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A first-in-human study of oral IAG933 in adult patients with advanced mesothelioma and other solid tumours

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

Declaration of Interests

Speaker: Dr Elena Garralda

Research: Novartis, Roche, Thermo Fisher, AstraZeneca, Taiho, BeiGene, Janssen, and Anaveon

Consultant/Advisor: Roche, Ellipses Pharma, Boehringer Ingelheim, Janssen Global Services, Seattle Genetics, Skypta, Sotio, Sanofi, Anaveon, AbbVie, Astex Therapeutics, Alentis Therapeutics, Marengo Therapeutics, Hengrui, Incyte, Medpace, Pfizer, Amgen, Genmab, Greywolf Therapeutics, Gilead Sciences, and Daiichi Sankyo

Speakers' Bureau: MSD, Roche, Novartis, Seagen, PPD Global, Aran, The Ricky Rubio Foundation, ESMO, Fundación SEOM, CDDF, Springer Nature, Karger Publishers, Doctaforum, Tactics, AEFI, Fundación ECO, MeetingPharma, AstraZeneca, Medscape, Alcura, Horizon CME, and European School of Oncology (ESO)

Employment: NEXT Oncology (IOB)

IAG933 is a LMW inhibitor of the protein–protein interaction between TEADs (all 4 paralogs) and YAP/TAZ

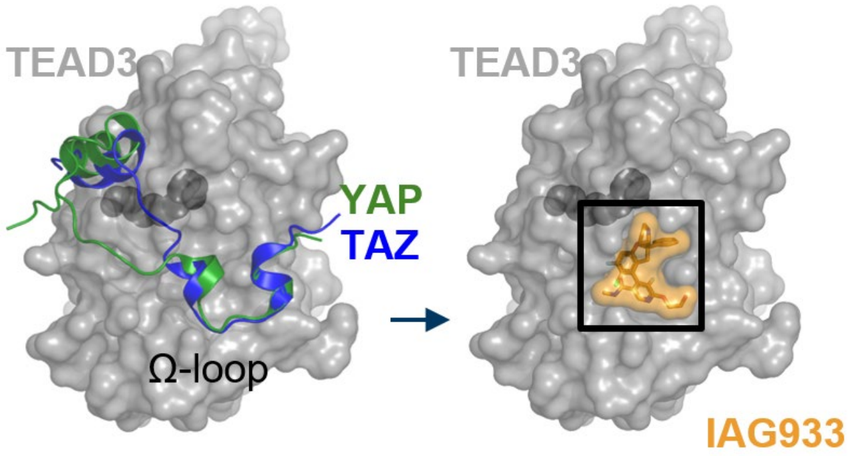
Hippo pathway

- YAP/TAZ–TEAD hyperactivation commonly occurs in cancers,[1-3] especially mesothelioma, due to frequent Hippo pathway mutations (e.g. NF2, LATS1/2)[4]
- Emerging data support TEAD inhibitors as promising Hippo pathway–targeted therapies[5]

IAG933 *YAP-TEAD direct PPI inhibitor*

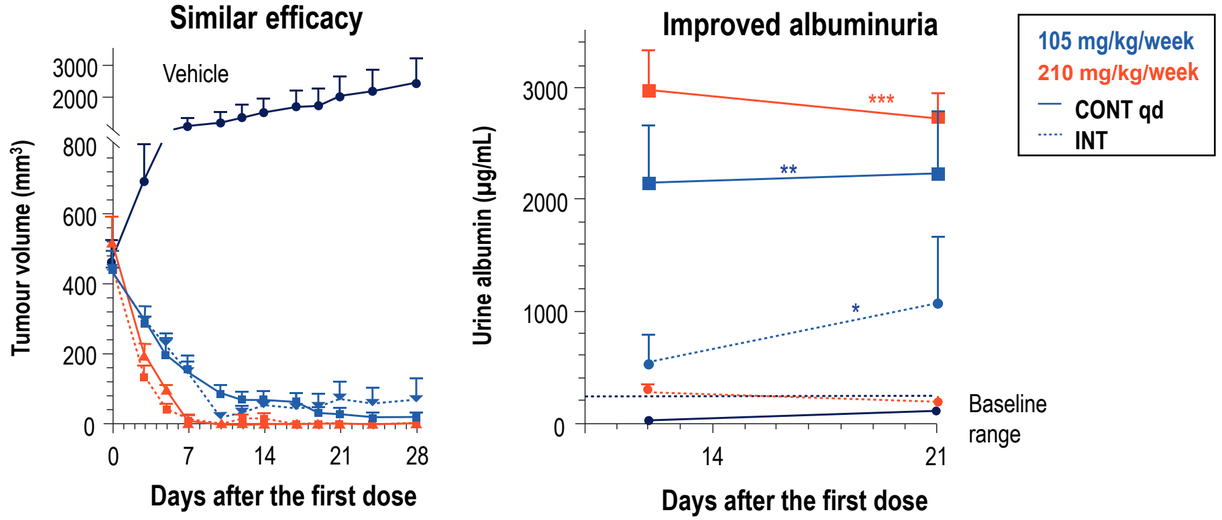
- An oral, selective, potent PPI inhibitor that binds to the TEAD coil site (Ω-loop) and directly displaces YAP and TAZ[6]
- We report dose-escalation data from the FIH study of IAG933 in mesothelioma (no mutation requirement) and other solid tumours with Hippo pathway alterations or YAP–TAZ fusions (e.g. EHE)

IAG933 mechanism of action



Intermittent schedule (qd vs 3 qw) at the same weekly dose

MSTO211H xenograft model, nude rats



CONT, continuous; EHE, epithelioid haemangioendothelioma; FIH, first-in-human; INT, intermittent; LATS1/2, large tumour suppressor kinase 1/2; LMW, low-molecular-weight; NF2, neurofibromin 2; PPI, protein–protein interaction; qd, once daily; qw, once weekly; TAZ, transcriptional coactivator with a PDZ-binding motif; TEAD, transcriptional enhanced associate domain; YAP, yes-associated protein.

1. Pobbati AV, et al. *Trends Biochem Sci.* 2023;48(5):450-462; 2. Muramatsu T, et al. *Carcinogenesis* 2011;32(3):389-398; 3. Eun YG, et al. *Oncotarget.* 2017;8(67):111130-111143; 4. Bueno R, et al. *Nat Genet.* 2016;48(4):407-416; 5. Yap T, et al. *Cancer Res.* 2023;83(8_Suppl):Abstract nr CT006; 6. Chapeau EA, et al. *Nat Cancer.* 2024;5(7):1102-1120.

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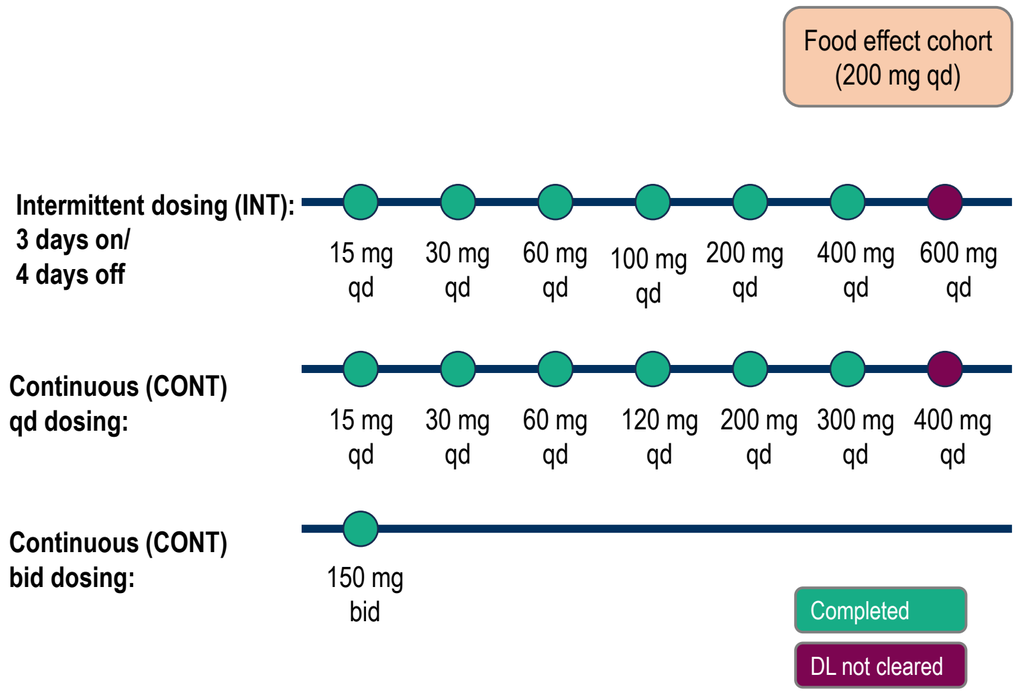
Study design: An ongoing, open-label, multicentre, phase 1, FIH study of IAG933 monotherapy

Key inclusion criteria

- Age ≥18 years
- ECOG PS score of 0 or 1
- Measurable disease, RECIST v1.1
- **Dose-escalation part:** Patients with advanced (unresectable or metastatic) mesothelioma without the required mutation testing or other solid tumours harbouring NF2/LATS1/LATS2 truncating mutations or deletions or tumours with functional YAP/TAZ fusions[a]
- Tumour amenable to biopsy

Dose escalation of IAG933 monotherapy



Key milestones
Clinical data cutoff: 2 July 2025
PK data cutoff: 14 February 2025

ClinicalTrials.gov: NCT04857372

Primary endpoints

- Incidence of DLTs
- Incidence and severity of AEs and SAEs
- Assess tolerability

Secondary endpoints

- ORR, DCR, PFS and DOR per mRECIST v1.1/RECIST v1.1/RANO
- Characterise the PK profile

Key exploratory endpoints

- Evaluate the effect of food on IAG933 exposure
- Assess changes in PD with paired biopsies
- Correlate genetic alterations with response

[a]Patients with a histological diagnosis of EHE can be enrolled without molecular evidence of YAP/TAZ fusions.

AE, adverse event; bid, twice daily; CONT, continuous; DCR, disease control rate; DL, dose level; DLT, dose-limiting toxicity; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EHE, epithelioid haemangioendothelioma; FIH, first-in-human; INT, intermittent; LATS1/2, large tumour suppressor kinase 1/2; mRECIST, modified RECIST; NF2, neurofibromin 2; ORR, overall response rate; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; qd, once daily; RANO, Response Assessment in Neuro-Oncology; RECIST, Response Evaluation Criteria in Solid Tumours; SAE, serious adverse event; TAZ, transcriptional coactivator with a PDZ-binding motif; YAP, yes-associated protein.

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Heavily pre-treated FIH population, with >50% of patients with pleural mesothelioma receiving >3 lines of prior therapy

- At data cutoff (2 July 2025), 136 patients were treated (INT dosing [3 days on/4 days off], n=42; CONT dosing, n=94)

Baseline demographics and clinical characteristics	All patients (N=136)		
	INT dosing (N=42)	CONT qd dosing (N=88)	CONT bid dosing (N=6)
Age (years), median (range)	63.5 (31.0-79.0)	67.5 (21.0-84.0)	63.5 (47.0-75.0)
Gender, n (%)			
Male	26 (61.9)	57 (64.8)	6 (100)
Female	16 (38.1)	31 (35.2)	-
Race, n (%)			
White	34 (81.0)	80 (90.9)	5 (83.3)
Asian	6 (14.3)	6 (6.8)	1 (16.7)
Black or African American	-	1 (1.1)	-
Unknown	2 (4.8)	1 (1.1)	-
Cancer diagnosis, n (%)			
Pleural mesothelioma	30 (71.4)	71 (80.7)	4 (66.7)
EHE	4 (9.5)	5 (5.7)	-
Peritoneal mesothelioma malignant	3 (7.1)	6 (6.8)	-
Meningioma	4 (9.5)	2 (2.3)	-
Others[a]	1 (2.4)	4 (4.5)	2 (33.4)
ECOG PS score, n (%)			
0	17 (40.5)	34 (38.6)	5 (83.3)
1	25 (59.5)	54 (61.4)	1 (16.7)

No. of prior antineoplastic regimens, n (%)	By indication		
	Pleural mesothelioma (N=105)	EHE (N=9)	Peritoneal mesothelioma (N=10)
1	11 (10.5)	3 (33.3)	2 (20.0)
2	39 (37.1)	1 (11.1)	1 (10.0)
3	25 (23.8)	1 (11.1)	4 (40.0)
≥4	30 (28.5)	2 (22.2)	3 (30.0)
Missing	0	2 (22.2)[b]	0

[a]Others include malignant peripheral nerve sheath tumour, multiple meningioma, nasal sinus cancer, non–small cell lung cancer, sarcoma uterus and mesothelioma; [b]Participants did not receive any prior systemic therapy.

bid, twice daily; CONT, continuous; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EHE, epithelioid haemangioendothelioma; FIH, first-in-human; INT, intermittent; qd, once daily.

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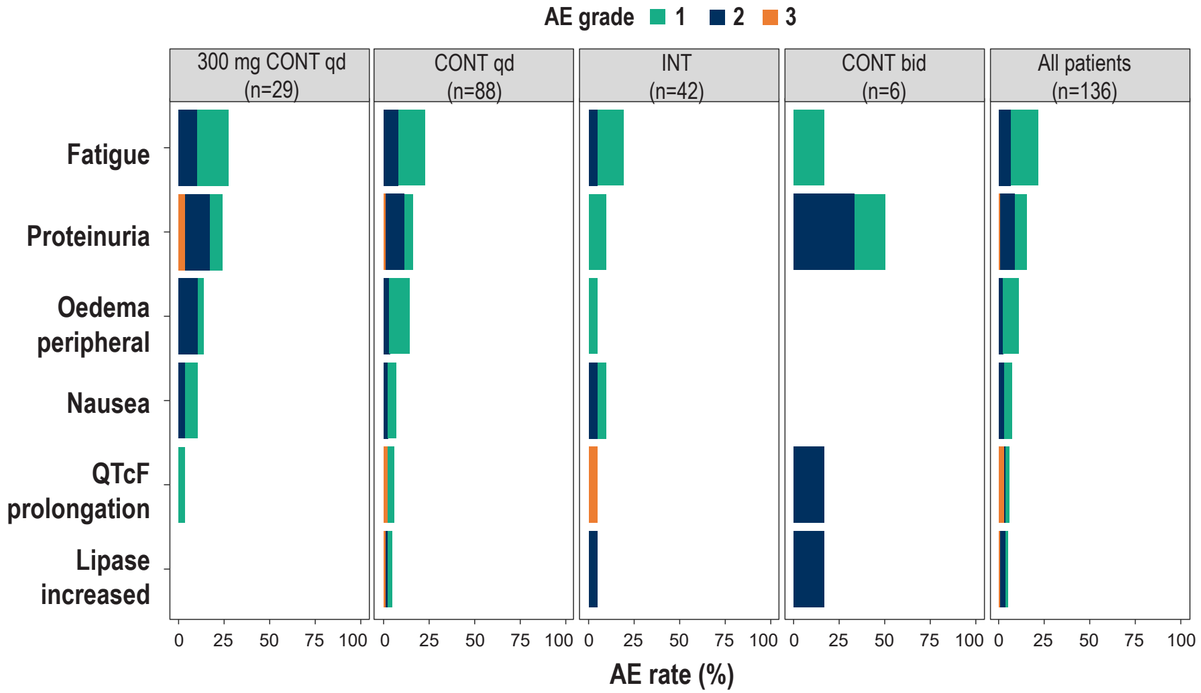
IAG933 was well-tolerated, and most TRAEs were grades 1 and 2, including reversible albuminuria

TRAEs with an overall incidence of >5%



uACRs were decreased on INT relative to qd dosing regimen

Dose/schedule	Median uACR (mg/g)	Mean uACR (mg/g)
200 mg INT	16.8	25.5
400 mg INT	25.7	53.1
600 mg INT	38.9	88.6
60 mg CONT qd	28.5	63.2
120 mg CONT qd	19.0	49.0
200 mg CONT qd	25.7	295.4
300 mg CONT qd	72.6	262.4
400 mg CONT qd	197.8	765.8
150 mg CONT bid	342.0	354.1

- Most TRAEs were grade 1 or 2; most common TRAEs in all patients were fatigue, proteinuria and peripheral oedema
  - Grade ≥3 TRAEs occurred in 9.5% (INT) and 5.7% (CONT qd) of patients
  - Suspected SAEs (i.e. atrial fibrillation, generalised oedema and proteinuria) were reported in 3.4% of patients in the CONT qd regimen
- DLTs were observed in 5 patients:
  - 4 for QTc prolongation (2 each on 600 mg INT schedule and 400 mg CONT schedule). QTc prolongation was otherwise grade1[a]
  - 1 DLT for grade 2 proteinuria on 300 mg qd CONT. Otherwise, albuminuria (and proteinuria) was manageable and reversible at all doses and schedules

[a]In one patient (150 mg bid CONT), an event of grade 2 QTcF prolongation was reported based on algorithm-derived QTcF; this AE was re-assessed as grade 0 after data cutoff (central cardiology review confirmed that the QTcF was grade 0).

AE, adverse event; bid, twice daily; CONT, continuous; DLT, dose-limiting toxicity; INT, intermittent; qd, once daily; QTc/QTcF, corrected QT interval (using Fridericia's formula); SAE, serious adverse event; TRAE, treatment-related adverse event; uACR, urine albumin-to-creatinine ratio.

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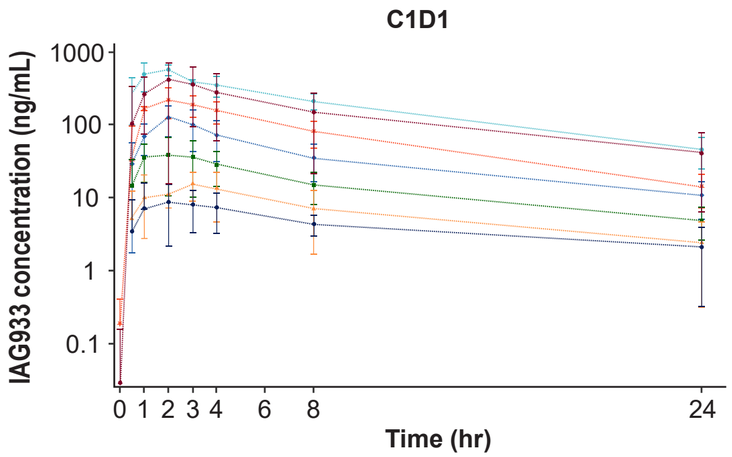
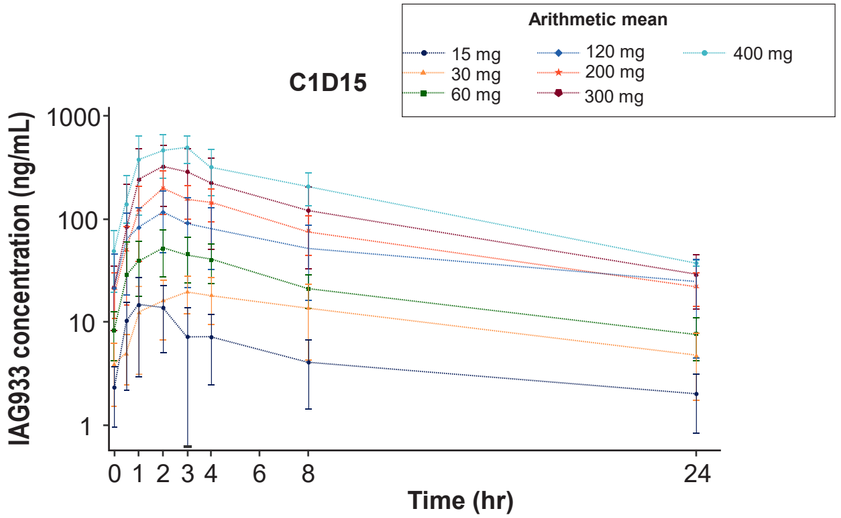
Dose proportional exposure with qd and INT dosing

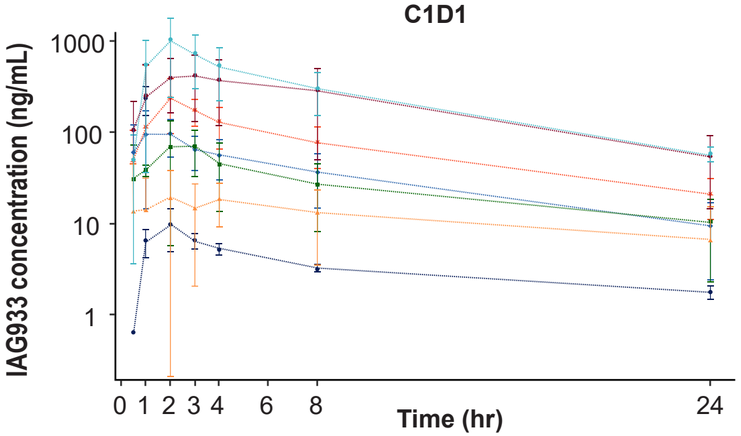
- Rapid oral absorption with a median T_{max} of ~2 hours
- Observed half-life (min-max): ~7-9 hours
- Generally, dose-proportional exposure and no significant accumulation were observed for the qd and INT regimens
- Effect of food (high-fat, high-calorie diet):
  - Decreased exposure by 22% and 34% vs those under the fasted condition
  - Time to C_{max} delayed by 1 hour

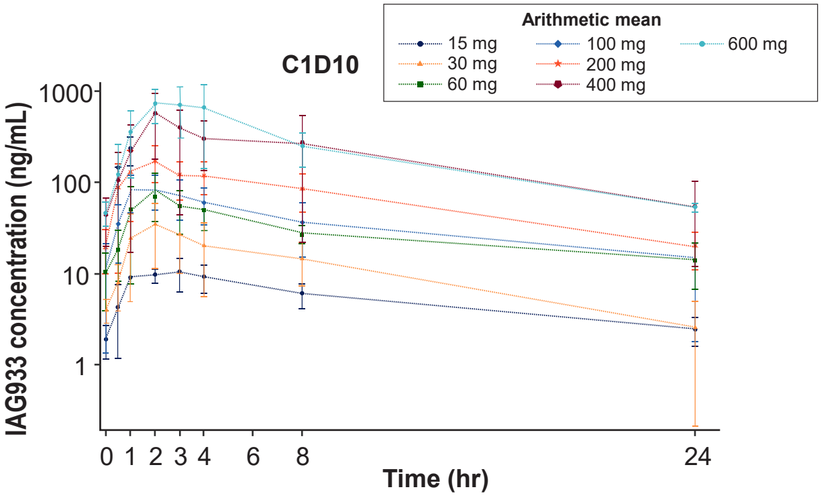
CONT qd dosing





INT dosing





C, cycle; C_{max}, maximum serum concentration; CONT, continuous; D, day; INT, intermittent; qd, once daily; T_{max}, time to reach the maximum drug concentrations in systemic circulation.

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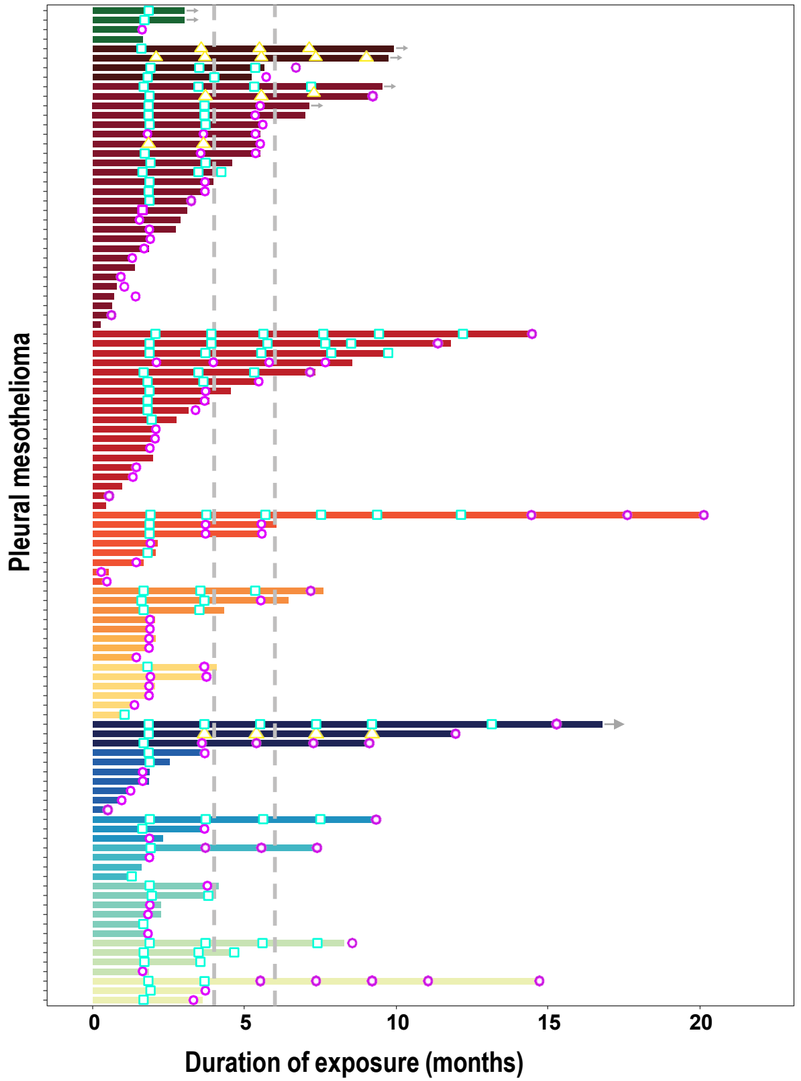
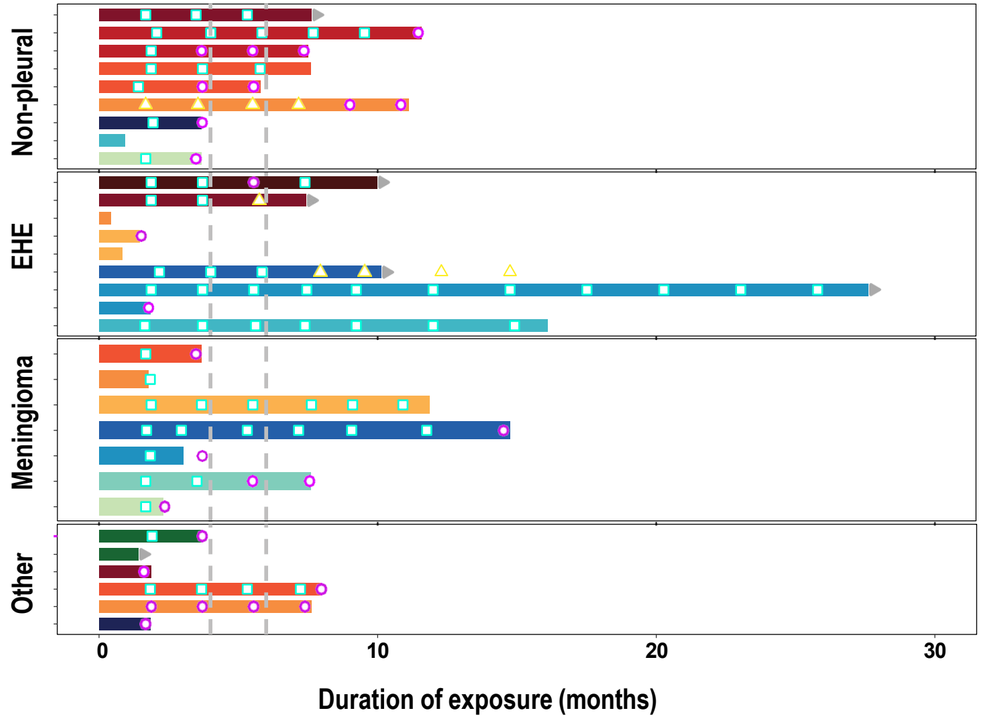
Duration of IAG933 treatment supports activity in multiple indications and on both schedules



Treatment
- 15 mg INT
- 30 mg INT
- 60 mg INT
- 100 mg INT
- 200 mg INT
- 400 mg INT
- 600 mg INT
- 15 mg CONT qd
- 30 mg CONT qd
- 60 mg CONT qd
- 120 mg CONT qd
- 200 mg CONT qd
- 300 mg CONT qd
- 400 mg CONT qd
- 150 mg CONT bid

Overall response
- PD
- PR
- SD

Note: The vertical markers indicate 4 and 6 months



- At data cutoff, 37 patients had a treatment duration of ≥6 months, including 7 patients with ≥12 months and 2 patients with ≥20 months
- **7 cPR:**
  - First responder in the study: peritoneal mesothelioma; 60 mg CONT
  - 1 with EHE (400 mg INT)
  - 5 with pleural mesothelioma (600 mg INT, n=1; 300 mg CONT and 400 mg CONT, n=2 each)
- **1 uPR :**
  - 1 with EHE (300 mg CONT)
- Median time to response for patients with a PR was 3.6 months

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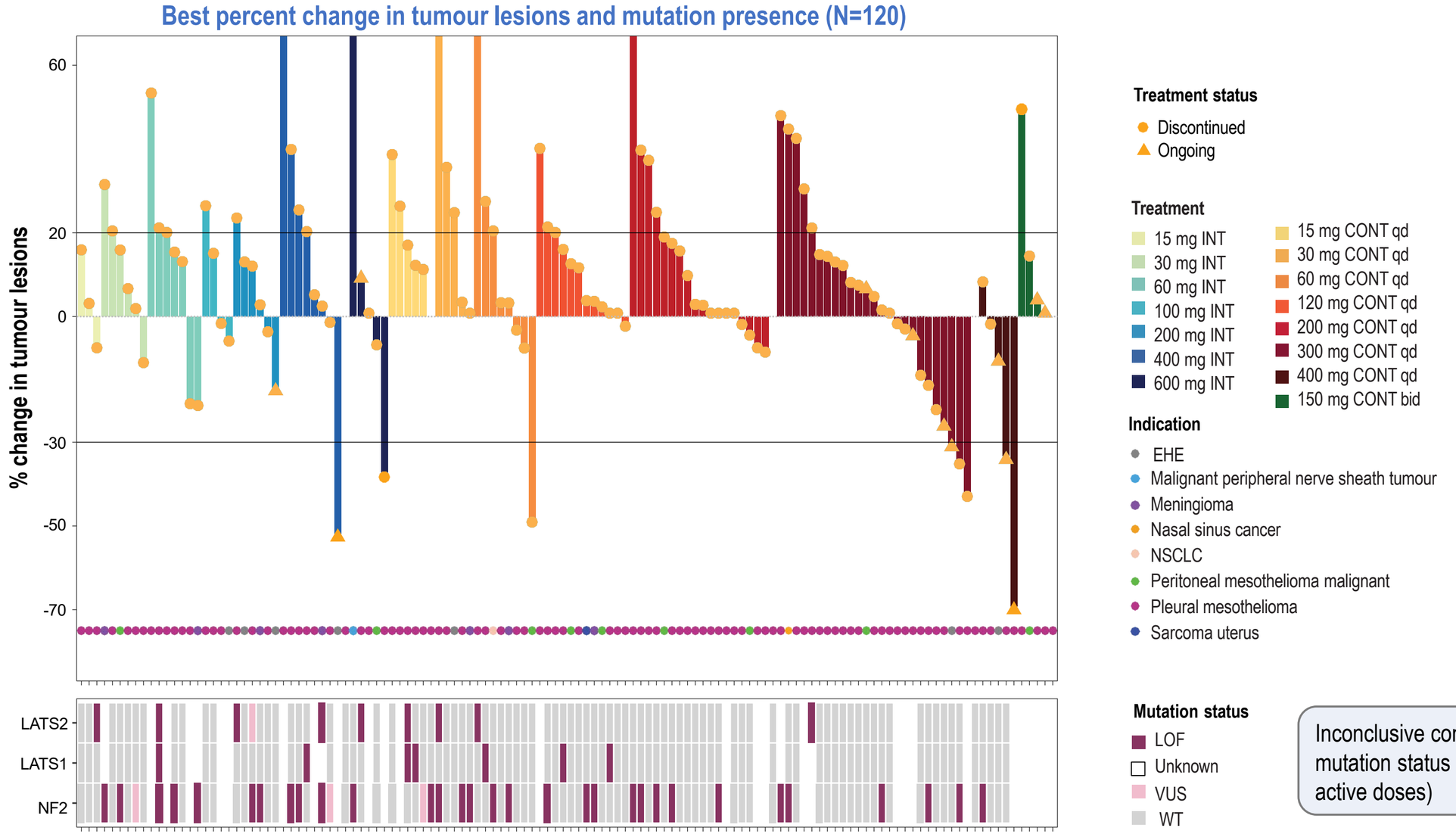
bid, twice daily; CONT, continuous; cPR, confirmed partial response; EHE, epithelioid haemangioendothelioma; INT, intermittent; PD, progressive disease; PR, partial response; qd, once daily; SD, stable disease; uPR, unconfirmed partial response.

IAG933 response by dose level and NF2/LATS1/LATS2 mutation status

Partial tumour control observed; mutation contribution inconclusive at active dose levels



Inconclusive contribution of NF2/LATS1/LATS2 mutation status to response (low numbers at active doses)

bid, twice daily; CONT, continuous; EHE, epithelioid haemangioendothelioma; INT, intermittent; LATS1/S2, large tumour suppressor kinase 1/2; LOF, loss of function (includes any truncating alteration or homozygous deletion); NF2, neurofibromin 2; NSCLC, non–small cell lung cancer; qd, once daily; VUS, variant of unknown significance (missense or indel); WT, wild-type.

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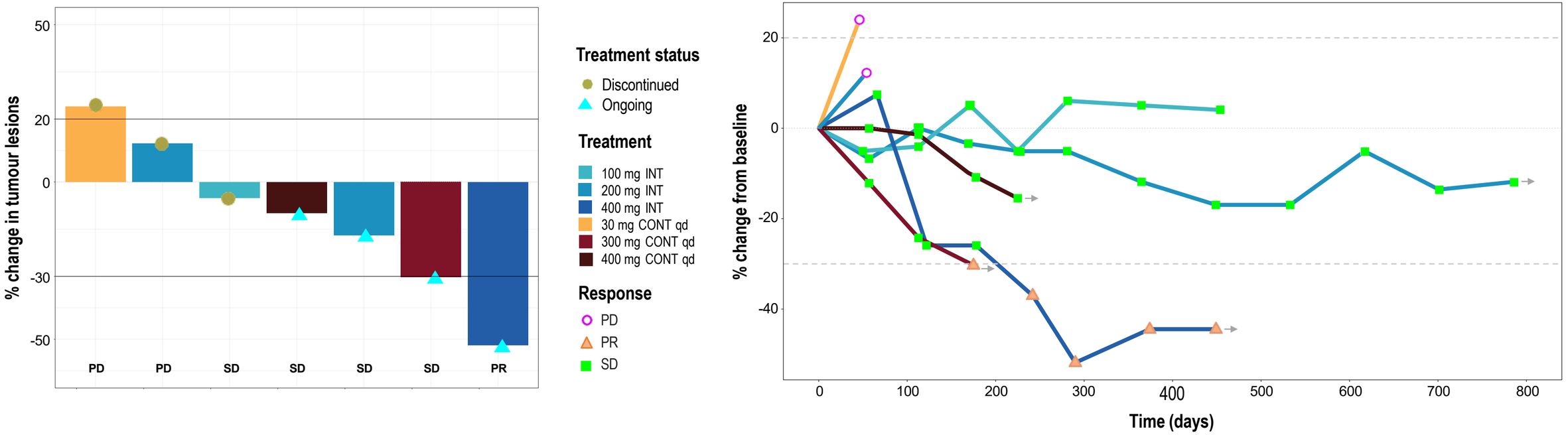
Efficacy with IAG933 in patients with EHE

EHE

- A rare malignant vascular sarcoma subtype with functional YAP-TAZ fusions (90% of WWTR-1-CAMTA1, 10% of YAP1–TFE3)[a]
- Limited treatment options are available for patients with metastatic disease

IAG933 experience in EHE[b]

- 1 cPR and 1 uPR[a] (both ongoing) in young patients with EHE among 9 patients treated[b]
- 3 patients with an SD of >300 days (1 with cPR), with the longest duration of SD being >27 months on the study (ongoing)
- mPFS was not reached
- Best response: 22%[c] ; DCR (cPR+SDs): 55%



[a]Source: Stacchiotti S, et al. *ESMO Open* 2021;6(3):100170; [b]Two patients with clinical progression and no post-baseline RECIST assessment; [c]22% includes uPR in EHE as confirmed by the investigator, awaiting database confirmation.

CAMTA1, calmodulin-binding transcription activator 1; CONT, continuous; cPR, confirmed partial response; DCR, disease control rate; EHE, epithelioid haemangioendothelioma; INT, intermittent; mPFS, median progression-free survival; PD, progressive disease; PR, partial response; qd, once daily; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease; TAZ, transcriptional coactivator with a PDZ-binding motif; TFE3, transcription factor E3; uPR, unconfirmed PR; WT, wild-type; WWTR1, WW domain–containing transcription regulator 1; YAP, yes-associated protein.

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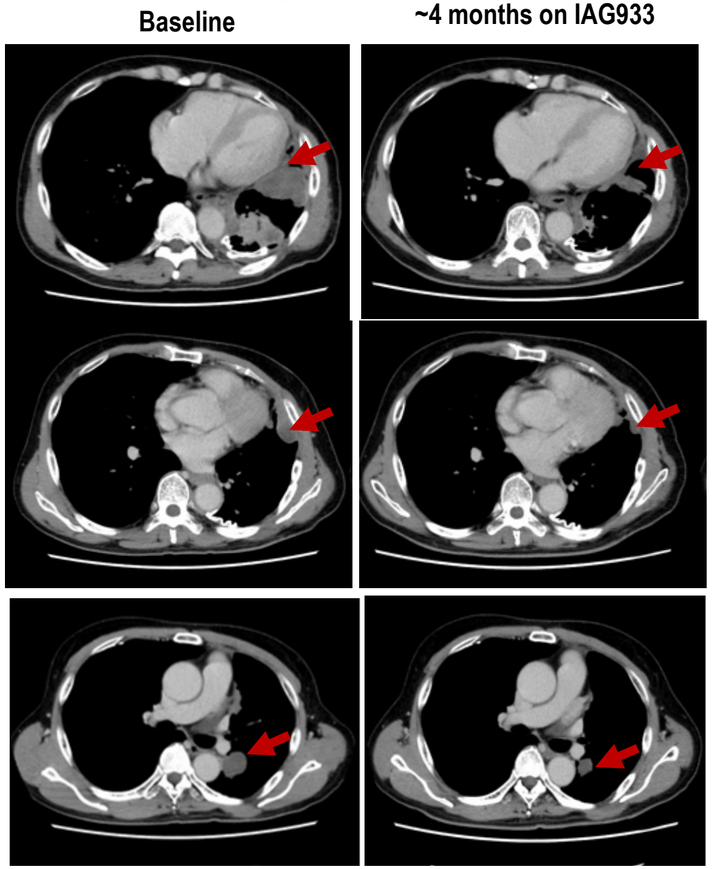
Partial responses observed with IAG933 in multiple indications at weekly doses of ≥420 mg

Tumour type (Histology)	Dose and schedule	Histology	NF2 alteration/ YAP/TAZ fusion	Maximum response
Peritoneal mesothelioma	60 mg qd	Epithelioid	Homozygous deletion[a]	cPR (−48.3%)
Pleural mesothelioma	600 mg INT	Epithelioid	Unknown[b]	cPR (−37.5%)
Pleural mesothelioma	300 mg qd	Epithelioid	Mutation	cPR (−34.4%)
Pleural mesothelioma	300 mg qd	Epithelioid	Unknown[b]	cPR (−42.1%)
Pleural mesothelioma	400 mg qd	Biphasic/mixed	Unknown[b]	cPR (−69.2%)
Pleural mesothelioma	400 mg qd	Epithelioid	WT	cPR (−33.3%)
EHE	400 mg INT	-	YAP/TAZ fusion[c]	cPR (−44.4%)
EHE	300 mg qd	-	YAP/TAZ fusion[c]	uPR (−30.3%)[d]

[a]Result from local testing, reported per investigator communication.
[b]No results from TSO-500, cfDNA testing or local data.
[c]No testing performed. Presence of YAP/TAZ fusion inferred from the prevalence of YAP/TAZ fusion in patients with EHE (Source: Stacchiotti S, et al. *ESMO Open* 2021;6(3):100170).
[d]uPR observed on 1st-post baseline imaging. 2nd-post baseline imaging with continued PR per PI (awaiting database confirmation) and patient is ongoing.

Pleural mesothelioma experience:

- Among 30 patients, 4 had cPR (2 of 4 patients on 400 mg CONT qd and 2 of 26 patients on 300 mg CONT qd); **ORR:** 13.3% across 300/400 mg CONT qd
- Both patients on 400 mg with a PR had a decrease to 300 mg for QTc prolongation (both <4 weeks at 400 mg)
- mPFS at 300 mg CONT qd in patients with pleural mesothelioma: 3.6 months



Courtesy: Dr. Yoshida, NCC (Japan)

Case: *A 61-year-old man with stage IV epithelioid pleural mesothelioma and prior cisplatin/pemetrexed and nivolumab/ipilimumab, with a baseline tumour burden of 140 mm, treated with 300 mg IAG933, achieving PR on C5D1, and a maximum response of −42.1% on C7D1 (cPR)*

C, cycle; cfDNA, cell-free DNA; CONT, continuous; cPR, confirmed partial response; D, day; EHE, epithelioid haemangioendothelioma; INT, intermittent; mPFS, median progression-free survival; ORR, overall response rate; PR, partial response; qd, once daily; TAZ, transcriptional coactivator with a PDZ-binding motif; uPR, unconfirmed PR; WT, wild-type; YAP, yes-associated protein.

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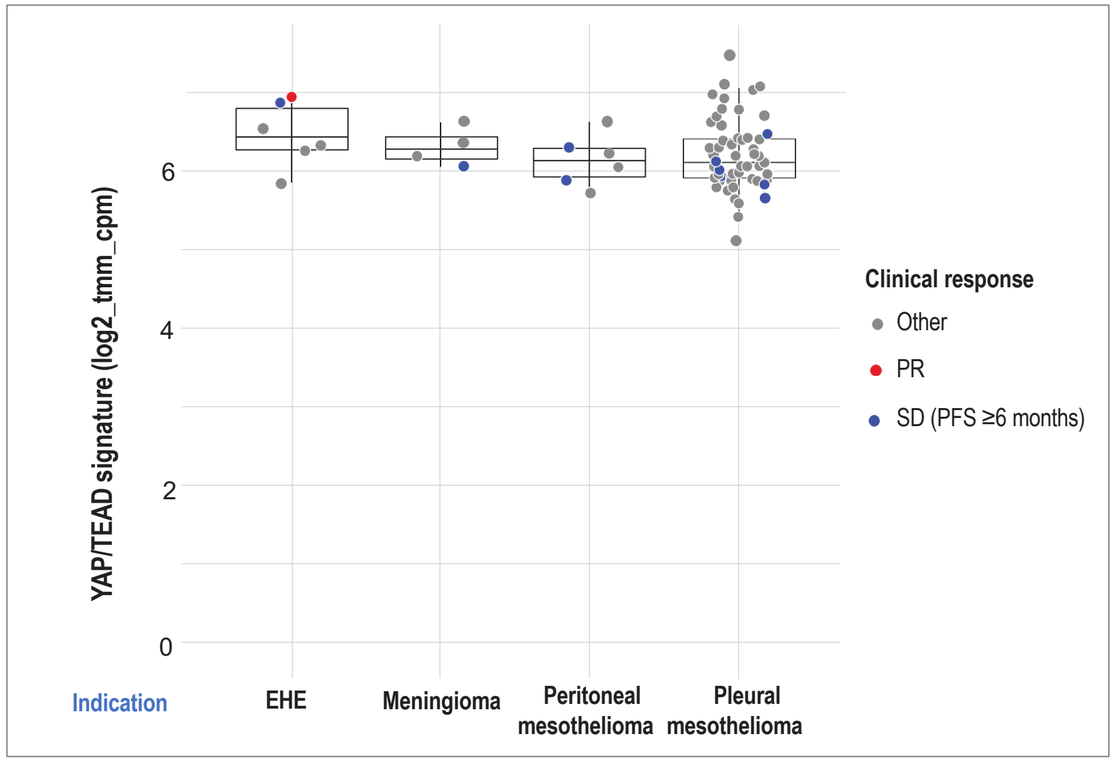
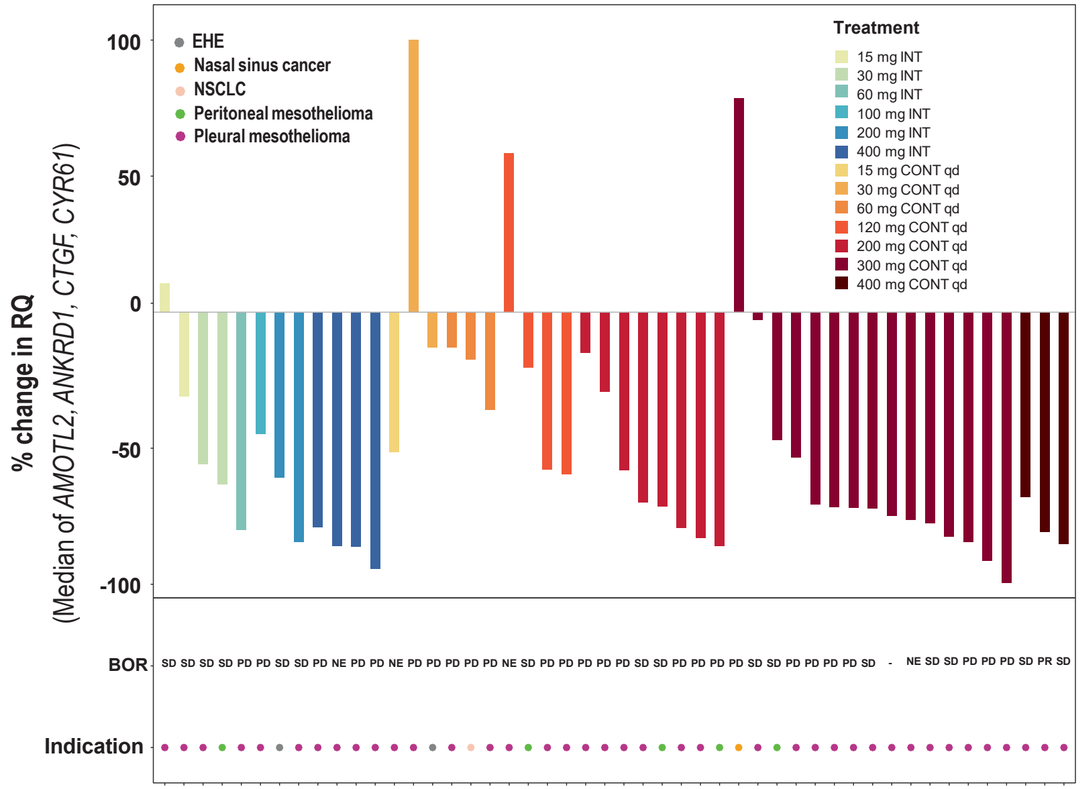
Evaluation of YAP-TEAD target gene expression at baseline and in paired biopsies

YAP–TEAD gene expression signature at baseline (tumour biopsy RNAseq)



Dose-dependent inhibition of TEAD target gene expression



- YAP/TEAD gene expression signature (*Liang et al., 2018*) was measured in baseline tumour biopsies as an indicator of TEAD activity
- EHE tended to show higher YAP signature levels
- Patients with a durable SD (lasting for >6 months) did not have the highest signature levels, and only one PR sample was available (EHE)

- YAP–TAZ/TEAD inhibition was assessed using RT-qPCR assay, measuring the suppression of 4 TEAD target genes in paired biopsies
- Dose-dependent gene inhibition occurred, with a strong pathway suppression at doses of ≥200 mg
- TEAD target gene suppression indicates IAG933 engagement but does not predict the response, consistent with preclinical data

Note: The dynamic range among patients is relatively narrow (~2-fold), consistent with the intent to enrol in indications with a high baseline TEAD activity.

BOR, best overall response; EHE, epithelioid haemangioendothelioma; INT, intermittent; NE, not evaluable; NSCLC, non–small cell lung cancer; PD, pharmacodynamics; PFS, progression-free survival; PR, partial response; RNAseq, RNA sequencing; RQ, relative quantity; RT-qPCR, reverse transcription quantitative real-time polymerase chain reaction; SD, stable disease; TAZ, transcriptional coactivator with a PDZ-binding motif; TEAD, transcriptional enhanced associated domain; YAP, yes-associated protein.

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Summary and conclusions

Safety

- IAG933 was safe and tolerable on multiple schedules, with manageable levels of proteinuria and predominantly grade 1 or grade 2 TRAEs
- While DLTs for QTc prolongation were observed at the highest INT (600 mg) and CONT qd (400 mg) schedules, QTc prolongation was mostly grade 1 and manageable
- Maximum tolerated dose was 300 mg on the CONT qd schedule

PK

- PK demonstrated dose proportionality and a $T_{1/2}$ of 7-9 hours

Activity

- Antitumour activity was observed in patients with mesothelioma, including 5 patients with a cPR in pleural mesothelioma and 1 with a cPR in peritoneal mesothelioma, along with 2 responses in patients with EHE (1 patient with a cPR and 1 patient with an ongoing uPR), as well as multiple patients across indications with a durable clinical benefit
- Active dose range is 200 to 300 mg CONT qd

Biomarkers

- Dose-dependent target gene inhibition was observed from paired biopsies
- Limited power to draw conclusion about the contribution of NF2 mutation status to response at an active dose level

CONT, continuous; cPR, confirmed partial response; DLT, dose-limiting toxicity; EHE, epithelioid haemangioendothelioma; INT, intermittent; NF2, neurofibromin 2; PK, pharmacokinetics; qd, once daily; $T_{1/2}$, half-life; TRAE, treatment-related adverse event; uPR, unconfirmed partial response.

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