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

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Background

- Lung cancer is the leading cause of brain metastases[1-9]
- Patients with NSCLC and brain metastases have associated aggressive clinical features (e.g., adenocarcinoma, advanced T and N stage)[10]
- *KRAS* mutations have a predictive role on brain metastasis incidence and survival in patients with NSCLC and can impact disease management[11,12]
- 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[13]
- This study's objective was to evaluate the incidence and progression of brain metastasis in *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 in 150+ countries over 20 years
- Anonymized data was pooled from historical phase II/III clinical trials for patients with previously treated aNSCLC (IIIB/IV), treated with docetaxel-containing regimens
  - Total of 836 aNSCLC participants with aNSCLC enrolled in docetaxel-containing regimen trials (**Figure 1**)
  - Of these participants, 595 had both *KRAS* mutations and a brain imaging assessment at baseline, and at least one follow-up brain imaging assessment after that during the treatment period and/or follow-up

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, with the exception of two patients who were clinically assessed

Endpoints

Endpoint	Definition
CNS Disease Control Rates (CNS-DCR) at 12 months	Estimated for patients with brain metastases at baseline; the 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
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)	Time from start of study treatment to time of death. If patient did not have the event of interest in the follow-up, censoring occurred at the last reported visit for which data was captured in the trial eCRF
Progression-free Survival (PFS)	Time from start of study treatment to time of progression or death, whichever is earlier. Same censoring rules as OS

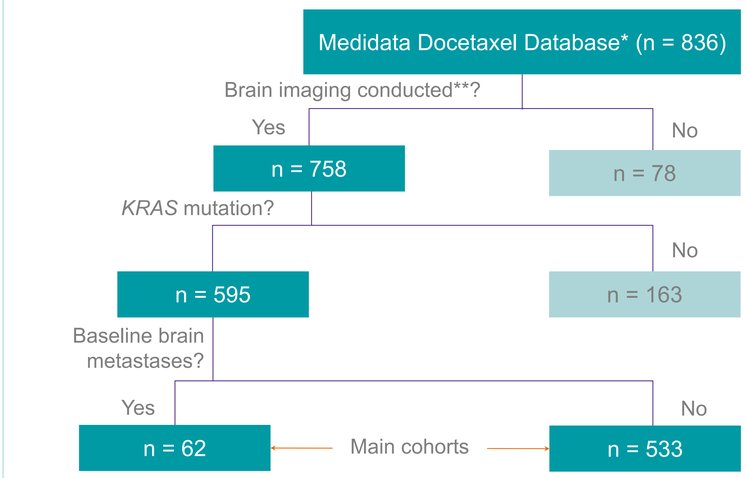
Statistical analysis

- Baseline demographics & clinical characteristics described for all patients
- Patients were stratified by baseline brain metastases status
  - For categorical variables, Pearson's chi-squared test 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

Study Population

Figure 1. Consort Diagram



*All patients are post-QL treatment
**2 patients did not receive brain imaging at baseline, were clinically assessed instead. Both patients had follow-up brain imaging

Baseline characteristics

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
Baseline & clinical characteristics				
Age Median (IQR)		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*	Adeno-carcinoma	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

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

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%
- Of the 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 DOCE alone and DOCE + 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, CI)	6.7 (5.3-8.8)	8.7 (7.6-9.6)
Progression free survival [months] (Median, CI)	3.6 (2.6-4.2)	5.6 (5.2-6.1)
CNS Progression (N, %)	17 (27.4%)	45 (8.4%)
CNS Disease Control Rate at 12 months (N, %)	47 (75.8%)	n/a

Figure 2. Overall Survival for Main Cohorts (Baseline brain metastases Present or Absent)

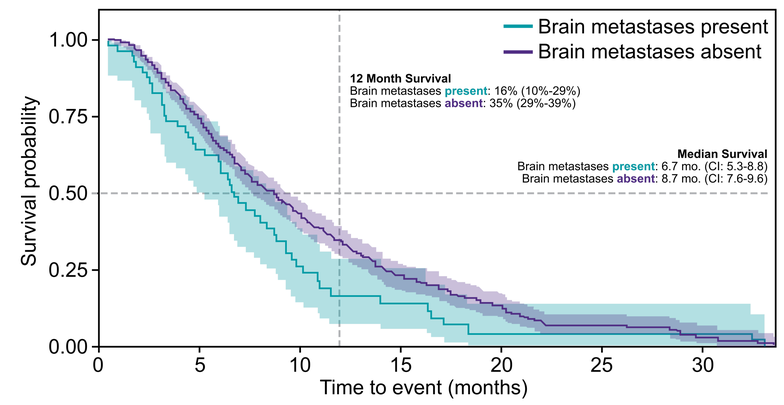
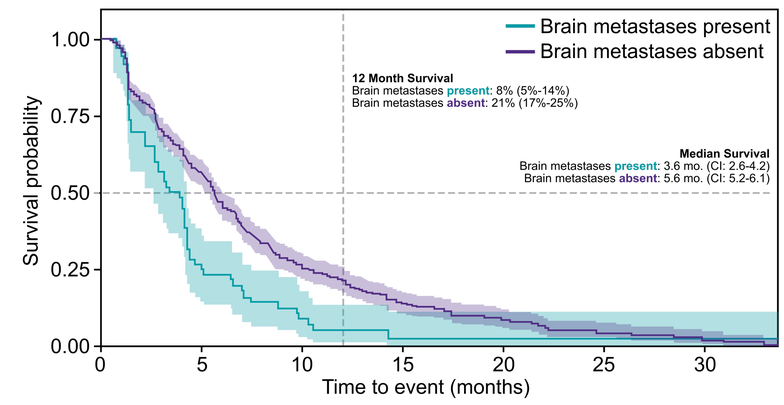


Figure 3. Progression Free Survival for Main Cohorts (Baseline brain metastases Present or Absent)



Discussion

- *KRAS* mutations are one of several factors associated with increased probability of brain metastases in NSCLC[10,14,15]
- Docetaxel is not known to have significant CNS penetration[16-18], although data is limited[19,20] and impact on CNS-DCR in *KRAS* mutated NSCLC is not known
- In this study of highly selected clinical trial populations of *KRAS*mut aNSCLC with pretreated stable brain metastases, docetaxel containing regimens resulted in a CNS-DCR at 12 months of 75.8%
- 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 duration of the clinical trials accrual periods
  - No patients received docetaxel in combination with an antiangiogenesis inhibitor. Brain metastases in *KRAS* G12C NSCLC are observed at similar frequency (40%) as other *KRAS* mutations.[21,22] Novel 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[23] and 85% (28/33) for adagrasib.[24] Adagrasib has also reported CNS-DCR (median follow-up of 6.6 months) of 84% (16/19) in cohort of Phase 1/1b patients with active untreated brain metastases[21,25]
- Similar to trials of *KRAS* G12C inhibitors, [23] in this study, docetaxel demonstrated numerically worse mPFS and mOS for patients 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
- Given the lack of data in patients with active brain metastases (including those with *KRAS* mutations) and its relevance to NSCLC, consideration should be given to proactively study such patients and their response to next therapies – both in RCTs[26,27] and in real-world data

www.medidata.com

References

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