Review of Updated Phase 2 Clinical Data of AL101 in Recurrent/Metastatic Adenoid Cystic Carcinoma with Notch mutations

Friday, September 18, 2020

Conference Call Participants

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Disclaimer

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. All statements contained in this presentation that do not relate to matters of historical fact should be considered forward-looking statements, including statements relating to our development of AL101 and AL102, the promise and potential impact of our preclinical or clinical trial data, the timing of and plans to initiate additional clinical trials of AL101 and AL102, the timing and results of any clinical trials or readouts and the sufficiency of cash to fund operations. These forward-looking statements are based on management's current expectations. The words ”may,” “will,” “should,” “expect,” “plan,” “anticipate,” “could,” “intend,” “target,” “project,” “estimate,” “believe,” “predict,” “potential” or “continue” or the negative of these terms or other similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

These statements are neither promises nor guarantees, but involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements, including, but not limited to, the following: the impact of the COVID-19 pandemic on our operations, including our preclinical studies and clinical trials, and the continuity of our business; we have incurred significant losses, are not currently profitable and may never become profitable; our need for additional funding; our cash runway; our limited operating history and the prospects for our future viability; the lengthy, expensive, and uncertain process of clinical drug development, including potential delays in regulatory approval; our requirement to pay significant payments under product candidate licenses; the approach we are taking to discover and develop product candidates and whether it will lead to marketable products; the expense, time-consuming nature and uncertainty of clinical trials; enrollment and retention of patients; potential side effects of our product candidates; our ability to develop or to collaborate with others to develop appropriate diagnostic tests; protection of our proprietary technology and the confidentiality of our trade secrets; potential lawsuits for, or claims of, infringement of third-party intellectual property or challenges to the ownership of our intellectual property; risks associated with international operations; our ability to retain key personnel and to manage our growth; the potential volatility of our common stock; costs and resources of operating as a public company; unfavorable or no analyst research or reports; and securities class action litigation against us.

These and other important factors discussed under the caption "Risk Factors" in our Form S-1 filed with the U.S. Securities and Exchange Commission (SEC) on May 4, 2020 and our other filings with the SEC, including Form 10-Q filed on August 12, 2020, could cause actual results to differ materially from those indicated by the forward-looking statements made in this presentation. Any such forward-looking statements represent management's estimates as of the date of this presentation. New risk factors and uncertainties may emerge from time to time, and it is not possible to predict all risk factors and uncertainties. While we may elect to update such forward-looking statements at some point in the future, except as required by law, we disclaim any obligation to do so, even if subsequent events cause our views to change. Although we believe the expectations reflected in such forward-looking statements are reasonable, we can give no assurance that such expectations will prove to be correct. These forward-looking statements should not be relied upon as representing our views as of any date subsequent to the date of this presentation.

Certain information contained in this presentation relates to or is based on studies, publications, surveys and other data obtained from third-party sources and our own internal estimates and research. While we believe these third-party sources to be reliable as of the date of this presentation, we have not independently verified, and we make no representation as to the adequacy, fairness, accuracy or completeness of any information obtained from third-party sources. In addition, all of the market data included in this presentation involves a number of assumptions and limitations, and there can be no guarantee as to the accuracy or reliability of such assumptions. Neither we nor our affiliates, advisors or representatives makes any representation as to the accuracy or completeness of the data included in this presentation or undertake to update such data after the date of this presentation. Finally, while we believe our own internal research is reliable, such research has not been verified by any independent source.

Welcome

Roni Mamluk, Ph.D.
Founder & Chief Executive Officer

Advancing a Pipeline of Novel Pan-Notch Inhibitors

Product Candidates	Program		Preclinical	Phase 1	Phase 2	Phase 3	Commercial Rights	Upcoming Milestones[1]
	Indication	Target						
AL101 (Intravenous)	R/M ACC	Notch Pathway					ayala pharmaceuticals	Initial data from 6mg cohort in H1'21
	R/M TNBC	Notch Pathway					ayala pharmaceuticals	Dose 1st patient in H2'20
	R/R T-ALL	Notch Pathway					ayala pharmaceuticals	Initiate a Phase 2 trial in H2'21
AL102 (Oral)	Desmoid Tumors	Notch Pathway					ayala pharmaceuticals	Initiate a Phase 2 trial in H1'21
	MM	BCMA					NOVARTIS	Initial clinical data (NVS to report)

1 Anticipated clinical milestones are subject to the impact of COVID-19 on our business

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R/M ACC = Recurring / Metastatic Adenoid Cystic Carcinoma; R/M TNBC = Recurring / Metastatic Triple Negative Breast Cancer; R/R T-ALL = Relapsed / Refractory T-cell Acute Lymphoblastic Leukemia; MM = Multiple Myeloma; BCMA = B-cell Maturation Antigen

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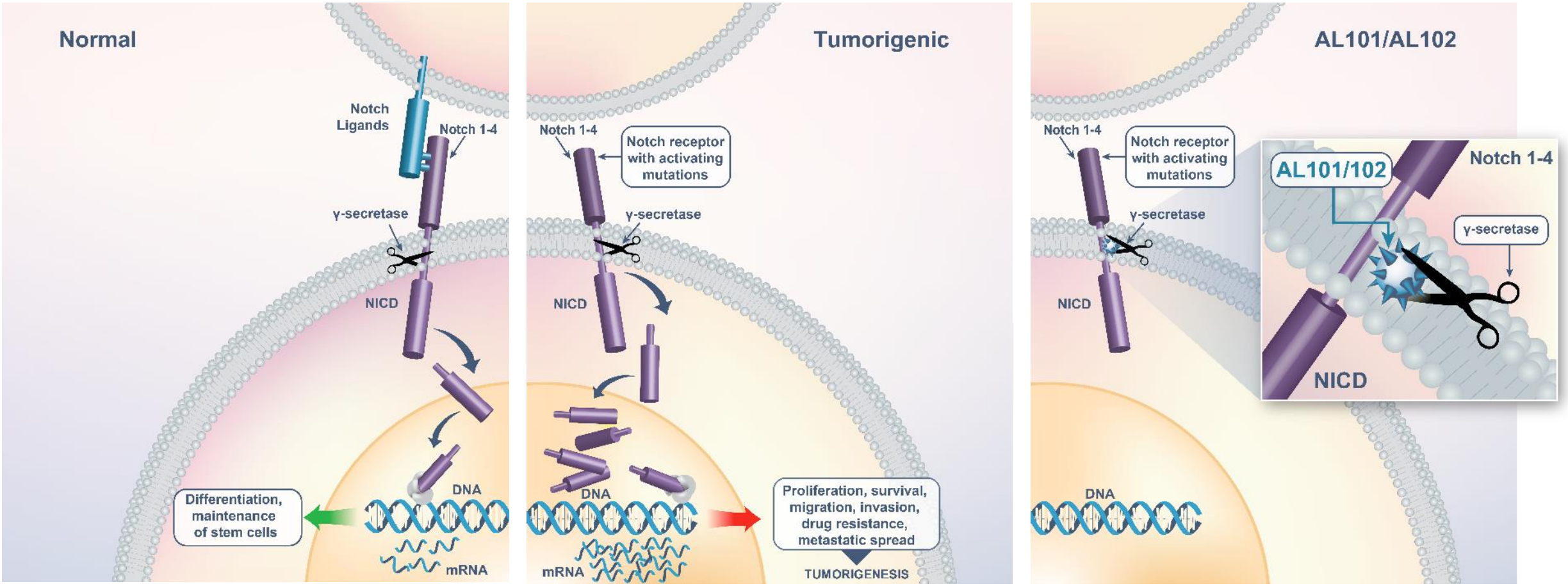
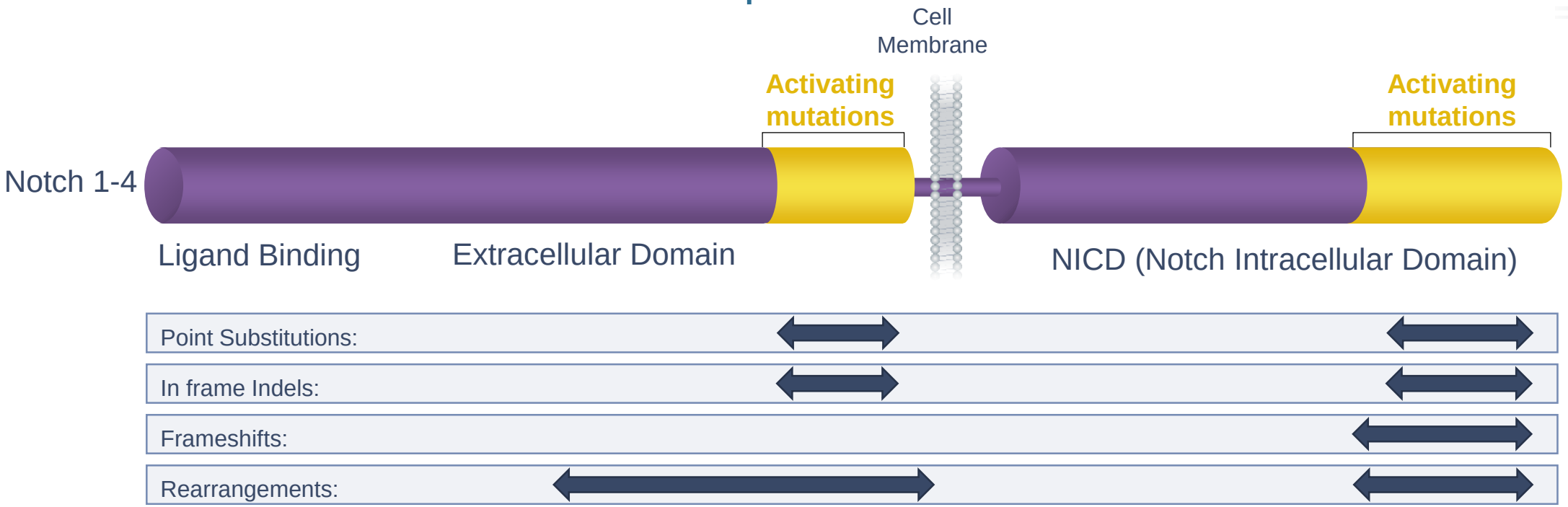
Gary Gordon M.D., Ph.D.
Chief Medical Officer

Notch is Tumorigenic in Defined Cancers and Involved in Cancer Hallmarks



Notch Activating Genetic Alterations Occur in Two Regions that are Similar Across the 4 Notch Receptors



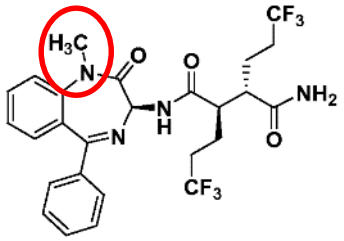
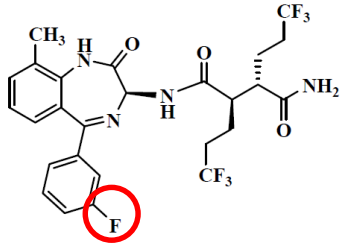
NGS-based Notch Alteration Screen:

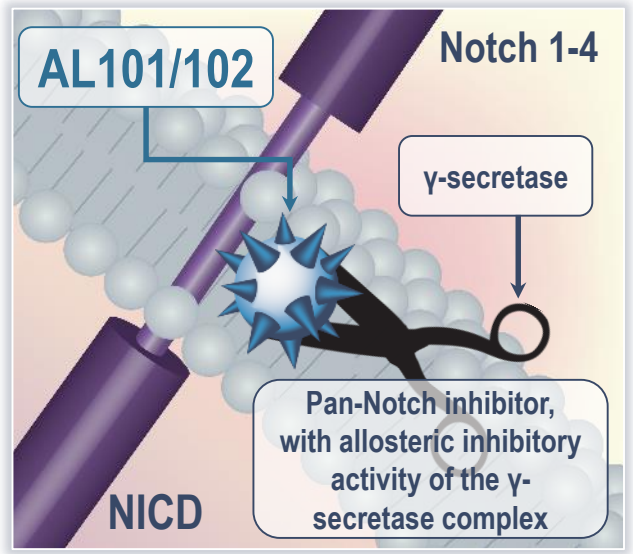
- Commercial assays for mutations
- LDT assays for rearrangements

LDT = Laboratory Developed Test

AL101 & AL102 are Allosteric Small Molecule GSIs

- Gamma secretase consists of 4 proteins that forms an intramembrane cleaving protease complex
- AL101 & AL102 are allosteric inhibitors that interfere with movement of substrates (Notch, BCMA) into the catalytic site

	AL101	AL102
Structure		
MW	556.5	574.5
Route of Administration	IV	PO
PK at Steady State:	ACCURACY[1]	BMS Phase I[2]
T_{max} (h)	1.04h	1-3h
$T_{1/2}$ (h)	64.6h	17-28h



Gaochao Tian et al. 2003; Earl E. Clarke et al 2006; Gertsik et al 2015
1 Ferrarotto et al, ESMO 2019
2 Aung et al, 2018

Alan L. Ho, MD, PhD
Geoffrey Beene Junior Faculty Chair and Medical Oncologist,
Memorial Sloan Kettering Cancer Center

DISCLOSURE INFORMATION

- Advisory Boards/Consulting: Ayala, Kura Oncology, Regeneron, Eisai, TRM Oncology, Sun Pharmaceuticals, Merck, Sanofi Aventis, BMS, Genentech, Genzyme, Novartis, Janssen (travel only), AstraZeneca, Hai-II, Guidepoint Global Advisors (no payment received), Ignyta (travel/lodging/conference fees only), CureVac, Rgenta, Prelude Therapeutics, Klus Pharma, McGivney Global Advisors, Excelexis

- Speaking engagements: Omniprex America LLC, Medscape, Novartis

- Research Funding (Principal Investigator): Ayala, Kura Oncology, AstraZeneca, Astellas, Eisai, Bayer, BMS, Koltan (Celldex) Pharm, Lilly, Genentech/Roche, Pfizer, Novartis, Daiichi Sankyo, Ayala Pharm, Merck, Allos Pharm, Elevar Therapeutics

- Leadership Roles: NCI Head and Neck Steering Committee (member), National Comprehensive Cancer Network (investigator steering committee member, non-melanoma skin guidelines committee member), Alliance for Clinical Trials (Head of the head and neck working group in the Experimental Therapeutics Committee), International Rare Cancer Initiative (co-chair of head/neck section), International Thyroid Oncology Group (board member, correlative science committee chair, member of the protocol committee), MSKCC Investigational New Drug Committee (chair)

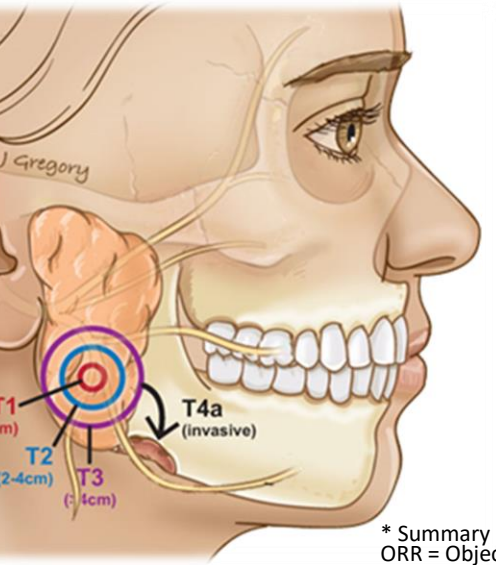
Adenoid Cystic Carcinoma (ACC)

ACC is a rare malignancy of secretory glands

- Mainly salivary gland tumors, but also in eye, trachea, breast, and lungs
- Tend to grow around nerves, spread more quickly and are tougher to take out by surgery

Current Treatment Landscape

- No FDA approved therapy, limited treatment options
- SOC surgery and radiation in early disease and chemo or lenvatinib for advanced disease



Total of 31 Phase 2 clinical trials in ACC*

- None has advanced for approval in ACC
- In 15 of the 31 trials, a 0% ORR was observed
- ORR average ~6%

Treatment modalities tested in ACC	
VEGFR	mTOR
FGFR	BCR-ABL
PDGFR	EGFR
KIT	NFKB
RAF	Chemotherapy
RET	26S Proteasome
PD-1	AKT
	HDAC

Annual US incidence ~3,400[1]

R/M ACC ~1,700[1]

Notch-activating mutations ~20%[2]

* Summary by ACCRF (Adenoid Cystic Carcinoma Research Foundation), as of August 2018
ORR = Objective Response Rate
1 The Nemetz Group Epidemiology analysis December 2019. 2 Company estimates: Frequency of Notch in ACC 2019.

NOTCH1 Alterations in ACC

Ferrarotto, R et. al. J Clin Oncol, 2016

Activating *NOTCH1* mutant ACCs define an aggressive subset:

- Poor recurrence-free and overall survival
- Distinct patterns of metastases (liver/bone/other)

Ho, AS...Morris, LGT. JCI, 2019

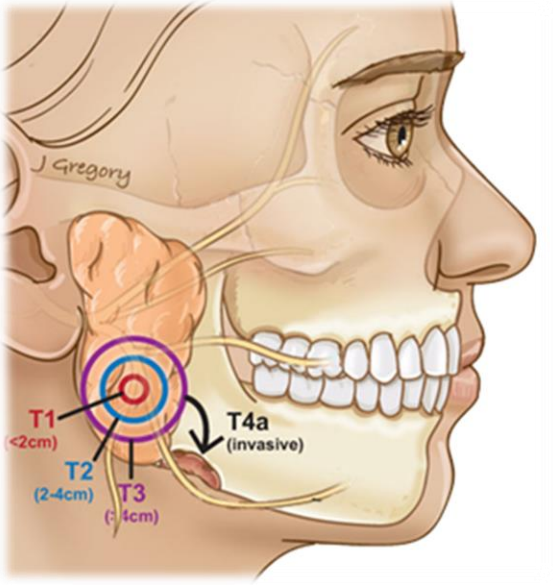
- When comparing 177 primary ACCs to 868 recurrent/metastatic ACCs, *NOTCH1* mutations were dramatically enriched in the latter (8.5% in primaries versus 26.3% in recurrent/metastatic tumors), consistent with a more aggressive disease phenotype.
- *NOTCH1* mutations were associated with significantly poorer survival (OS 55.1 (mutant) vs. 204.5 months (wild-type), $P = 1.10 \times 10^{-4}$).

NOTCH1 mutant ACC is an aggressive variant associated with a poorer prognosis

Quality of Life for ACC

- ACC impact on QOL can range from no symptoms at all to severe/debilitating.
- ACCs can arise anywhere in the upper aerodigestive tract of the head/neck and metastasize distantly, leading to cosmetic and/or physical symptoms

  - Pain
  - Cosmetic deformity (facial droop, plastic reconstruction, orbital exenteration)
  - Cranial nerve dysfunction
  - Dysphagia
  - Trismus
  - Fistulas
  - Dysarthria
  - Loss of voice
  - Shortness of breath,
  - Cough
  - Pneumonia
  - Organ failure
  - Fluid accumulation



VIRTUAL 2020 ESMO congress

ACCURACY a Phase 2 trial of AL101, a selective gamma secretase inhibitor, in subjects with recurrent/metastatic adenoid cystic carcinoma harboring Notch activating mutations

Abstract #4418; Mini Oral #919MO (NCT03691207)

Discussion with Alan L. Ho, MD, PhD

Geoffrey Beene Junior Faculty Chair and Medical Oncologist,
Memorial Sloan Kettering Cancer Center

ACCURACY Study

Schema and Baseline Characteristics[a]

- Recurrent/metastatic (R/M) adenoid cystic carcinoma (ACC)
- Notch-activating mutations
- Disease progression within prior 6 months
- ECOG <2

Cohort 1: AL101 4 mg QW (n=45)

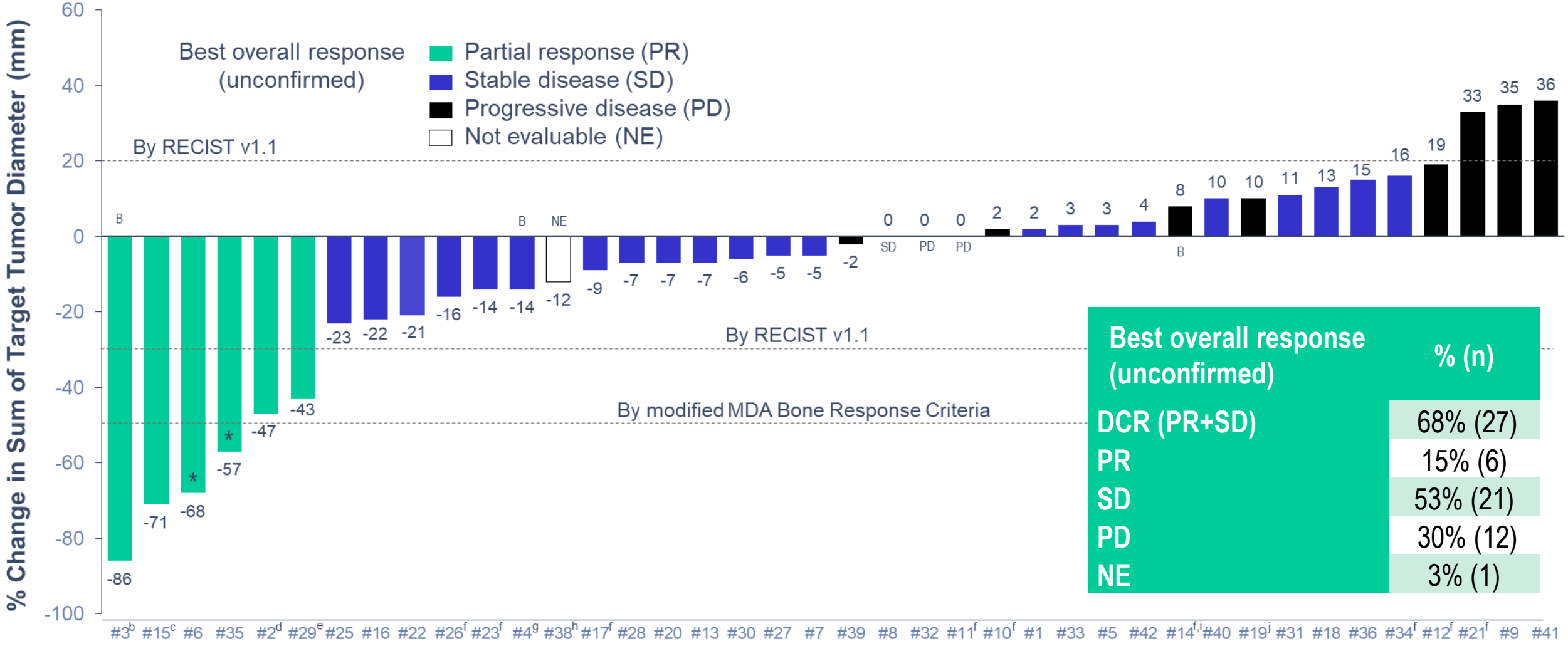
Cohort 2: AL101 6 mg QW (n=42)
Currently enrolling

Primary endpoint – ORR per RECIST v1.1 or modified MDA Bone Response Criteria, by Investigator
Secondary endpoints – DoR, PFS, OS, Safety, PK
Global study: North America, Europe, and Israel

Cohort 1	
Subject Disposition	
Subjects enrolled and treated, n	45
Subjects with at least one post-baseline scan, n	40
Baseline Characteristics (N=45)	
Median age, years (range)	50 (25-79)
Male/female, %	44/56
Prior chemotherapy treatment, %	60
Prior radiation therapy, %	93
Metastatic disease, %[b]	91
Locally recurrent disease, %[b]	27
Treatment naïve and metastatic, %[b]	9
Most common sites of recurrence, %	
Lung	44
Bone	27
Liver	18

[a]Data cutoff: July 30, 2020. [b]Subjects may select more than one category. MDA, MD Anderson.

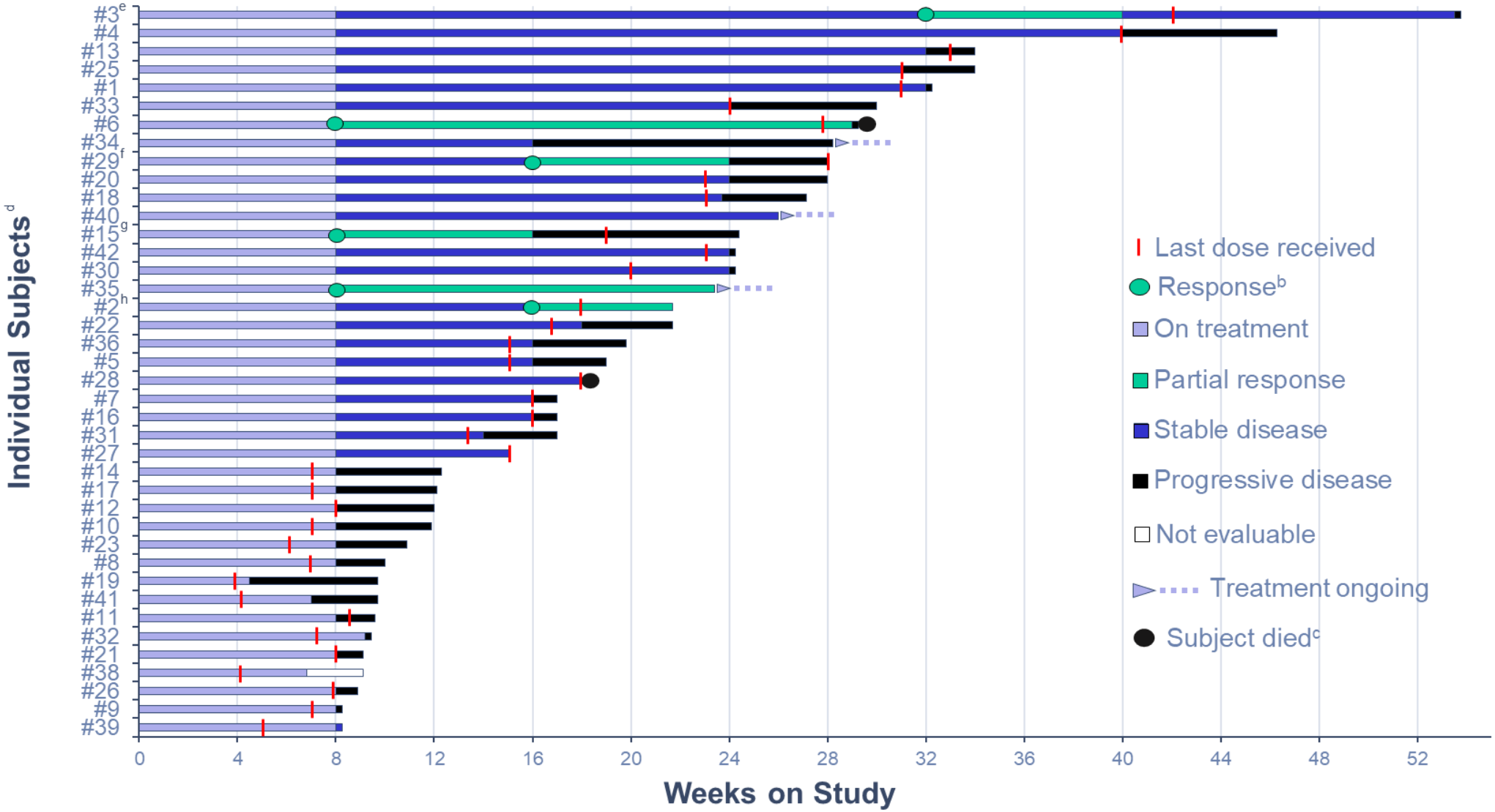
Best Overall Responses by Investigator Review (n=40)[a]



Best overall response (unconfirmed)	% (n)
DCR (PR+SD)	68% (27)
PR	15% (6)
SD	53% (21)
PD	30% (12)
NE	3% (1)

*confirmed responses. B, bone-only disease. [a]Includes efficacy-evaluable subjects only (data cutoff: July 30, 2020); #24 not included because the patient withdrew consent; #37 not included because died before disease assessment. [b]Subject #3, with bone-only disease, had an unconfirmed PR at week 32 by the investigator per modified MDA Bone Response Criteria. [c]Subject #15 had an unconfirmed PR at week 8. [d]Subject #2 had an unconfirmed PR at week 16. [e]Subject #29 had an unconfirmed PR at week 16. [f]These subjects had clinical PD. [g]Subject #4, with bone-only disease, had SD at week 16 by the investigator per modified MDA Bone Response Criteria. [h]Subject #38 was NE because only one scan demonstrating SD was performed at week7. [i]Subject #14, with bone-only disease, had PD at week 8 by the investigator per modified MDA Bone Response Criteria. [j]Subject #19 had radiographic PD.

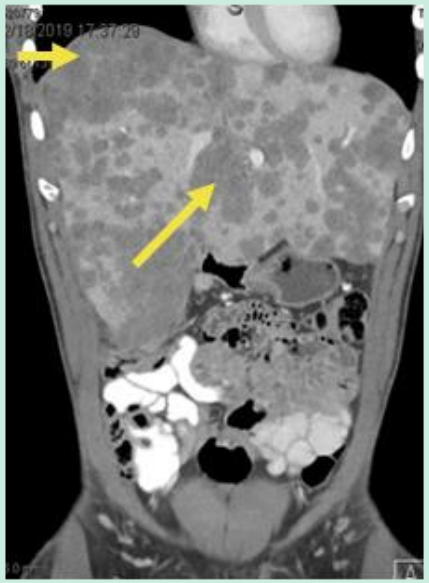
Time on Study and Response by Investigator (n=40)[a]



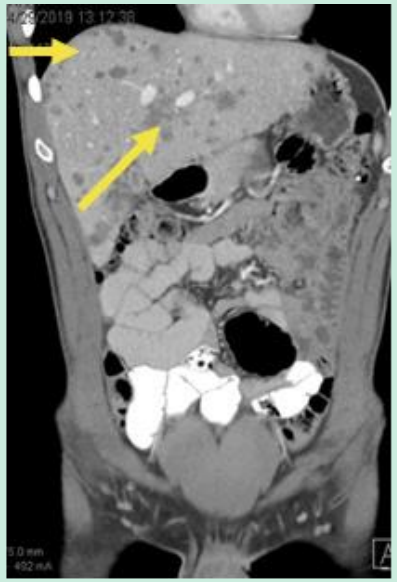
[a]Represents all efficacy-evaluable subjects (Data cutoff: July 30, 2020); #24 not included because the patient withdrew consent; #37 not included because died before disease assessment. [b]Response as assessed by investigator per RECIST v1.1. [c]Only deaths occurring within 30 days after the last dose are shown. [d]Subject #3, Subject #4 and Subject #14 had bone-only disease. [e]Subject #3 had an unconfirmed PR at week 32 by the investigator per modified MDA Bone Response Criteria. [f]Subject #29 had an unconfirmed PR at week 16. [g]Subject #15 had an unconfirmed PR at week 8. [h]Subject #2 had an unconfirmed PR at week 16.

SCANS of Subjects With Partial Response per RECISTv1.1

Subject #6

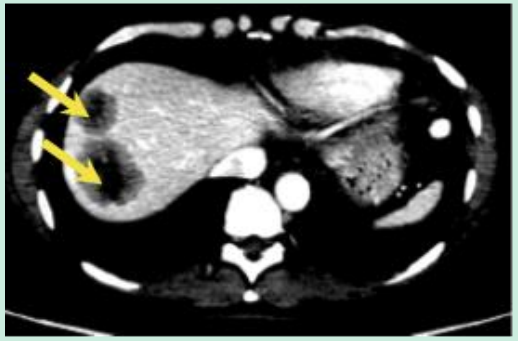


Baseline Scan

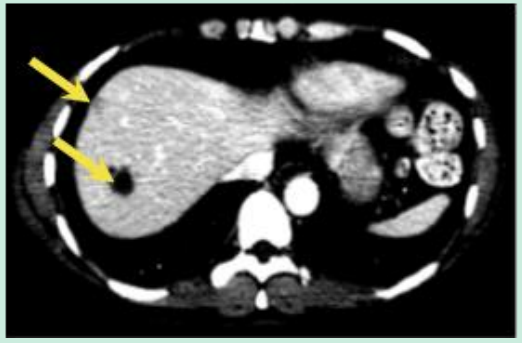


Post-treatment Scan (C3/D1): PR

Subject #15

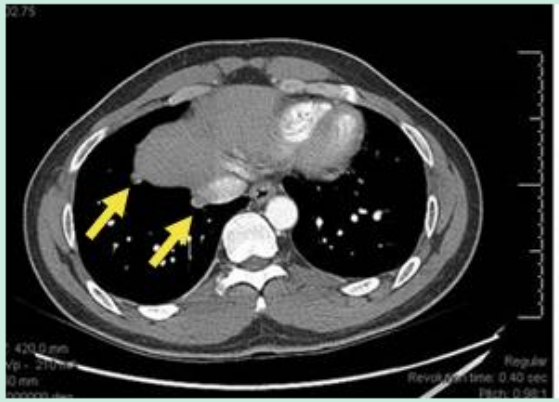


Baseline Scan

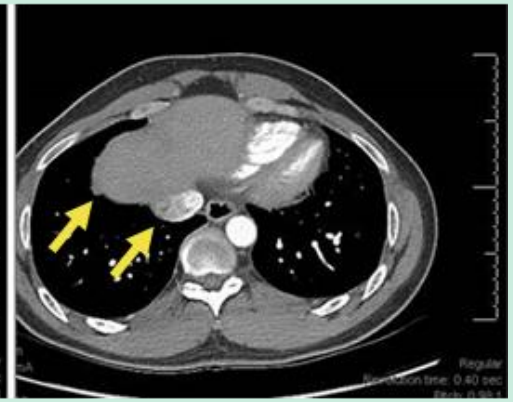


Post-treatment Scan (C3/D1): PR

Subject #29

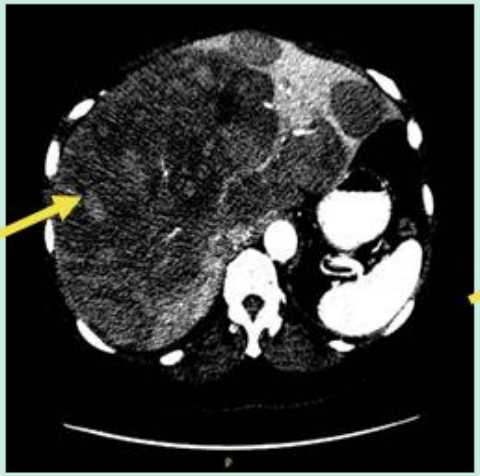


Baseline Scan

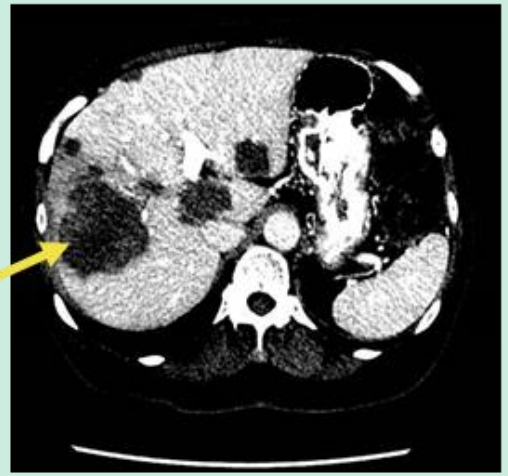


Post-treatment Scan (C3/D8): PR

Subject #35



Baseline Scan



Post-treatment Scan (C3/D1): PR

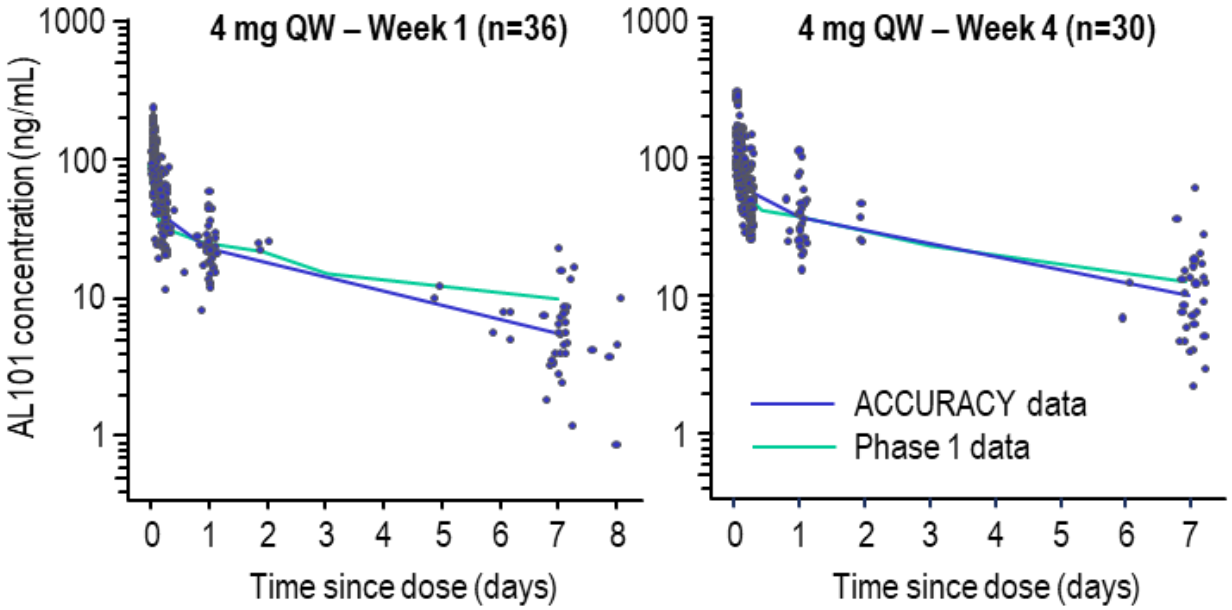
Treatment-Related AEs (TRAEs) Reported in ≥15% of Subjects[a]

	Safety Population (N=45)[b] 4 mg IV QW	
	Any Grade, n (%)	Grade 3/4, n (%)
Any TRAE	**45 (100)**	**9 (20)**
Diarrhea	27 (60)	2 (4)
Fatigue	23 (51)	2 (4)
Nausea	22 (49)	1 (2)
Hypophosphatemia	19 (42)	2 (4)
Cough	12 (27)	0
Vomiting	12 (27)	0
Epistaxis	9 (20)	0
Rash maculo-papular	8 (18)	0
Decreased appetite	7 (16)	1 (2)
Dysgeusia	7 (16)	0

[a]Data cutoff: July 30, 2020. [b]There was 1 subject with a Grade 4 TRAE of hyponatremia and one subject who died due to pneumonia, which was possibly treatment-related.

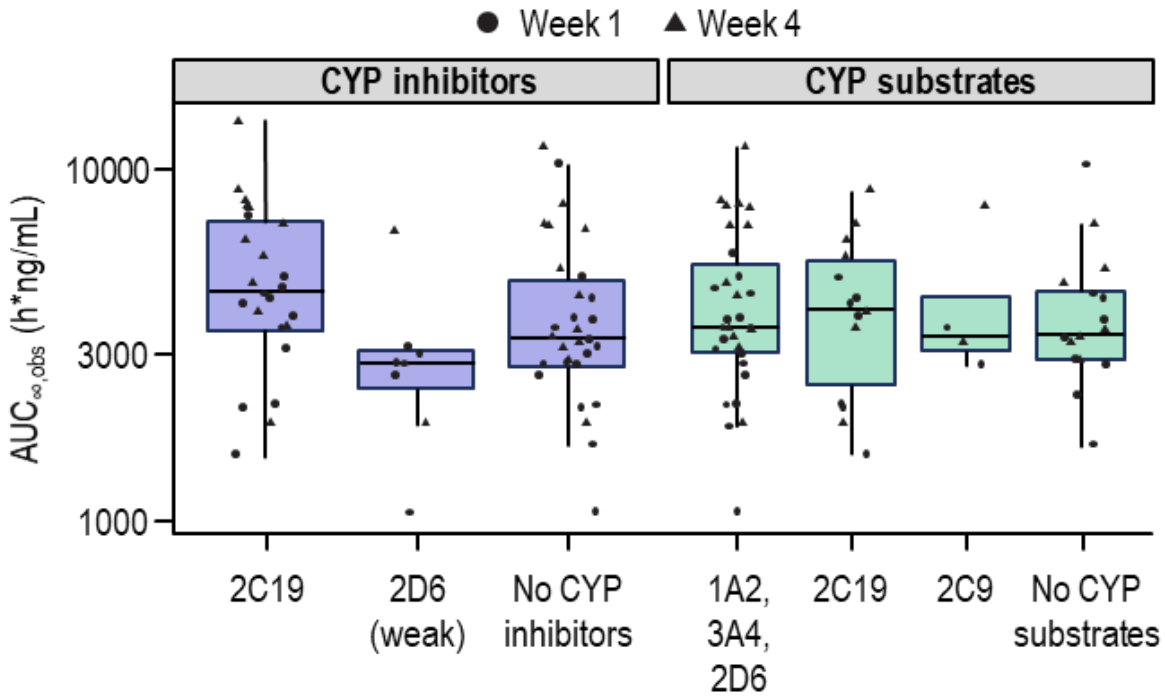
AL101 Pharmacokinetics[a]

AL101 plasma concentration over time[b]



- Plasma PK concentration-time curves for 36 patients on 4 mg dose are equivalent to the PK profile from the earlier phase 1 study[1] (n=43 at 4 mg)

Effect of CYP inhibitors and substrates on AL101 PK[c]



- Analysis of PK AUC with concomitant medications does not indicate a significant effect of CYP inhibitors or substrates on AL101 exposure

[a]Data cutoff: July 30, 2020. [b]Dots: individual patient data; lines: geometric means. [c]Box plots represent median, 25/75 percentile, and 2/98 percentile; groups with >1 patient represented are shown in the figure.

1. El-Khoueiry AB, et al. *J Clin Oncol*. 2018;36(Suppl 15):Abstract 2515.

Conclusions and Observations

- The aggressiveness of *NOTCH* mutant ACC is distinct from *NOTCH* WT disease, representing a distinct biologic and clinical entity.
- Therefore, historical ACC trial data may not be a relevant reference, as the NOTCH mutant population was not prospectively characterized and analyzed.
- AL101 can induce dramatic tumor regressions in this aggressive disease population, validating *NOTCH* mutations are oncogenic drivers in ACC.
- 40% of the subjects (16 out of 40) were on study for at least 24 weeks (or 6 months) or are still on drug not having reached 24 weeks. This included 2 subjects treated beyond progression.
- May be a promising clinical signal given the disease aggressiveness in this patient population.
- The AE profile is in keeping with known toxicities of this class and were manageable.
- PK analysis suggests that higher doses may optimize the therapeutic window and enhance therapeutic efficacy.

Acknowledgements

- We gratefully acknowledge the patients who participated and their families
- We also thank ACCURACY investigators and the clinical study teams
- The ACCURACY trial is sponsored by Ayala Pharmaceuticals

- Coauthors include: Renata Ferrarotto,[1] Lori J. Wirth,[2] Jameel Muzaffar,[3] Cristina P. Rodriguez,[4] Bing Xia,[5] Cesar A. Perez,[6] Daniel W. Bowles,[7] Eric Winquist,[8] Sebastien J. Hotte,[9] Robert Metcalf,[10] Caroline Even,[11] Gary B. Gordon[12], Gilad Gordon,[13] and Alan L. Ho[14]

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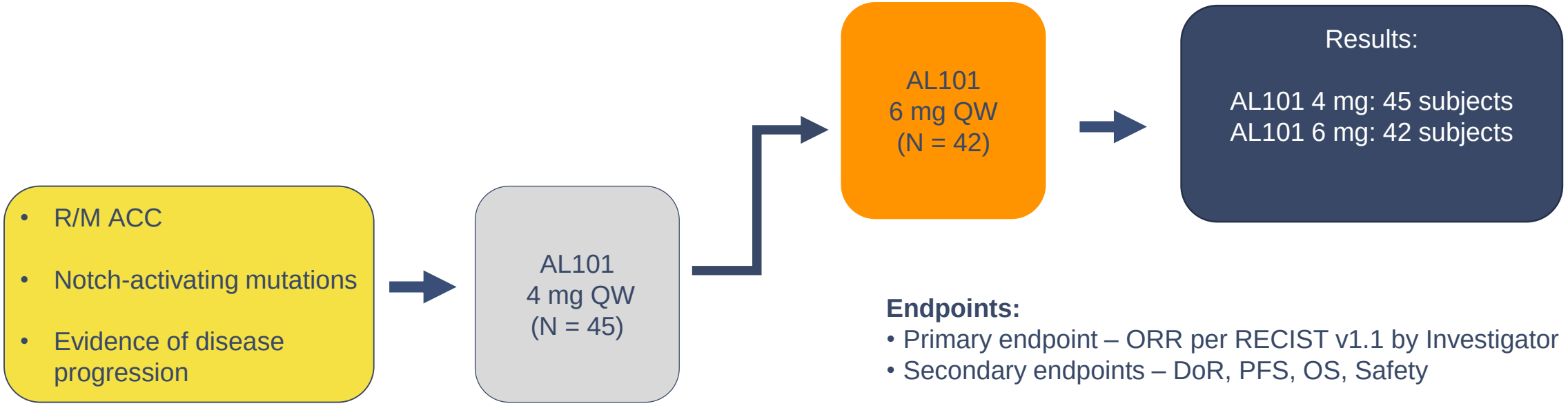
Roni Mamluk, Ph.D.
Founder & Chief Executive Officer

Ongoing Phase 2 ACCURACY Trial in R/M ACC with Notch-activating Mutations



Endpoints:
- Primary endpoint – ORR per RECIST v1.1 by Investigator
- Secondary endpoints – DoR, PFS, OS, Safety

Global Study with Sites in:
- North America
- Europe
- Israel

R/M = Recurring / Metastatic; ORR = objective response rate; DoR = duration of response; PFS = progression-free survival; OS = overall survival; QW = once weekly

Upcoming Potential Milestones[1]

- H2 20 – Dose 1st patient in Phase 2 clinical trial in R/M TNBC
- H1 21 – Initiate Phase 2 clinical trial in Desmoid
- H1 21 – Initial data from 6mg cohort of Phase 2 ACCURACY study in R/M ACC
- H2 21 – Initiate Phase 2 clinical trial in R/R T-ALL

1 Anticipated clinical milestones are subject to the impact of COVID-19 on our business

Questions & Answers

Thank you.

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