Brain Metastases in Patients with *KRAS* Mutant Advanced NSCLC Receiving Docetaxel: Pooled Clinical Trial Data Analysis

Jacob Aptekar, MD, Ph.D.[1], Rahul Jain, Ph.D.[1], Beata Korytowsky[2], Afrah Shafquat, Ph.D.[1], Jacob Hendershot[1], Aniketh Talwai[1], Yahav Itzkovich[1], Sukhmani K. Padda, MD[3]

[1]Medidata, a Dassault Systèmes company, New York, NY, 10014; [2]Mirati Therapeutics, San Diego, CA 92121;[3]Cedars-Sinai Samuel Oschin Cancer Center, Los Angeles, CA 90048

Background

- Lung cancer is the leading cause of brain metastases[1-11]
- Patients with NSCLC and brain metastases have associated aggressive clinical features (e.g., advanced T and N stage)[12]
- *KRAS* mutations appear to have a predictive role on brain metastasis incidence and survival in patients with NSCLC and can impact disease management[13,14]
- The risk of central nervous system (CNS) progression in *KRAS* mutant (*KRAS*mut) locally advanced or metastatic NSCLC (aNSCLC) has not been well-described in clinical trial (CT) cohorts, which exclude patients with poor functional status or unstable, symptomatic brain metastases[15]
- This study's objective was to evaluate the incidence and progression of brain metastasis in previously treated *KRAS*mut aNSCLC clinical trial participants treated with docetaxel-containing regimens

Methods

Data source

- Pooled clinical trial data was sourced from the Medidata platform, comprising more than 27,000 historical clinical trials with 8 million patients across 150+ countries over 20 years
- Anonymized data was pooled from historical phase II/III clinical trials of docetaxel-containing regimens for patients with previously treated aNSCLC (IIIB-IV)
  - Total of 836 aNSCLC patients enrolled in docetaxel-containing regimen trials (**Figure 1**)
  - Of these, 595 had both a *KRAS* mutation and a brain imaging assessment at baseline, and at least one follow-up brain imaging assessment during the treatment period and/or follow-up period

Study population

- Patients from pooled docetaxel clinical trials met the following inclusion/exclusion criteria for this study:
  - aNSCLC (Stage IIIB-IV; majority AJCC Version 7)
  - Disease progression or relapse after at least one prior line of systemic anti-cancer therapy
  - No baseline brain metastases except if asymptomatic, treated and stable
  - *KRAS*mut positive, confirmed through tissue-based testing
  - No prior MEK (Mitogen-activated protein kinase) tyrosine kinase inhibitor (TKI) for docetaxel + MEK TKI combination trials
  - No prior docetaxel treatment
  - Had brain imaging conducted at baseline (except for two patients who were clinically assessed)

Endpoints

Endpoint	Definition
CNS Disease Control (CNS-DCR) at 12 months	Proportion of patients with CNS disease control (partial/complete response or stable disease per RECIST 1.1) at 12 months after the start of treatment **Estimated for patients with brain metastases at baseline*
CNS Progression	Per RECIST 1.1, unequivocal progression in baseline brain metastases or new brain metastases identified on follow-up brain imaging
Overall Survival (OS)[a]	Time from start of study treatment to time of death
Progression-free Survival (PFS)[a]	Time from start of study treatment to time of progression or death, whichever is earlier

[a]If patient did not have the event of interest, censoring occurred at the last reported visit for which data was captured in the trial eCRF

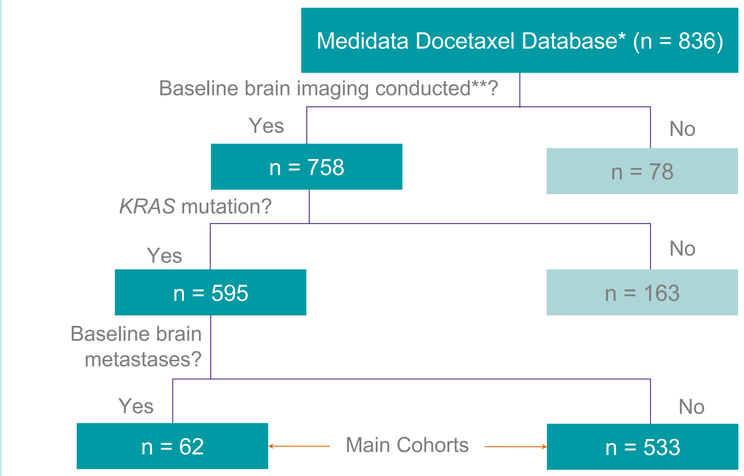
Statistical analysis

- Baseline demographics & clinical characteristics described for all patients
- Patients were stratified by baseline brain metastasis status (present vs. absent)
  - For categorical variables, Pearson's chi-squared tests were used
  - For continuous variables, Wilcoxon rank sum tests were used
  - Two-tailed alpha of 0.05 level of significance was used
- Kaplan-Meier method was employed to estimate the OS and PFS for both cohorts
- Statistical analyses were performed using R version 4.0.3, SAS 9.4, and Python 3.9

Results

Advanced or Metastatic NSCLC Study Population

Figure 1. Consort Diagram



*All patients are previously treated with aNSCLC
**2 patients did not receive brain imaging at baseline, were clinically assessed instead. Both patients had follow-up brain imaging

Baseline characteristics

- A total of 595 patients met the eligibility criteria for this analysis (**Figure 1**)
- In this clinical trial population, 10% had baseline brain metastases. Both extent of disease & smoking status showed a statistical difference between the cohorts ($p < 0.01$)
- The clinical trial cohort was predominantly white: presence vs. absence of baseline brain metastases, 90% and 94%, respectively

Table 1. Demographics and Baseline Characteristics of Cohorts of Present vs. Absent Baseline Brain Metastases

		Baseline Brain Metastases Present (N=62; 10%)	Baseline Brain Metastases Absent (N=533; 90%)	Statistical Comparison
Variables				
Age Median (IQR), years		60 (11)	61 (11)	p = 0.24
Gender	Male	44%	55%	p = 0.08
	Female	56%	45%	
Race	White	90%	94%	p = 0.71
	Black or African-American	5%	2%	
	Asian	2%	1%	
	Other	3%	2%	
Smoking Status	Current	37%	21%	**p < 0.01**
	Former	63%	70%	
	Never	0%	9%	
ECOG*	0	42%	41%	p = 0.9
	1	53%	55%	
Histologic Type*	Adenocarcinoma	95%	89%	p = 0.43
	Squamous	3%	8%	
Extent of Disease	Metastatic	100%	75%	**p < 0.01**
	Locally adv.	0%	25%	

*Other/unknown not reported

Outcomes

- Of patients with baseline brain metastases, 27.4% (17/62) had CNS progression, with 82% (14/17) as the first-site-of-progression. CNS-DCR at 12 months was 75.8% (**Table 2**)
- Of patients without baseline brain metastases, 8.4% (45/533) developed new brain metastases, with 89% (40/45) as the first-site of disease progression
- CNS-DCR rates were similar between docetaxel alone and docetaxel + MEK TKI cohorts (data not shown)

Table 2. Outcomes of Cohorts of Present vs. Absent Baseline Brain Metastases

	Baseline Brain Metastases Present (N=62; 10%)	Baseline Brain Metastases Absent (N=533; 90%)
Outcomes		
Brain Metastasis		
CNS Progression (N, %)	17 (27.4%)	45 (8.4%)
CNS Disease Control Rate at 12 months (N, %)	47 (75.8%)	n/a
Survival		
Overall survival [months] (Median, 95% CI)	6.7 (5.3-8.8)	8.7 (7.6-9.6)
Progression-free survival [months] (Median, 95% CI)	3.6 (2.6-4.2)	5.6 (5.2-6.1)

Figure 2. Overall Survival for Main Cohorts (Baseline Brain Metastases)

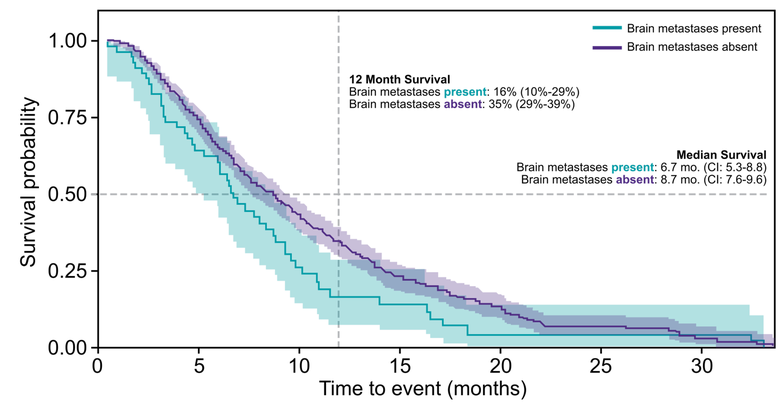
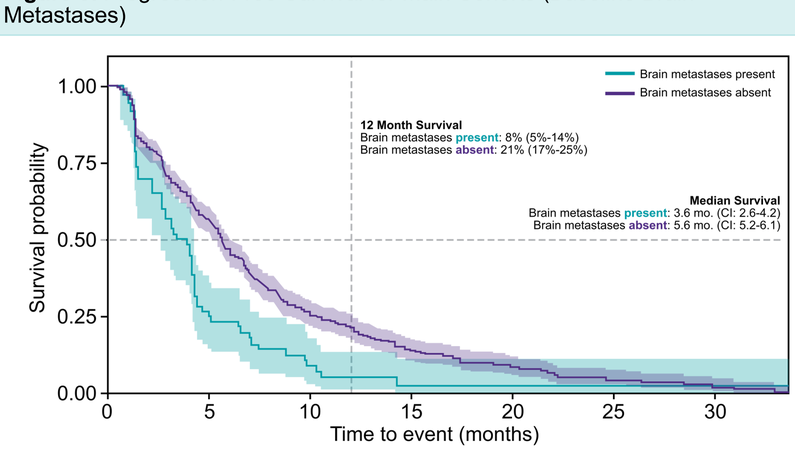


Figure 3. Progression-Free Survival for Main Cohorts (Baseline Brain Metastases)



Discussion

- *KRAS* mutations are one of several factors associated with increased probability of brain metastases in NSCLC[12,16,17]
- Docetaxel is not known to have significant CNS penetration[18-20], although data is limited[21,22], and the impact on CNS-DCR in *KRAS* mutated NSCLC is not known
- In this study, comprised of a highly selected clinical trial population of pretreated *KRAS*mut aNSCLC patients with stable brain metastases, docetaxel-containing regimens resulted in a CNS-DCR of 75.8% at 12 months
- Limitations of Study
  - CNS-DCR does not account for competing risk of mortality and brain imaging assessments not mandated at predefined intervals
  - Minority (<4%) of patients received prior immune checkpoint inhibitor therapy due to the clinical trials accrual periods
  - No patients received docetaxel in combination with an anti-angiogenic therapy
- Brain metastases in *KRAS* G12C NSCLC are observed at similar frequency (40%) as other *KRAS* mutations.[23,24] Allosteric *KRAS* G12C inhibitors have reported CNS-DCR at 12 months per RANO-BM criteria in cohorts with treated stable brain metastases, including 88% (16/19) for sotorasib[25] and 85% (28/33) for adagrasib.[26] Adagrasib has also reported CNS-DCR (median follow-up of 6.6 months) of 84% (16/19) in a cohort of patients with active untreated brain metastases based on Phase 1/1b data[23,27]
- Similar to trials of *KRAS* G12C inhibitors,[25] in this analysis, docetaxel demonstrated numerically worse mPFS and mOS for patients presenting with baseline brain metastases

Conclusion

- High level data is lacking for many standard of care therapies (e.g. chemotherapy, immunotherapy) and their impact on brain metastases in aNSCLC
- Furthermore, given the lack of data in patients with active brain metastases (including those with *KRAS* mutations) and its relevance to NSCLC, such patients should be proactively studied in both RCTs[28,29] and in real world data

References

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Author contact: Sukhmani.Padda@cshs.org

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Author contact: Sukhmani.Padda@cshs.org