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Targeting cancer, differently.

Susan M. Molineaux, Ph.D. | Founder, President & Chief Executive Officer

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Calithera Today

- Core expertise in oncology, discovering and developing novel small molecule enzyme inhibitors
  - Primary focus is on precision oncology
  - Nimble and well-versed in conducting biomarker-driven early and late-stage clinical trials
- Recent addition of two mature mid-stage clinical assets to our pipeline
  - With this acquisition from Takeda Pharmaceuticals, we fully own all development and commercial rights
  - We have developed a new biomarker-driven clinical strategy for both compounds
  - Potential for rapid approval paths in genetically-defined patient populations
- Discovery engine creating a preclinical pipeline of synthetic lethal targets
  - Discovery of novel series of VPS4 inhibitors will be presented at AACR
- Experienced leadership team across a fully-integrated biopharmaceutical company

Strong Management

Experienced Leadership

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Founder, President & Chief Executive Officer

PROTEOLIX rigel MERCK

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New Clinical and Preclinical Pipeline

Mivavotinib

SYK inhibitor

Biomarker-defined clinical activity in ABC DLBCL

Ph 2A/2B trial in ABC DLBCL initiating in 1H22

Ph2A single agent data expected by 1Q23

Sapanisertib

mTORC1/2 inhibitor

Biomarker-defined clinical activity in NRF2m sqNSCLC

Ph 2A/2B trial in NRF2m sqNSCLC initiating in 1H22

Ph2A single agent data expected by 1Q23

Synthetic Lethality

VPS4A/VPS4B (ATPases)

Preclinical program: paralogs

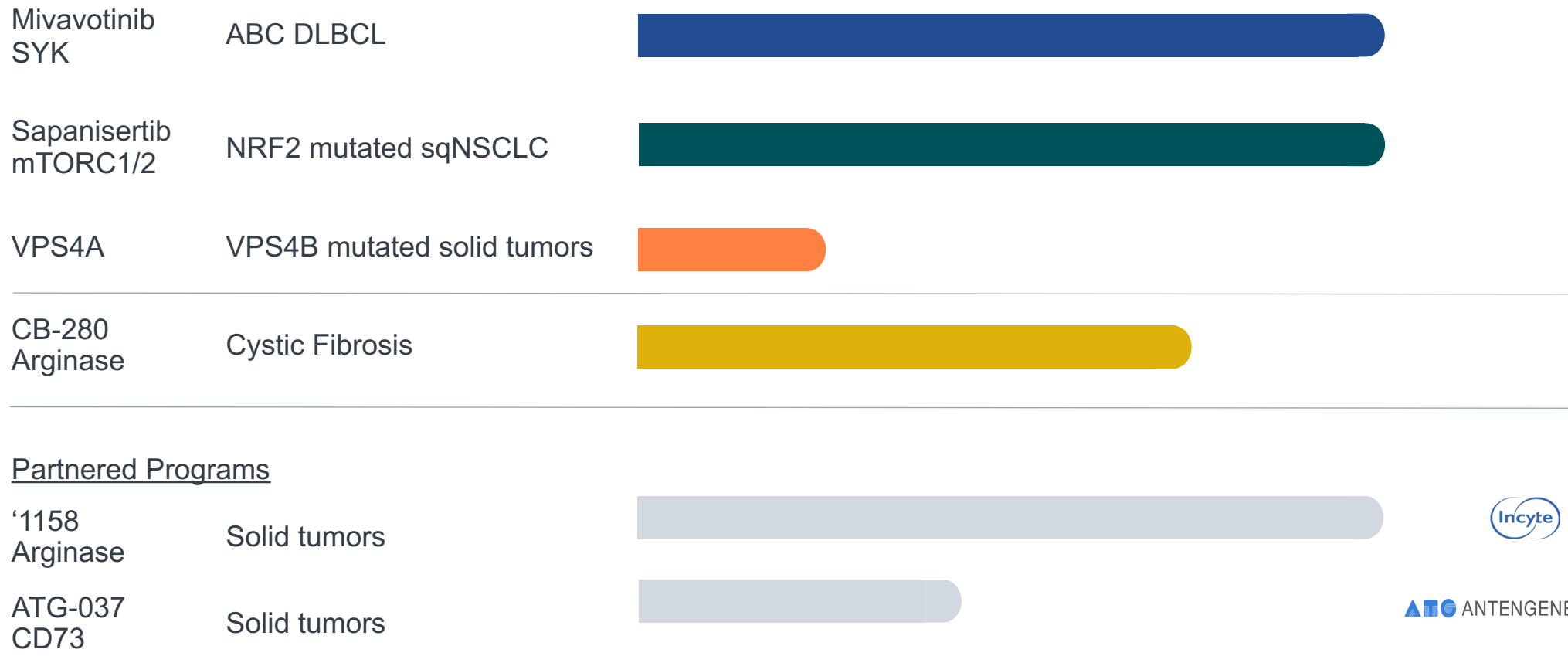
Inhibitor to target tumors with one deleted paralog

NGS biomarker defined

Potential for large market

Calithera Pipeline: Focus on Precision Oncology

Program Target	Indication	DISCOVERY	PRE-IND	PHASE 1	PHASE 2	PHASE 3
Mivavotinib SYK	ABC DLBCL					
Sapanisertib mTORC1/2	NRF2 mutated sqNSCLC					
VPS4A	VPS4B mutated solid tumors					
CB-280 Arginase	Cystic Fibrosis					
Partnered Programs						
‘1158 Arginase	Solid tumors					
ATG-037 CD73	Solid tumors					



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SYK inhibitor for NHL

Mivavotinib

Mivavotinib Overview

SYK Inhibitor Entering a Phase 2 Trial in Diffuse Large B-Cell Lymphoma (DLBCL)

- In NHL trials mivavotinib was active, with durable single agent responses in DLBCL[1]
- Our initial development is in ABC DLBCL where BCR signaling and SYK activation are central drivers of tumor growth, and mivavotinib is most active
- ~50%[2,3] of ABC DLBCL have MYD88 and/or CD79b mutations that hyperactivate SYK and are predicted to have enhanced sensitivity to mivavotinib
- Fast-to-market opportunity in a biomarker-defined DLBCL population
- Biomarker-specific clinical data expected by 1Q23

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[1]Gordon, Clin Cancer Res 2020;26:3546-56.
C34001 and C34004 CSRs (Unpublished data on file)
[2]Schmitz, N Engl J Med 2018;378:1396-407
[3]Wilson, Cancer Cell 2021;39:1-11

Mivavotinib has Durable Single Agent Responses in R/R DLBCL

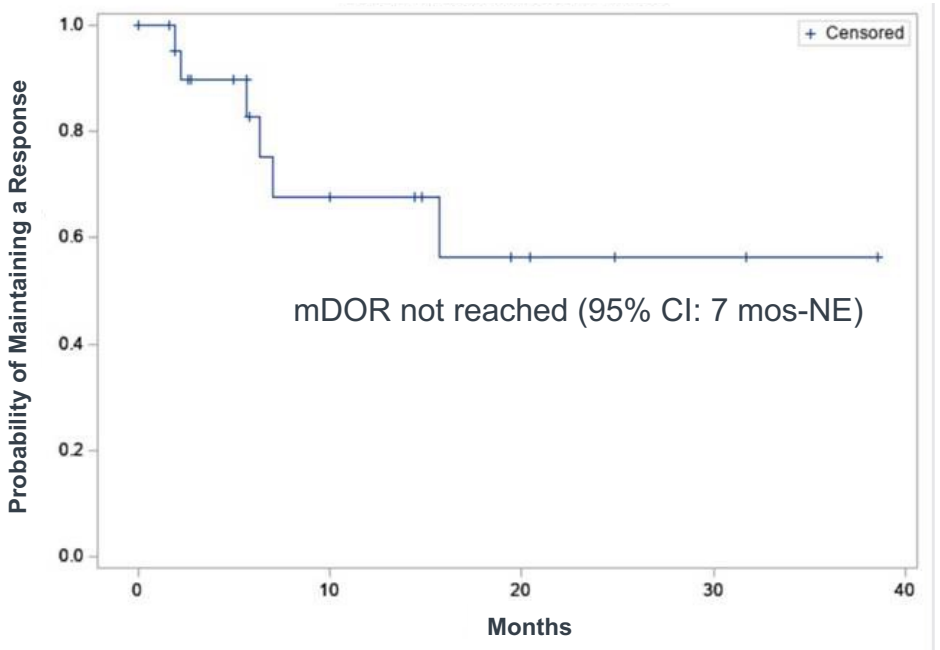
- Mivavotinib is an orally dosed, potent and selective SYK kinase inhibitor
  - IP protection through 2036 US/2035 EU assuming full 5-year patent term extension
- In NHL trials[1], mivavotinib had impressive single agent activity in late stage DLBCL patients
- Responses were durable over several months, with mDOR not reached

Response Rate in DLBCL

Pts	N*	CR	ORR
R/R DLBCL	81	16% (13/81)	33% (27/81)

*Mivavotinib 100 mg QD
Response evaluable population

Duration of Response



[1] Unpublished data on file (studies C34001 and C34004)

Mivavotinib is Differentiated from Other SYK Inhibitors

Higher clinical activity could be due to higher tissue penetration and duration of target engagement

Mivavotinib has higher response rates in DLBCL

SYK Inhibitor	ORR
Mivavotinib[1]	33% (27/81)*
Entosplentinib[2]	0% (0/43)**
Fostamatinib[3]	3% (2/68)**
Cerdulatinib[4]	8% (1/12)**

*Response evaluable, 100 mg QD
**ITT

Mivavotinib achieves higher tissue and tumor exposure

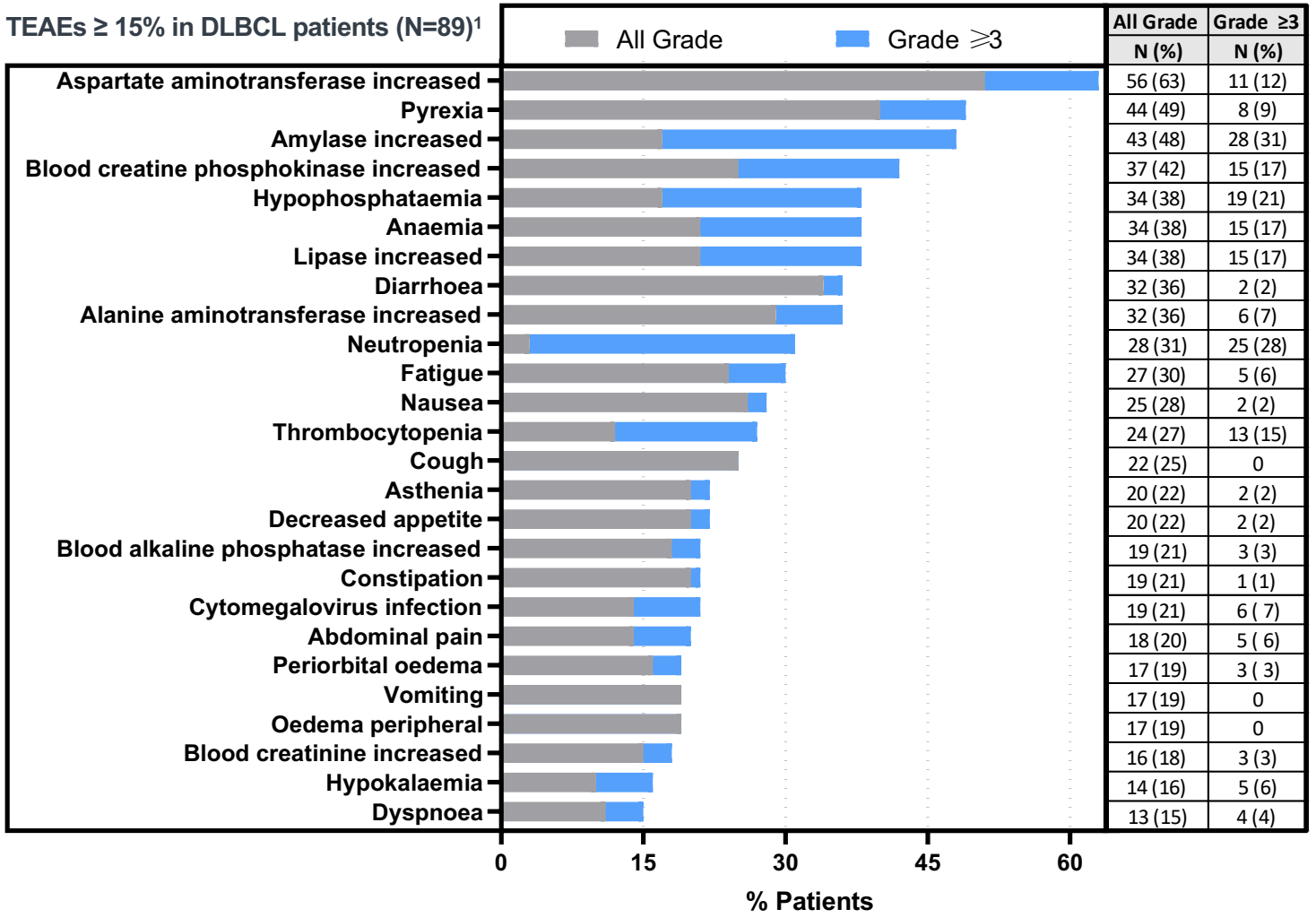
Assay	Species	Mivavotinib[5]	Entospletinib
Vol of Distribution (L/kg)	Rat	9.5	0.5[6]
	Dog	6.7	1.4[6]
Tumor/Plasma AUC Ratio	Mouse	3.6*	-
Protein Binding	Human	54.9%	97.1%[6]
Plasma Half-Life	Human	38 hrs	9-15 hrs[7]

*Plasma and tumor concentrations of mivavotinib following oral dosing in MV411 tumors

[1]Unpublished data on file (studies C34001 and C34004)
[2]Burke, Clin Lymphoma, Myeloma & Leukemia 2018;18:e327-e331.
[3]Flinn, Eur J Cancer 2016;54:11-7
[4]Coffey, Clin Cancer Res 2019;25:1174-84.
[5] Unpublished data on file
[6]Currie et al, J of Med Chem 2014; 57: 3856-73
[7]Ramanathan Clin Drug Investig 2017 37:195-205

Safety Profile of Mivavotinib in DLBCL is Favorable For Development as Monotherapy or in Combination with Other Drugs

- >300 patients with heme malignancies treated with mivavotinib
- Favorable safety profile
- Most common AEs were asymptomatic and reversible laboratory abnormalities
- Mivavotinib is combinable with bendamustine-rituximab, ibrutinib[2], and R-CHOP[3]



	All Grade N (%)	Grade ≥3 N (%)
Aspartate aminotransferase increased	56 (63)	11 (12)
Pyrexia	44 (49)	8 (9)
Amylase increased	43 (48)	28 (31)
Blood creatine phosphokinase increased	37 (42)	15 (17)
Hypophosphataemia	34 (38)	19 (21)
Anaemia	34 (38)	15 (17)
Lipase increased	34 (38)	15 (17)
Diarrhoea	32 (36)	2 (2)
Alanine aminotransferase increased	32 (36)	6 (7)
Neutropenia	28 (31)	25 (28)
Fatigue	27 (30)	5 (6)
Nausea	25 (28)	2 (2)
Thrombocytopenia	24 (27)	13 (15)
Cough	22 (25)	0
Asthenia	20 (22)	2 (2)
Decreased appetite	20 (22)	2 (2)
Blood alkaline phosphatase increased	19 (21)	3 (3)
Constipation	19 (21)	1 (1)
Cytomegalovirus infection	19 (21)	6 (7)
Abdominal pain	18 (20)	5 (6)
Periorbital oedema	17 (19)	3 (3)
Vomiting	17 (19)	0
Oedema peripheral	17 (19)	0
Blood creatinine increased	16 (18)	3 (3)
Hypokalaemia	14 (16)	5 (6)
Dyspnoea	13 (15)	4 (4)

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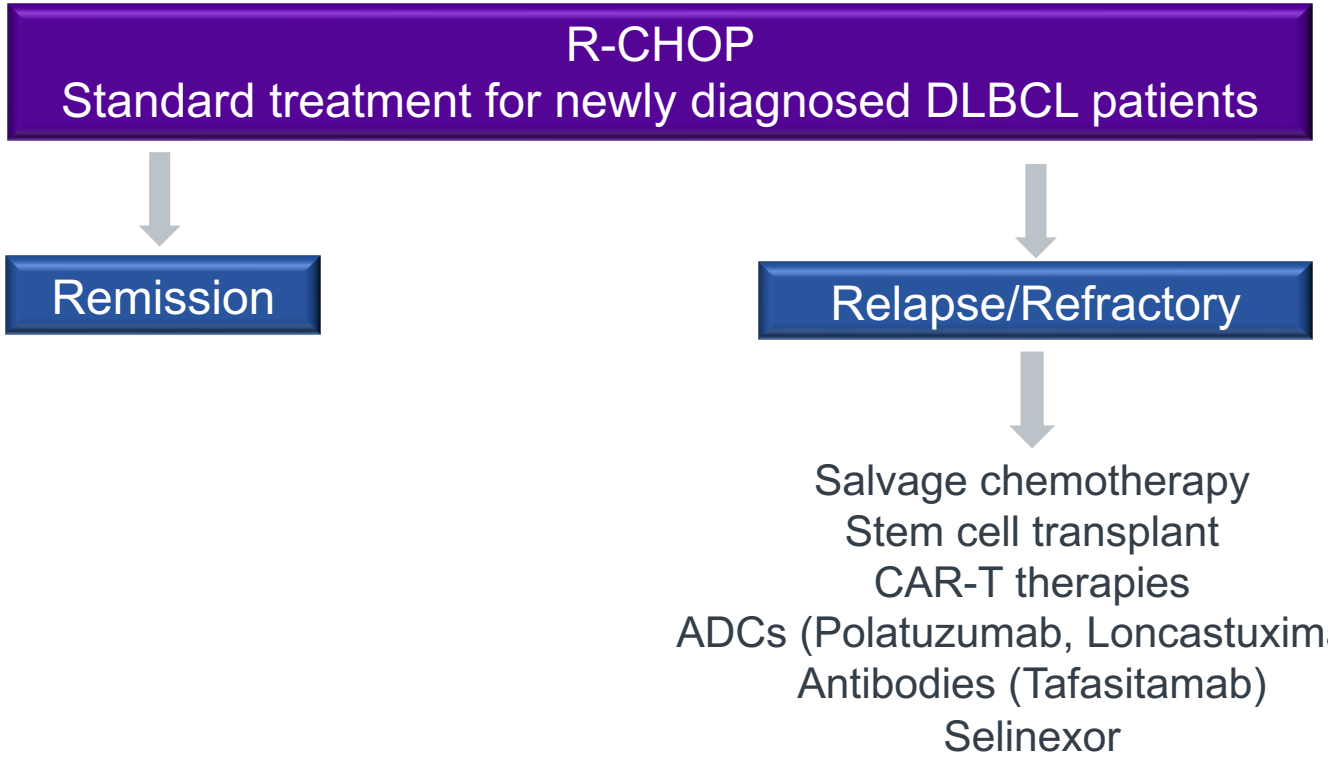
[1] Unpublished data on file (study C34001 study)
[2]Assouline, EHA Poster 2018
[3]Karmali, ASH Poster 2021

Current DLBCL Treatment Landscape

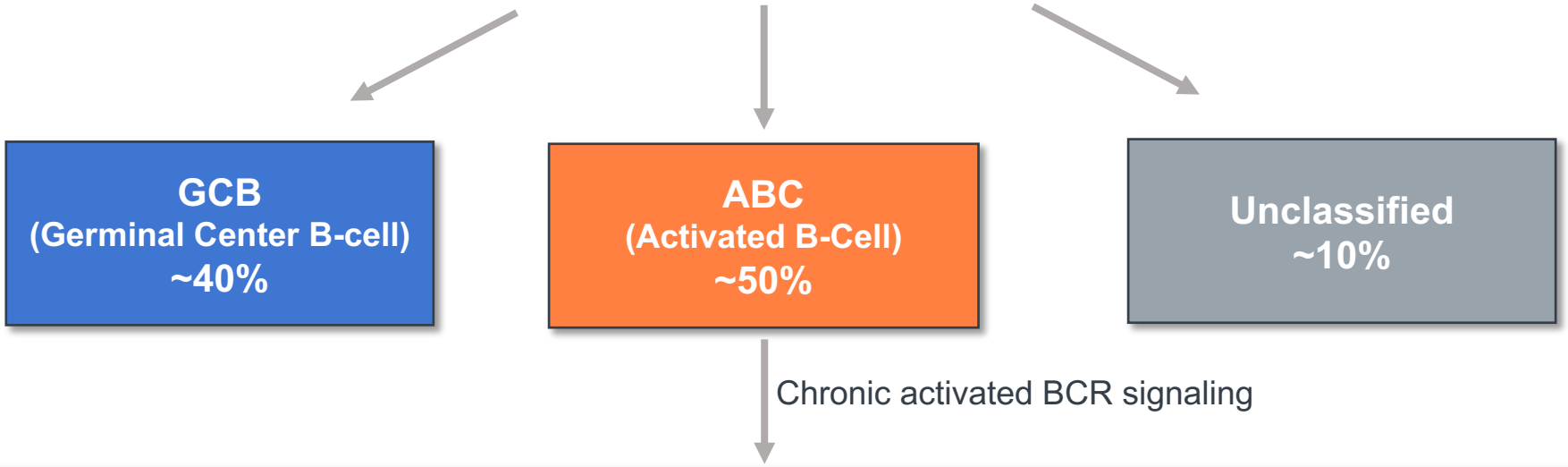


- *High unmet need remains for patients who are ineligible for, or relapse after, CAR-T or transplant*
- *Currently no defined patient selection strategies to optimize therapy for patients with R/R DLBCL*
- *A fully oral regimen with enriched efficacy in a biomarker-defined subset of DLBCL meets a key unmet need*

DLBCL Disease Characteristics

DLBCL is the most common form of lymphoma, representing ~30% of all NHL diagnoses[1,2]
~24,000 people diagnosed in the US each year, with ~60% 5-year survival[1,2,3]

DLBCL treatments are the same for all patients, despite the fact that it is a biologically heterogeneous disease[4]



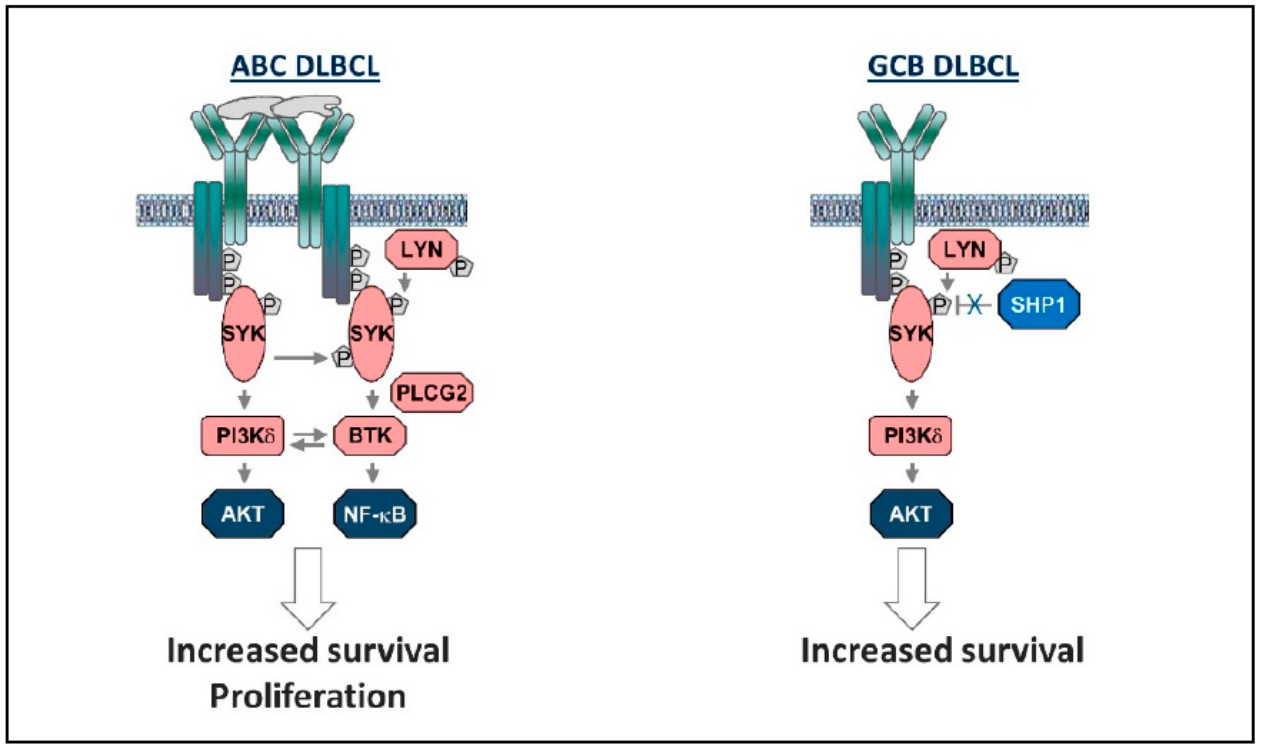
ABC patients have a poorer prognosis

- *Fewer curative responses to R-CHOP and shorter OS[4,5]*
- *Currently no approved treatments specific for ABC patients*

[1]American Cancer Society. *Cancer Facts & Figures 2022*. Atlanta, Ga: American Cancer Society; 2022. https://www.cancer.org/cancer/non-hodgkin-lymphoma/about/key-statistics.html#references
[2]NCCN, B-Cell Lymphomas; April 2021 https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf
[3]https://seer.cancer.gov/statfacts/html/dlbcl.html
[4]Mareschal, Haematologica 2011;96:1888-90.
[5]Schmitz, N Engl J Med 2018;378:1396-407

SYK Controls Central Activation Pathways in ABC DLBCL

- The ABC DLBCL subgroup is defined by chronic activation of the BCR signaling pathway
- In ABC DLBCL, SYK activates NF-kb and PI3K pathways, driving both proliferation and survival
- In contrast, in GCB DLBCL SYK activates the PI3K pathway
- Pathway biology predicts SYK inhibitors to be active in both ABC and GCB, with higher activity in ABC



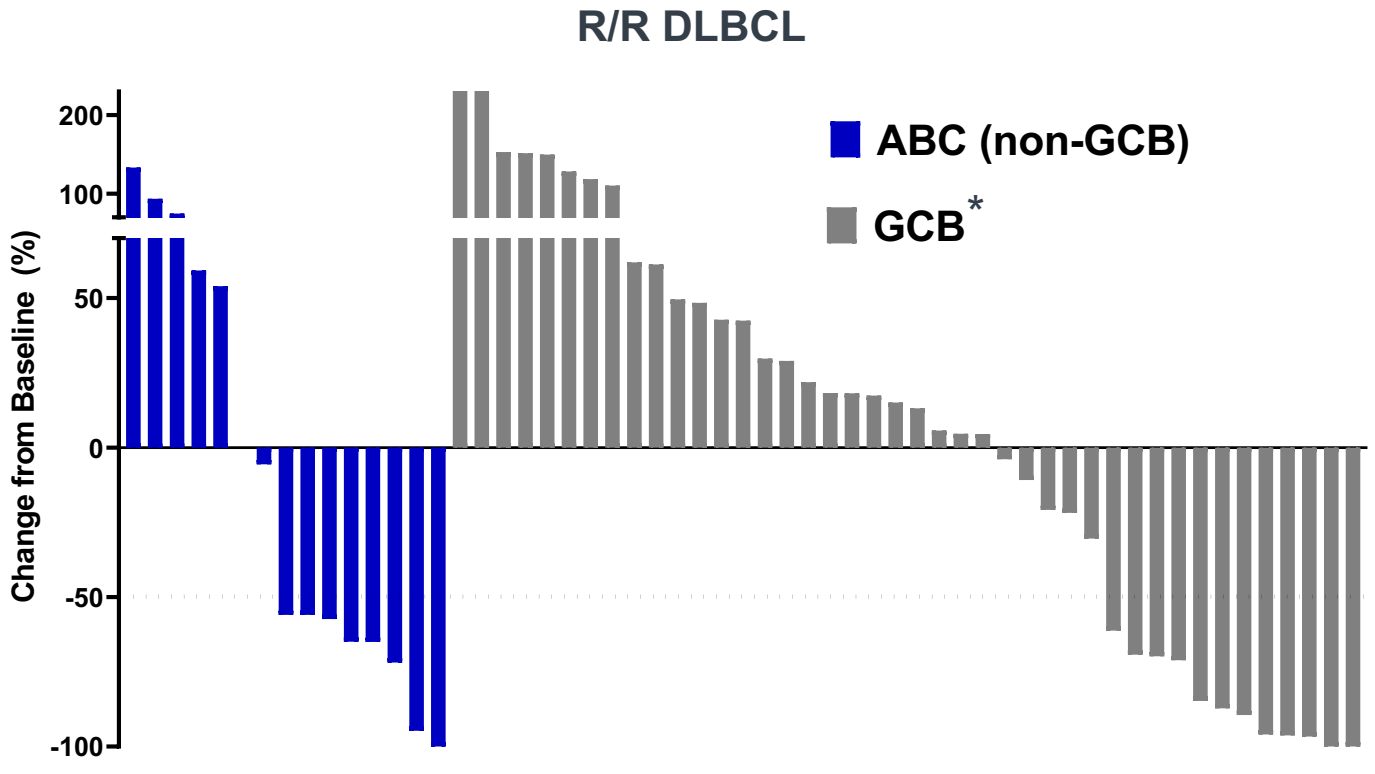
Efremov, Cancers 2020;12:1396-1434.

Mivavotinib Activity is Highest in ABC DLBCL

Retrospective analysis of ORR by cell of origin shows enriched activity in ABC patients

Cell of Origin	N*	ORR
ABC (non-GCB)	15	53%
GCB	45	22%

*Response evaluable population
Patients of unknown cell-of-origin are excluded



*3 pts with PD as best response not graphed (target lesions not recorded)

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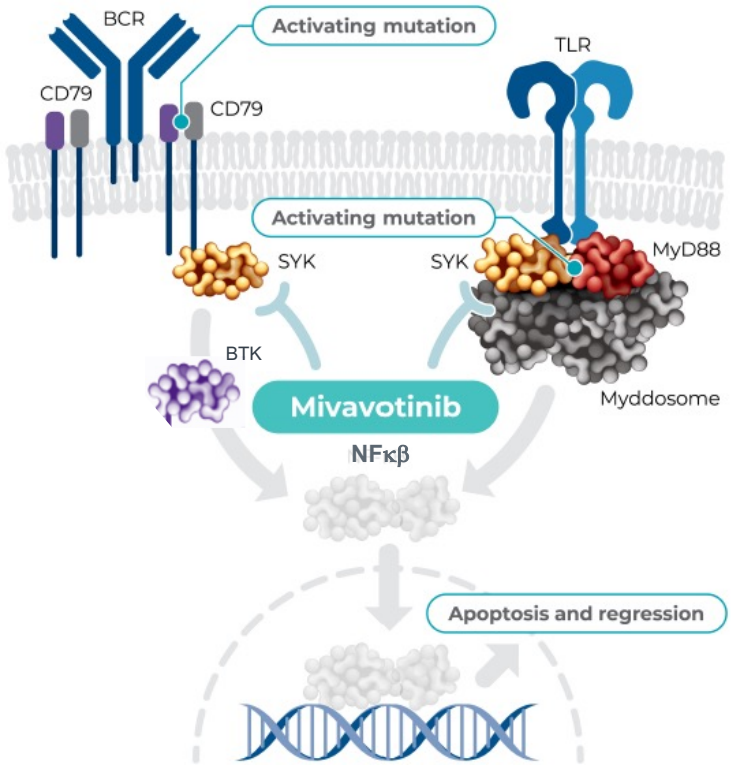
MYD88 and CD79b Mutations Hyperactivate SYK

~50% of ABC DLBCL tumors have one or both mutations[1,2]

Mivavotinib expected to be active in CD79b and MYD88 mutated DLBCL
In a retrospective analysis, 2 out of 3 patients with known CD79b mutations had CRs (1 DLBCL, 1FL)

<u>CD79m</u>
SYK is hyperactivated
Drives BCR signaling

<u>CD79m and CD79m/MYD88m</u>
BTK inhibitors active[6]



<u>MYD88m</u>
SYK is hyperactivated
Drives BCR and TLR signaling[3,4,5]

<u>MYD88m (~70% occur w/o CD79m)</u> [6,7]
BTK inhibitors not active[8]

[1]Schmitz, N Engl J Med 2018;378:1396-407
[2]Wilson Cancer Cell 2021;39:1-11.
[3]Munshi, Blood Cancer J 2020;10:12
[4]Phelan, Nature 2018;560:387-391.
[5]deGroen, Haematologica 2019;104:2337-48
[6] Ngo, Nature 2011 February 3; 470(7332): 115–119.
[7]Vermaat Haematologica 2020, 105(2):424-434
[8]Wilson Nat Med. 2015; 21(8): 922–926

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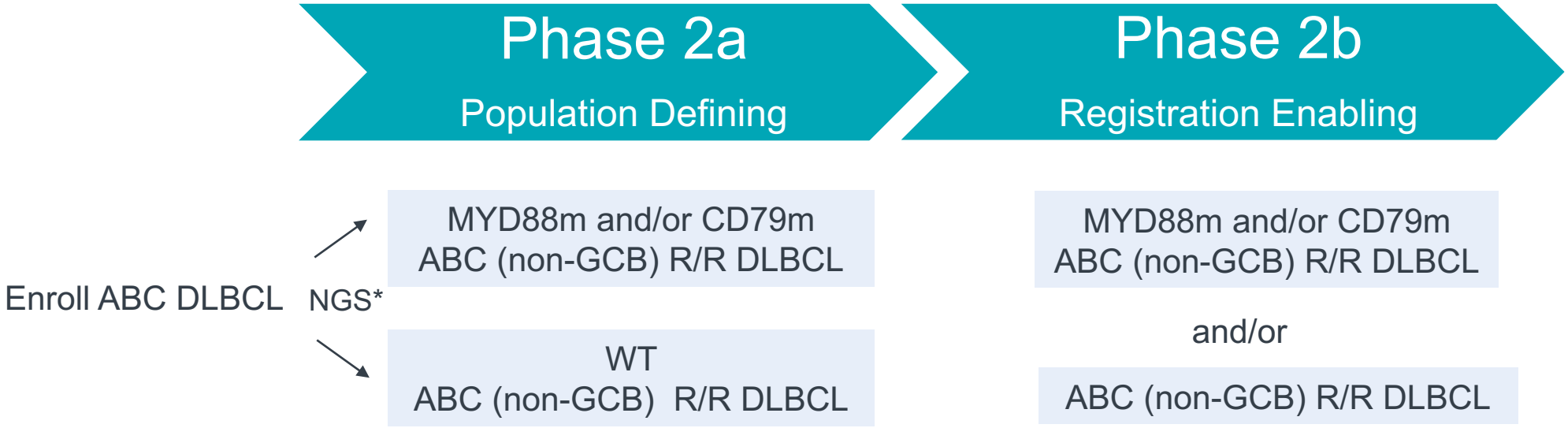
Trial Design for Mivavotinib in R/R ABC DLBCL



Objectives

Further define patient population and refine RP2D dose**

- Safety and tolerability
- Anti-tumor efficacy
- Biomarker validation

FPI expected in 1H22

Enroll biomarker defined cohorts for potential accelerated approval study

- Primary endpoint: ORR
- Safety and tolerability
- Secondary endpoints: DOR, PFS, OS

*ctDNA based liquid NGS performed in parallel to enroll a pre-specified number of patients harboring MYD88/CD79b mutations

** Doses: 100 mg QD or 120 mg QD for 2 wks, 80 mg QD

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Clinical Expansion of Mivavotinib Into Other Indications

Earlier Stage DLBCL and Other Heme Malignancies

DLBCL

Monotherapy (R/R DLBCL)
ABC (including MYD88/CD79bm)
GCB (biomarker exploration)

Combination
Mivavotinib + SOC DLBCL drugs

Waldenstrom's Macroglobulinemia

Monotherapy (R/R WM)
MYD88 mutant (95%)

Combination (earlier lines of therapy)
Mivavotinib + SOC WM drugs

Potential for further development
In FL, CLL and AML

Mivavotinib Summary

Market Opportunity and Unmet Need

- DLBCL projected to be ~$8B market by 2026
- High unmet need in R/R DLBCL for treatments with biomarkers to identify patients most likely to benefit
- Potential to expand beyond initial line of therapy based on activity as a single agent and combinability as a tolerable, oral agent

- Deep and durable single agent activity in DLBCL and other NHL
- Mivavotinib has enhanced activity in ABC DLBCL, where unmet need is high, and potential in MYD88 and CD79b patients
- DLBCL provides a near term clinical readout and a fast-to-market strategy
- Potential to be the first biomarker-driven drug in DLBCL

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mTORC1/2 Inhibitor for NRF2-mutated Squamous NSCLC

Sapanisertib

Sapanisertib Overview

mTORC1/2 Inhibitor Entering a Phase 2 Trial in NRF2-Mutated Squamous NSCLC (sqNSCLC)

- A recent Ph 2 trial showed durable single agent activity of sapanisertib in a NRF2m* subset of sqNSCLC patients, a genetically defined group with poorer prognosis[1]
- Sapanisertib has a well-established and manageable safety profile
- Initial development of sapanisertib will be in R/R NRF2m sqNSCLC
- Potential to be the first approval in a NRF2m patient population
- Possible future expansion to NRF2m populations in other tumor types

*NFE2L2

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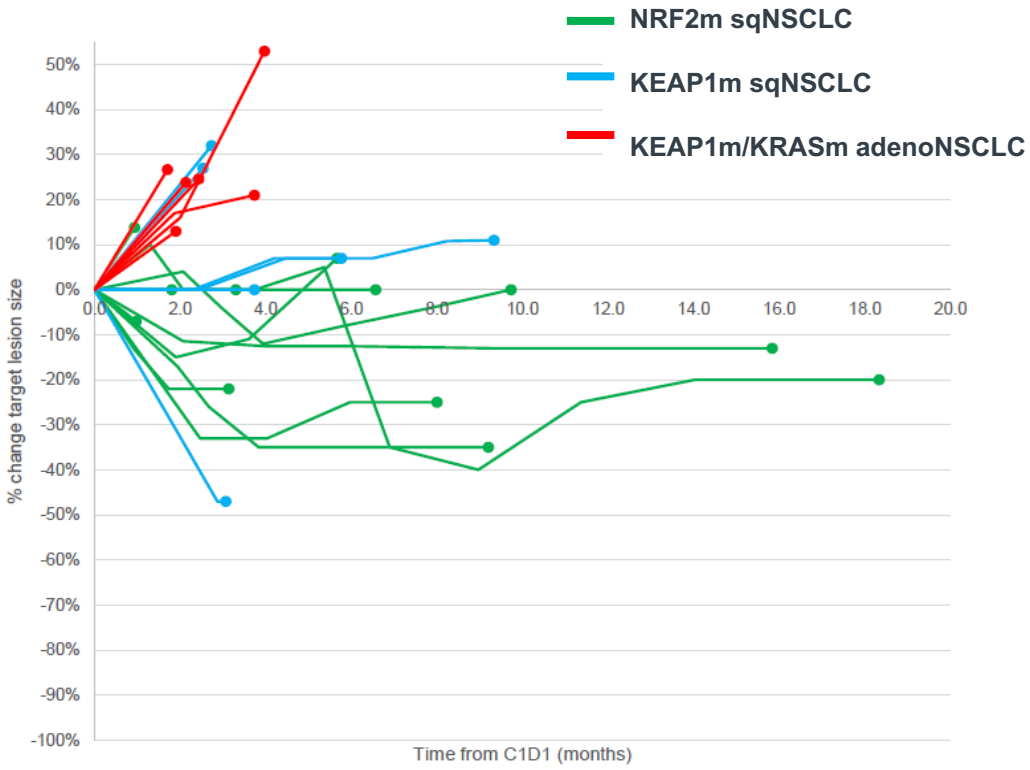
[1]Paik, J Clin Oncol 2020;38 15 suppl: 9607

Sapanisertib has Durable Single Agent Activity in NRF2m R/R SqNSCLC Patients

- Sapanisertib is a potent and selective oral inhibitor of mTORC1/TORC2
  - IP protection through 2036 US/2034 EU assuming full 5-year patent term extension
- Sapanisertib has single agent activity (27% ORR) in heavily pre-treated NRF2m sqNSCLC patients
- Responses were durable with a mPFS of 8.9 months (95% CI [7m, NR])

Mutation	Indication	ORR *	mPFS
NRF2m	SqNSCLC	27% (3/11)	8.9 mo
KEAP1m	SqNSCLC	17% (1/6)	
KEAP1m + KRASm	Adeno NSCLC	0% (0/5)	

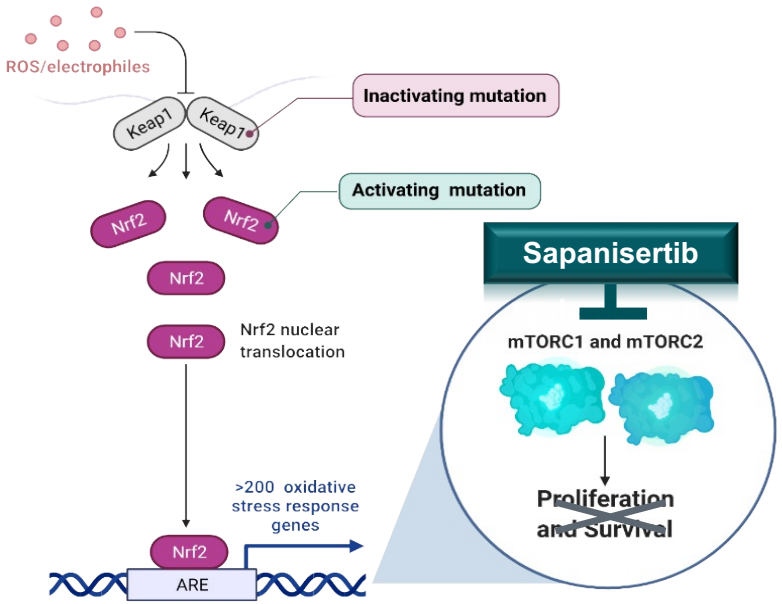
*Sapanisertib at 3 mg QD
Response evaluable population



Paik, J Clin Oncol 2020;38 15 suppl: 9607

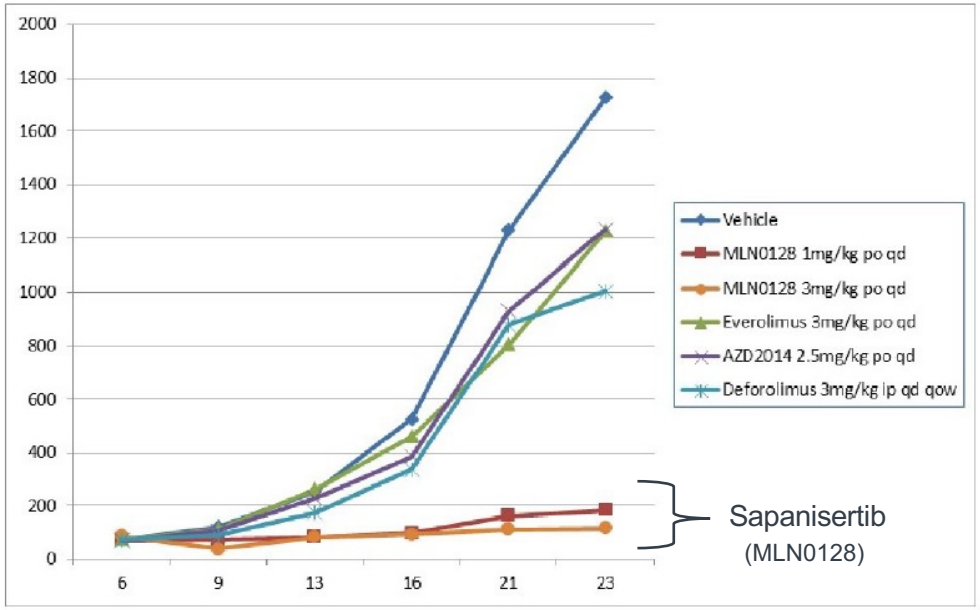
Sapanisertib is More Active than Other mTOR Inhibitors in NRF2m sqNSCLC Animal Models

- NRF2 or KEAP1 mutant tumors constitutively activate the oxidative stress pathway to support survival
- NRF2 activation upregulates mTOR activity
- Sapanisertib inhibits mTORC1/2, blocking proliferation and inducing cell death



- Several mTOR inhibitors (sapanisertib [MLN0128]), everolimus, AZD2014 (vistusertib), and deforolimus) were dosed in a NRF2m sqNSCLC xenograft
- Sapanisertib was the only inhibitor to have strong single agent efficacy
- TORC1 inhibitors (everolimus and deforolimus) were not active

NRF2m LK-2 Xenograft



- Paik, J Clin Oncol 2020;38 15 suppl: 9607
- Shibata, Cancer Res. 2010;70:9095-105.
- Bendavit, J Biol Chem 2016;291:25476-88.

Sapanisertib was Well-tolerated in R/R Solid Tumor Patients

Ph 2 Studies of Sapanisertib in Patients With Solid Tumors

Grade ≥3 Adverse Events of any Cause in ≥2% of Total Patients

Adverse Event	3 mg QD[1]	3 mg QD[2]	4 mg QD[2]	4 mg QD[3]	5 mg QD[3]	Total
	(N=30)	(N=11)	(N=6)	(N=7)	(N=39)	(N=93)
Hyperglycemia	14 (47)	1 (9)	1 (17)	2 (29)	5 (13)	23 (25)
Rash macular	2 (7)	1 (9)	1 (17)	0	3 (8)	7 (8)
Fatigue	0	0	2 (33)	0	5 (13)	7 (8)
Hypophosphatemia	0	0	0	0	4 (10)	4 (4)
Stomatitis	0	0	0	0	3 (8)	3 (3)
Abdominal pain	0	1 (9)	0	0	3 (8)	4 (4)
Hyponatremia	0	1 (9)	1 (17)	1 (14)	1 (3)	4 (4)
Hyperkalemia	0	0	0	1 (14)	2 (5)	3 (3)
Dyspnea	0	0	0	0	2 (5)	2 (2)
Acute kidney inj.	0	0	0	0	2 (5)	2 (2)
Thrombocytop.	0	0	0	0	2 (5)	2 (2)
Hematuria	0	0	0	0	2 (5)	2 (2)
Pneumonia	0	0	0	0	2 (5)	2 (2)

- Sapanisertib on a QD schedule (3-5 mg QD) was evaluated in 3 separate trials in NSCLC and other solid tumor patients
- Predominantly Gr1/2 TEAEs
- Most commonly observed TEAE was hyperglycemia
  - Well controlled with oral hypoglycemic therapy and home glucose monitoring[4]
- Only one discontinuation (1/93) for hyperglycemia at these QD doses[3]

[1] Paik, J Clin Oncol 2020;38 15 suppl: 9607 (NSCLC)
[2] Moore, ESMO Open 2018;3:1-11. (Solid tumors);
[3] Unpublished data on file (study INK128-001)
[4] Voss et al., Brit J Cancer 2020;123:1590–8. (Solid tumors)

Squamous NSCLC Landscape

50,000-60,000 squam patients diagnosed in the US each year, or 25-30% of all NSCLC[1]

Only 1-5% of tumors have actionable mutations such as EGFR, KRAS, etc.[2]

Five-year metastatic survival rate is 7%[1]

1L SOC

anti PD-1 and chemo[3]

2L SOC

Salvage chemo[3,4]

(mPFS 3-4.5 mo)[5]

15% NRF2 mutants[2]

Prognosis is poorer in patients with these mutations[6]

1. https://seer.cancer.gov/statfacts/html/lungb.html
2. Data from TCGA BioPortal https://www.cbioportal.org/
3. https://www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq#_359
4. NCCN NSCLC guidelines June 2021
5. Garon, Lancet 2014;384:665-73.
6. Rizvi, Oral Abstract OA04.07: World Conference on Lung Cancer, 2019 for all NSCLC

Clinical Development Plan for Sapanisertib

Objectives

Refine RP2D and validate NRF2m patient selection strategy

- Safety and tolerability
- Anti-tumor efficacy
- Validate NRF2m biomarker

FPI expected in 1H22

Enroll NRF2m sqNSCLC expansion cohort for single arm or randomized study

- Primary endpoint: ORR (potential accel approval)
- Secondary endpoints: DOR, PFS, OS
- Primary endpoint: PFS (full approval)
- Safety and tolerability

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RP2D= Randomized phase 2 dose

Potential to Treat NRF2/KEAP1 Mutations in Other Tumor Types

Many patients could potentially benefit from treatments specific to this pathway

Histology	NRF2 mutation frequency	KEAP1 mutation frequency	Total mutation frequency
NSCLC squamous	15%	12%	27%
NSCLC adeno	2%	19%	21%
Bladder	9%	3%	12%
Esophagus	9%	3%	12%
HNSCC	5%	4%	9%
HCC	4%	5%	9%
Cholangiocarcinoma	3%	6%	9%
Uterine	6%	2%	8%
Cervical	6%	0.5%	6.5%
Gastric	0.5%	2.5%	3%
papRCC	2%	1%	3%
CRC	1%	2%	3%
ccRCC	1.5%	0.5%	2%
Melanoma	1%	1%	2%
Pancreatic	0%	1%	1%
Breast	0.3%	0.4%	0.7%

Data from TCGA BioPortal https://www.cbioportal.org/

Sapanisertib Summary

NRF2m SqNSCLC
Market Opportunity and Unmet Need

- SqNSCLC is expected to be a $4.5B market by 2026[1]
- NRF2 mutations account for 15% of all sqNSCLC patients
- High unmet need for biomarker-driven treatments in sqNSCLC patients

Sapanisertib Potential

- Single agent activity with durable responses in NFR2m sqNSCLC
- Safety profile favorable for development as monotherapy and/or in combination
- Potential first-in-class treatment for NRF2m sqNSCLC patients
- Potential to expand into NRF2 mutant populations in other cancers

[1]DRG Nov 2021

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Arginase Inhibitor for Cystic Fibrosis

CB-280

Rationale for Arginase Inhibitors in Cystic Fibrosis

Despite recent advances with CFTR modulators, many patients still have impaired lung function

- Arginase plays a critical role in CF airway disease[1, 2, 3]
  - Decreases nitric oxide (NO) production[4], increases production of polyamines and proline
- Inhibition of arginase should increase NO, increasing anti-microbial activity and improving airway function[5]
- Potential for additional benefit when combined with standard of care therapies[6]
- Potential benefit in all CF patients, regardless of CFTR genotype

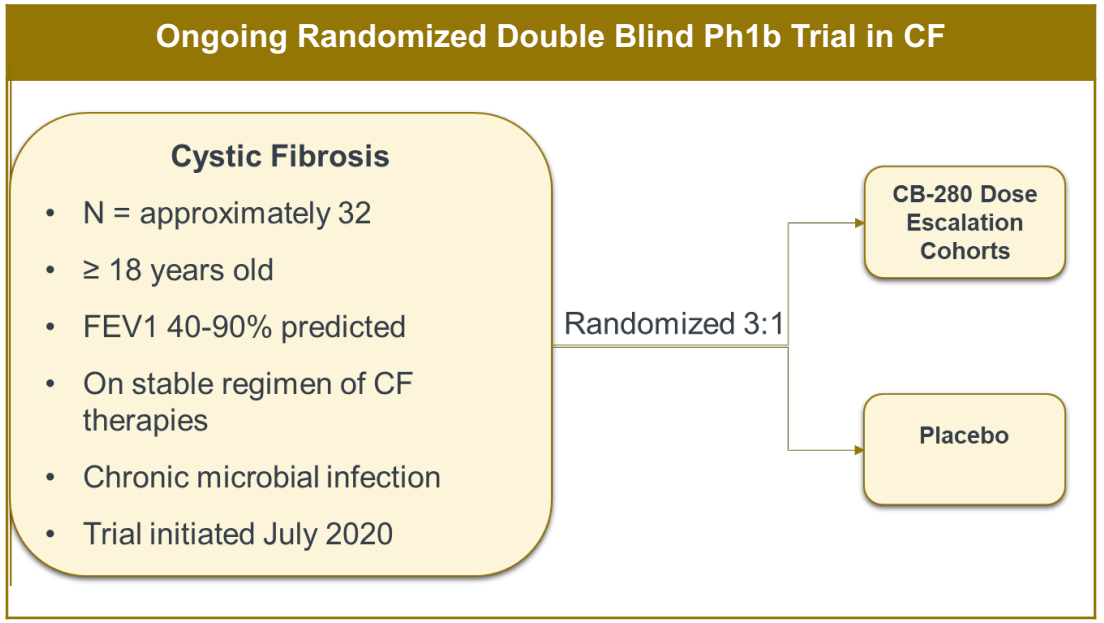
CB-280 is an investigational first-in-class orally-dosed arginase inhibitor in Phase 1b trials supported by a grant from the Cystic Fibrosis Foundation

1. Grasemann et al., Am J Respir Crit Care Med 172: 1523-1528, 2005
2. Grasemann et al., Respiratory Research 7: 87, 2006
3. Jaecklin et al., J Appl Physiol 117: 284-288, 2014
4. Grasemann et al., Eur Respir J 25: 62-68, 2005
5. Mermis et al, NACF-2020-CX-280-202-TIP-POSTER-08Sep2020
6. Wu, Mol Pharmacol 96:515-525, 2019

Ph1b Interim Data Presented at North American Cystic Fibrosis Conference

Interim Analysis Key Conclusions

- CB-280 was well-tolerated, showed linear PK and demonstrated robust dose-related PD effects
- Encouraging trends seen in disease biomarkers including increased FeNO and decreased sweat chloride
- Early positive trend seen in FEV1, a safety endpoint
- Cohort 4 (300 mg) enrollment and analysis is complete
- Evaluation of next steps is ongoing



- **Primary Endpoint**: Safety
- **Secondary Endpoints**: PK/PD: arginase inhibition and arginine increase assessed in plasma and sputum
- **Exploratory Endpoints**: FENO, sweat chloride, sputum colonization

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Boas et al. Abstract 529 North American Conference for Cystic Fibrosis, November 2021.

CALITHERA

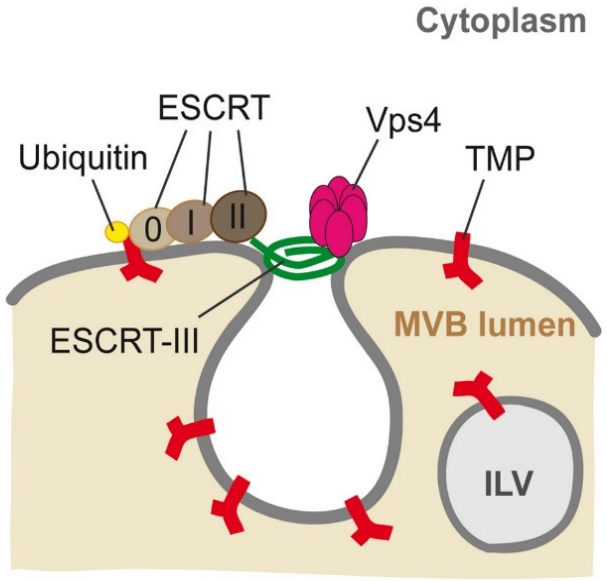
VPS4A Program

Synthetic Lethality in Solid Tumors

Synthetic Lethality Research Pipeline: VPS4

VPS4 is our most advanced synthetic lethality program

- VPS4A and VPS4B are paralog ATPases essential for remodeling intracellular organelle membranes[1,2]
  - Loss of function of both paralogs is lethal
- VPS4B homozygous deletion occurs in 1-3% of several solid tumor types[3]
  - VPS4B is frequently co-deleted with tumor suppressors SMAD2/4
- VPS4B heterozygous deletion is common across solid tumor cancers[2,3]
  - Most notably in CRC and PDAC (~65%)
- Heterozygous or homozygous loss of VPS4B in cancer cells makes them vulnerable to inhibition of VPS4A[2]
- Calithera has identified small molecule inhibitors of VPS4
- We will present data on these novel VPS4 inhibitors at AACR 2022



ESCRT mediated ILV budding

Adell FEBS Journal 283 (2016) 3288-3302

[1]Szymanska EMBO Molecular Medicine 2020 12:e10812
[2]Neggers Cell Rep 2020 33 (11): 108493
[3]Data from TCGA BioPortal https://www.cbioportal.org/

Calithera Today: Significant Value Creation

Three clinical stage programs

Biomarker-defined clinical development for our two oncology drugs

Upcoming Milestones

Data for mivavotinib and sapanisertib expected by 1Q23

Research pipeline for synthetic lethality targets in biomarker defined patient populations

Leveraging an experienced management team