A phase I/II study of ALK inhibitor CH5424802 in patients with ALK-positive NSCLC; safety and efficacy interim results of the phase II portion

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Disclosure

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  CHUGAI, Pfizer, Novartis

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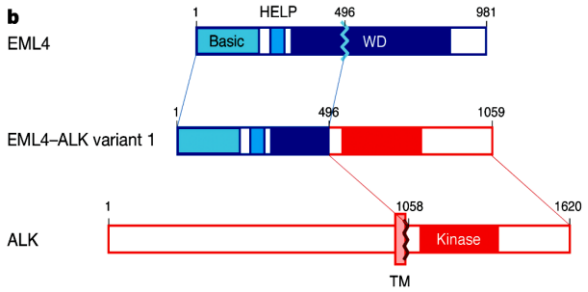
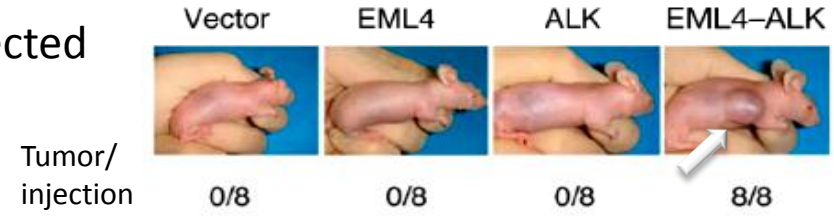
EML4-ALK: A new target for NSCLC therapy

- **Identification of the transforming *EML4-ALK* fusion gene in NSCLC**

A subset of NSCLC patients (pts) express oncogenic fusion gene consisting of *EML4* and *ALK,* which is a promising candidate for a therapeutic target.

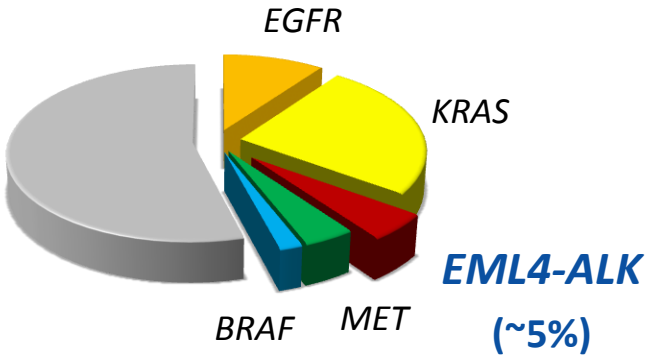


Subcutaneous injection of the transfected 3T3 cells into nude mice



- **Frequency of ALK rearrangements in NSCLC**

Mutually exclusive of EGFR or KRAS mutation



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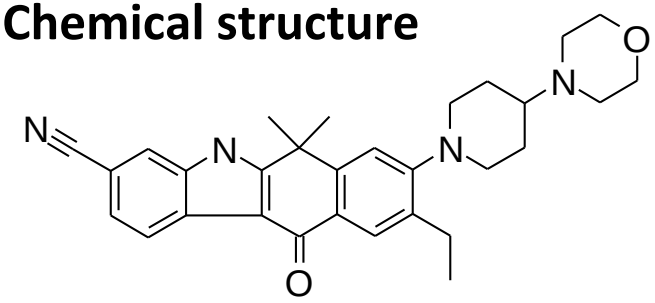
Soda et al., Nature, 448, 561-6 (2007), modified

CH5424802: A selective ALK inhibitor

- **Chemical structure**

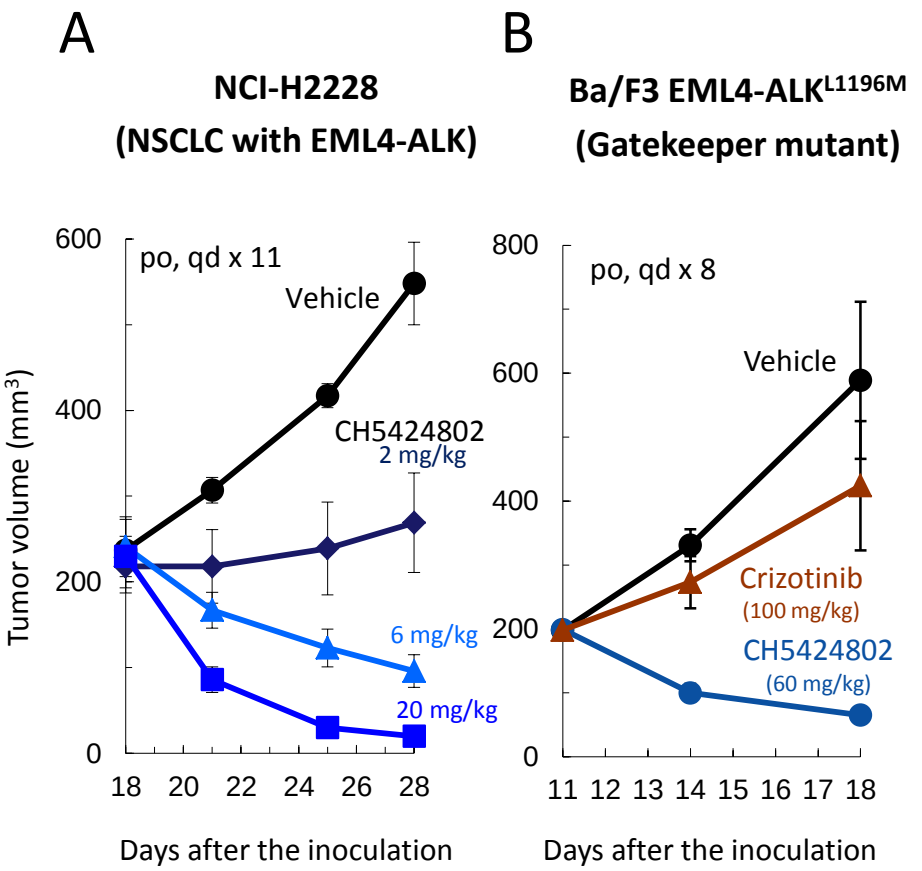


- **Inhibitory activities against kinases**

Kinases	IC_{50} (nM)
ALK	1.9
ALK C1156Y*	0.93
ALK L1196M*	2.1
INSR	550
KDR	1,400
ABL, EGFR, FGFR2, HER2, IGF1R, JAK1, KIT, MET, PDGFRβ, SRC, AKT1, AuroraA, CDK1, CDK2, MEK1, PKA, PKCα, PKCβ1, PKCβ2, Raf-1	>5,000

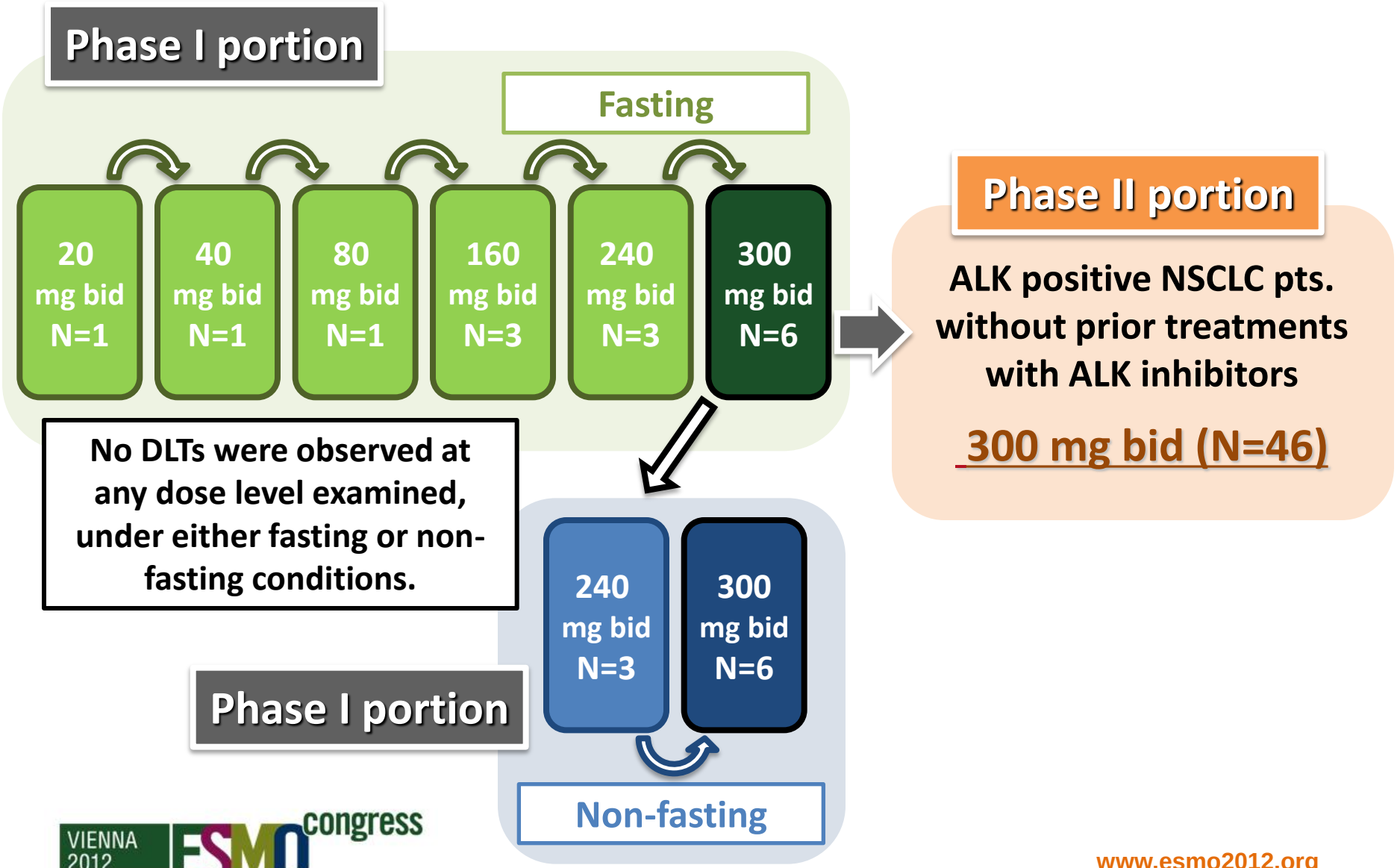
*Point mutations identified in crizotinib-resistant pts.

- **Efficacies in s.c. mouse xenograft models**



Sakamoto et al., Cancer Cell, 19, 679–690 (2011), modified

Overviews of a phase I/II study for CH5424802



Phase II portion: Key eligibility criteria and primary endpoints

- **Key eligibility criteria for pts recruited**
  - Histologically or cytologically confirmed advanced or metastatic NSCLC
  - ECOG performance status of "0-1"
  - ALK fusion gene confirmed in tissues (IHC* and FISH) or cell samples (RT-PCR)
  - One or more prior chemotherapies undergone
  - No prior treatment with ALK inhibitors

- **Primary endpoints**
  - Objective response rate (ORR) (IRC** assessment)

** IRC, independent review committee

** Takeuchi et al., Clin. Cancer Res., 15, 3143-9 (2008)*

Patient's characteristics

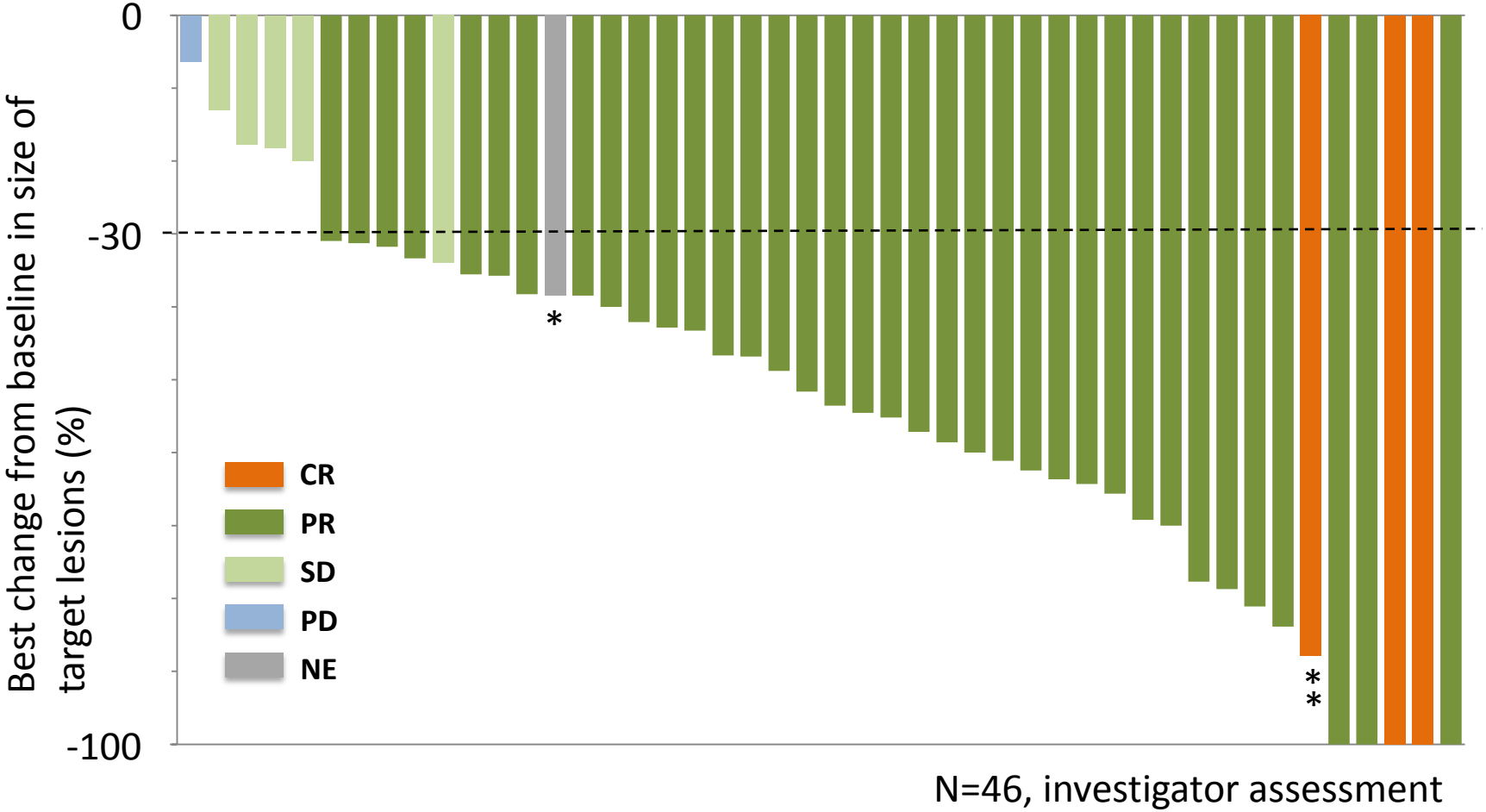
Demographics		Phase II portion N = 46, n (%)
Age	Median (ranges)	48.0 (26-75)
Sex	Male Female	22 (48%) 24 (52%)
ECOG Performance status	0 1	21 (46%) 25 (54%)
Smoking history	Non-smokers Current smokers Past smokers	27 (59%) 1 (2%) 18 (39%)
Histology	Adenocarcinoma	46 (100%)
ALK diagnosis	IHC and FISH RT-PCR	39 (85%) 7 (15%)
Prior regimens	1 2 ≥ 3	16 (35%) 12 (26%) 18 (39%)

Clinical efficacy of CH5424802

	Investigator assessment N=46
CR	3
PR	36
SD	5
PD	1
NE	1
Total of response	39
ORR [95% CI]	85% [71.1-93.7]

- **Treatment duration: 2-46+ weeks**
- **40 out of 46 pts are still on study treatments**

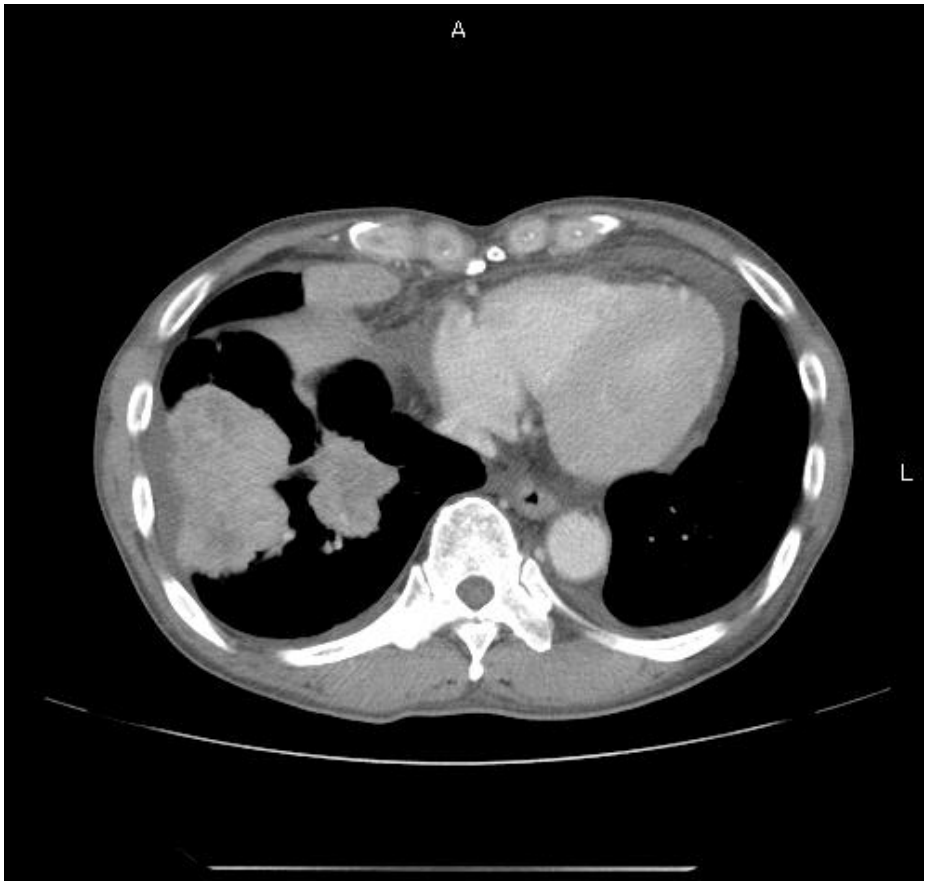
A waterfall plot of tumor shrinkage



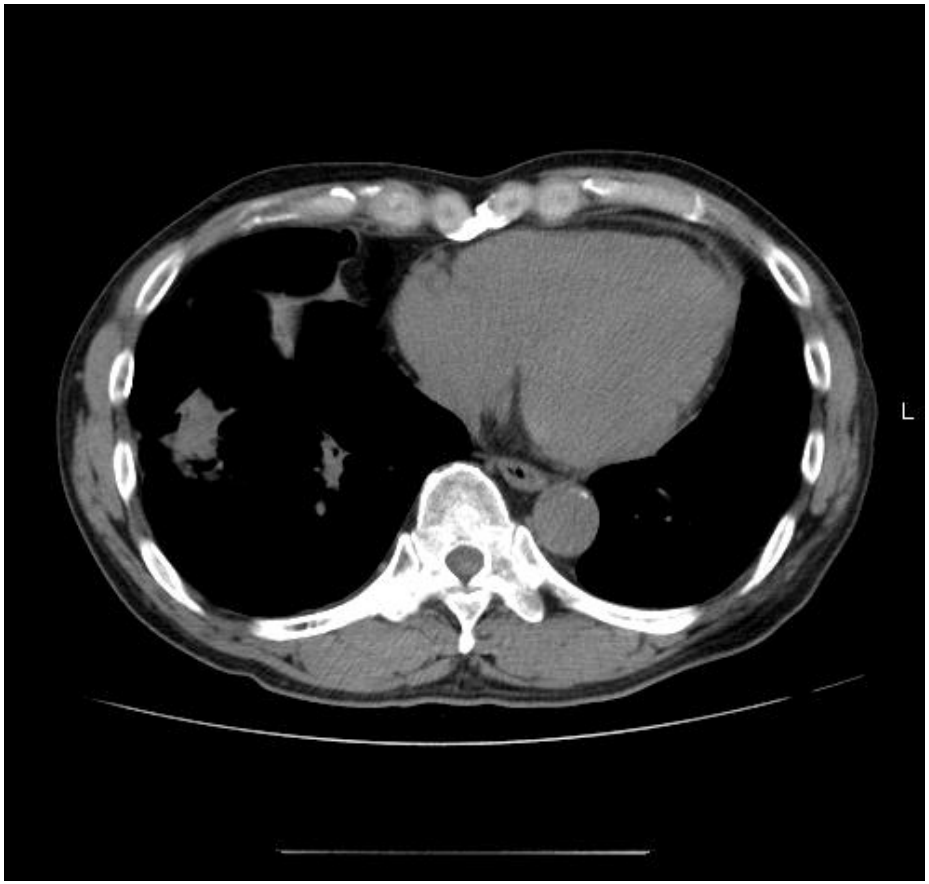
*Indeterminate response by early stopping due to safety reasons

**Per RECIST 1.1, percent change from baseline for subjects with response of CR can be less than 100% when lymph nodes are identified as target lesions.

Anti-tumor activity of CH5424802

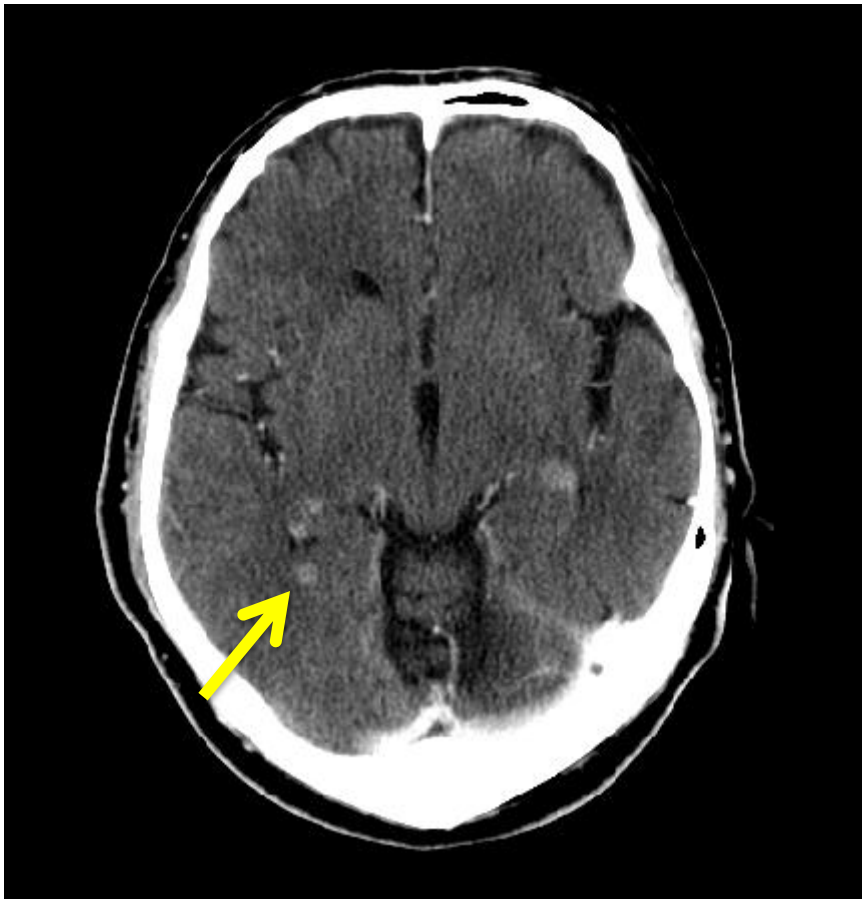


Before treatment

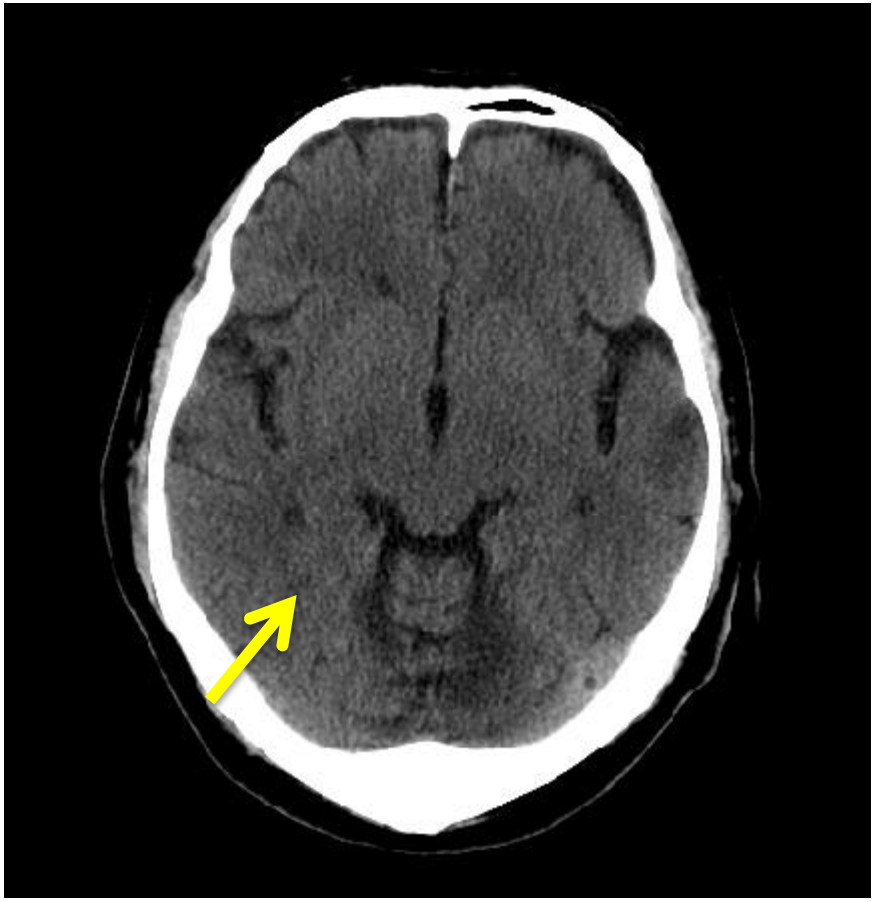


After 26 weeks of CH5424802 treatment

Anti-tumor activity in brain metastases



Before treatment



After 33 weeks of CH5424802 treatment

Treatment related AEs (≥ 10%)

Adverse event	Total, n (%)	Grade 3, n
Dysgeusia	14 (30%)	0
AST increased	13 (28%)	0
Rash*	11 (24%)	2
Constipation	11 (24%)	0
ALT increased	10 (22%)	1
Blood creatinine increased	10 (22%)	0
Neutrophil count decreased	8 (17%)	2
Blood bilirubin increased	8 (17%)	0
Blood CPK** increased	7 (15%)	2
Nausea	6 (13%)	0
Stomatitis	6 (13%)	0
Myalgia	5 (11%)	0
Blood ALP*** increased	5 (11%)	0
Total Treatment related AEs	**43 (93%)**	**11**

*rash, rash maculo-papular, rash pustular ; **CPK, creatine phosphokinase;
***ALP, alkaline phosphatase

Treatment related AEs

Body system	Adverse event	Total, n (%)	Grade 3, n
Visual disorder	vision blurred	1 (2%)	0
	visual impairment	1 (2%)	0
	vitreous haemorrhage	1 (2%)	0
Gastrointestinal disorder	Nausea	6 (13%)	0
	Diarrhea	2 (4%)	0
	Vomiting	1 (2%)	0

Visual disorders were rare and GI toxicities were mild.

Treatment related AEs

- No dose reductions were required.

- Treatment related AEs leading to a discontinuation were observed in 3 pts.

  Cholangitis sclerosing, interstitial lung disease, and tumor haemorrhage

Summary

- **CH5424802 had good activity in ALK positive NSCLC patients.**
  - ORR: 85% [95% CI: 71.1-93.7]
  - Significant and rapid tumor shrinkage occurred in most patients.
  - CH5424802 is potentially active against metastatic brain tumors.

- **CH5424802 was well tolerated.**
  - The majority of adverse events were grade 1 or 2
  - No dose reduction were required.
  - Visual disorders were rare and GI toxicities were mild.

Conclusions

- **CH5424802 is a new potent ALK inhibitor for NSCLC.**
- **We look forward to further investigation with CH5424802 and exploring optimal ALK inhibitor applications in NSCLC.**

Acknowledgements

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- Hokkaido Cancer Center
- Kurashiki Central Hospital
- National Shikoku Cancer Center
- National Cancer Center Hospital East
- Shizuoka Cancer Center
- National Cancer Center Hospital