UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): October 31, 2022

CYCLACEL PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**0-50626**	**91-1707622**
(State or other jurisdiction of incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

200 Connell Drive, Suite 1500
Berkeley Heights, NJ 07922
(Address of principal executive offices and zip code)

Registrant's telephone number, including area code: (908) 517-7330

(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (*see* General Instruction A.2. below):

☐ **Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)**

☐ **Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)**

☐ **Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))**

☐ **Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))**

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Trading Symbol(s)**	**Name of each exchange on which registered**
Common Stock, par value $0.001 per share	CYCC	The Nasdaq Stock Market LLC
Preferred Stock, $0.001 par value	CYCCP	The Nasdaq Stock Market LLC

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 8.01 Other Events.

On October 31, 2022, Cyclacel Pharmaceuticals, Inc. (the "Company") hosted a research and development day, whereby the Company provided a program update on its CDK2/9 inhibitor, oral fadraciclib, and oral PLK1 inhibitor, CYC140, for the treatment of advanced solid tumors and lymphoma. A copy of the slides presented are attached hereto as Exhibit 99.1 and are incorporated by reference herein.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits.

Exhibit No.	**Description**
99.1	Slide Presentation dated October 31, 2022.
104	Cover Page Interactive Data File (embedded with the Inline XBRL document).

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the Registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

CYCLACEL PHARMACEUTICALS, INC.

By: /s/ Paul McBarron
Name: Paul McBarron
Title: Executive Vice President-Finance,
Chief Financial Officer and Chief Operating Officer

Date: October 31, 2022

Exhibit 99.1


CYCLACEL
Translating cancer biology into medicines
R&D Day - October 31, 2022
Update on Oral CDK2/9 and PLK1 Inhibitor Programs in Solid Tumors and Lymphoma

Disclaimer

This presentation contains certain forward-looking statements that involve risks and uncertainties that could cause actual results to be materially different from historical results or from any future results expressed or implied by such forward-looking statements. Such forward-looking statements include statements regarding, among other things, the efficacy, safety and intended utilization of Cyclacel's product candidates, the conduct and results of future clinical trials, plans regarding regulatory filings, future research and clinical trials and plans regarding partnering activities. Factors that may cause actual results to differ materially include the risk that product candidates that appeared promising in early research and clinical trials do not demonstrate safety and/or efficacy in larger-scale or later clinical trials, trials may have difficulty enrolling patients, Cyclacel may not obtain approval to market its product candidates, the risks associated with reliance on outside financing to meet capital requirements, and the risks associated with reliance on collaborative partners for further clinical trials, development and commercialization of product candidates. You are urged to consider statements that include the words "may," "will," "would," "could," "should," "believes," "estimates," "projects," "potential," "expects," "plans," "anticipates," "intends," "continues," "forecast," "designed," "goal," or the negative of those words or other comparable words to be uncertain and forward-looking. For a further list and description of the risks and uncertainties the Company faces, please refer to our most recent Annual Report on Form 10-K and other periodic and other filings we file with the Securities and Exchange Commission and are available at www.sec.gov. Such forward-looking statements are current only as of the date they are made, and we assume no obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise.

Agenda

Time (EDT)	Topic	Speaker
10:00AM	Welcome and Introductions	Spiro Rombotis *Cyclacel, President & CEO*
10:10AM	An Overview of the Unmet Medical Needs in the Treatment of T Cell Lymphoma	Jasmine Zain, MD *City of Hope National Medical Center*
10:25AM	Unmet Medical Needs and Current Treatment Options for Hepatobiliary Cancers	Do-Youn Oh, MD, PhD *Seoul National University Hospital*
10:40AM	Oral CDK2/9 inhibitor fadraciclib clinical update	Mark Kirschbaum, MD *Cyclacel, SVP & Chief Medical Officer*
11:00AM	Oral PLK1 inhibitor CYC140 clinical update	Mark Kirschbaum, MD *Cyclacel, SVP & Chief Medical Officer*
11:10AM	Q&A; Discussion	Moderator; All

Cyclacel Summary

- **STRATEGY:** Leverage understanding of biology to bring Rx candidates to proof-of-concept
- **HUMAN CAPITAL:** Small, focused team of skilled drug developers committed to strategy
- **SCIENCE**: Leader in cell cycle checkpoint control and oncology drug innovator
- **ASSETS**: Multiple data readouts from registration-directed, Ph 1/2 studies
  - **Fadraciclib** (CYC065, CDK2/9 inhibitor): Ph 1/2 solid tumors and lymphoma ongoing
    - Single agent responses in unselected dose escalation in both solid tumors and lymphoma
    - PoC cohort stage 1H 2023
  - **CYC140** (PLK1 inhibitor): Ph 1/2 solid tumors and lymphoma ongoing
    - Early indication of activity, interim dose escalation data 1H 2023

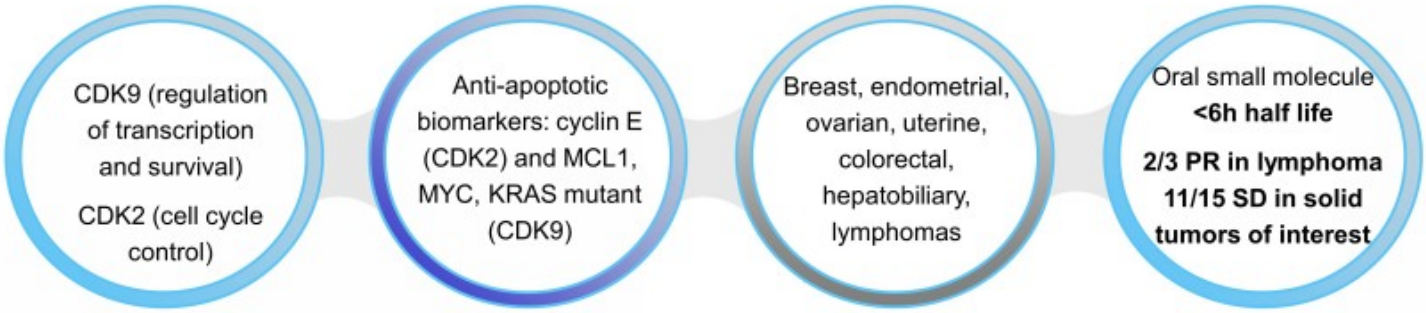
CYCLACEL

Therapeutic Strategy: Enabling Apoptosis

- **Durably suppress** proteins/genes associated with cancer resistance → enable **apoptosis**
- Suppress multiple, **redundant** mechanisms with a **single drug**
- Optimize **mechanistically**-relevant, **dosing** strategy
- Venetoclax: only FDA-approved apoptosis enabler

CYCLACEL

Fadraciclib (formerly CYC065) Summary



Ongoing Ph 1/2: biologically-optimal schedules require continuous dosing

Jasmine Zain, MD

Overview of the Unmet Medical Needs in the Treatment of T Cell Lymphoma

Jasmine Zain, MD,
Professor, Department of Hematology & Hematopoietic Cell Transplantation and Director, T cell Lymphoma Program at the Toni Stephenson Lymphoma Center, City of Hope National Medical Center

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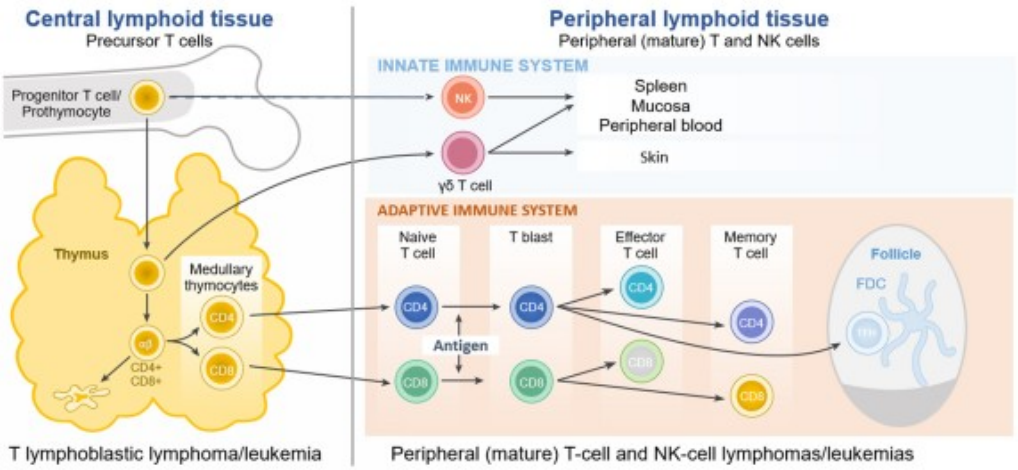
City of Hope

WHAT IS T-CELL LYMPHOMA

Jasmine Zain, MD
Director T-Cell Lymphoma Program
Professor Hematology and Hematopoietic Stem Cell Transplantation
City of Hope National Medical Center

T-CELL LYMPHOMAS ARISE FROM POST-THYMIC T LYMPHOCYTES



FDC, follicular dendritic cells.

Jaffe ES, et al. *Blood.* 2008;112:4384-4399

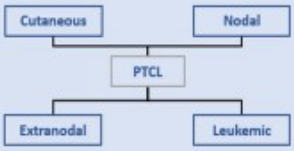
PTCLS REPRESENT A RARE GROUP NON-HODGKIN LYMPHOMAS

~4,800-8,000 cases per year in the U.S.[1]

Median age in US is **62 years**, varies by subtype and race[2]

Slightly **more common in men**[2]

Many types and variations of T-cell NHL, each with different symptoms, survival rates, and prognoses, due to differences in the origin of cells[1,3-5]



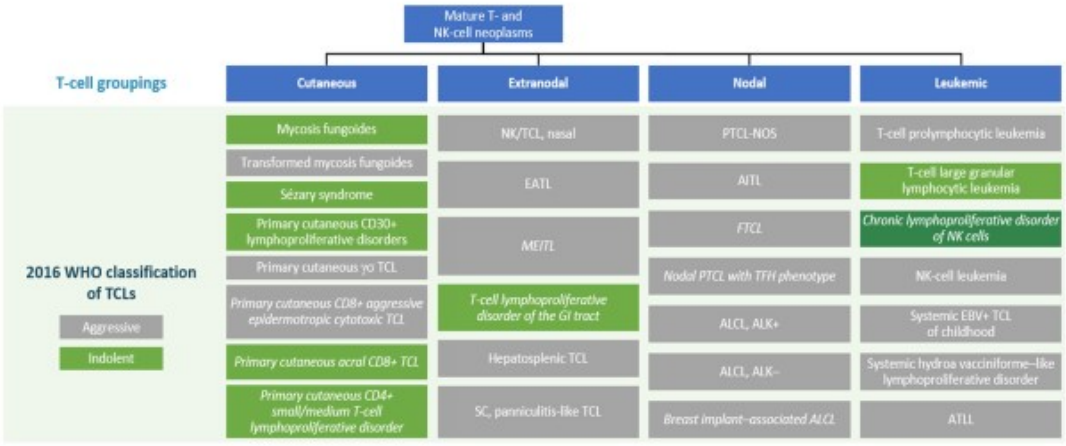
- PTCL-NOS more common in North America[2]
- EBV-associated lymphomas seen in Asia and Central and South America[2]
- EATL is related to celiac disease[2]
- ALK-positive ALCL and hepatosplenic T-cell lymphoma can be seen in young patients[2]

Commonly presents with **advanced stage disease**[3]

Associated with increased risk

- History of eczema or psoriasis
- Family history of hematologic malignancies
- Smoking for 40+ years
- Alcohol consumption
- Being a textile worker
- Celiac disease (EATL)

PTCLS REPRESENT A RARE GROUP NON-HODGKIN LYMPHOMAS

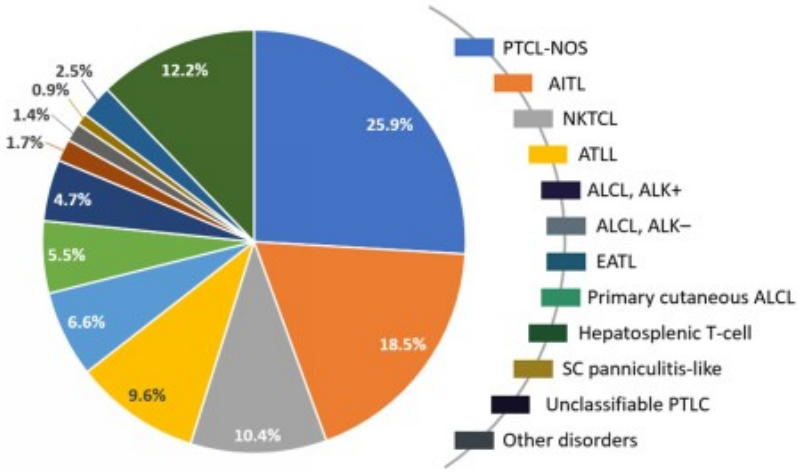


[a]PTCL does not refer to anatomic sites, but the involvement of more mature (post-thymic) T cells vs pre-thymic or immature T cells; provisional entities are listed in italics.[1]

AITL, angioimmunoblastic T-cell lymphoma; ATLL, adult T-cell leukemia/lymphoma; FTCL, follicular TCL; GI, gastrointestinal; MEITL, monomorphic epitheliotropic intestinal T-cell lymphoma; NK, natural killer; SC, subcutaneous; TCL, T-cell lymphoma; TFH, T-follicular helper phenotype; WHO, World Health Organization.

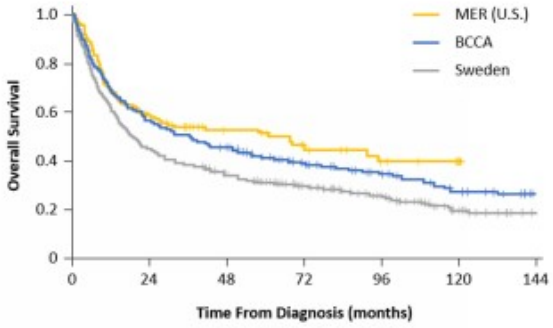
1. Armitage JO, et al. *Ann Oncol*. 2006;15:1487-1489. 2. Swerdlow SH, et al. *Blood*. 2016;127:2375-2390. 3. Marchi E, et al. *CA Cancer J Clin*. 2020;70:47-70. 4. Zizani PL, et al. *Crit Rev Oncol Hematol*. 2016;99:214-227. 5. Pinter-Brown L. *Hematology Am Soc Hematol Educ Program*. 2020;154-159. 6. Shi M, et al. *Clinical Case Rep*. 2015;3:740-743. 7. Guitart J, et al. *Mod Pathol*. 2017;30:781-772. 8. Guo N, et al. *Diagn Pathol*. 2019;14:82. doi.org/10.1186/s13000-019-0859-4.

DISTRIBUTION OF SUBTYPES



Vose al. *J Clin Oncol.* 2008;26:4124-4130

ASSOCIATED WITH A POOR PROGNOSIS



Demographics and OS

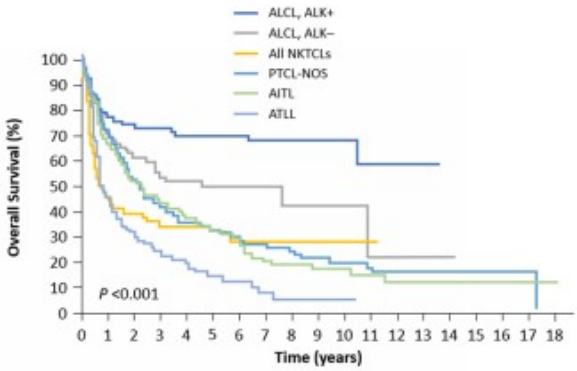
N = 775	MER* (n=138)	BCCA (n=215)	SWE* (n=422)
>60 years	46%	49%	64%
Male	66%	60%	63%
ALK– ALCL	17%	25%	21%
AITL	25%	20%	19%
PTCL-NOS	43%	45%	43%
Other	14%	10%	17%
5-year OS	51.5%	41.5%	32.5%
5-year OS by subgroups		Combined	
▪ Stage I/II		53.6 %	
▪ Stage III/IV		28.6 %	
▪ ECOG PS 0-1		45.2%	
▪ ECOG PS 2-4		24.3%	
3-year OS from progression for ASCT		11.8%	

Variability in outcomes may be secondary to differences in baseline and treatment characteristics between the 3 cohorts

*Excluded ALK+ ALCL.
ASCT, autologous stem-cell transplantation; BCCA, British Columbia Cancer Agency; ECOG, Eastern Cooperative Oncology Group; MER, Molecular Epidemiology Resource; OS, overall survival; PS, performance status; SWE, Sweden.
Maurer MJ, et al. *J Clin Oncol*. 2017;35:4019-4026.

SUBTYPES DIFFER IN CLINICAL OUTCOMES

Overall Survival of Patients With the Most Common Subtypes of PTCL

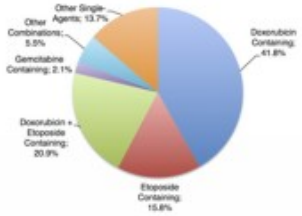


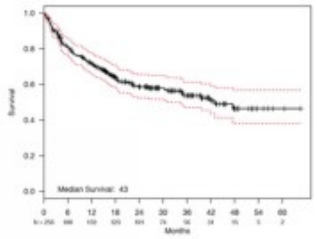
Survival by Histologic Type

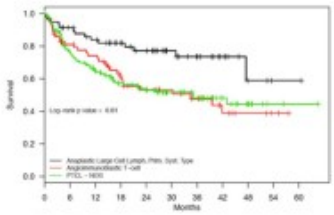
Diagnosis	5-year OS (%)
PTCL-NOS	32
AITL	32
Nasal NKTCL	42
Extranasal NKTCL	9
ATLL	14
ALCL, ALK+	70
ALCL, AKL–	49

Vose JM, et al. *J Clin Oncol*. 2008;26:4124-4130.

COMPLETE - COMPREHENSIVE ONCOLOGY MEASURE FOR PERIPHERAL T-CELL LYMPHOMA

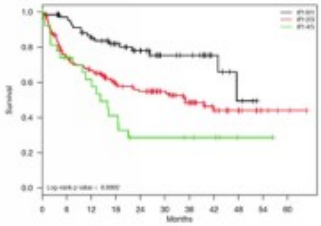


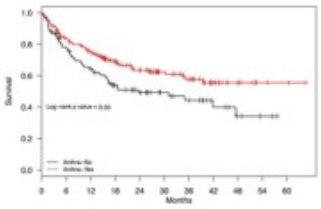




Induction regimen for PTCL

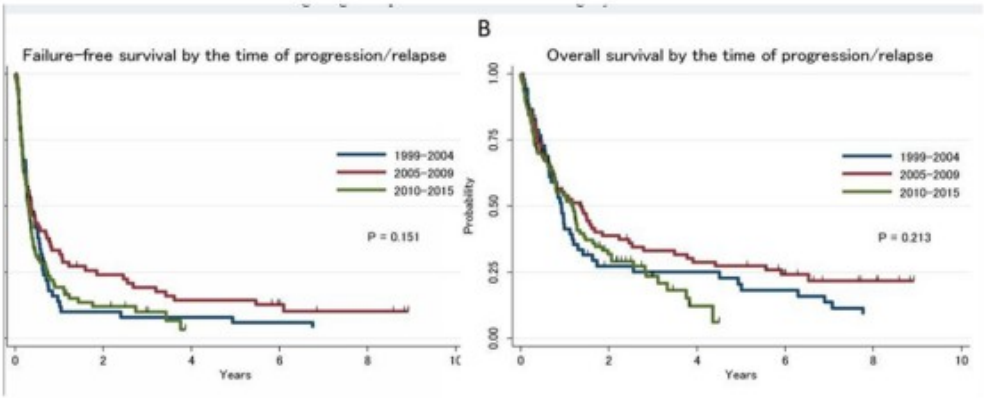
- 51% had nodal disease
- No clear standard of therapy in the US for PTCL





Carson, et al. 2017. Cancer.

NO CHANGE IN FFS OR OS IN PTCL – NOS AND AITL

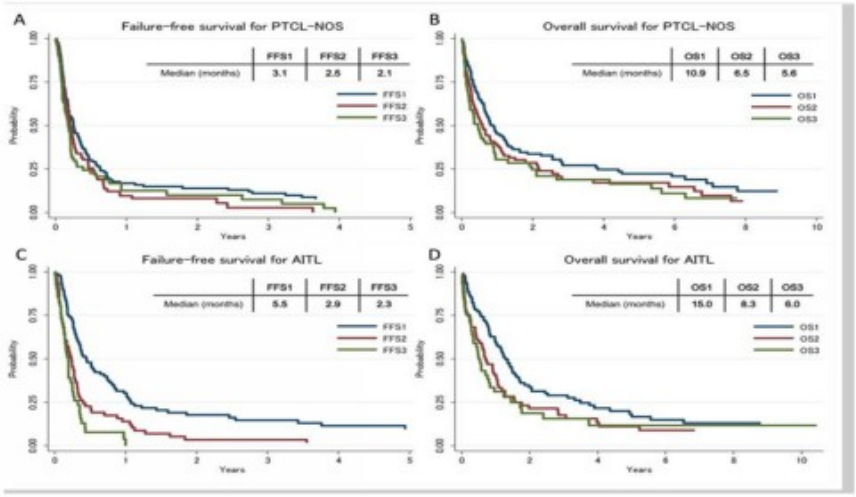


Chiara et al. British Journal of Hematology 2017

WHAT WE KNOW SO FAR

- CHOP based therapies remain the back bone of upfront therapy (CR 31-67%)
- **For CD30+ lymphomas and ALCL- ----- BV+CHP – based on randomized data and shown to impact survival – best effect seen in ALCL, other subtypes not so much**
- Role of Etoposide if the upfront regimen continues to be debated. Best data is by Schimdt, et al. <60, normal LDH, improved OS. CHOEP followed by high dose ASCT has been used by several groups. Metanalysis by Deng et al did not show a difference between CHOP and CHOPE (Onco targets 2019)
- CHOP+Romdepsin (Ro-CHOP) – Initial results ORR 78% including 66% CR. Randomized phase 3 is NEGATIVE
- CHOP+Pralatrexate - ORR 89%, CR 67%
- CHOP+Belinostat – ORR 86%, CR 67%, PR 19%
- CHOEP+Revlimid – ORR 88% and CR 38%. Len maintenance arm
- CHEP+BV – Ongoing. Possible EPCH+BV?
- Chidamide + CHOP, Chidamide + CHOEP (ORR 68%, CR 43%)
- Non – CHOP based therapies
- Mogamulizumab combinations – EPOCH, mLSG15

PROGNOSIS FOR PATIENTS WITH RELAPSED REFRACTORY PTCL



Dismal out comes for relapsed disease

Chiara et al: British Journal of Hematology 2017

APPROVED AGENTS FOR THE TREATMENT OF RR PTCL

AGENT	HISTOLOGY	ORR/CR	ORR/CR	DURATION
PRALATREXATE 2009	PTCL- all subtypes	29%/11%	PTCL- nos 32% sALCL- 35% AITL- 8% other – 38%	DOR = 10.1 months (,1-22.1)
ROMIDEPSIN 2009	PTCL- all subtypes	25%/15%	PTCL- nos—29/14 AITL- 30/19 Alk-ve ALCL -24/19	DOR 28 months (1-48) Median OS= 11.3 months Time to CR =3.7months
BELINOSTAT 2014	PTCL- all subtypes	26%/11%	PTCL-nos-23% AITL-46%/18% ALCL- 15% ENKTCL-50%	DOR= 13.6 months (4.5-29.4)
BRENTUXIMAB VEDOTIN 2011	sALCL	86%/59%	Highest responses in ALCL- other subtypes much less	DOR = 13.2 (5.7-26.3) OS- 70% at 1 yr. 64% at 4 yrs
MOGAMULIZUMAB 2012	ATLL	50/31	Approved for CTCL in the US, ATLL and CCR4 expressing PTCL in Japan	Median PFS 5.2 months
CHIDAMIDE 2014	PTCL	28/14	Approved in China	Median PFS 2.1 month, OS 21.4 months

ALTERNATIVE APPROACHES TO TREAT R/R PTCL

AGENT	N	HISTOLOGICAL SUBTYPES N	ORR/CR (%)	RESPONSE BY HISTOLOGY ORR/CR	OUTCOMES	COMMENTS
ICE	40	PTCL	70/35		Median PFS= 6 months	68% went to transplant 83% relapsed at 3 years
ESHAP	22	All PTCL	32/18		Median PFS= 2.5 months	
BENDAMSUTINE	58	AITL- 32 PTCL- nos 23 ALCL- 2 EATL- 1	50/28		Median DOR= 3.5 months 1-21)	Median OS 6.3 months
GEM/DEX/CISPLATIN	51	PTCL	69/19		Median PFS= 4 months	72% went to auto or stem cell transplant
ALEMTUZUMAB	PTCL-nos 10 AITL – 4	2(1-4)	36/21			
CRIZOTINIB	Alk+ ALCL=9		89/78		NR	

HOW TO CHOOSE THE NEXT LINE OF THERAPY

National Comprehensive Cancer Network®

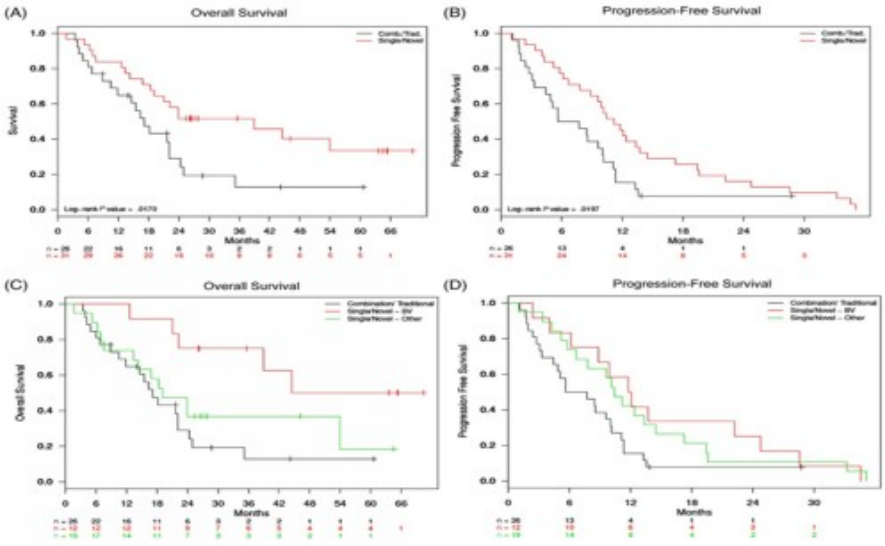
NCCN Guidelines Version 2.2022
Peripheral T-Cell Lymphomas

NCCN Guidelines Index
Table of Contents
Discussion

SUGGESTED TREATMENT REGIMENS[a]

INITIAL PALLIATIVE INTENT THERAPY		
PTCL-NOS; EATL; MEITL[f]	**AITL, INCLUDING NODAL PTCL, TFH and FTCL**	**ALCL**
• Clinical trial preferred Preferred regimens (alphabetical order) • Belinostat • Brentuximab vedotin for CD30+ PTCL[d,g] • Pralatrexate • Romidepsin Other recommended regimens (alphabetical order) • Alemtuzumab[j] • Bendamustine[d] • Bortezomib[j] (category 2B) • Cyclophosphamide and/or etoposide (intravenous [IV] or oral [PO]) • Duvelisib[k] • Gemcitabine • Lenalidomide[d] • RT[l]	• Clinical trial preferred Preferred regimens (alphabetical order) • Belinostat • Brentuximab vedotin for CD30+ AITL[d,g] • Romidepsin Other recommended regimens (alphabetical order) • Alemtuzumab[j] • Bendamustine[d] • Bortezomib[j] (category 2B) • Cyclophosphamide and/or etoposide (IV or PO) • Cyclosporine[m] • Duvelisib[k] • Gemcitabine • Lenalidomide[d] • Pralatrexate[n] • RT[l]	• Clinical trial preferred Preferred regimens • Brentuximab vedotin[d] Other recommended regimens (alphabetical order) • Alectinib (ALK+ ALCL only)[o] • Belinostat • Bendamustine[d] • Bortezomib[j] (category 2B) • Cyclophosphamide and/or etoposide (IV or PO) • Crizotinib (ALK+ ALCL only) • Duvelisib[k] • Gemcitabine • Pralatrexate • RT[l] • Romidepsin

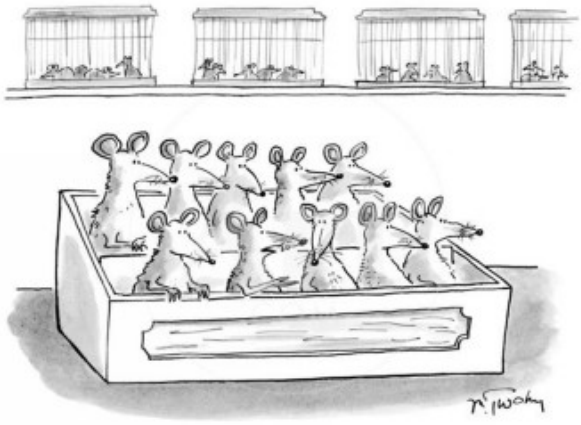
SINGLE AGENT VS COMBINATION CHEMOTHERAPY IN RR PTCL



Results from COMPLETE registry

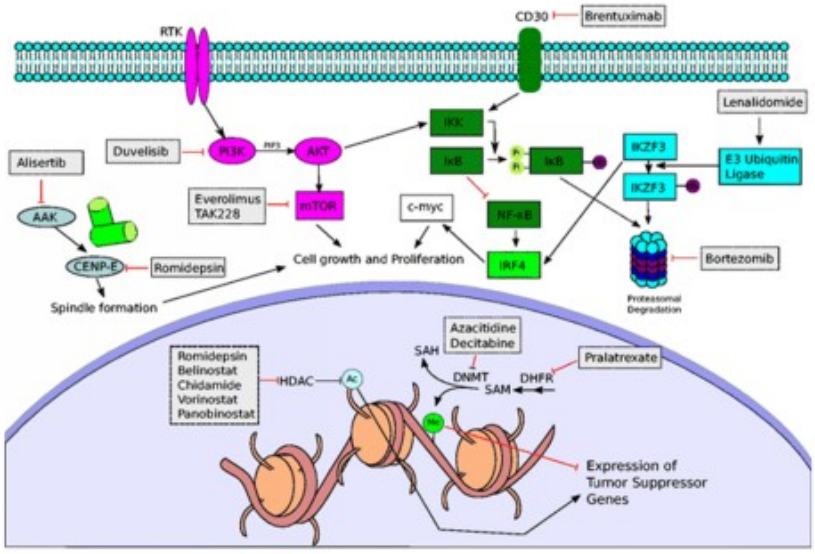
Stuver et al- American Journal Hematology 2019

UPCOMING THERAPIES



"I'll tell you, mock jury duty beats cancer testing."

POTENTIAL THERAPEUTIC TARGETS FOR PTCL



Ma et al : Current Hema malignancy reports 2018


© Guy & Rodd/Distributed by Universal Uclick via CartoonStock.com
PEANUT BUTTER
JELLY
CARTOONSTOCK
Search ID: gra050219
IT TURNS OUT THEY DON'T GO TOGETHER SO WELL.

DOUBLETS AND TRIPLETS –TARGETED AGENTS

COMBINATION	N	RESULTS	MAIN TOXICITY/DLT
PRALATREXATE + ROMIDEPSIN-2018	14	ORR 71%, PFS 4.4 months	Mucositis, thrombocytopenia
DUVELISIB+ROMI-2017	29	ORR 50%- median TTR 51 days	
DUVELISIB + BORETEZOMIB- 2017		ORR 53%- median TTR 52 days	
ALISERTIB + ROMIDEPSIN-2017	3	ORR 25%	Hematologic, fatigue, infection
CHIDAMIDE+THALIDOMIDE+CYCLOPHOSPHAMIE- 2017	12	ORR 83%,CR41%, PR33%	Neutorpenia, thrombocytopenia
ROMIDEPSIN+ AZACITIDINE- 2019	31	ORR73%, CR55 %	Neutropenia, thrombocytopenia
LENALIDOMIDE+VORINOSTAT- 2014	8	ORR 25%, PFS 2.2 months , OS 6.7 months	hematologic
ROMIDEPSIN PLUS LENALIDOMIDE- 2017	21	ORR in PTCL 50%. Median EFS 15.5 weeks, Median OS not reached	Neutropenia, thrombocytopenia
ROMIDEPSIN+LENALIDOMIDE+CARFLIZOMAB- 2017	16	ORR 45%, CR 36%, PR 9%- median EFS 13.6 months	Hematologic, DVT, infection
PANOBINOSTAT + BORETEZOMIB-2015	23	ORR 43% median DOR 5.6 months	Thrombocytopenia, diarrhea, neuropathy
DURVALUMAB + ROMIDEPSIN+ 5 AZA	Ongoing		
DURVALUMAB + PRALATREXATE	Ongoing		

COMBINATION THERAPIES IN THE UPFRONT SETTING

COMBINATION	N	RESULTS	ADVERSE EVENTS
LENALIDOMIDE + CHOEP- 2018	39	ORR 69% CR=48%	Hematologic toxicity
LENALIDOMIDE+ CHOP- 2015	37	ORR 54%	Hematologic toxicity
PRALATREXATE PLUS CHOP- FOL-CHOP	12	ORR 89%, CR 67%	No added toxicities noted
COEP ALTERNATING WITH PRALATREXATE-2016	33	ORR- 70%, CR 52%, 2 year PFS 39%- 2 yr OS 60%	
EVEROLIMUS + CHOP-2016	30	ORR 90%, 2 year OS 70%, 2 yr PFS 33%	Mucositis, hematologic
ROMIDEPSIN +CHOP-2014 RANDOMIZATION AGAINST CHOP IS GOING ON - 2015	19	ORR 68%, PFS 57%-18 months, OS 76.5%	Neutropenia, thrombocytopenia, anemia
CHIDAMIDE+CHOP-2019	30	CR 46%- PFS at 12 months is 54% and OS is 100%	

NOVEL SINGLE AGENTS FOR PTCL- RECENT UPDATES

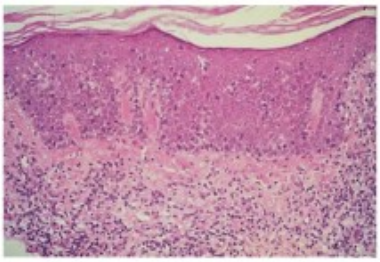
Agent	Mechanism of action	RR	N	ORR	CR	PFS/OS
Alisertib	Aurora A inhibitor	PTCL	37	30%	14%	3 months
Crizotinib	ALK inhibitor	ALK+ALCL	9	100%	100%	
Duvelisib	PI3K-δ inhibitor	16	19	54	15	8.4 months
Tenalisib	PI3Kγ δ Inhibitor	PTCL/CTCL	58	46%	18%	Median DOR 4.91 months. 6.53 months – PTCL 3.8 months CTCL
Ruxolitinib	Jak1/2 inhibitor	PTCL	48	23%	6%	Median DOR 7.3months
Cerdulatinib	JAK and SYK inhibitor	PTCL/CTCL	60	55% 35%for CTCL	41%	Median DOR pending
CDK9 inhibitors	Targets CDK9 Inhibits proliferation, survival, cell cycle regulation	Ongoing studies				

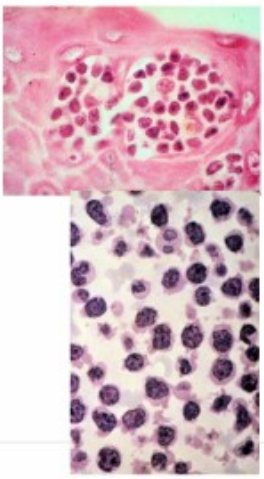
PRIMARY CUTANEOUS LYMPHOMAS

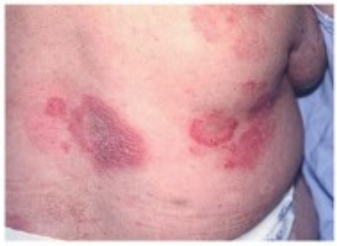
- B- or T- cells neoplasm that primarily involves the skin with no extracutaneous disease at the time of diagnosis
- T cell subtype more common than B cell
- Mycosis Fungoides (MF) and Sezary Syndrome (SS) are the most common cutaneous lymphomas – Epidermotropic CTCLs – 50%

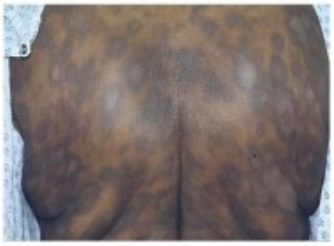
WHO-EORTC CLASSIFICATION OF CUTANEOUS LYMPHOMAS	WHO CLASSIFICATION OF LYMPHOID NEOPLASMS
CUTANEOUS T-CELL AND NK-CELL LYMPHOMAS	**MATURE T-CELL AND NK-CELL NEOPLASMS**
MYCOSIS FUNGOIDES folliculotropic MF pagetoid reticulosis granulomatous slack skin **sézary syndrome**	**MYCOSIS FUNGOIDES**
	SEZARY SYNDROME
ADULT T-CELL LEUKEMIA/LYMPHOMA	**ADULT T- CELL LEUKEMIA/LYMPHOMA**
PRIMARY CUTANEOUS CD30⁺ LYMPHOPROLIFERATIVE DISORDERS Primary cutaneous anaplastic large cell lymphoma Lymphomatoid papulosis	**PRIMARY CUTANEOUS CD30 POSITIVE T-CELL LYMPHOPROLIFERATIVE DISORDERS** Lymphoamatoid Papulosis Primary cutaneous anaplastic large cell lymphoma
SUBCUTANEOUS PANNICULITIS-LIKE T-CELL LYMPHOMA*	**PRIMARY CUTANEOUS GAMMA DELTA T- CELL LYMPHOMA**
EXTRANODAL NK/T-CELL LYMPHOMA, NASAL TYPE	**EXTRANODAL NK/T-CELL LYMPHOMA, NASAL TYPE**
PRIMARY CUTANEOUS PERIPHERAL T-CELL LYMPHOMA, UNSPECIFIED **Primary cutaneous aggressive epidermotropic CD8⁺ T-cell lymphoma (provisional)** **Cutaneous gamma/delta T-cell lymphoma** (provisional) Primary cutaneous CD4⁺ small/medium-sized pleomorphic T-cell lymphoma (provisional)	**PRIMARY CUTANEOUS CD8+ AGGRESSIVE EPIDERMOTROPIC CYTOTOXIC T CELL LYMPHOMA**
	PRIMARY CUTANEOUS CD4+ SMALL/MEDIUM T CELL LYMPHOMA

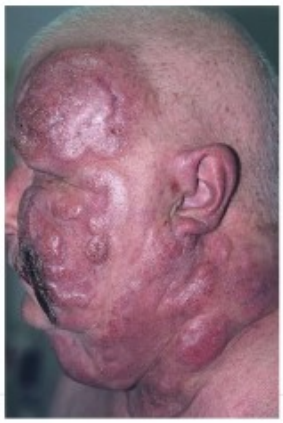
CLINICOPATHOLOGIC FEATURES OF MF

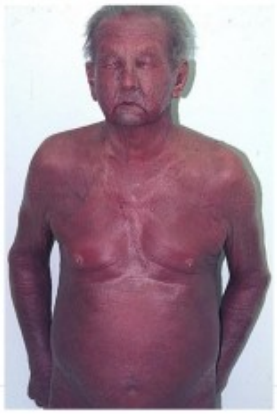






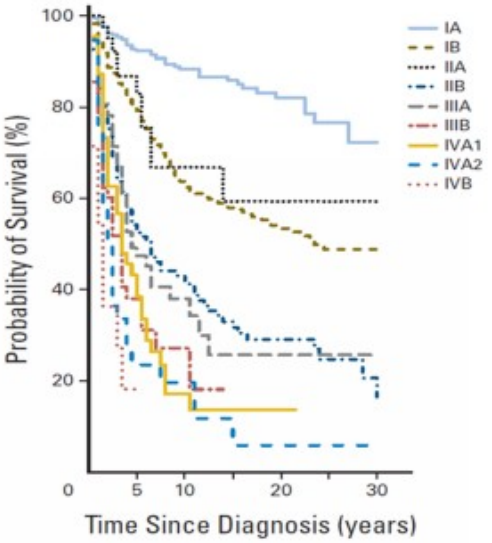






POOR PROGNOSIS FOR LATER-STAGE CTCL

Overall Survival by Clinical Stage[8]



Expected OS Rates by Clinical Stage[9]		
Stage	**5-Year OS, %**	**10-Year OS, %**
IA	91-100	80-100
IB	72-86	58-75
IIA	49-73	45-49
IIB	40-65	20-39
III	40-57	20-40
IVA	15-40	5-20
IVB	0-15	0-5

10/31/2022

CTCL, cutaneous T-cell lymphoma; OS, overall survival.
8. Reprinted from Agar NS, et al. *J Clin Oncol*. 2010;28(31):4730-4739; 9. Adapted from Scarisbrick JJ, et al. *Br J Dermatol*. 2014;170(6):1226-1236.

CONCLUSION

- T– Cell lymphoma are a heterogenous group of diseases
- Systemic T- cell lymphomas are aggressive, and the prognosis is poor
- Cutaneous T- cell lymphomas can be indolent in early stages, but a small percentage of patients can have aggressive features
- Treatment options for T- cell lymphomas are limited and not curative
- There is a need for new therapeutic approaches

Cancer Treatment Centers of America

part of City of Hope

Do-Youn Oh, MD, PhD

New Drug Development in Biliary Tract Cancer

Do-Youn Oh, MD, PhD,

Professor, Division of Medical Oncology, Department of Internal Medicine, Seoul National University and Seoul National University College of Medicine

CYCLACEL

New Drug Development in Biliary Tract Cancer

Do-Youn Oh, MD., PhD.

Medical Oncology, Seoul National University Hospital
Cancer Research Institute,
Seoul National University College of Medicine

31 Oct 2022, Cyclacel R&D Day

COI

- **Consultant/Advisory Board:**

AstraZeneca, Novartis, Genentech/Roche, Merck Serono , Bayer, Taiho, ASLAN, Halozyme, Zymeworks, BMS/Celgene, BeiGene, Basilea, Turning Point, Yuhan, Arcus Biosciences, IQVIA, MSD

- **Research Grant :**

AstraZeneca, Novartis, Array, Eli Lilly, Servier, BeiGene, MSD, Handok

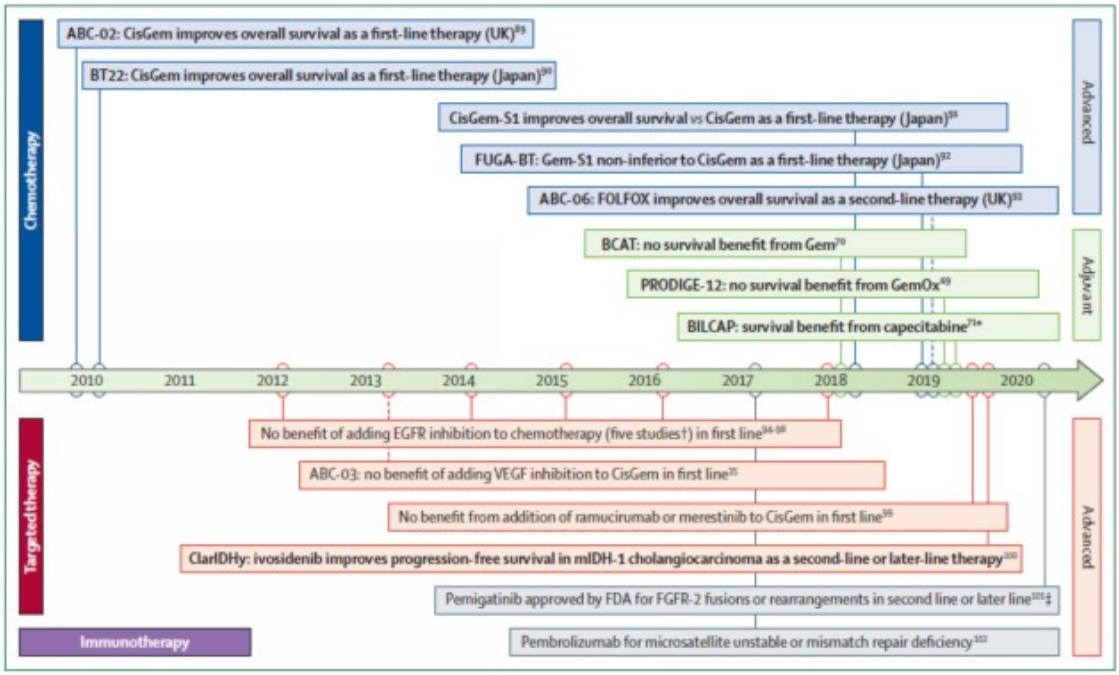
BTC: NON-RARE Cancer in Korea

Incidence of **cholangiocarcinoma**

Incidence of **gallbladder cancer**

Valle JW, Oh DY, et al. Lancet. 2021

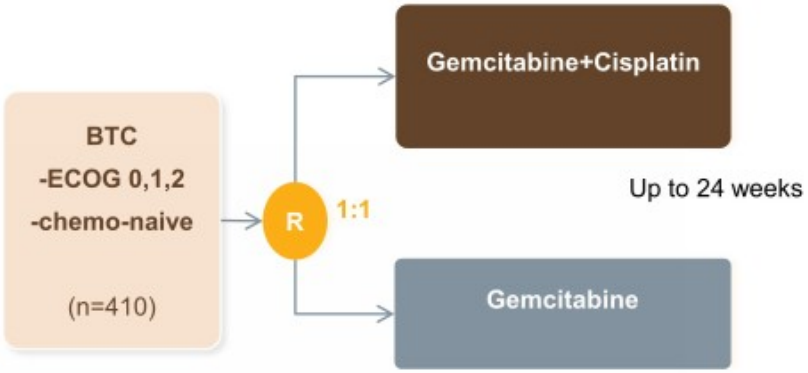
Developments in systemic therapy of BTC



Valle JW, Oh DY, et al. Lancet. 2021

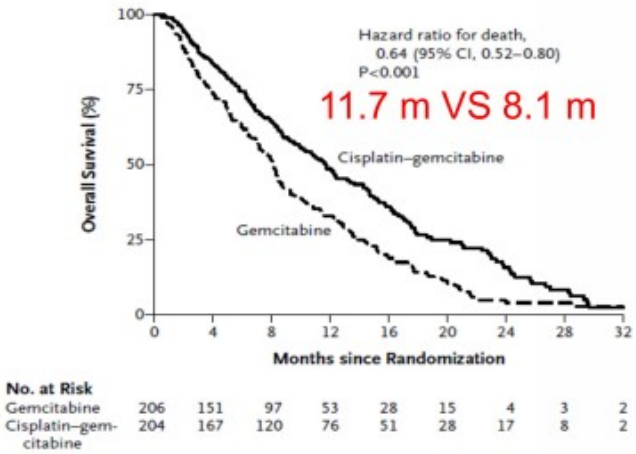
1st-line, BTC

✓ ABC-02, UK



→ **Primary endpoint:** OS

OS



No. at Risk									
Gemcitabine	206	151	97	53	28	15	4	3	2
Cisplatin–gemcitabine	204	167	120	76	51	28	17	8	2

Valle J et al. NEJM 2010

Clinical trials, 1L, BTC

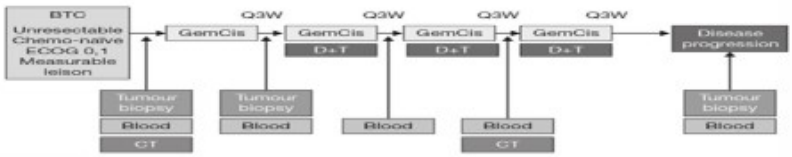
	Phase	Control	Experimental	OS (m)	HR
ABC-02	III	Gem	GemCis	8.1 vs 11.7	0.64
BT22	II	Gem	GemCis	7.7 vs 11.2	0.69
JCOG1113	III	GemCis	Gem+S1	13.4 vs 15.1	0.95 (non-inferiority)
KHBO1401-MITSUBA	III	GemCis	GemCis+S1	12.6 vs 13.5	0.79 (0.60-1.04)
Lee et al	III	GemOx	GemOx+Erlotinib	9.5 vs 9.5	0.93
BINGO	II	GemOx	GemOx+Cetuximab	12.4 vs 11.0	
Hezel et al	II	GemOx	GemOx+Panitumumab	10.2 vs 9.9	
JSBF	II	GemCis	GemCis+ Ramucirumab GemCis+Merestinib	13.0 vs 10.5 13.0 vs 14.0	1.33 (0.96-1.86) 0.95 (0.67-1.34)
NuTide	III	GemCis	NUC1031+Cis	negative	

IO+Chemotherapy in BTC

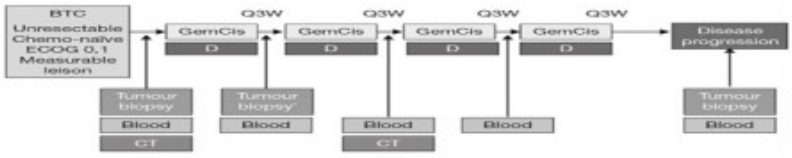
- Durvalumab+ Chemotherapy, 1L, BTC

➢BTC-1st MEDITREME

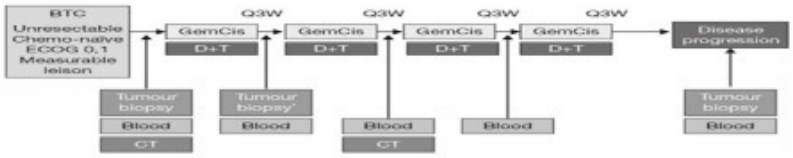
Cohort 1: GC->GC+D+T



Cohort 2: GC+D



Cohort 3: GC+D+T



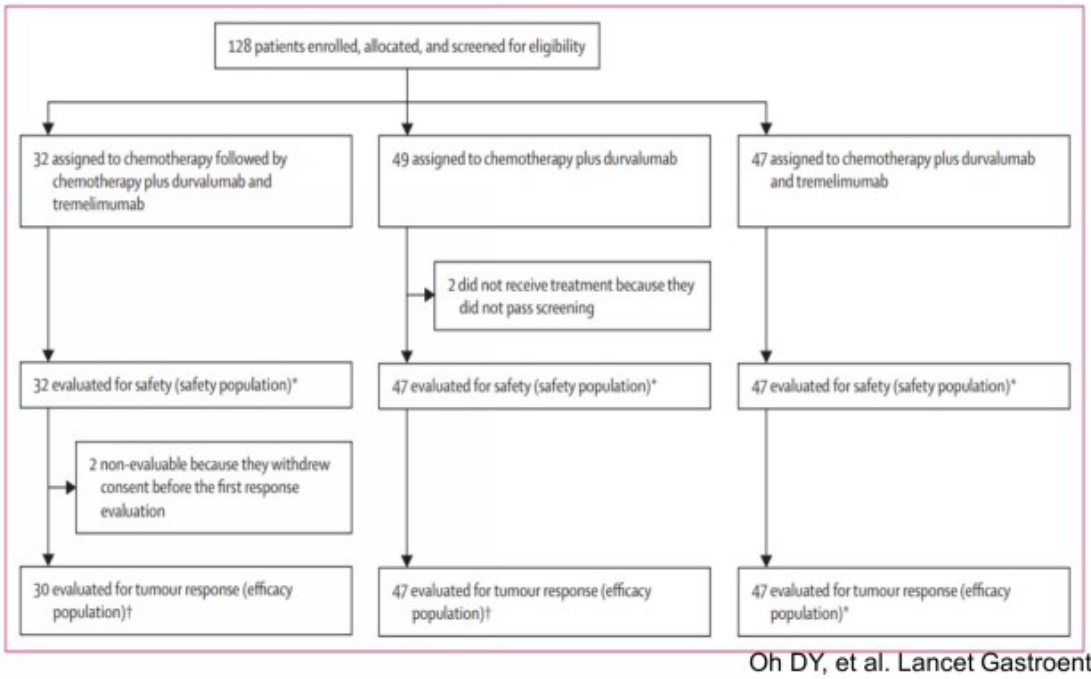
GC:GemCis
D:Durvalumab,
T: Tremelimumab, maximum 4 cycles

ClinicalTrials.gov Identifier: NCT03046862

Oh DY, et al. Lancet Gastroenterol Hepatol 2022

BTC-1st MEDITREME

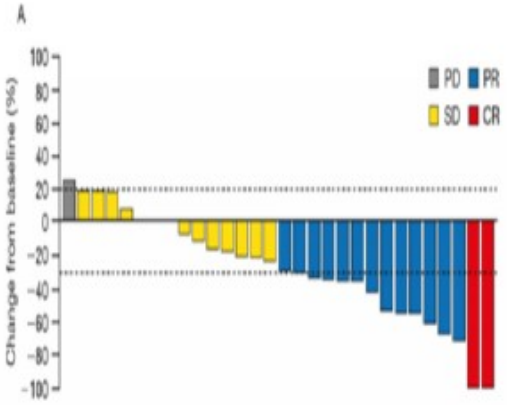
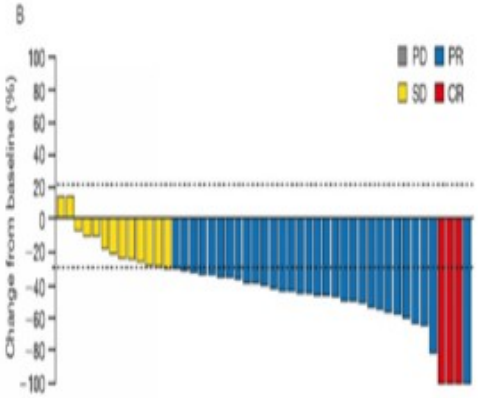
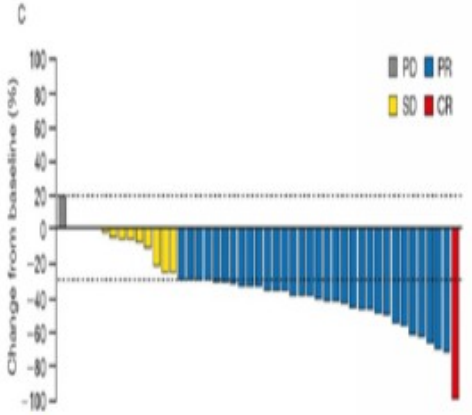
- Patient enrollment



Oh DY, et al. Lancet Gastroenterol Hepatol 2022

BTC-1st MEDITREME

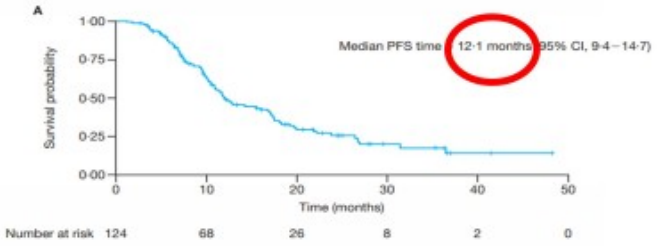
➢ Treatment response

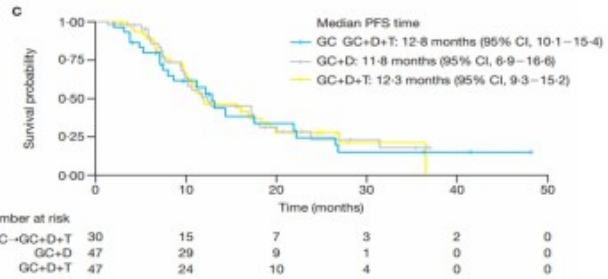
Cohort 1: GC->GC+D+T	Cohort 2: GC+D	Cohort 3: GC+D+T
		
ORR: 50% (95% CI, 33–67)	ORR: 72% (95% CI, 58-83)	ORR: 70% (95% CI, 56-81)

Oh DY, et al. Lancet Gastroenterol Hepatol 2022

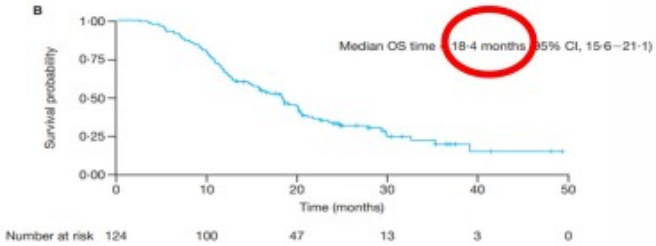
BTC-1st MEDITREME

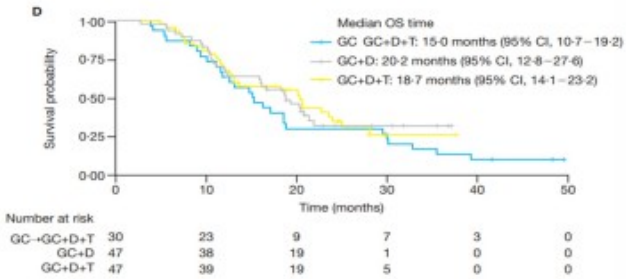
➢ PFS





➢ OS





Oh DY, et al. Lancet Gastroenterol Hepatol 2022

TOPAZ-1 study design

TOPAZ-1 is a double-blind, multicenter, global, Phase 3 study

Key eligibility
- Locally advanced or metastatic BTC (ICC, ECC, GBC)
- Previously untreated if unresectable or metastatic at initial diagnosis
- Recurrent disease >6 months after curative surgery or adjuvant therapy
- ECOG PS 0 or 1

Stratification factors
- Disease status
  - (initially unresectable versus recurrent)
- Primary tumor location
  - (ICC versus ECC versus GBC)

R (1:1)
N=685

Durvalumab 1500 mg Q3W + GemCis (up to 8 cycles) → Durvalumab 1500 mg Q4W until PD

Placebo Q3W + GemCis (up to 8 cycles) → Placebo Q4W until PD

Primary objective
- Overall survival

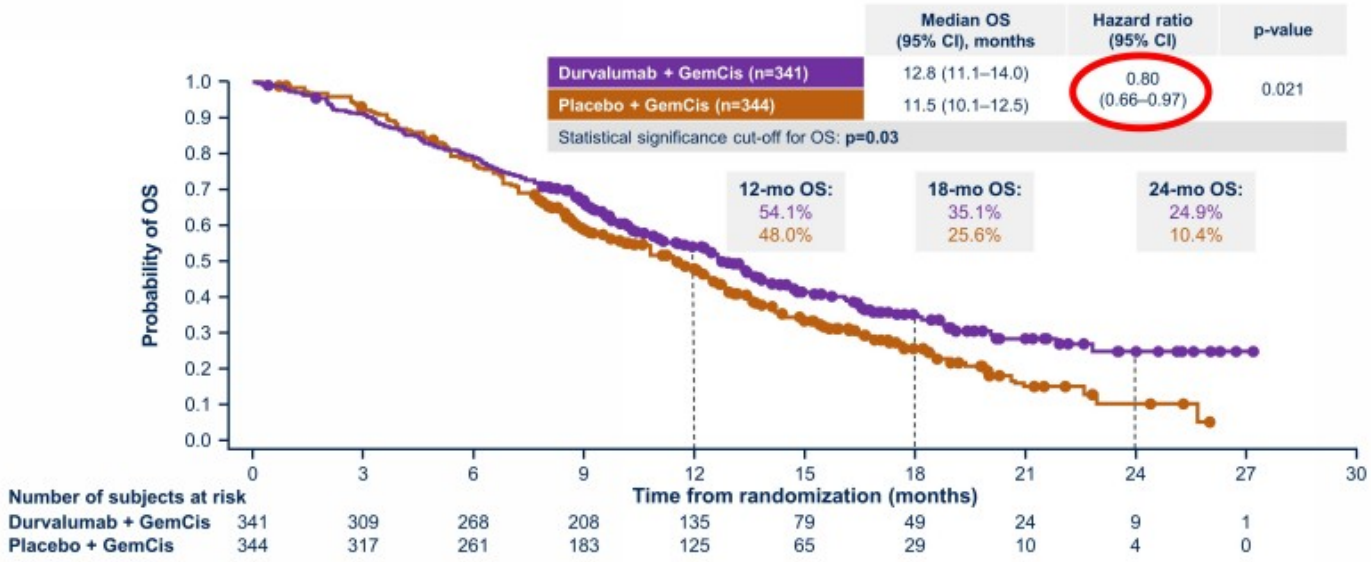
Secondary objectives
- Progression-free survival
- Objective response rate
- Duration of response
- Efficacy by PD-L1 status
- Safety

GemCis treatment: gemcitabine 1000 mg/m2 and cisplatin 25 mg/m2 on Days 1 and 8 Q3W administered for up to 8 cycles.

BTC, biliary tract cancer; ECC, extrahepatic cholangiocarcinoma; ECOG, Eastern Cooperative Oncology Group; GBC, gallbladder cancer; GemCis, gemcitabine and cisplatin; ICC; intrahepatic cholangiocarcinoma; PD, progressive disease; PD-L1, programmed cell death ligand-1; PS, performance status; QnW, every n weeks; R, randomization.

Oh DY, et al. ASCO GI 2022

TOPAZ-1, Primary endpoint: OS

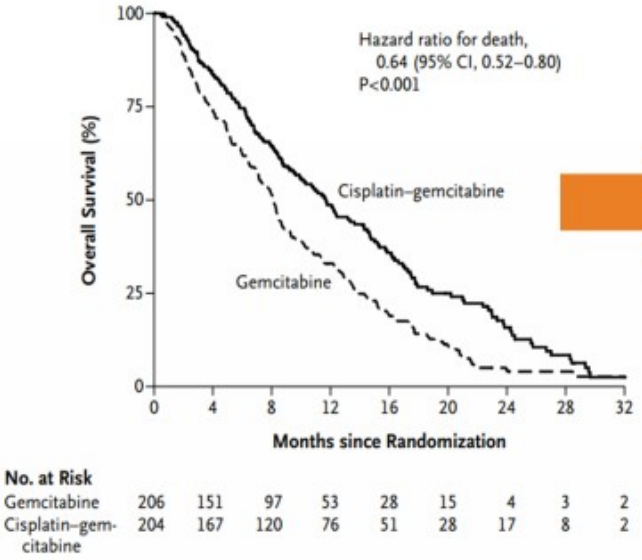


Median duration of follow-up (95% CI) was 16.8 (14.8–17.7) months with durvalumab + GemCis and 15.9 (14.9–16.9) months with placebo + GemCis.
CI, confidence interval; GemCis, gemcitabine and cisplatin; HR, hazard ratio; mo, month; OS, overall survival.

Oh DY, et al. NEJM Evidence 2022

BTC, 1L, OS

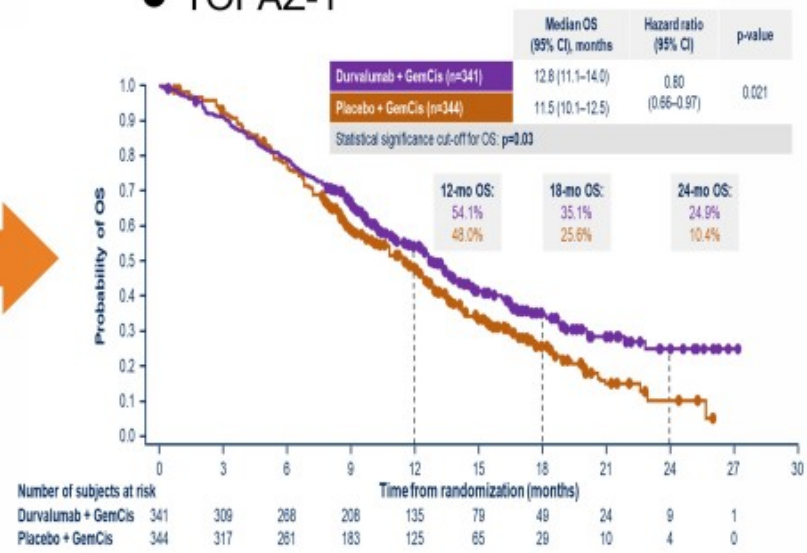
- ABC-02



No. at Risk									
Gemcitabine	206	151	97	53	28	15	4	3	2
Cisplatin–gemcitabine	204	167	120	76	51	28	17	8	2

Valle J, et al. NEJM 2010

- TOPAZ-1



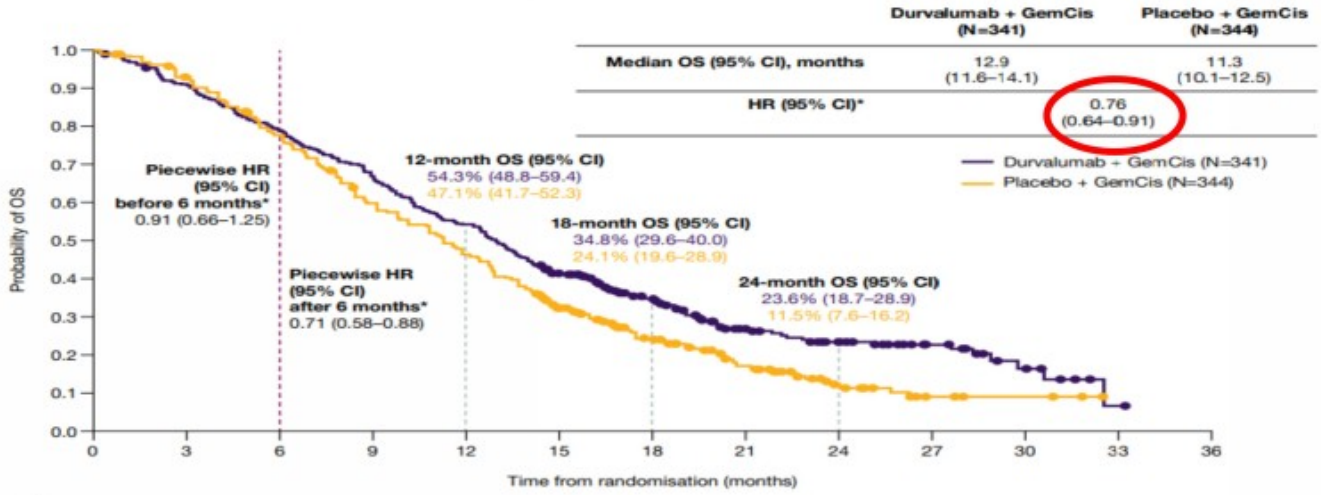
Number of subjects at risk										
Durvalumab + GemCis	341	309	268	208	135	79	49	24	9	1
Placebo + GemCis	344	317	261	183	125	65	29	10	4	0

Oh DY, et al. NEJM Evidence 2022

Long-term FU (+6.5 months more FU)

Data cut-off: 25 Feb 2022
OS event maturity: 76.9%

- Overall Survival



No. at risk

Durvalumab + GemCis	341	331	324	309	294	278	268	252	240	227	208	194	184	169	152	134	117	96	88	74	61	52	47	44	36	33	27	21	17	10	8	5	3	1	0
Placebo + GemCis	344	337	329	316	298	282	260	241	222	198	187	175	158	138	125	104	92	76	65	53	47	37	29	21	14	11	9	5	3	3	3	2	1	0	0

*Durvalumab + GemCis versus placebo + GemCis. An HR <1 favours durvalumab + GemCis
CI, confidence interval; GemCis, gemcitabine and cisplatin; HR, hazard ratio; OS, overall survival

Oh DY, et al. ESMO 2022

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2022
Biliary Tract Cancers

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

Primary Treatment for Unresectable and Metastatic Disease

Preferred Regimens

- Gemcitabine + cisplatin[4] (category 1)
- Durvalumab + gemcitabine + cisplatin (category 1)[d,5]

Other Recommended Regimens

- 5-fluorouracil + oxaliplatin
- 5-fluorouracil + cisplatin (category 2B)
- Capecitabine + cisplatin (category 2B)
- Capecitabine + oxaliplatin
- Gemcitabine + albumin-bound paclitaxel
- Gemcitabine + capecitabine
- Gemcitabine + oxaliplatin
- Gemcitabine + cisplatin + albumin-bound paclitaxel[1] (category 2B)
- Single agents:
  - 5-fluorouracil
  - Capecitabine
  - Gemcitabine

Useful in Certain Circumstances

- For *NTRK* gene fusion-positive tumors:
  - Entrectinib[6-8]
  - Larotrectinib[9]
- For MSI-H/dMMR tumors:
  - Pembrolizumab[e,f,10,11]
- For *RET* fusion-positive tumors:
  - Pralsetinib (category 2B)[12]

d Durvalumab + gemcitabine + cisplatin is also a recommended treatment option for patients who developed recurrent disease >6 months after surgery with curative intent and >6 months after completion of adjuvant therapy

5. Oh DY, He AR, Qin S, et al. Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer. NEJM Evid 2022:1-11. Epub ahead of print.

FDA Approval, 02 Sep 2022

U.S. FOOD & DRUG ADMINISTRATION

Search | Menu

Home / Drugs / Development & Approval Process | Drugs / Drug Approvals and Databases / Resources for Information | Approved Drugs / FDA approves durvalumab for locally advanced or metastatic biliary tract cancer

FDA approves durvalumab for locally advanced or metastatic biliary tract cancer

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Resources for Information | Approved Drugs

Oncology (Cancer) / Hematologic Malignancies Approval Notifications

Ongoing | Cancer Accelerated Approvals

Verified Clinical Benefit | Cancer Accelerated Approvals

On September 2, 2022, the Food and Drug Administration approved durvalumab (Imfinzi, AstraZeneca UK Limited) in combination with gemcitabine and cisplatin for adult patients with locally advanced or metastatic biliary tract cancer (BTC).

Efficacy was evaluated in TOPAZ-1 (NCT03875235), a randomized, double-blind, placebo-controlled, multiregional trial that enrolled 685 patients with histologically confirmed locally advanced unresectable or metastatic BTC who had not previously received systemic therapy for advanced disease.

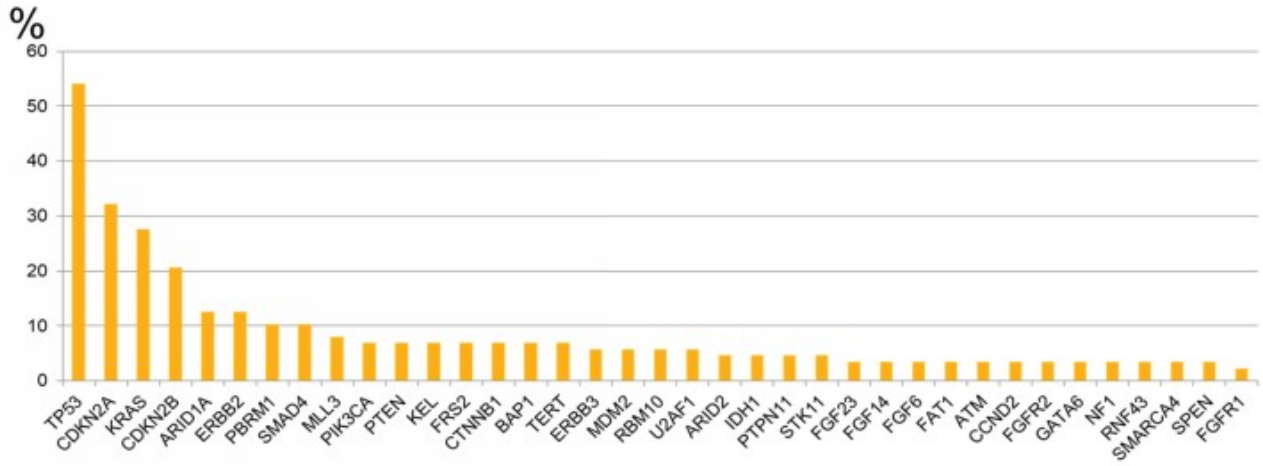
Trial demographics were as follows: 56% Asian, 37% White, 2% Black, and 4% other race; 7% Hispanic or Latino; 50% male and 50% female; median age was 64 years (range 20-85) and 47% were 65 years or older. Fifty-six percent had intrahepatic cholangiocarcinoma, 25% had gallbladder cancer, and 19% had extrahepatic cholangiocarcinoma.

Content current as of:
09/02/2022

Regulated Product(s)
Drugs

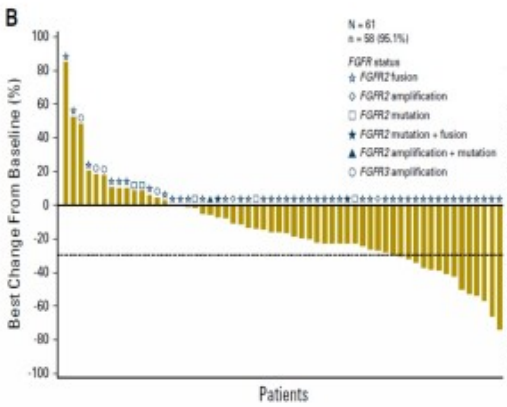
Molecular spectra of BTC

SNUH, BTC, Foundation One



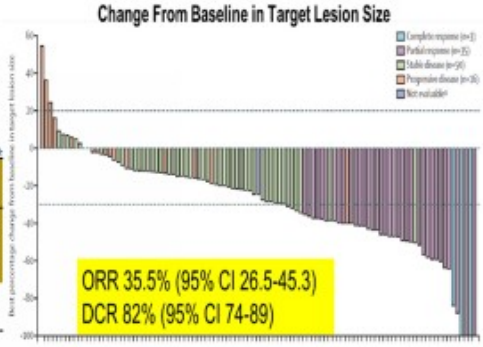
Targeting FGFR2 fusion/translocation in BTC

Infigratinib (BGJ398)



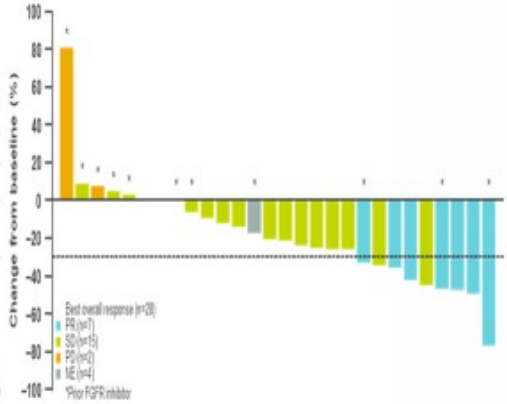
May 2021, FDA Approval

Pemigatinib (INCB54828)



Apr 2020, FDA Approval

Futibatinib (TAS-120)

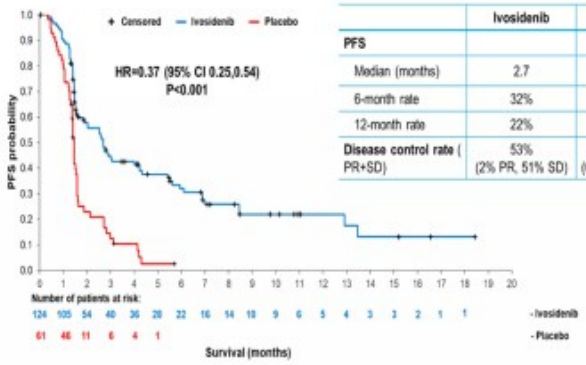


Sep 2022, FDA Approval

Targeting IDH1 in BTC

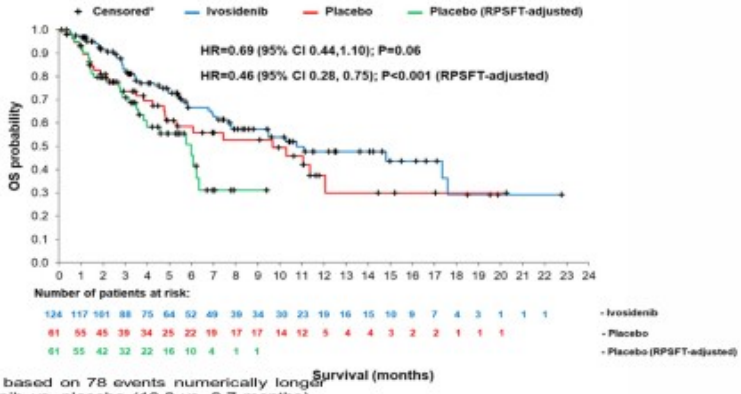
✓ ClarIDHy, IDH1 Mutation (+) CC, Phase III

PFS



	Ivosidenib	Placebo
PFS		
Median (months)	2.7	1.4
6-month rate	32%	NE
12-month rate	22%	NE
Disease control rate (PR+SD)	53% (2% PR, 51% SD)	28% (0% PR, 28% SD)

OS



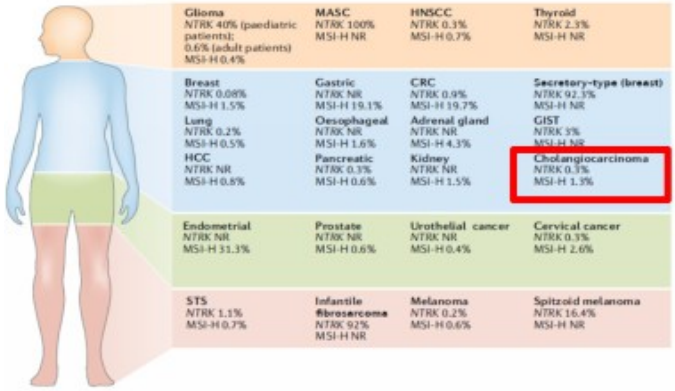
- Median OS based on 78 events numerically longer with ivosidenib vs. placebo (10.8 vs. 9.7 months).
  - OS rates at 6- and 12-months for ivosidenib: 67% and 48% vs. 59% and 38% for placebo.
- Rank-preserving structural failure time (RPSFT)[1,2] method used to reconstruct the survival curve for the placebo subjects as if they had never crossed over to ivosidenib.
- With the RPSFT method, the median OS with placebo adjusts to 6 months.

Aug 2021, FDA Approval

Abou-Alfa GK, Oh DY, et al. Lancet Oncol 2020

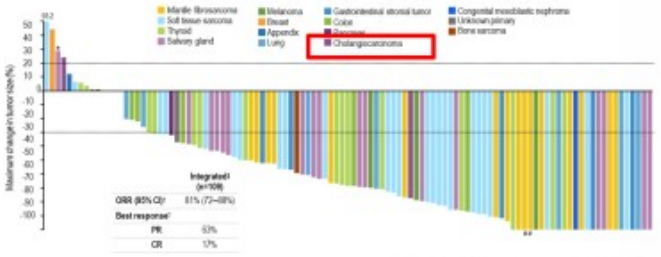
Targeting MSI-H, NTRK in BTC

●Tissue-agnostic approach



Pestana RC, et al. Nat Rev Clin Oncol 2020

➢ Larotrectinib is efficacious regardless of tumor type



Ulrik L, Oh DY, et al. ESMO 2018

● Pembrolizumab

➢ Solid tumours exhibiting dMMR or MSI-H

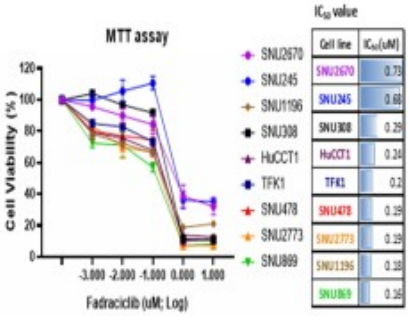
➢ Data supporting pembrolizumab approval by FDA

- ✓ 15 Different tumor types
- ✓ ORR: 39.6% (CR 7%)
- ✓ Response duration: 1.6+ m~ 22.7+ m
- ✓ 78% of response lasting> 6months

Source: Keytruda labeling, BLA submission, FDA review documents

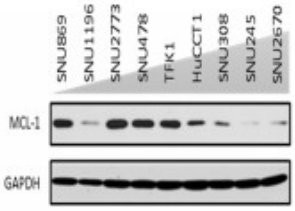
Targeting CDK2/9 in BTC

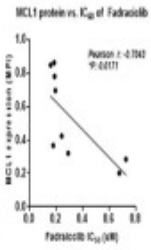
- Fadraciclib (CYC-065) controls BTC cell growth.
  - BTC cells with high MCL1 are relatively sensitive to Fadraciclib

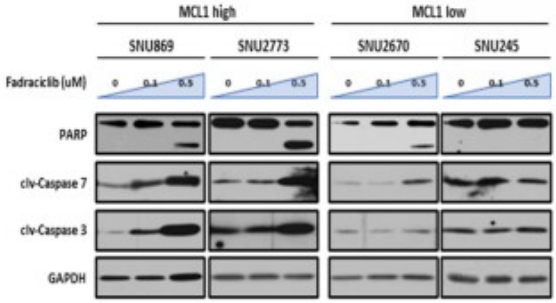


IC_{50} value

Cell line	IC_{50}(uM)
SNU2670	0.73
SNU245	0.68
SNU308	0.29
HuCCT1	0.24
TFK1	0.2
SNU478	0.19
SNU2773	0.19
SNU1196	0.18
SNU869	0.16



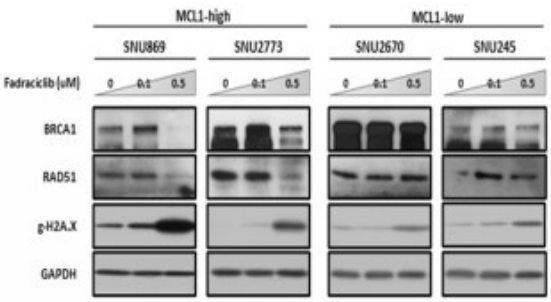


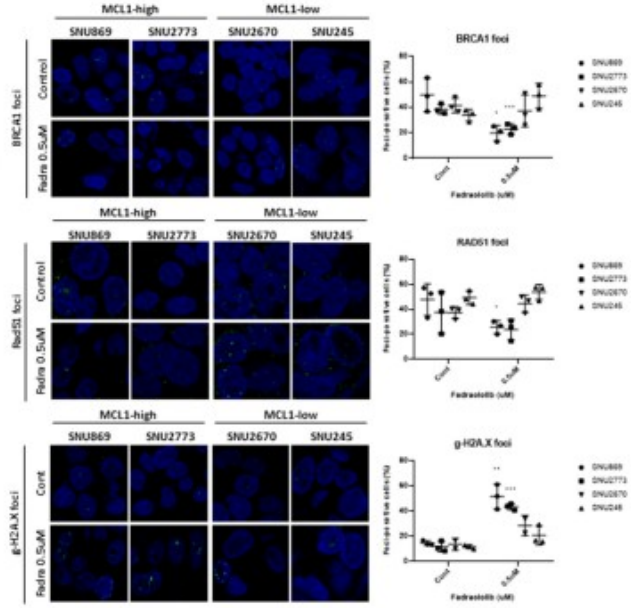


Kim JM, Oh DY, et al. Unpublished data

Targeting CDK2/9 in BTC

- Fadraciclib (CYC-065) downregulates the expression of HR factors.

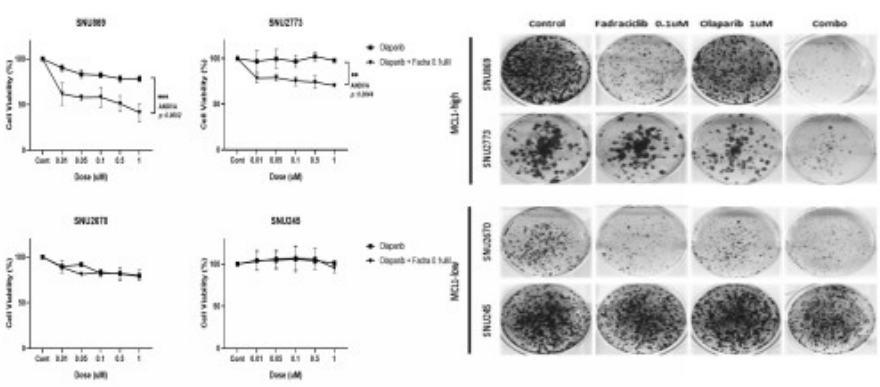


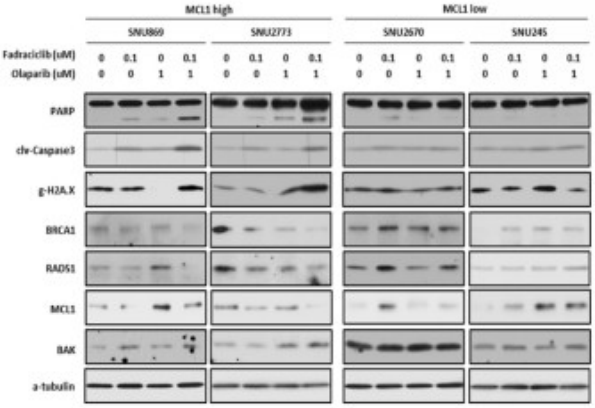


Kim JM, Oh DY, et al. Unpublished data

Targeting CDK2/9 in BTC

- Fadraciclib (CYC-065) sensitizes MCL1-high BTC cells to olaparib (PARP inhibitor)

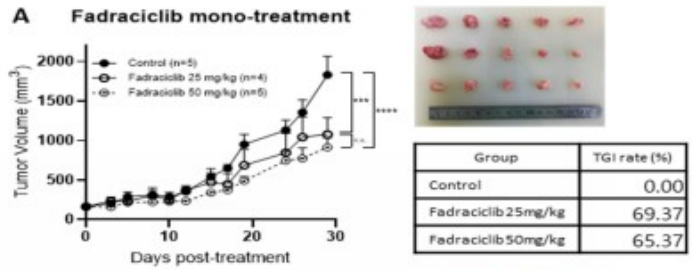




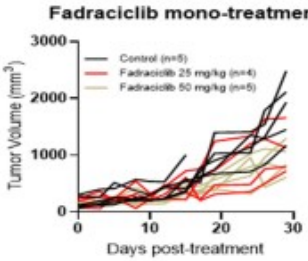
Kim JM, Oh DY, et al. Unpublished data

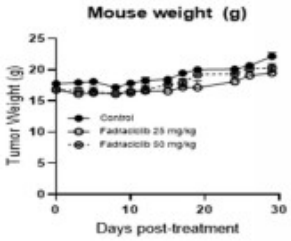
Targeting CDK2/9 in BTC

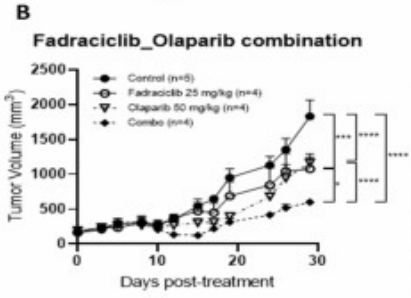
- Fadraciclib (CYC-065) shows antitumor effects in BTC xenograft model.

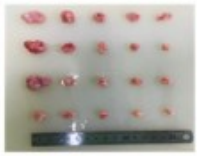


Group	TGI rate (%)
Control	0.00
Fadraciclib 25mg/kg	69.37
Fadraciclib 50mg/kg	65.37

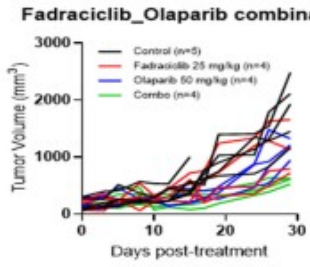


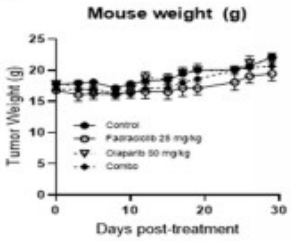






group	TGI rate (%)
Control	0.00
Fadraciclib 25mg/kg	69.37
Olaparib 50mg/kg	51.49
Combo	79.76





Kim JM, Oh DY, et al. Unpublished data

Current status and future perspectives in BTC

- New SOC in 1L using immunotherapy+chemotherapy combination.
- Targeting genetic subsets (FGFR2 fusion, IDH1 mutation) has shown success.
- Many clinical trials for various targets (genetic subset, immune, etc) are ongoing in BTC.

Blue Ocean in New Drug Development

Fadraciclib CDK2/9 Inhibitor Clinical Update

Mark Kirschbaum, MD
Chief Medical Officer,
Cyclacel Pharmaceuticals, Inc.

Dual Inhibition of CDK2 & CDK9= Multiple Antitumor Mechanisms

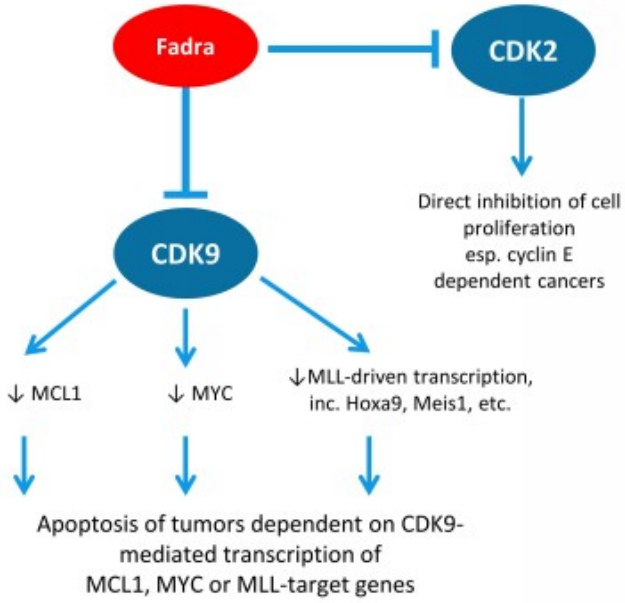
Anti-**apoptotic** protein (MCL1, MYC, MYCN, MYB, MDM2, etc. …[1,2]) overexpression in **solid tumors** & **leukemias**

Cyclin E (*CCNE*) overexpression > drug resistance in **women's cancers**, e.g.

- HR +ve CDK4/6 inhibitor refractory breast cancer
  - *Palbociclib + HR regimen failure stat sig correlated with cyclin E overexpression (PALOMA-3)* [3]
- HER2 +ve refractory breast cancer
  - *Cyclin E amplification/overexpression is a mechanism of trastuzumab (Herceptin®) resistance* [4]

CDK2 is an escape mechanism for CDK9

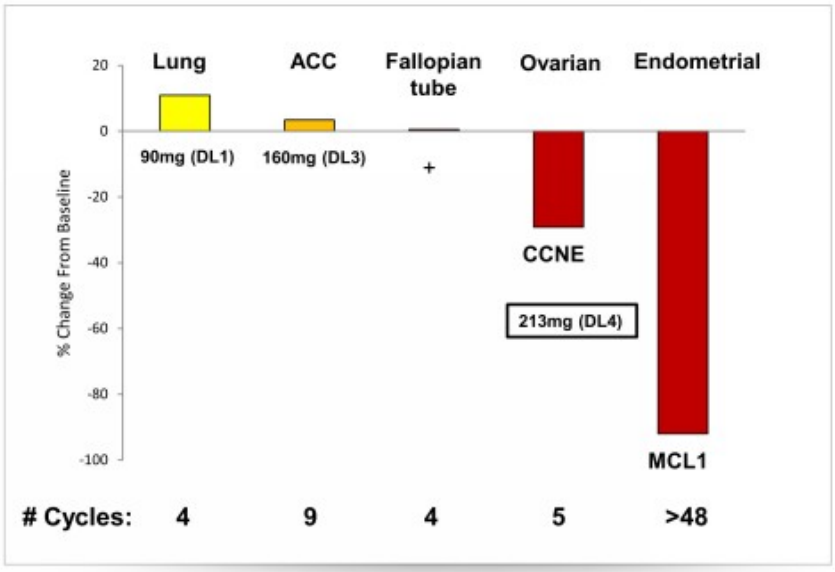
CDK2 also degrades MCL1



CYCLACEL

[1] Poon E et al, JCI 2020. [2] Frame S et al, PLOS One, 2020. [3] Turner NC et al; JCO 2019. [4] Scaltriti M et al, PNAS, 2011.

Fadraciclib IV 065-01 Ph 1 Part 2 Data *(unselected, late line)*



Tumors with MCL1 and CCNE overexpression respond to fadraciclib single agent

- Improved efficacy with more frequent 1h infusions on d1, 2, 8, 9 every 3wk
- SD >4 cycles in cyclin E amplified ovarian cancer; 29% shrinkage of all target lesions
- Confirmed PR at 4 cycles (MCL1 amplified endometrial cancer); 100% shrinkage of all baseline target lesions and CR at 1.5 years; deep ongoing response at 3 years

CYCLACEL® *Data on file. + Non-measurable target tumor lesion.*

Fadraciclib Oral 065-101 Ph 1/2 Solid Tumor *(ongoing, unselected, late line)*

- Currently evaluating 150mg bid daily 4 out of 4 weeks (level 6 of up to 7 dose levels)
- 18 patients treated across 5 cohorts without dose limiting toxicities up to 100mg bid daily 4 out of 4 weeks
- PoC part of the study across multiple tumor types expected to begin 1H 2023

Dose Escalation*
(3+3; unselected, all comer, late line)

	Active
7th Dose Level *200mg bid daily M to F (4/4 wk)*	
6th Dose Level **150mg bid daily M to F (4/4 wk)**	
5th Dose Level (n=6) *100mg bid daily M to F (4/4 wk)*	✓
4th Dose Level (n=3) *100mg bid daily M to F (3/4 wk)*	✓
3rd Dose Level (n=3) *75mg bid daily M to F (3/4 wk)*	✓
2nd Dose Level (n=3) *50mg bid daily M to F (3/4 wk)*	✓
Starting Dose Level (n=3) *50mg bid daily MWF (3/4 wk)*	✓

Proof of Concept (PoC)**
(Simon 2-stage; 2nd /3rd line)

Cohort 1: Endometrial, Ovarian

Cohort 2: Cholangiocarcinoma

Cohort 3: Hepatocellular Carcinoma

Cohort 4: Breast (post-CDK4/6i, TNBC, HER-2 refractory)

Cohort 5: Lymphoma (B-cell)

Cohort 6: Lymphoma (T-cell)

Cohort 7: mCRC (including KRAS mutated)

Cohort 8 Basket: biomarker selected suspected to have related MoA (expand if responses seen)

Pivotal
(if randomized study not needed)

Single-arm, open label, study for n=TBD cancer patients in a histology from PoC

Pivotal indication to be determined based on clinical data from PoC

ClinicalTrials.gov Identifier: NCT04983810.

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**Single agent **Single agent; followed by combination TBD: To be disclosed.*

Fadraciclib Oral 065-101 Safety (*Interim Results*)

- Single agent well tolerated thus far up to and including DL5
- No DLTs related to study drug

Fadraciclib Oral 065-101 SAE List *(interim, ongoing study)*

ID	Cohort	Event Preferred Term	CTCAE Grade	Causal Relationship
102-001	Dose Level 1	Abdominal pain	2	Not related
102-002	Dose Level 1	Accidental overdose	1	Not Applicable
		Wound secretion	2	Not related
		Obstructive airways disorder	2	Not related
		Productive cough	3	Not related
		Dysphagia	2	Not related
102-004	Dose Level 2	Acute respiratory failure	2	Not related
		Dyspnoea	2	Not related
		Urinary retention	2	Not related
		Disease Progression	5	Not related
		Spinal cord compression	3	Not related
102-009	Dose Level 2	Hyperglycaemia	3	Not related
		Accidental overdose	1	Not Applicable
101-010	Dose Level 3	Cerebral haemorrhage	3	Not related
		Brain edema	3	Not related
		Cerebral haematoma	3	Not related
101-013	Dose Level 3	Abdominal Pain	3	Not related
		Blood bilirubin increased	4	Not related
		Hyponatremia	3	Not related
302-016	Dose Level 4	Cholangitis	3	Not related
		Pain	2	Not related
102-024	Dose Level 5	Seizure	2	Not related

CYCLACEL® *Data on file.*

Fadraciclib Oral 065-101 Related TEAE List *(interim, ongoing study)*

Cohort	TEAE by Preferred Term	All Grades, n	Grade ≥ 3, n
Dose Level 1	Decreased appetite	1	0
	Lymphocyte count decreased	1	1
	Chills	1	0
	Anaemia	1	0
	Hypoalbuminaemia	1	1
	Hypocalcaemia	1	0
	Nausea	1	0
	Accidental overdose	1	0
	Weight decreased	1	0

Fadraciclib Oral 065-101 Related TEAE List *(interim, ongoing study)*

Cohort	TEAE by Preferred Term	All Grades, n	Grade ≥ 3, n
Dose Level 2	Decreased appetite	2	0
	White blood cell count decreased	1	1
	Vomiting	3	0
	Nausea	2	0
	Thrombocytopenia	3	1
	Diarrhoea	1	0
	Fatigue	2	1
	Rash maculo-papular	1	0
	Dry mouth	1	0
	Blood triglycerides increased	1	1
	Accidental overdose	1	0
	Lymphocyte count decreased	1	1
	Dehydration	1	0
	Hyperglycaemia	1	1
	Insomnia	1	0
	Taste disorder	1	0
	Visual impairment	1	0

CYCLACEL® *Data on file.*

Fadraciclib Oral 065-101 Related TEAE List *(interim, ongoing study)*

Cohort	TEAE by Preferred Term	All Grades, n	Grade ≥ 3, n
Dose Level 3	Thrombocytopenia	1	0
	Diarrhoea	1	0
	Ageusia	1	0
	Decreased appetite	1	0
	Vomiting	1	0
	Nausea	1	0
	Taste disorder	1	0
Dose Level 4	Diarrhoea	1	0
	Nausea	3	0
	Dry mouth	1	0
Dose Level 5	Blood creatinine increased	2	0
	Diarrhoea	3	0
	Fatigue	2	0
	Nausea	3	0
	Vomiting	2	0
	Abdominal pain	1	0
	Neutrophil count decreased	1	0
	Lymphocyte count decreased	1	1
	Gastritis	1	0
	Thrombocytopenia	1	0
	Hyperglycaemia	1	0

Data on file.

Fadraciclib Oral 065-101 Response Data (*interim*)

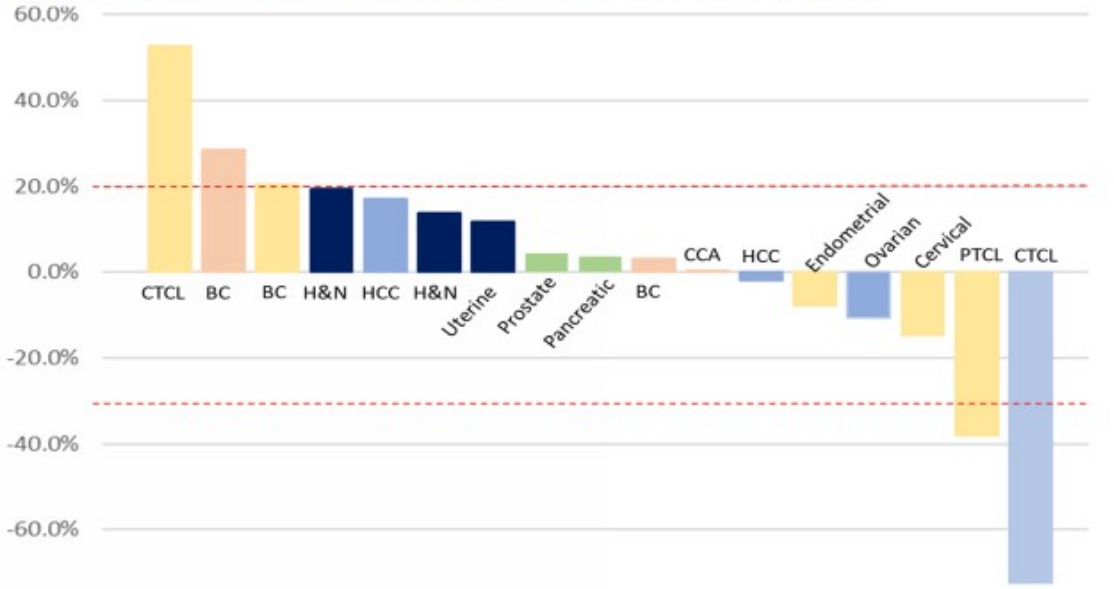
Best Overall Response	*n/N*
Complete Response (CR)	-
Partial Response (PR)	2/18*
Stable Disease (SD)	11/18
Progressive Disease (PD)	5/18
Activity by dosing level (DL)	***n/N (PR+SD)***
DL5 *(3 pts ongoing; 200mg/d x5 days continuously)*	3/6 (1+2)
DL4	1/3 (0+1)
DL3	3/3 (0+3)
DL2	3/3 (1+2)
DL1	2/3 (0+2)

PR or SD by histology	*n/N*
Gyn (endometrial, ovarian, cervical/uterine)	4/4
T-cell lymphoma	2/3
Breast	0/3
Hepatocellular	2/2
Prostate	2/2
Head & neck	1/2
Cholangiocarcinoma	1/1
Pancreatic	1/1

CYCLACEL® *Data on file * CTCL, PTCL.*

Fadraciclib Oral 065-101 Interim Data *(ongoing, unselected, late line)*

Best percentage change from baseline in target lesions (all response types)



Response Criteria by:

- RECIST 1.1 (N=14)
- mSWAT (N=1)
- Lugano (N=2)

BC=breast cancer

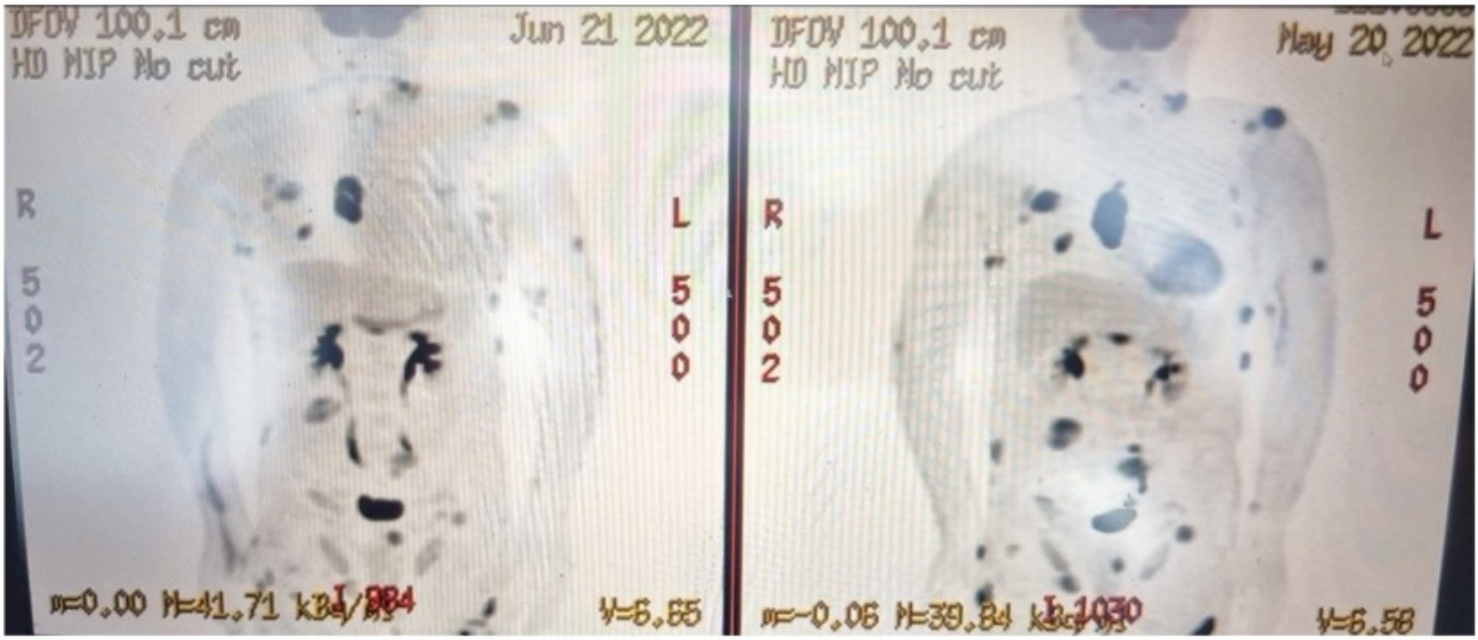
CCA=cholangiocarcinoma

H&N=head & neck cancer

HCC=hepatocellular cancer

CYCLACEL® *Data on file.*

PR in angioimmunoblastic PTCL pt. *(oral 065-101 DL5 Lugano criteria)*



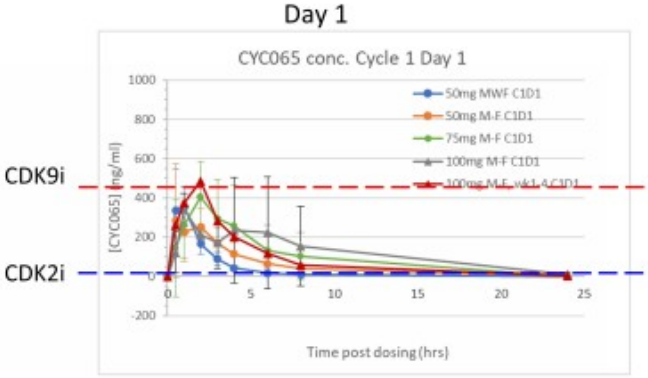
CYCLACEL® *Data on file. PET scan images kindly provided by the principal investigator.*

Target Engagement Levels Achieved for ~5h Continuous Dosing

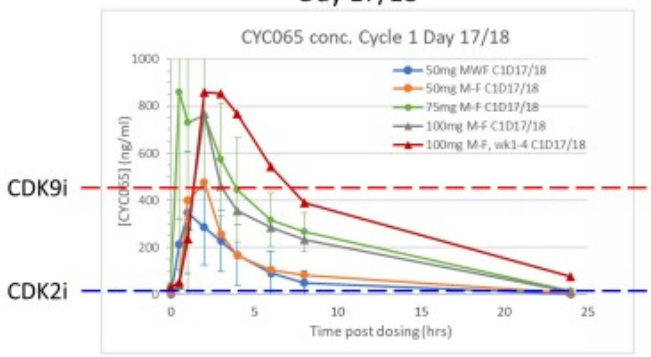
Plasma Concentration Post Oral Fadraciclib DL1-5 Patients (Interim)

CDK9 target engagement
CDK2 target engagement

Day 1



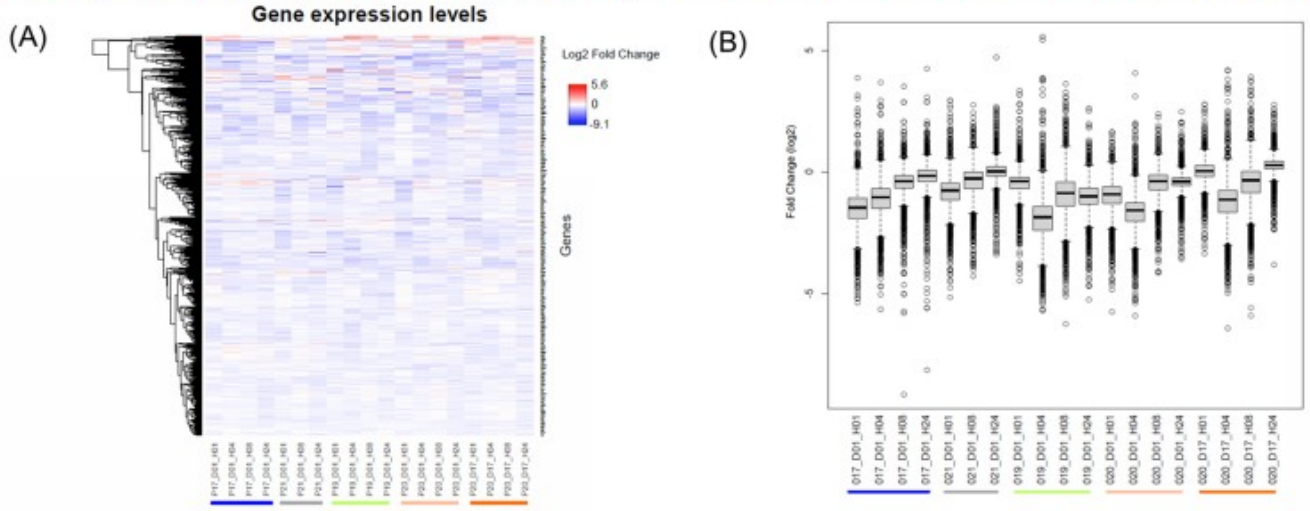
Day 17/18



Plasma concentration (mean ± SD) from PK samples collected from patients on Cycle 1 Day 1 and Cycle 1 Day 17/18 in 065-101 Ph 1/2 Solid Tumor Study (*Interim Results*).

CDK9 Inhibition at DL5 Induces Broad Transcriptional Inhibition

Pharmacodynamic Response in Whole Blood by RNAseq Oral Fadraciclib 065-101 Solid Tumor DL5 Patients (Interim)



PD samples at baseline, 1, 4, 8, 24 h post-treatment on Cycle 1 Day 1 and C1 D17/18. TPM by mRNAseq. Differential gene expression determined relative to baseline after normalization to housekeeping genes. (A) For 1h or 4h timepoints average fold change (across samples) in gene expression is ≥2 for 3347 protein-coding genes (heatmap illustrates differential gene expression). (B) Boxplot shows distribution of gene expression fold changes across samples. Horizontal line = mean, 2nd to 3rd quartiles boxed, 1st to 4th quartiles dashed, statistical outliers to normal distribution circles. Samples labelled by "Subject No.Day Hour". Data on file.

Fadraciclib Oral 065-101 Interim Results Summary

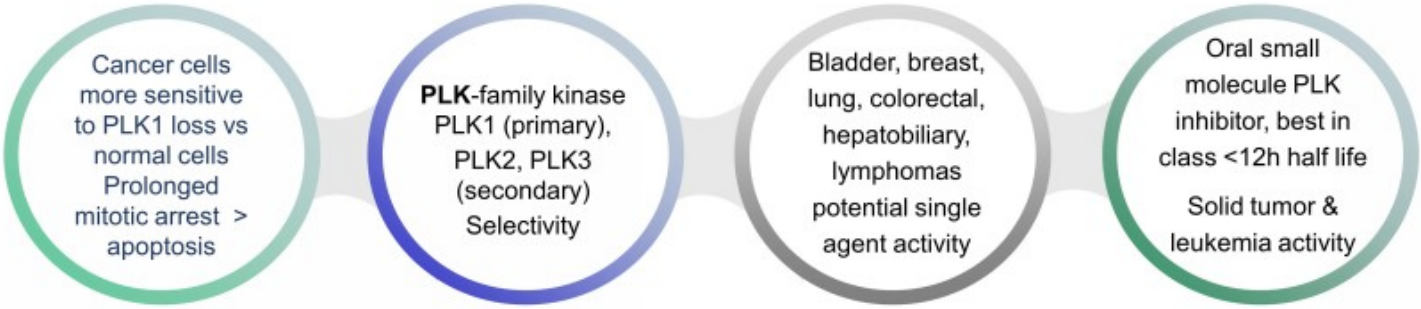
- 18 pts evaluable with advanced solid tumors or lymphoma treated in DL 1-5 (median treatment duration is 2.4 cycles; range 1-5 cycles)
- Well tolerated in all dose levels thus far (including DL5 100mg bid, M-F, week 1-4 in 28-day cycles)
- Two PRs in T-cell lymphoma pts; 4 pts (cervical, endometrial, HCC, ovarian cancer) showed target lesion reduction and a pancreatic cancer pt stable disease for 5 cycles
- Target engagement levels achieved for ~5 hours per dose on continuous dosing
- Enrollment continues at DL6 (150mg bid, M-F, week 1-4)
- Confirmed CR continues for 3 years in a subject with MCL1-amplified endometrial cancer dosed at 213mg IV d1,2,8,9 q3w in earlier Phase 1 study of fadraciclib IV

CYCLACEL® •Data on file

CYC140 PLK1 Inhibitor Preclinical & Clinical Update

Mark Kirschbaum, MD
Chief Medical Officer,
Cyclacel Pharmaceuticals, Inc.

CYC140 A Differentiated PLK1 Inhibitor



Ongoing Ph 1/2: biologically-optimal schedules require continuous dosing

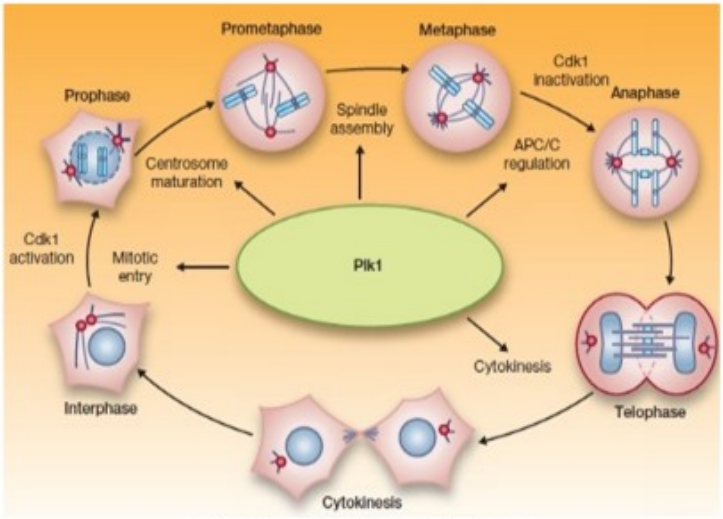
CYC140 Scientific Rationale: Inhibit PLK1 Key Mitotic Regulator

Oncogene with key role in regulation of

- mitotic entry and exit
- spindle formation
- cytokinesis

Cancer very sensitive to PLK1 depletion, esp.

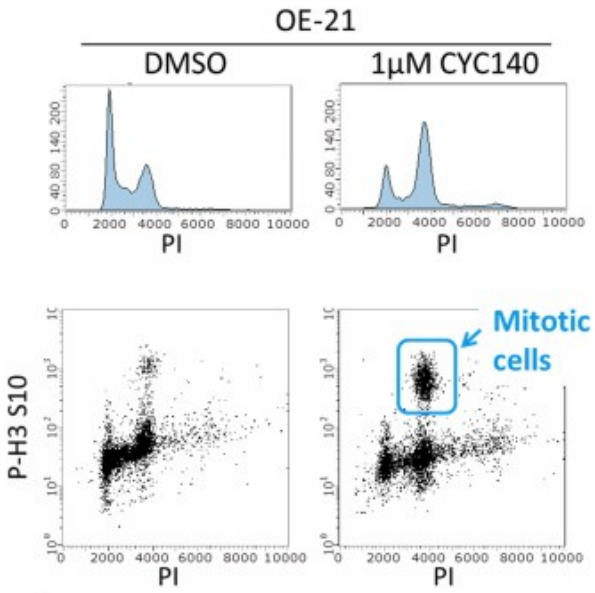
- mutated KRAS and p53(-)
- blocks proliferation by prolonged mitotic arrest
- onset of apoptotic death in cancer cells
- normal cells with intact checkpoints less sensitive



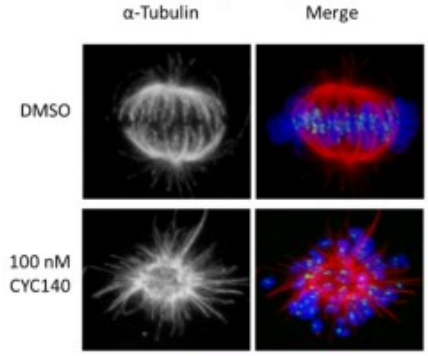
Medema RH et al. (2011) Clin Can Res 17(20):6459-66

Characteristic PLK1i Mitotic Effects in Cells

CYC140 increases mitotic cell number



CYC140 induces monopolar spindle formation

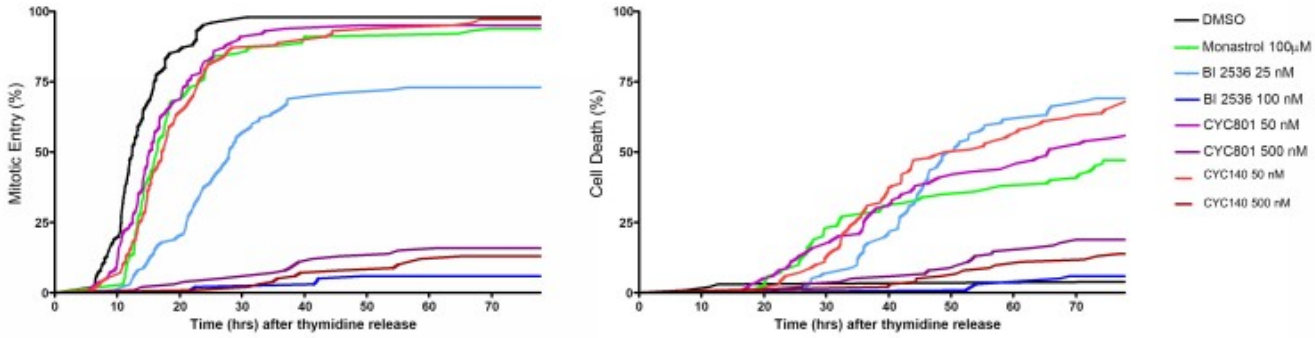


	DMSO	250nM CYC140
% mitotic cells (n>250 cells/field)	2.4%	69.0%
% of mitotic cells with monopolar spindles (n=50 mitotic cells)	4%	74%

Left: Moureau S. et al. ENA 2016 Abs 355. Right: Medema RH et al. (2011) Clin Can Res 17(20):6459-66.

Optimizing PLK1i Exposure Can Enhance Cell Death Induction – Rationale for Lower, Prolonged Dosing

RKO colon carcinoma cell line - Single thymidine block and release prior to treatment



At high doses, PLK1i treatment stops growth; at lower doses PLK1i starts cell cycle and then more tumor cells die.

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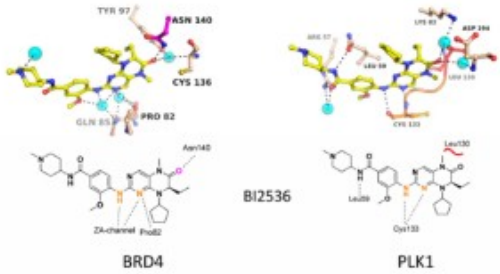
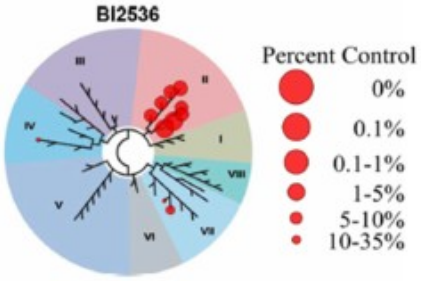
Aspinal et al., Oncotarget, 2015, 6, 36472-88 and company data on file.

Dual PLK1 and BRD4 Inhibitor Landscape

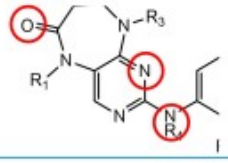
Hydrogen bonding interactions of BI2536 in BRD4 and PLK1



Profiling of BI2536 against panel of 32 human BRDs.



Key BI2536 groups spatially maintained in CYC140



Compound	BRD4 Kd (μM)	BRD4-1 IC_{50} (μM)
BI2536	0.052	0.067
CYC140	0.057	0.153
volasertib	0.110	0.220
TAK-960	0.170	0.397
GSK461364	*> 10*	*> 10*
Onvansertib	*> 10*	*> 10*
JQ-1	*0.018*	*0.016*

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Ember et al. ACS Chem Biol. 2014, 9, 1160-1171.

PLK Inhibitors in Clinical Development

Volasertib
(Boehringer Ingelheim; i.v. BI-6727 discontinued)

- BTD in AML Ph2 data; but Ph 3 POLO-1 in AML failed; imbalance of deaths likely due to myelosuppression; long terminal half-life ~110h
- Dose intensity led to single agent activity

Onvansertib
(Cardiff; p.o., selectivity primarily PLK1, secondarily CDK9, etc.*)

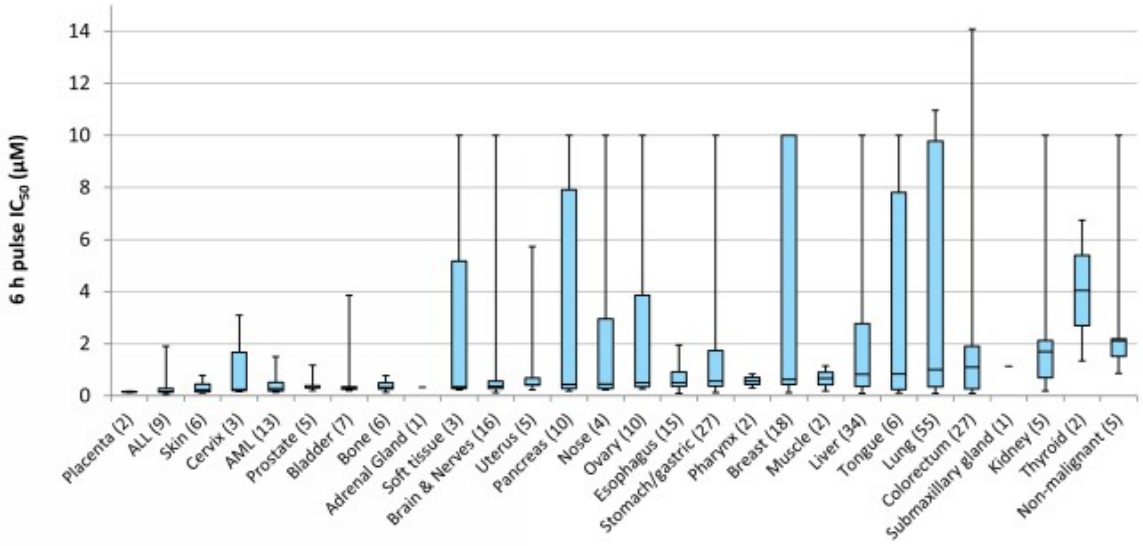
- Signal in KRASmut mCRC with bevacizumab/FOLFIRI; terminal $t_{1/2}$ ~24h
- Ph 1b studies in AML with chemo; prostate with abiraterone; mPDAC with chemo

CYC140
(Cyclacel; p.o., selectivity primarily PLK1, secondarily PLK2, PLK3)

- Preclinical activity in multiple solid tumors and leukemias; terminal $t_{1/2}$ ~11h
- Streamlined, dose intense, registration-enabling, Ph 1/2 in multiple **solid tumors** in progress

CYCLACEL® *Data on file. *Valsasina B et al Mol Can Ther 2012 11 1006; https://mct.aacrjournals.org/content/11/4/1006.figures-only.*

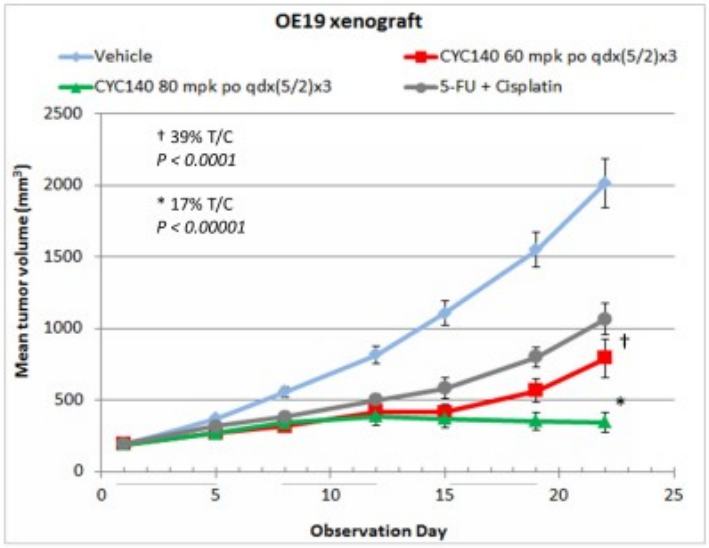
CYC140 Pulse Treatment Highlights Multiple Sensitive Indications

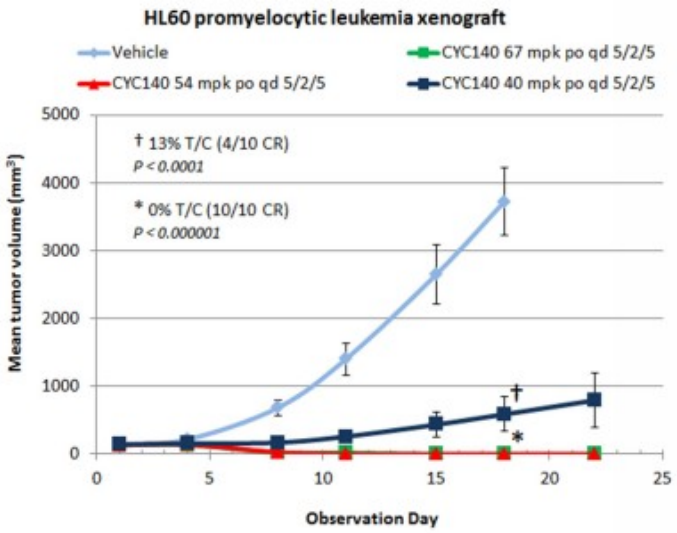


Cellular cytotoxicity: 72h IC_{50} from 6 h CYC140 exposure identifies sensitive cancer cell subsets, incl. acute leukemias, skin, prostate, bladder, bone, brain & nerves, uterus, esophagus. Where IC_{50} not reached maximum concentration tested (10 µM) is plotted. Data on file.

CYC140 Preclinical Efficacy in Esophageal & Leukemia Models

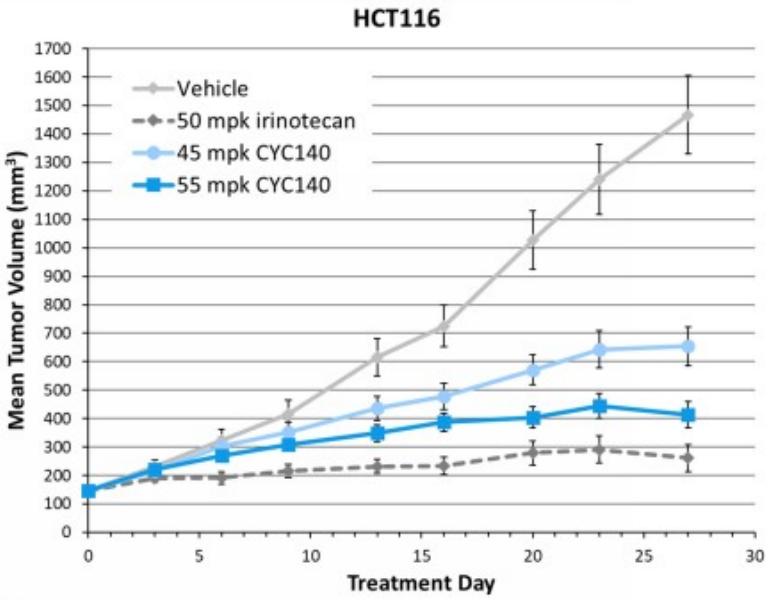
Potent and selective inhibitor (PLK1 IC_{50} ~3 nM)





CYCLACEL® *Data on file.*

CYC140 Preclinical Efficacy in KRAS G13D mut Colorectal Cancer



Treatment	Route/ Schedule	Efficacy
50 mpk irinotecan	ip Q4D x 4 wk	Not tolerated >10% Mean BW Loss 18% T/C (Day 27)
45 mpk CYC140	po (qdx5/wk) x 4 wk	45% T/C (Day 27)
55 mpk CYC140	po (qdx5/wk) x 4 wk	28% T/C (Day 27)

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Data on file. HCT116 is a human colorectal carcinoma cell line. T/C=tumor over control.

CYC140 Oral Ph1/2 Solid Tumor Study Design

Dose Escalation*
(3+3; unselected, all comer, late line)

- **7th Dose Level (n=3)** *20mg qd M to F (wk 1 to 3)*
- **6th Dose Level (n=3)** *20mg qd M to F (wk 1 & 3)*
- **5th Dose Level (n=3)** *15mg qd M to F (wk 1 to 3)*
- **4th Dose Level (n=3)** *15mg qd M to F (wk 1 & 3)*
- **3rd Dose Level (n=3)** *10mg qd M to F (wk 1 to 3)*
- **2nd Dose Level (n=3)** *10mg qd M to F (wk 1 & 3)* — Active ✓
- **Starting Dose Level (n=3)** *5mg qd M to F (wk 1 to 3)*

Schedule: 3-4 wk/cycle.

Proof of Concept (PoC)**
(Simon 2-stage; 2nd /3rd line)

Cohort 1: Bladder cancer

Cohort 2: Breast cancer (TNBC)

Cohort 3: Lung cancer (NSCLC and SCLC])

Cohort 4: Hepatocellular carcinoma (HCC) and biliary tract cancer

Cohort 5: Metastatic colorectal cancer (mCRC) including KRAS-mutated

Cohort 6: B-cell lymphoma including diffuse large B-cell lymphoma (DLBCL)

Cohort 7: T-cell lymphoma (CTCL/PTCL)

Cohort 8 Basket: tumors suspected to have related MoA (expand if responses)

Pivotal
(if randomized study not needed)

Single-arm, open label, study for n=TBD cancer patients

Indication in pivotal study to be determined based on clinical data from PoC

CYCLACEL® *Single agent **Single agent; followed by combination TBD: To be disclosed.

CYC140 Summary

- Optimized short half life and oral dosing
- Improved kinase profile over other PLK1 inhibitors
  - BRD4 inhibition at low nM range (important epigenetic target)
- Broad single agent preclinical activity supports single agent trial design
- Single agent Phase 1/2 solid tumor and lymphoma (140-101) ongoing at DL2
  - Anticancer Activity: stable disease in patient with NSCLC (non-small cell lung cancer) for 6 cycles (ongoing), and patient with Ovarian cancer for 4 cycles
  - No DLTs thus far
  - Report interim data in 1H23

Cyclacel Summary

- Differentiated, targeted oncology medicines with 1st or 2nd mover advantage
- Fadra: oral CDK2 & CDK9 inhibitor; PR in women's cancers, lymphomas
- Big pharma committed to the class, focused on breast indication
- CYC140: oral PLK inhibitor with novel MoA; potential best-in-class properties
- Multiple short- & mid-term catalysts; addressing large unmet patient needs