Safety, Pharmacokinetics, and Pharmacodynamic Effects of ALKS 4230 in Patients With Advanced Solid Tumors From the Ongoing Dose Escalation Portion of a First In Human (FIH) Study

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BACKGROUND

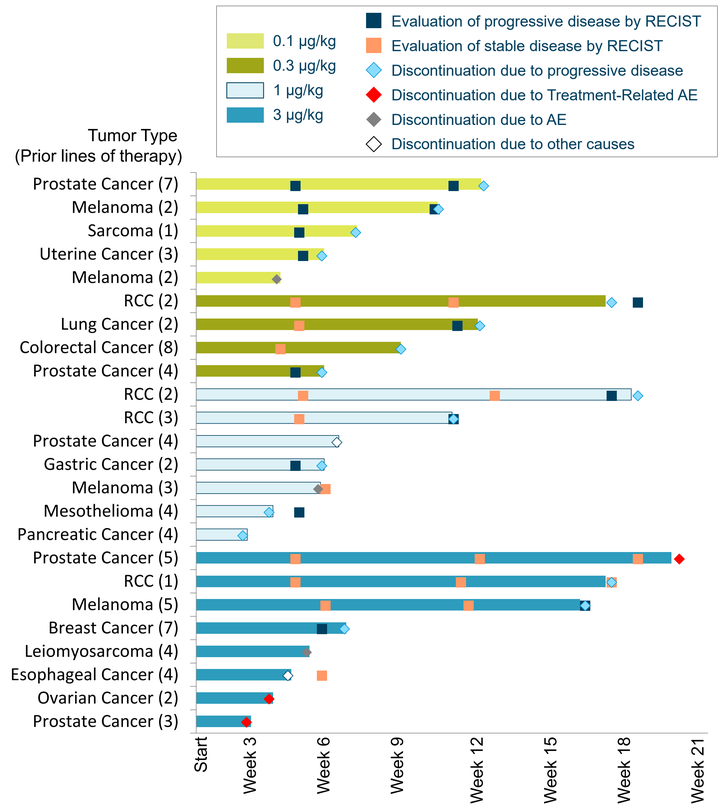
- ALKS 4230 is a fusion of circularly permuted IL-2 and IL-2 Receptor α (IL-2Rα) designed to selectively activate the intermediate-affinity IL-2R, comprised of IL-2Rβ and γ, for activation of cytotoxic CD8⁺ T cells and NK cells.
- The intermediate-affinity IL-2R is expressed predominantly on effector lymphocytes, which play an important role in driving antitumor immune responses.[1]
- Wild-type IL-2 activates the high-affinity IL-2R, comprised of IL-2Rα, β, and γ_c, driving the expansion of immunosuppressive CD4⁺ regulatory T (T_{reg}) cells at concentrations below those at which intermediate-affinity IL-2R-bearing effector cells are activated.[2]
- Selective activation of the intermediate affinity IL-2R has the potential to enhance tumor killing, and was shown to possess enhanced antitumor activity relative to IL-2 in murine models.[3]

METHODS

- ALKS 4230 is being studied in a FIH Phase 1 study in subjects with advanced refractory solid tumors
- ALKS 4230 is administered as a 30 minute intravenous infusion once daily for 5 consecutive days repeating in treatment cycles of 14 days (first cycle) or 21 days (subsequent cycles)
- The first part of the study is a dose escalation with the primary objective of investigating the safety and tolerability of ALKS 4230 and to determine the MTD and the RP2D
- Other assessments include pharmacokinetics, lymphocyte sub-population expansion, immunogenicity, and anti-tumor activity

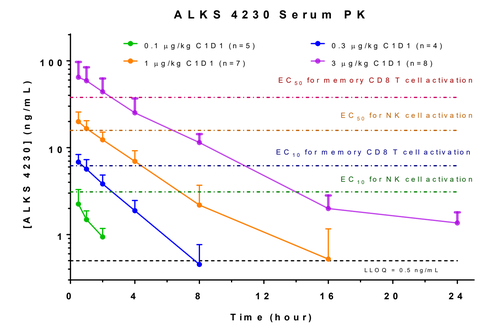
RESULTS

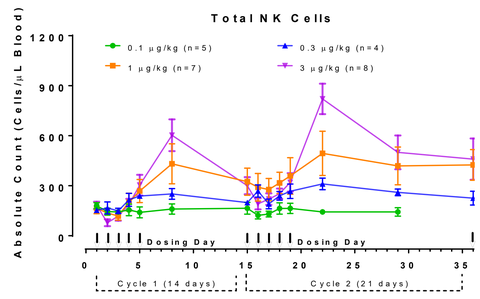
Patient Duration on Study

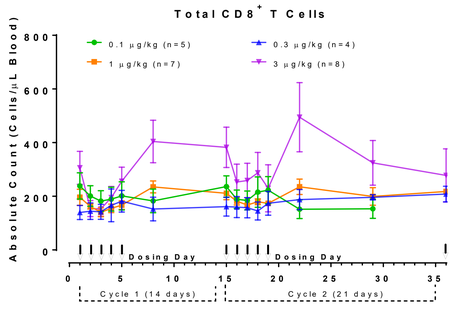


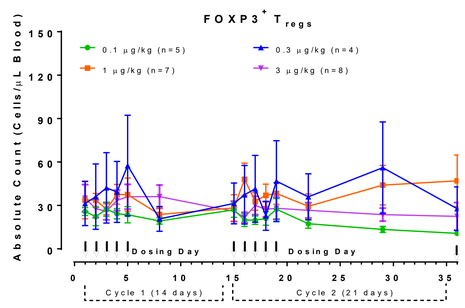
RESULTS

ALKS 4230 Pharmacokinetics and Pharmacodynamic Effects









- Systemic exposure to ALKS 4230 increased with increasing dose
- Maximum ALKS 4230 serum concentrations at the 3 µg/kg/day exceeded the EC_{50} values for NK and CD8⁺ T cell activation determined by *in vitro* pharmacology studies
- ALKS 4230 induced a dose-dependent increase in circulating NK and CD8⁺ T cells with an approximately 4-fold and 2-fold expansion at 3 µg/kg/day, respectively, and minimal, non-dose dependent change in T_{regs}, as compared to a more robust expansion of T_{regs} over CD8⁺ T cells and NK cells observed in patients treated with high-dose IL-2 (SITC 2018 abstract P123)

Treatment-Emergent Adverse Events

Preferred Term	Treatment-Emergent Adverse Events Occurring in ≥20% of Patients, All Grades (1-3)				
	0.1 µg/kg (N=5)	0.3 µg/kg (N=4)	1 µg/kg (N=7)	3 µg/kg (N=8)	Total (N=24)
Pyrexia		2 (50%)	5 (71%)	8 (100%)	15 (63%)
Chills		2 (50%)	5 (71%)	8 (100%)	15 (63%)
Vomiting	2 (40%)	2 (50%)	2 (29%)	4 (50%)	10 (42%)
Fatigue	4 (80%)	1 (25%)	2 (29%)	3 (38%)	10 (42%)
Constipation	2 (40%)	1 (25%)	2 (29%)	4 (50%)	9 (38%)
Anemia	1 (20%)	1 (25%)	3 (43%)	3 (38%)	8 (33%)
Nausea	2 (40%)	1 (25%)	1 (14%)	4 (50%)	8 (33%)
Dyspnea	2 (40%)	1 (25%)	1 (14%)	3 (38%)	7 (29%)
Blood creatinine increased			3 (43%)	3 (38%)	6 (25%)
Decreased appetite	1 (20%)	1 (25%)	1 (14%)	3 (38%)	6 (25%)
Myalgia	1 (20%)		1 (14%)	3 (38%)	5 (21%)
Dizziness		1 (25%)	2 (29%)	2 (25%)	5 (21%)
Abdominal pain	1 (20%)		2 (29%)	2 (25%)	5 (21%)
Hypertension	1 (20%)	1 (25%)	1 (14%)	2 (25%)	5 (21%)

Data shown as "n subjects (% of category)"
Among these AEs occurring in ≥ 20% of subjects, all were Grade 1 or 2, except Grade 3 anemia that occurred in N=4 subjects
No Grade 4 or 5 events have occurred to date

Grade 3 Treatment-Related Adverse Events

Preferred Term	ALKS 4230-Related Adverse Events, Grade 3 (N=24)
Neutrophil count decreased	2 (8%)
White blood cell count decreased	2 (8%)
Cholangitis	1 (4%)
Diarrhea	1 (4%)
Febrile neutropenia[1]	1 (4%)
Hyperbilirubinaemia	1 (4%)
Hypoalbuminaemia[2]	1 (4%)
Jaundice cholestatic	1 (4%)
Lymphocyte count decreased	1 (4%)

Data shown as "n subjects (% of category)"
[1] Occurred in a subject with a transient fever that occurred on Cycle 2 Day 2 (C2D2) 3-6 hrs post-infusion with a high temperature of 39.7°C. ANC was 4200/mm³ on C2D2 but subsequently dropped to 810/mm³ on C2D4. ANC recovered to 1700/mm³ by C2D10. No antibiotics or other medical intervention was needed.
[2] Occurred on C1D4 in a subject who had previously had Grade 3 hypoalbuminemia four days prior to C1D1. Hypoalbuminemia had recovered to Grade 2 on C1D1, but worsened again by C1D4.

- Consistent with other cytokine therapies, pyrexia and chills were the most common treatment-emergent ALKS 4230-related adverse events
- Overt capillary leak syndrome has not been observed to date
- No Grade 4 or 5 adverse events have been reported
- At the 3 µg/kg dose level, one incident each of Grade 3 febrile neutropenia and Grade 3 hypoalbuminemia met the protocol definitions for dose-limiting toxicities (DLT). After discussion with the investigators it was determined that these should not be considered DLTs, and DLT definitions were amended, allowing continued dose escalation.

Elevation of Serum Cytokine Levels

ALKS 4230 Dose	Maximum IL-6		Maximum IFN-γ	
	Concentration (pg/mL)	Fold-change from baseline	Concentration (pg/mL)	Fold-change from baseline
0.1 µg/kg (N=5)	55.3 (19.4-329.7)	4.0 ± 6.0	20.3 (7.4-63.2)	2.5 ± 3.0
0.3 µg/kg (N=4)	87.8 (12.6-208.5)	2.2 ± 1.0	20.9 (5.0-39.2)	1.7 ± 0.9
1 µg/kg (N=7)	88.7 (17.3-799.5)	10.9 ± 13.9	10.9 (3.8-29.5)	2.1 ± 1.5
3 µg/kg (N=8)	809.8 (22.1-4698.4)	25.9 ± 35.8	41.6 (3.8-607.1)	11.4 ± 17.3

Data shown as "median (range)" or "mean ± SD"

- Dose-dependent elevations of serum IL-6 and IFN-γ levels were observed in response to treatment with ALKS 4230
- IL-6 levels peaked at 4 hours post-dose and recovered to baseline at 8-10 hours post-dose
- Fever coincided with the time of maximum IL-6 and recovered to baseline 8-12 hours post-dose

CONCLUSIONS

- ALKS 4230 was generally well-tolerated at the doses tested, with treatment-related AEs that were generally manageable and transient
- The 3 µg/kg/day dose level induced expected immunologic effects, supporting the rationale for assessing combination therapies with ALKS 4230, as well as continued dose escalation in the monotherapy setting
- In addition to assessing combination therapies at the 3 µg/kg dose level, monotherapy dose escalation (up to 6, 10, and 15 µg/kg/day) is ongoing

The authors thank the patients and families who participated in the study

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Abbreviations: AE=adverse event; DLT=dose limiting toxicity; FIH=first in human; IFN-γ=Interferon gamma; IL-2=Interleukin-2; MTD=maximum tolerated dose; N/D=not detectable; NK=natural killer cells; RCC=renal cell carcinoma; RECIST=Response Evaluation Criteria in Solid Tumours v1.1; RP2D=recommended Phase 2 dose; T_{reg}=regulatory T cells

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