Consolidative Therapy (LCT) Improves Overall Survival (OS) Compared to Maintenance Therapy/Observation in Oligometastatic Non-Small Cell Lung Cancer (NSCLC): Final Results of a Multicenter, Randomized, Controlled Phase 2 Trial

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Disclosure for Dr. Gomez

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Background

- Biologic state of "oligometastasis" still being defined
 - Defining patients in-between locally advanced state and true metastases that could be "cured"
- In 2012, we initiated phase II randomized study examining this question
 - Key eligibility criteria:
 - Diagnosis of stage IV NSCLC
 - ≤3 metastases after standard front-line systemic therapy
 - Four cycles of platinum-doublet chemotherapy or 3 months of EGFR/ALK targeted therapy for appropriate molecular alterations
 - ECOG performance status 0-2
 - Eligible for "local consolidative therapy" (surgery/radiation therapy=LCT) to all sites of disease
 - Treatment arms:
 - A) Standard = maintenance therapy/observation (MT/O)
 - B) Experimental = local consolidative therapy (LCT)



Background

Maintenance Therapy/Observation (MT/O)



Secondary Endpoints: Overall survival, safety/toxicity, time to appearance of new lesions Balanced randomization: 1) Number of metastases (0-1 vs. 2-3), 2) Response to first-line systemic therapy (stable disease vs. partial response), 3) N0-N1 vs. N2-N3, 4) CNS vs. no CNS metastases, 5) EGFR/ALK alteration vs. wild type

Gomez et al., Lancet Oncol 2016

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Background





Gomez et al., Lancet Oncol 2016

Iyengar et al., JAMA Oncol 2017



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Conclusions/Remaining Questions

- Since 2016, benefit of consolidative therapy in PFS endpoint has been demonstrated in at least four prospective randomized trials
 - Two in lung cancer (Gomez et al., Iyengar et al), one in prostate cancer (Ost et al., *JCO* 2018), one in colorectal cancer (Ruers et al., *JNCI* 2017)
- However, does PFS benefit translate to OS improvement?
 - Particularly relevant in current trial because crossover allowed between arms
 - Will "late LCT" (e.g. at time of progression) lead to similar OS times as "early LCT," when measured from the time of randomization?



Progression Free Survival



Median 4.4 months in MT/O arm [95% CI 2.2-8.3] and 14.4 months in LCT arm [95% CI 7.4-23.1, p=0.022]

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No additional Grade 3 or higher adverse events in either arm

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Overall Survival



Median 17.0 months MT/O [HR=0.40, 95% CI 10.1–39.8, *P*=0.017] vs. 41.2 months LCT [95% CI 18.9–not reached]



Survival After Progression



Median 37.6 months LCT [95% CI 9.0-not reached] vs. 9.4 months MT/O [95% CI 5.9–19.6, P=0.034]

Patients that received complete LCT at the time of progression (in either arm) did better than those that did not!



Subgroup Analysis of Prognostic Factors on OS



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Limitations/Conclusions

Limitations included stopped early/small size, heterogeneity of maintenance arm treatments, no immunotherapy

1) With long-term follow-up, compared to MT/O, LCT in patients with oligometastatic disease who do not progress after front-line systemic therapy:

- Improves PFS
- Is associated with an improvement in OS
- 2) LCT with acceptable tolerance, long-term follow-up did not reveal further high-grade toxicity in either arm
- 3) Survival after progression improved in LCT arm
 - Complete LCT at the time of progression may improve OS compared to patients that do not receive this treatment

4) Identified patient subgroups that appeared to benefit from LCT Less nodal burden, less metastases, no CNS metastases

