Binimetinib, pemetrexed and cisplatin, followed by maintenance of binimetinib and pemetrexed in patients with advanced non-small cell lung cancer (NSCLC) and KRAS mutations. The phase 1B SAKK 19/16 trial.

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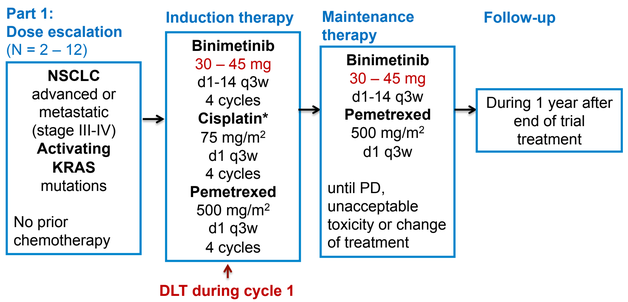
Abstract: 2892

Background

- KRAS mutations are found in 20-25% of non-squamous non small cell lung cancer (NSCLC) patients and therapeutic recommendations do not differ compared to the ones for NSCLC without oncogenic driver alterations.[1]
- There is a need for more effective therapies for patients with a NSCLC driven by the RAS/MEK/ERK pathway
- Binimetinib, an oral selective ATP-non-competitive inhibitor of MEK1 and MEK2[2], is approved by FDA in combination with encorafenib for advanced BRAF-mutant melanoma and showed clinical benefit in combination with encorafenib and cetuximab in patients with metastatic BRAF-mutant colorectal cancer[3,4]
- Based on clinical evidence, binimetinib plus platinum-based chemotherapy is promising in a heterogenous cohort of non-squamous NSCLC patients.[5]

Methods

Figure 1 Phase IB Trial design



Part 2: Dose expansion (N = max. 6): Follow the same schedule and medications as in part 1 with the maximum tolerated dose of Binimetinib.

*Creatinine clearence 45-< 60ml/min after at least one cycle cisplatin: cisplatin replaced by carboplatin AUC5 in all subsequent induction cycles

Primary endpoint (EP)
- DLT (dose-limiting toxicity) during first cycle in dose escalation

Secondary endpoints (EPs)
- Best response (ORR=CR+PR by RECIST1.1) per dose level (DL) of binimetinib
- Progression-free survival (PFS)
- Overall survival (OS)
- Adverse events (AEs) according to CTCAE version 4.03

Results

Between May, 2017 and December, 2019 18 patients were registered into this trial, 13 of which were included in the dose escalation part and 5 in the dose expansion cohort.

Table1 Study population

	Phase I part (Dose escalation)		Expansion cohort
	30 mg Binimetinib (DL1)	45 mg Binimetinib (DL2)	45 mg Binimetinib
Recruited patients	6	7	5
Evaluable for DLT	3	6	-
Evaluable for efficacy EPs	5	6	3
Evaluable for safety EPs	6	6	4

Fifteen patients received binimetinib in combination with platinum and pemetrexed. Median number of cycles was 2 (1-17, range). Reasons for treatment discontinuation were disease progression (33%), patients refusal (13%), permanent discontinuation of binimetinib (13%) and withdrawal by physician (13%). In the dose escalation phase 9 patients (3 in DL1, 6 in DL2) were evaluable for DLT and no DLT occurred. DL 2 (45 mg bid) was the recommended phase 2 dose.

Table 2 Patient characteristics

	N=16*	%
Age, median (range)	60 (48-73)	
Male	10	63%
WHO PS - 0 - 1	 5 11	 31% 69%
Smoking status - Current smoker - Former smoker - Non smoker - Not known	 4 9 1 2	 25% 56% 6% 13%
Tumor stage - Stage IIIB - Stage IV	 2 14	 13% 88%
KRAS mutation - Codon 12 - Codon 13 - Codon 61	 14 1 1	 87% 7% 7%

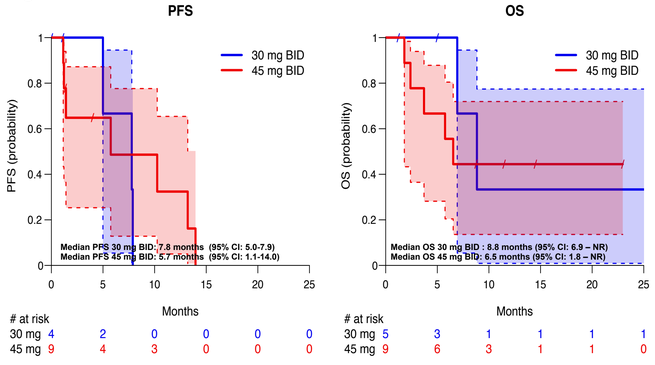
* Number of patients who took at least one dose of trial medication.

Table 3 Responses

Response (N=14*)	No. of patients (%)	
	Cisplatin** 75mg/m², pemetrexed 500mg/m² with **Binimetinib 30 mg (N=5)**	Cisplatin**75mg/m², pemetrexed 500mg/m² with **Binimetinib 45 mg (N=9)**
Overall response rate	**20%**	**33%**
Complete response	0	0
Partial response	1 (20%)	3 (33%)
Stable disease	3 (60%)	2 (22%)
Progressive disease	0	3 (33%)
Not assessed	1 (20%)	1 (11%)

- Two patients excluded from efficacy analysis: one patient due to major eligibility violation (patient had no measurable disease), and one patient because he received no binimetinib but only chemotherapy
- **4 patients received at least one cycle with carboplatin AUC5

Figure 2 Survival outcomes



One patient with 30 mg was censored at registration date (Month=0) for PFS, because this patient was lost to follow-up during first cycle. No tumor assessment was performed

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Table 4 ≥G3 adverse events (>10%)

Adverse event	N= 16 (%)	Possible related*	Probable related*	Definite related*
Lung infection	4 (25%)	1	-	-
Anemia	3 (19%)	1	1	-
Fatigue	3 (19%)	-	3	-
Nausea	2 (12%)	-	-	2
Hypertension	2 (12%)	-	-	-
Hyponatremia	2 (12%)	1	1	-
Thromboembolic event	2 (12%)	2	-	-
General worsening of health status	2 (12%)	-	-	-

*treatment-related SAEs during binimetinib 30 mg or 45 mg in combination with cisplatin** and pemetrexed
No SAE was reported related to binimetinib alone
No G3 ocular or cardiac AE occurred

**4 patients received at least one cycle with carboplatin AUC5

Conclusions

- No DLT occurred during the dose escalation part.
- Patients treated in this phase IB study with combination of cisplatin, pemetrexed and binimetinib at 45 mg bid presented no unexpected adverse event.
- No early signal of increased efficacy of the addition of binimetinib to chemotherapy was observed in therapy-naïve patients with KRAS-mutant advanced NSCLC.
- Promising results for the combination of immune checkpoint inhibitors with MEK inhibitors for KRAS-mutant lung cancer in animal models[6] justify further evaluation in a clinical setting, the results of which are eagerly awaited[7].

References

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