Patient-specific drug combinations in relapsed/ refractory lymphoma

Anand D Jeyasekharan *MBBS MRCP (UK) PhD FAMS (Medical Oncology)*
Senior Consultant, Department of Haematology-Oncology, National University Hospital, Singapore
Principal Investigator, Cancer Science Institute, National University of Singapore

National University Cancer Institute Singapore

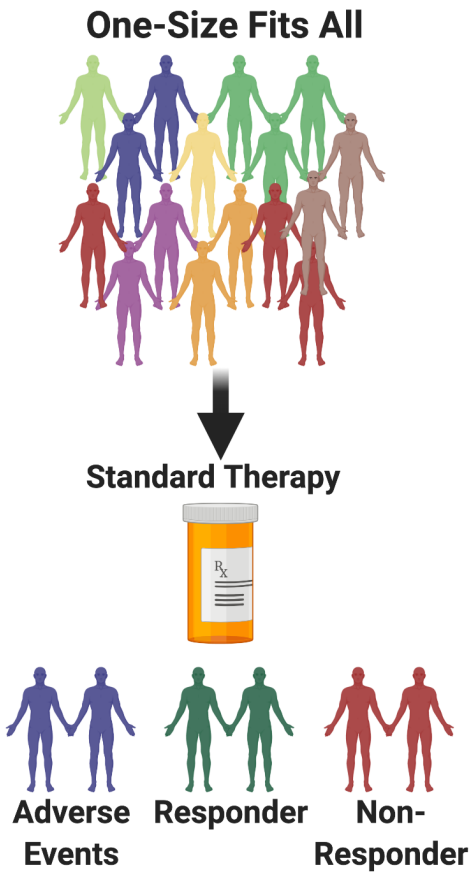
DISCLOSURES OF COMMERCIAL SUPPORT

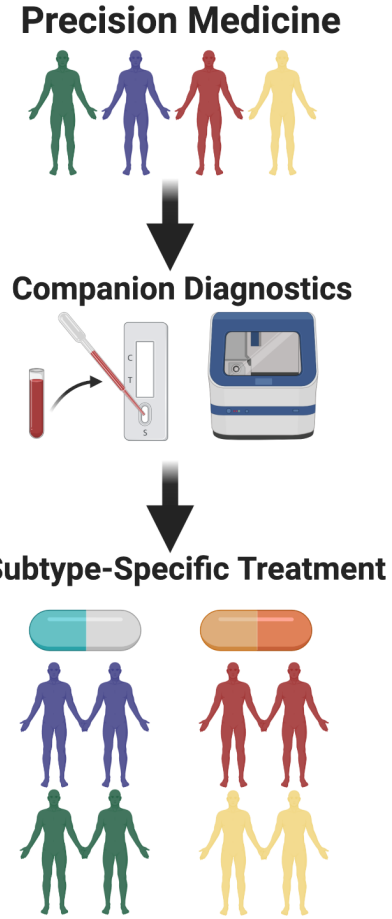
Name of Company	Research support/ collaboration	Employee	Consultant	Stockholder	Speaker's Bureau	Advisory Board	Other
Astrazeneca	X				X	X	
Janssen	X					X	
MSD						X	
Roche	X					X	
Gilead/ Kite						X	
Beigene						X	
Turbine Ltd			X				
Antengene						X	
PerkinElmer					X		

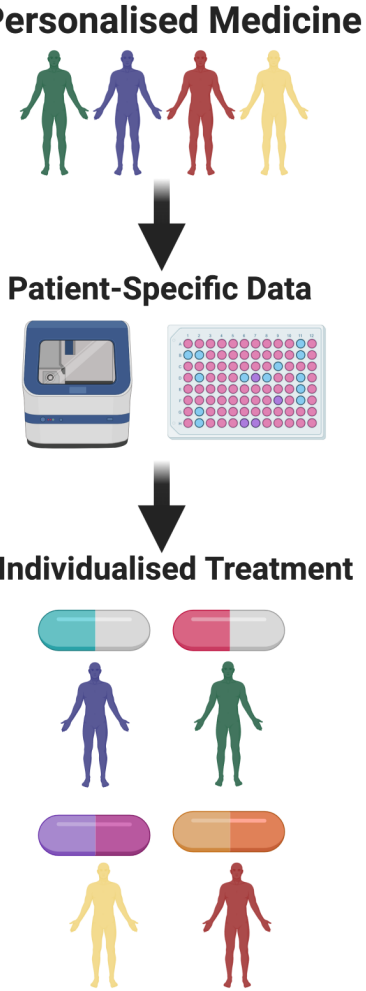
The methods and approaches discussed in this presentation are not licensed for routine clinical use

ADJ is an inventor on NUS owned Patent PCT/SG2020/050595 (16 October 2020); Method For Predicting A Suitable Therapy

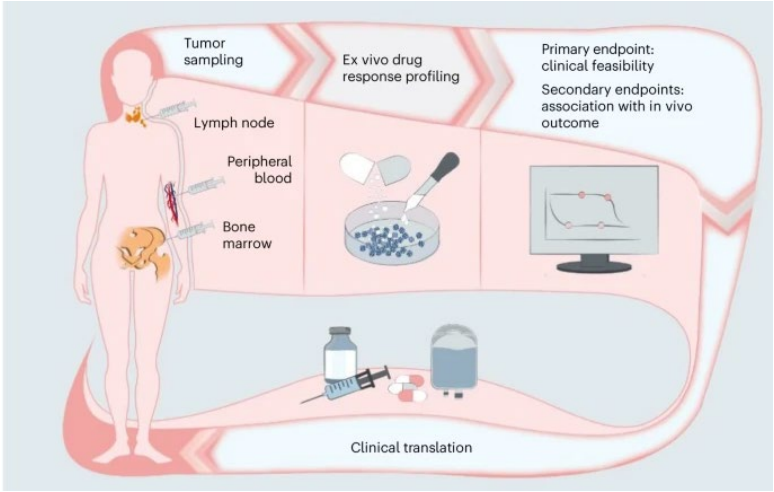
Personalized medicine in lymphoma

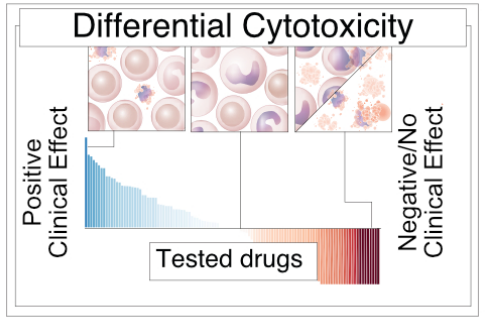






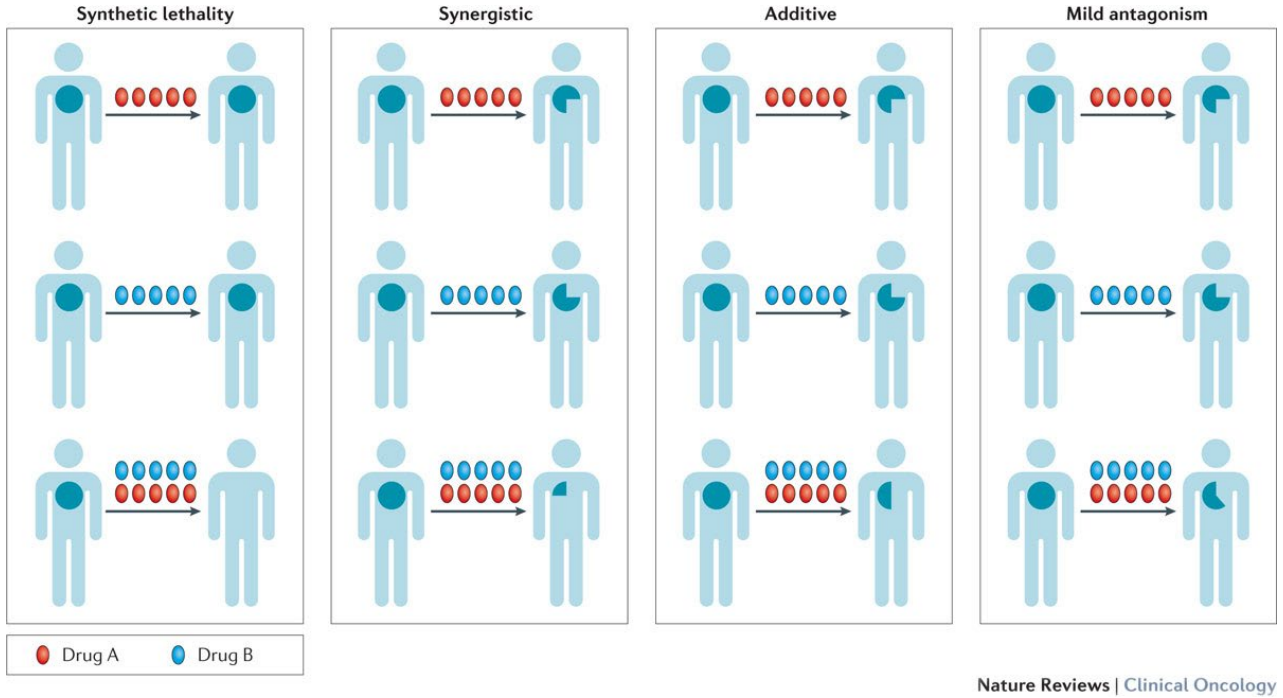
Ex-vivo analytics for personalized treatment; the functional precision medicine approach



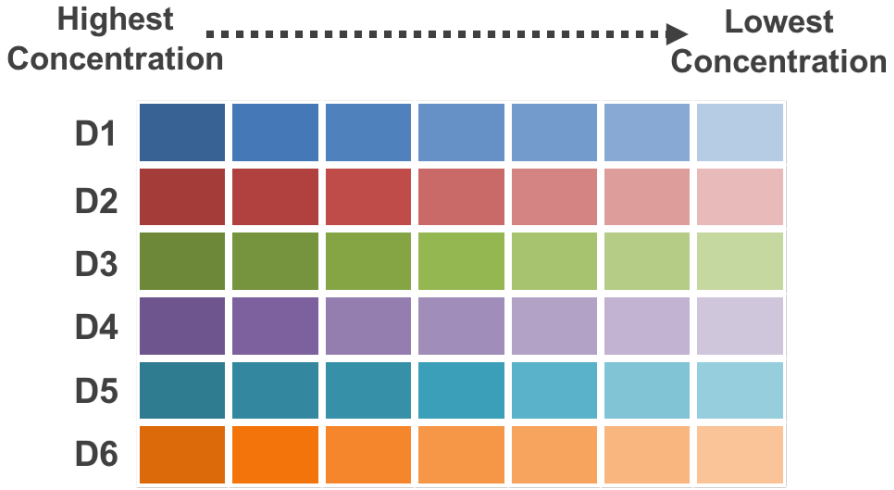


EXALT-2 trial, NCT04470947
SMARTrial; NCT03488641

Personalization of Combinations?



Lopez, J. S. & Banerji, U. (2016) Combine and conquer: challenges for targeted therapy combinations in early phase trials *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2016.96



6 drugs at 7 concentrations

$7^{6=}$ 117,649 combinations

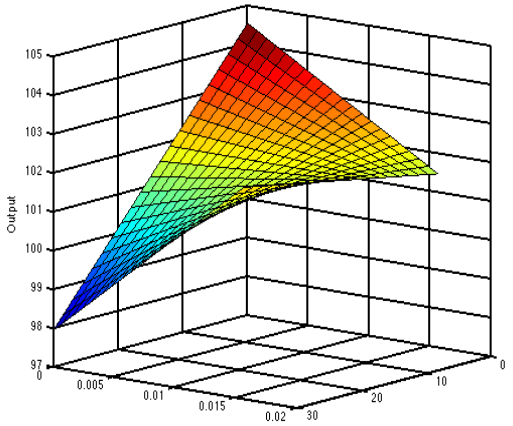
Quadratic Phenotypic Optimization Platform (QPOP)

National University Cancer Institute Singapore

Defined inputs (Drugs)

Quantifiable Output (Viability, Tumor Volume, Response Biomarker)

Bayesian modelling (*parabolic response surfaces*)



Output (Viability) =
$C_1 + C_2x + C_3y + C_4xy + C_5x^2 + C_6y^2$,

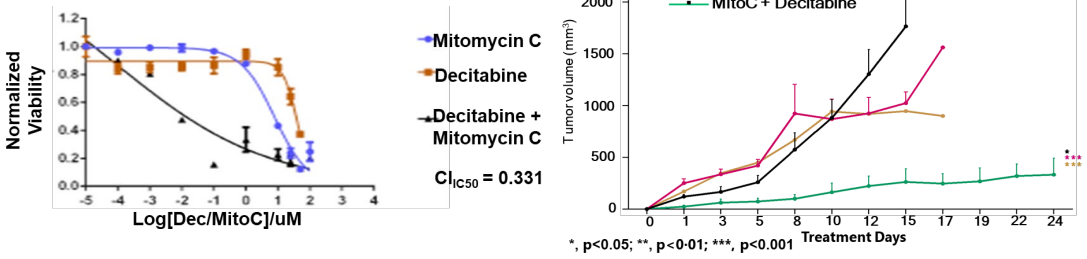
where C_1 , C_2 , C_3 , C_4 , C_5 and C_6 are patient specific coefficients while x and y are the two interacting drugs.

Rank interactions for specific combinations

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

Optimizing drug combinations against multiple myeloma using a quadratic phenotypic optimization platform (QPOP)



Myeloma mouse models

- **12 Drug Search Set**
- **Uses 1 Million Cancer Cells**
- **Results in Less than 1 Week**
- **Ranks Therapeutic Combinations**
- **Identify Patient-Specific Drug Combinations**

(Al-Shyoukh et al. BMC Systems Biology 2011)

M. Rashid et al (Edward Chow lab); Science Translational Medicine 2018

Case Study: 55yM with Hepatosplenic Gamma-Delta T-Cell Lymphoma

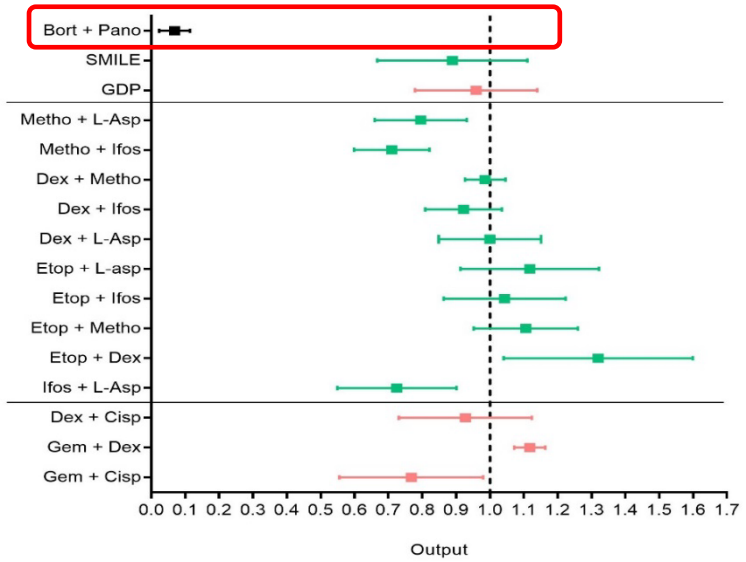
National University Cancer Institute Singapore

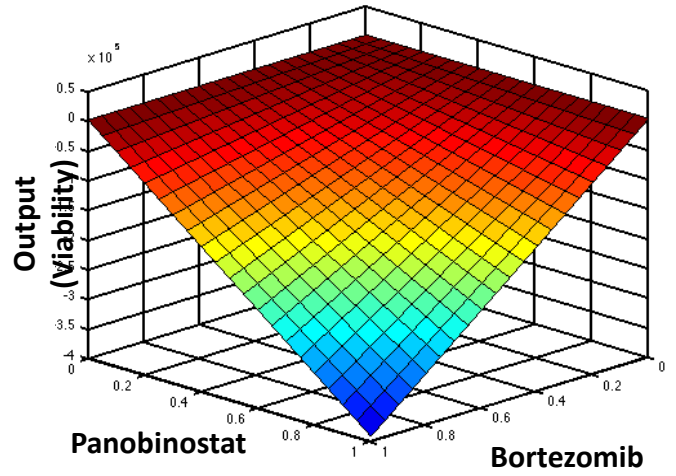
Correspondence | Open Access | Published: 27 January 2020

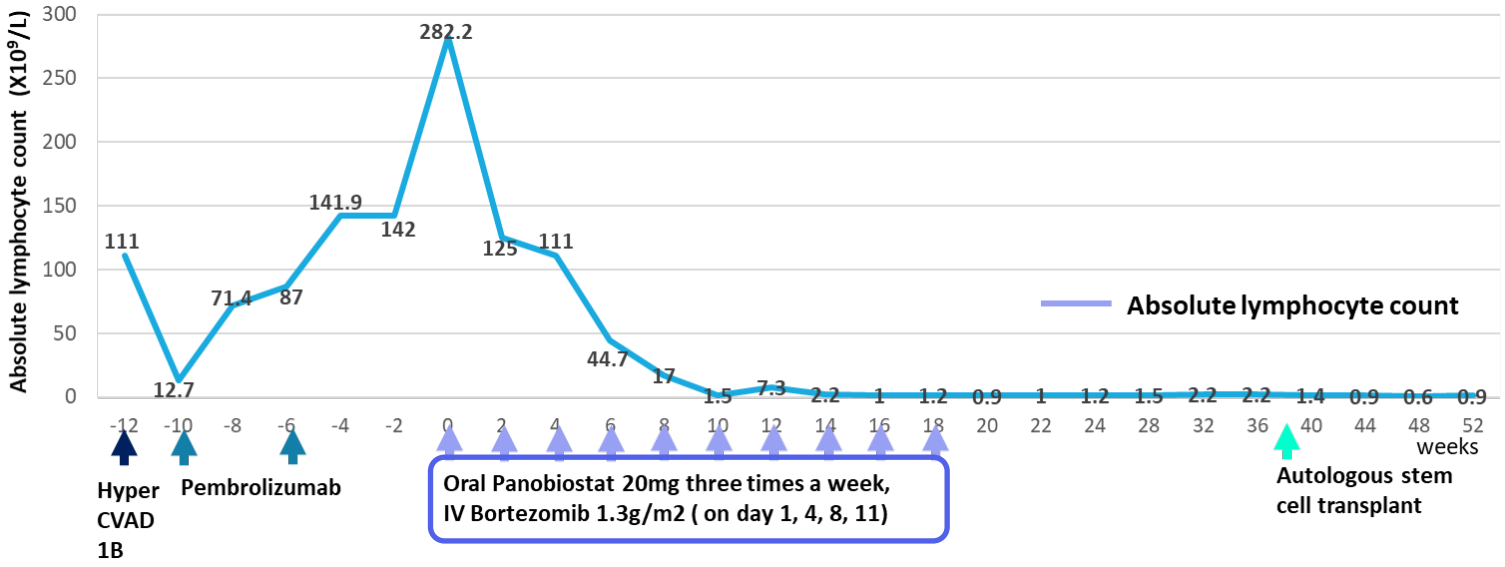
Application of an ex-vivo drug sensitivity platform towards achieving complete remission in a refractory T-cell lymphoma

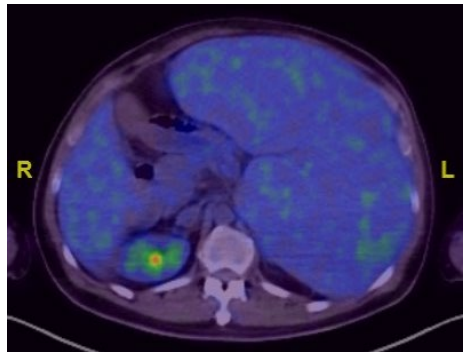
Sanjay de Mel, Masturah B. M. Rashid, [...] Anand D. Jeyasekharan

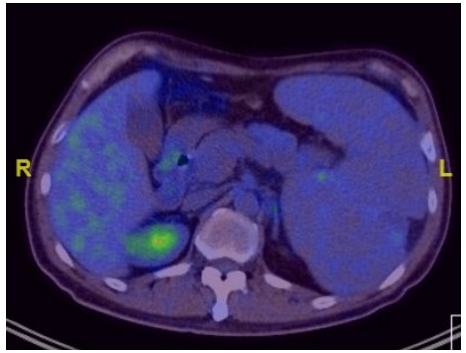
Blood Cancer Journal **10**, Article number: 9 (2020) | Cite this article

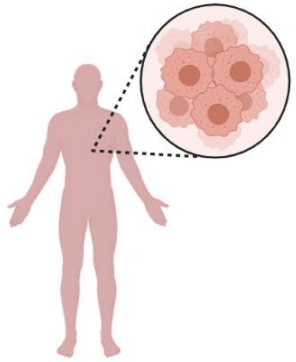












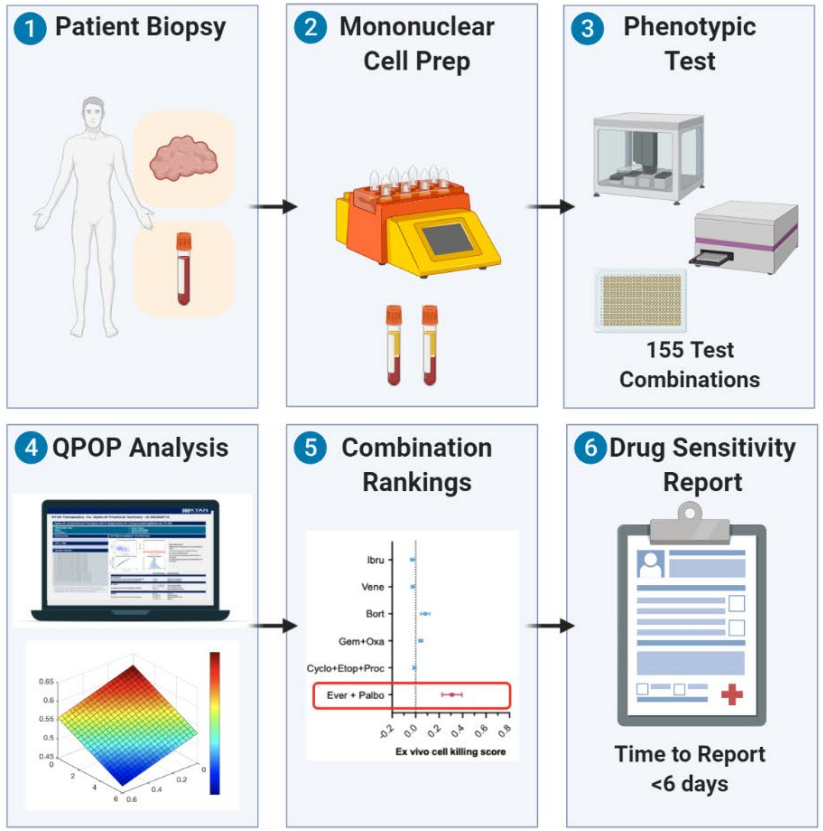
DSRB 2019/00271

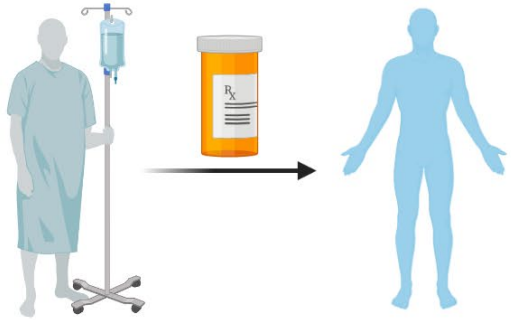
Prospective Clinical Study

Patients:

r/r Non-Hodkin Lymphoma (all subtypes; WHO 2016); age > 21 years

Due for tumour sampling by tissue biopsy/venepuncture/bone marrow aspiration





Results shared with treating physician

Off-label therapy with QPOP-derived combination therapy in absence of standard of care options or clinical trial

Regular follow up with study team for response assessment

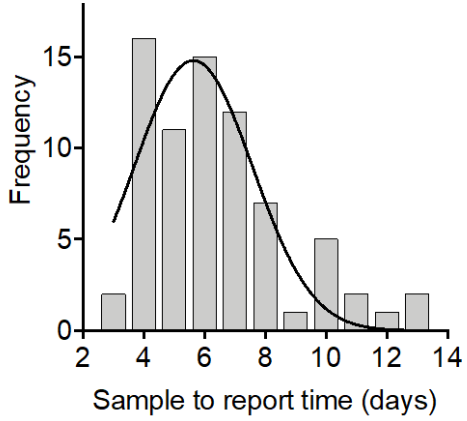
Patients recruited (n=81)
- T/NK-NHL (n=37)
- B-NHL (n=44)

Performed QPOP (n=77)
- T/NK-NHL (n=34)
- B-NHL (n=43)

Generated QPOP data (n=70)
- T/NK-NHL (n=29)
- B-NHL (n=41)

Excluded (n=4)
Cells were not viable

Excluded (n=7)
Did not pass QC (n=2)
Non-NHL (n=5)



- **12 drugs per patient**
- **All with established clinical safety/ dosing**
- **Preclinical/ clinical activity in lymphoma as single agents**
- **2 dose levels, kept << Cmax**

Table 1: Concentrations of drugs used in QPOP

		IC_0 (μM)	IC_{15} (μM)	IC_{30} (μM)	PK_{max} (μM)*
D1	Vinorelbine	0	0.12	0.24	0.811
D2	Olaparib	0	3	6	13.1
D3	Everolimus	0	0.001	0.002	0.064
D4	Palbociclib	0	0.015	0.03	0.101
D5	Dasatinib	0	0.04	0.08	0.264
D6	Brentuximab	0	0.3135	0.627	0.209
D7	Bortezomib	0	0.000648	0.001296	0.312
D8	Panobinostat	0	0.0003	0.0006	0.082
D9	Azacitidine	0	0.3	0.6	3.07
D10	Procarbazine	0	0.3	0.6	3.13
D11	Copanlisib	0	0.3	0.6	9.63
D12	Ruxolitinib	0	0.15	0.3	1.09

**Liston & Davis, Clin Can Res, 2017*

Top-ranking single drugs, 2- and 3-drug combinations

	H	L
Copanlisib	0.41399	0.58860
Dasatinib	0.49274	0.68735
Vinorelbine	0.67230	0.80925

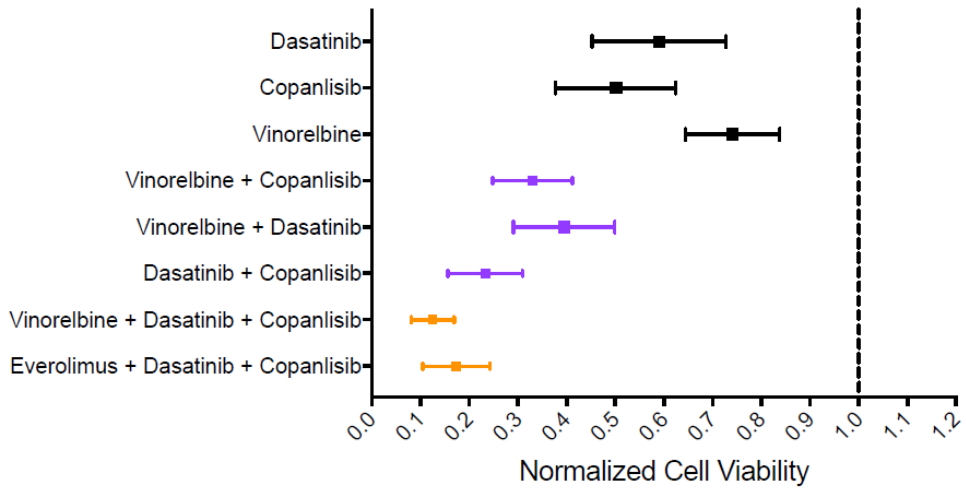
	HH	HL	LH	LL
Dasatinib + Copanlisib	0.15776	0.20736	0.22736	0.33947
Vinorelbine + Copanlisib	0.24183	0.33918	0.30151	0.43749
Vinorelbine + Dasatinib	0.27865	0.41696	0.35930	0.52576

	HHH	HLH	HHL	LHH	LHL	LLH	HLL	LLL
Vinorelbine + Dasatinib + Copanlisib	0.09821	0.11151	0.07054	0.10158	0.11255	0.14303	0.14634	0.21651
Everolimus + Dasatinib + Copanlisib	0.08841	0.13897	0.13801	0.12308	0.17269	0.18316	0.25108	0.29528

Dead — Normalized Cell Viability — Live

L	Lower concentration (i.e. IC_{15})
H	Higher concentration (i.e. IC_{30})

Forrest plot of top-ranking combinations



Experience summary

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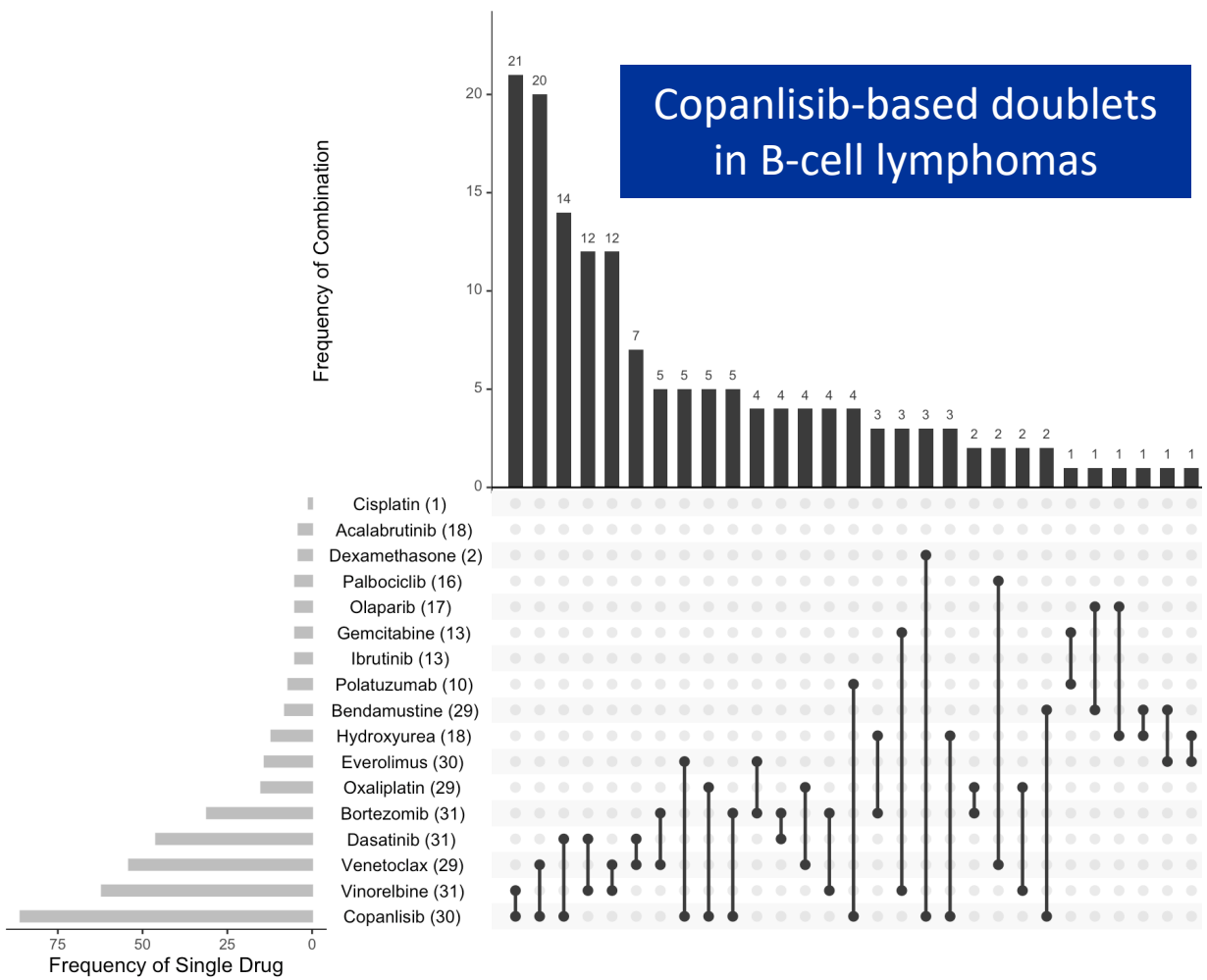
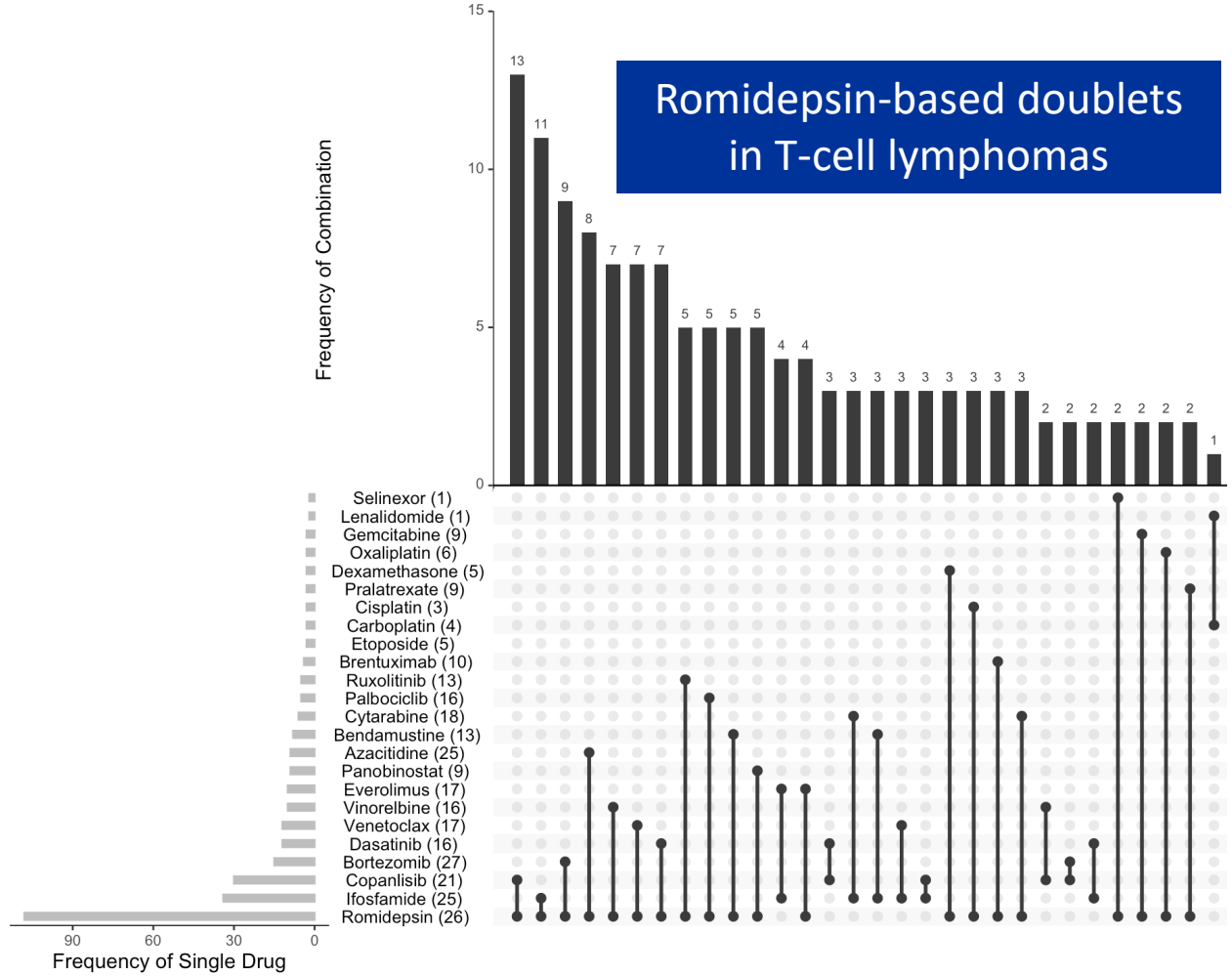
BCL



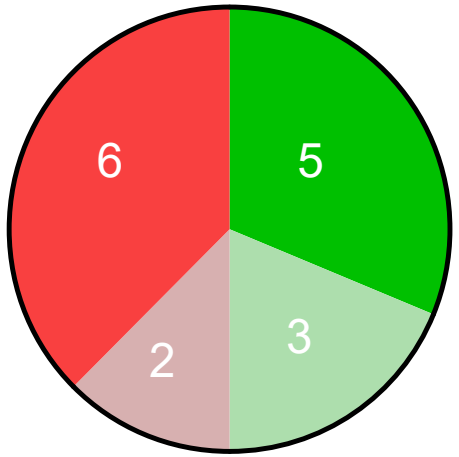
TCL



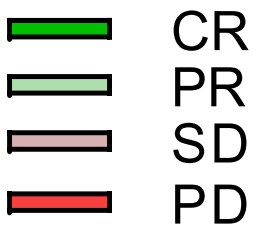
Subset of patients received QPOP directed off-label therapy *(Physician/ patient choice, affordability)*

National University Cancer Institute Singapore

QPOP-guided treatments

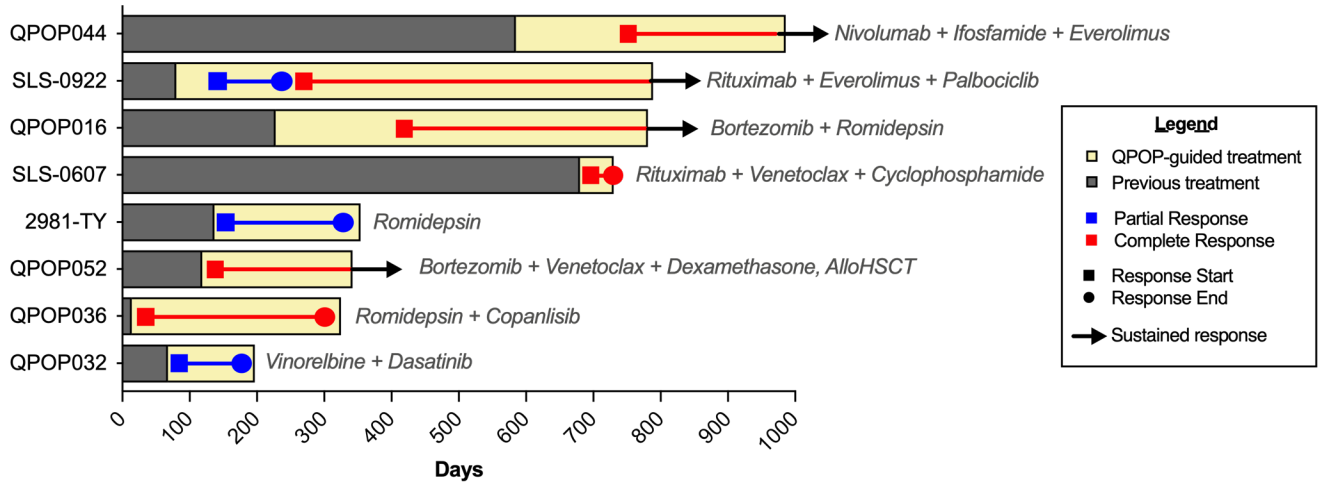


n = 16



CR
- Bortezomib-Romidepsin
- Bortezomib-Venetoclax
- Copanlisib-Romidepsin
- Everolimus-Palbociclib
- Venetoclax-Cyclophosphamide

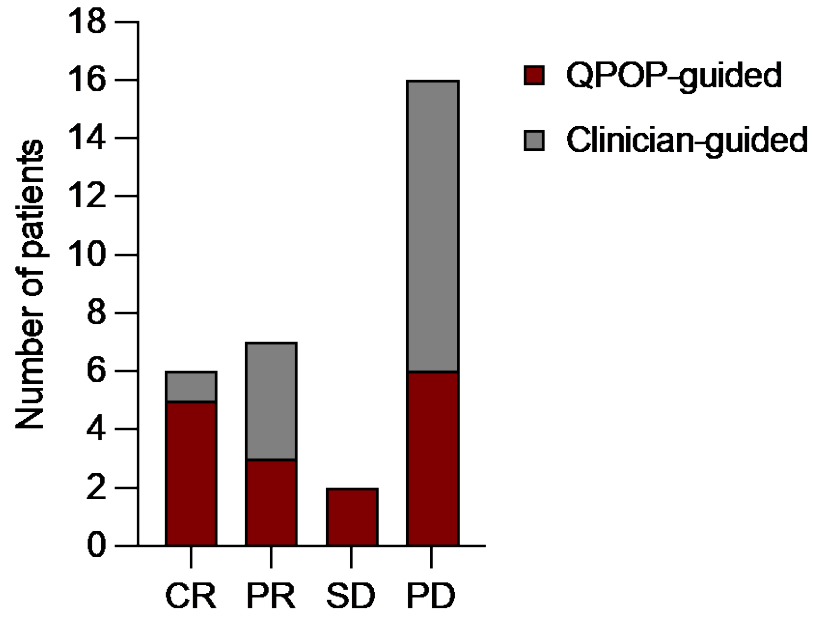
PR:
- Vinrorelbine-Dasatinib
- Ifosfamide-Everolimus
- Romidepsin-Ifosfamide

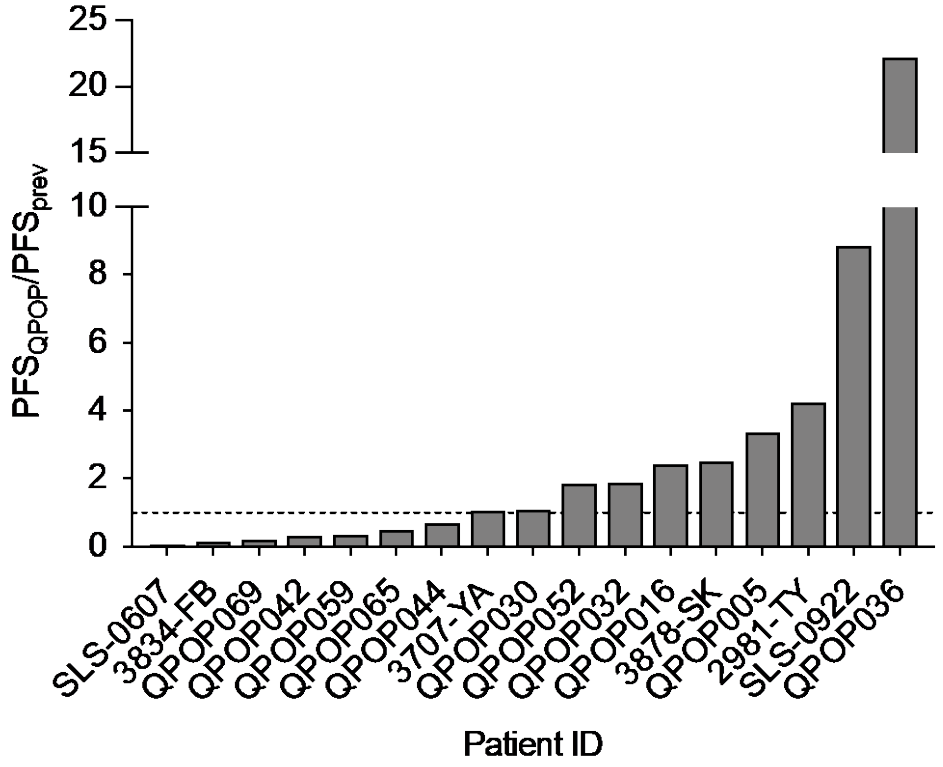


48% response rate in highly refractory lymphomas

6 G3/G4 toxicities
1 G5 toxicity (neutropenic sepsis; vinorelbine+dasatinib)

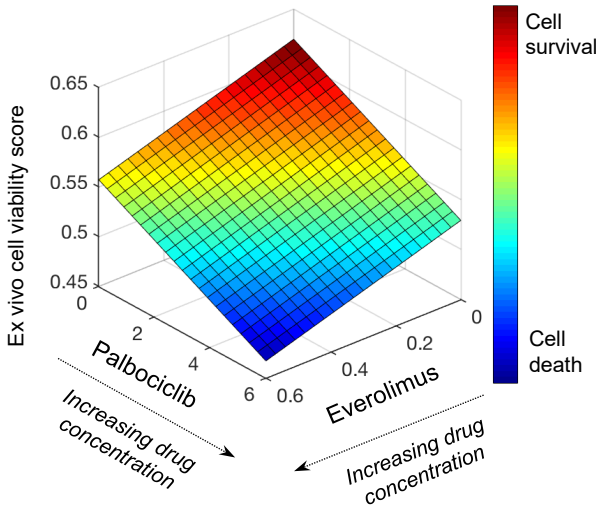
“Controls” for personalized medicine studies

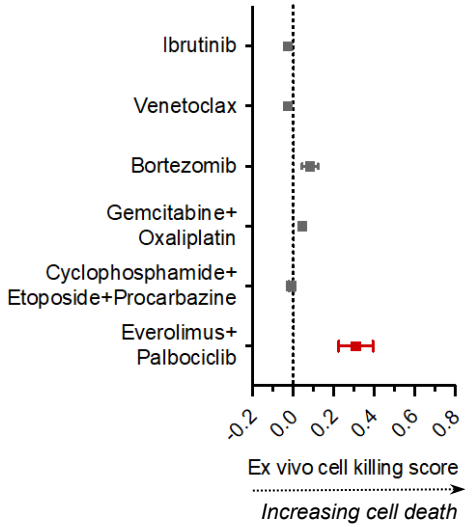




Example responder (B-cell subset)

- **74yF with relapsed/ refractory DLBCL (transformed MZL)**
- **Treated with BR, R-CHOP, ineligible for transplant, no suitable clinical trials/ CAR-T**

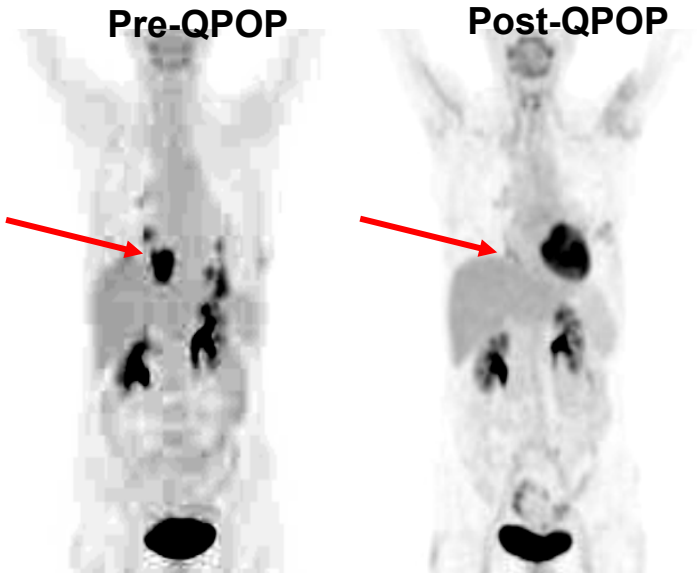




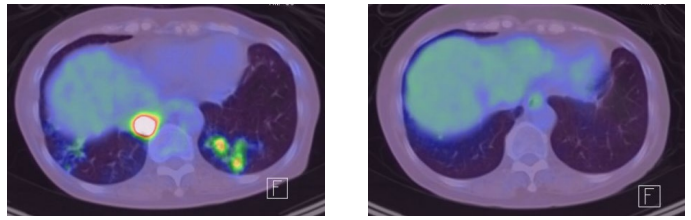
Combination of Everolimus + Palbociclib studied in breast cancer

RP2D
PALBO 100 mg/day (21 of 28 days) + EVE 5mg/day

NCT02871791, Barroso-Sousa et al



Diagnosis	QPOP	Treatment received	QPOP prediction	Treatment outcome	Treatment received	QPOP prediction	Treatment outcome
DLBCL		R-GDP	No response	**PD**	Everolimus + Palbociclib	Response	**CR**



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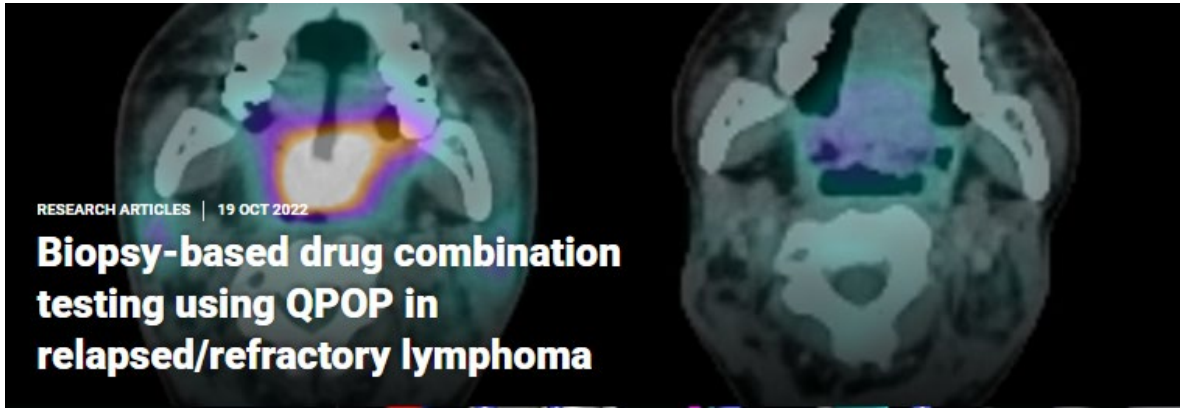
Science Translational Medicine



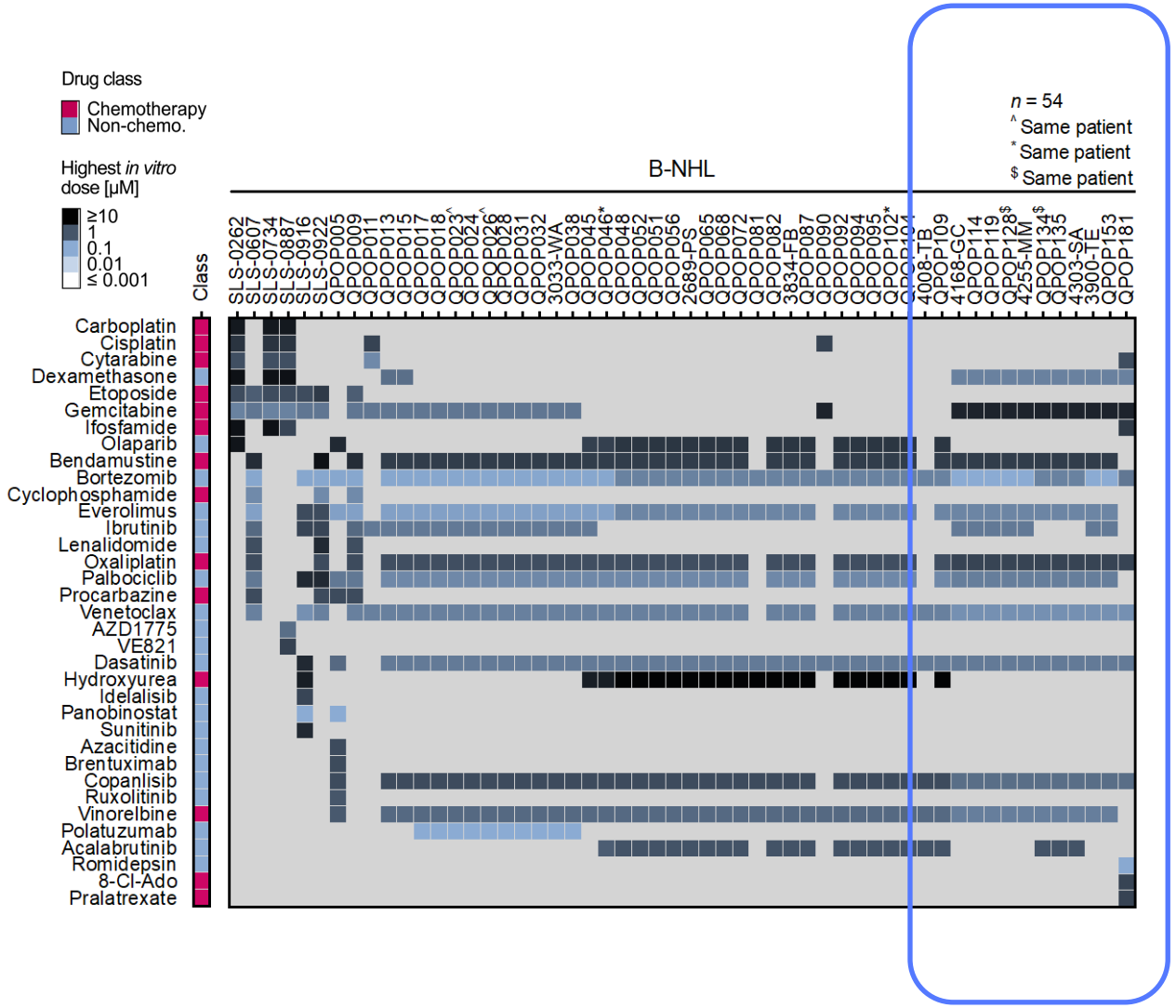
THE STRAITS TIMES INTERNATIONAL EDITION

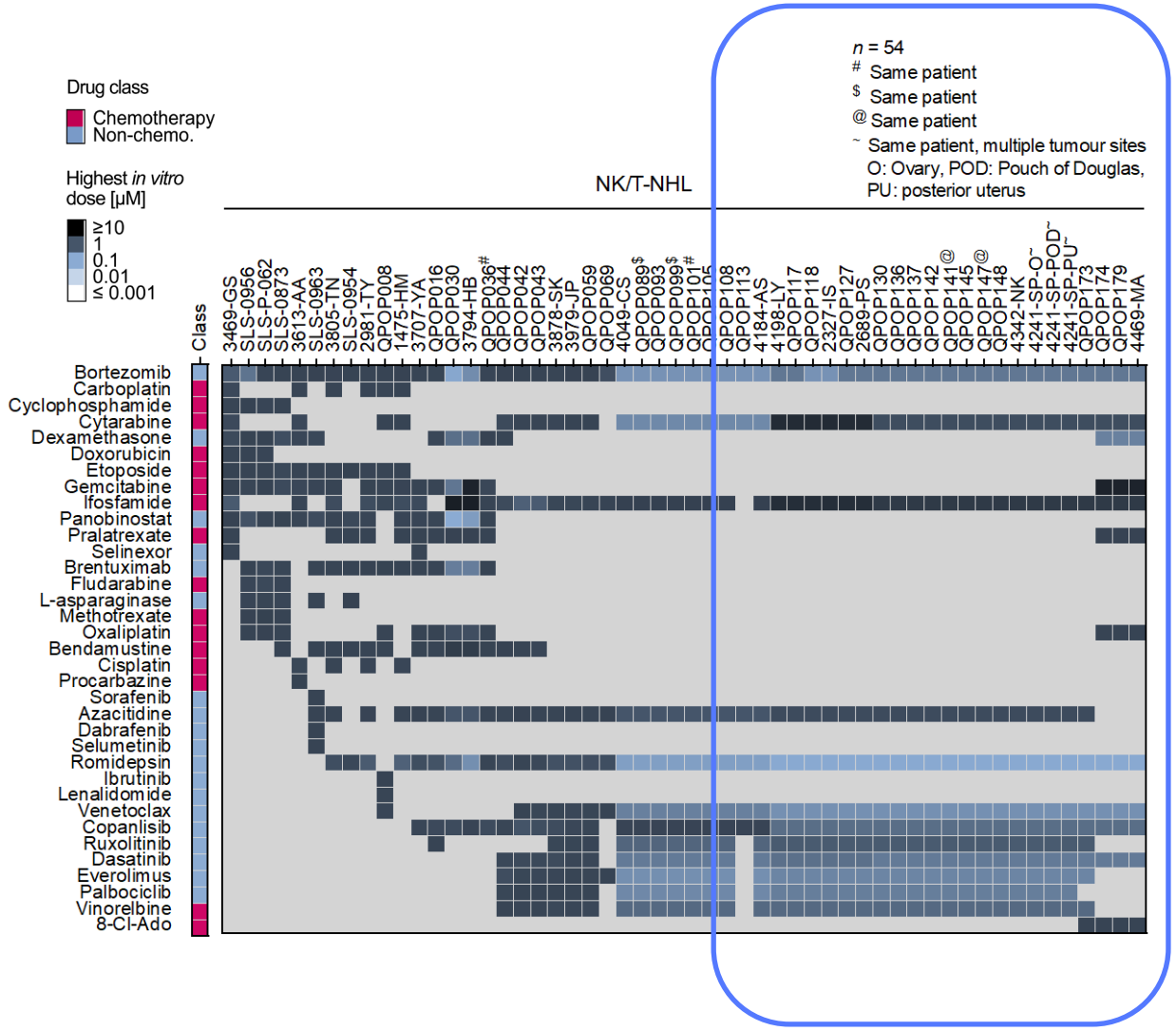
SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

An ex vivo platform to guide drug combination treatment in relapsed/refractory lymphoma

Jasmine Goh[1†], Sanjay De Mel[2,3†], Michal M. Hoppe[1], Masturah Bte Mohd Abdul Rashid[4], Xi Yun Zhang[1], Patrick Jaynes[1], Esther Ka Yan Ng[1], Nur'Atiqa Diana Binti Rahmat[1], Jayalakshmi[1], Clementine Xin Liu[3], Limei Poon[2,3], Esther Chan[2,3], Joanne Lee[2,3], Yen Lin Chee[2,3], Liang Piu Koh[3], Lip Kun Tan[5], Teck Guan Soh[5], Yi Ching Yuen[6], Hoi-Yin Loi[7], Siok-Bian Ng[1,2,8], Xueying Goh[9], Donovan Eu[9], Stanley Loh[7], Sheldon Ng[7], Daryl Tan[10,11], Daryl Ming Zhe Cheah[12], Wan Lu Pang[12], Dachuan Huang[12], Shin Yeu Ong[11], Chandramouli Nagarajan[11], Jason Yongsheng Chan[13,14], Jeslin Chian Hung Ha[13], Lay Poh Khoo[13], Nagavalli Somasundaram[13], Tiffany Tang[13], Choon Kiat Ong[12,15,16], Wee-Joo Chng[1,2,3,17], Soon Thye Lim[13,14,18], Edward K. Chow[1,2,19,20,21*], Anand D. Jeyasekharan[1,2,3,17*]


Drug class
Chemotherapy
Non-chemo.
Highest in vitro dose [μM]
≥10
1
0.1
0.01
≤ 0.001
Class
B-NHL
n = 54
^ Same patient
* Same patient
$ Same patient
SLS-0262
SLS-0607
SLS-0734
SLS-0887
SLS-0916
SLS-0922
QPOP005
QPOP009
QPOP011
QPOP013
QPOP015
QPOP017
QPOP018^
QPOP023^
QPOP024^
QPOP026*
QPOP028
QPOP031
QPOP032
3033-WA
QPOP038
QPOP045*
QPOP046*
QPOP048
QPOP052
QPOP051
QPOP056
2689-PS
QPOP065
QPOP068
QPOP072
QPOP081
QPOP082
3834-FB
QPOP087
QPOP090
QPOP092
QPOP094
QPOP095*
QPOP102*
QPOP104
4008-TB
QPOP109
4168-GC
QPOP114
QPOP119
QPOP128$
4255-MM
QPOP134$
QPOP135
4303-SA
3900-TE
QPOP153
QPOP181
Carboplatin
Cisplatin
Cytarabine
Dexamethasone
Etoposide
Gemcitabine
Ifosfamide
Olaparib
Bendamustine
Bortezomib
Cyclophosphamide
Everolimus
Ibrutinib
Lenalidomide
Oxaliplatin
Palbociclib
Procarbazine
Venetoclax
AZD1775
VE821
Dasatinib
Hydroxyurea
Idelalisib
Panobinostat
Sunitinib
Azacitidine
Brentuximab
Copanlisib
Ruxolitinib
Vinorelbine
Polatuzumab
Acalabrutinib
Romidepsin
8-Cl-Ado
Pralatrexate


Drug class
Chemotherapy
Non-chemo.
Highest in vitro dose [μM]
≥10
1
0.1
0.01
≤ 0.001
Class
NK/T-NHL
n = 54
# Same patient
$ Same patient
@ Same patient
~ Same patient, multiple tumour sites
O: Ovary, POD: Pouch of Douglas,
PU: posterior uterus
3469-GS
SLS-0956
SLS-P-062
SLS-0873
3613-AA
SLS-0963
3805-TN
SLS-0954
2981-TY
QPOP008
1475-HM
3707-YA
QPOP016
QPOP030
3794-HB
QPOP036#
QPOP044
QPOP042
QPOP043
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QPOP099$
QPOP101#
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QPOP113
4184-AS
4198-LY
QPOP117
QPOP118
2327-IS
QPOP127
2689-PS
QPOP130
QPOP136
QPOP137
QPOP142@
QPOP145@
QPOP147@
QPOP148
4342-NK
4241-SP-O~
4241-SP-POD~
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QPOP179
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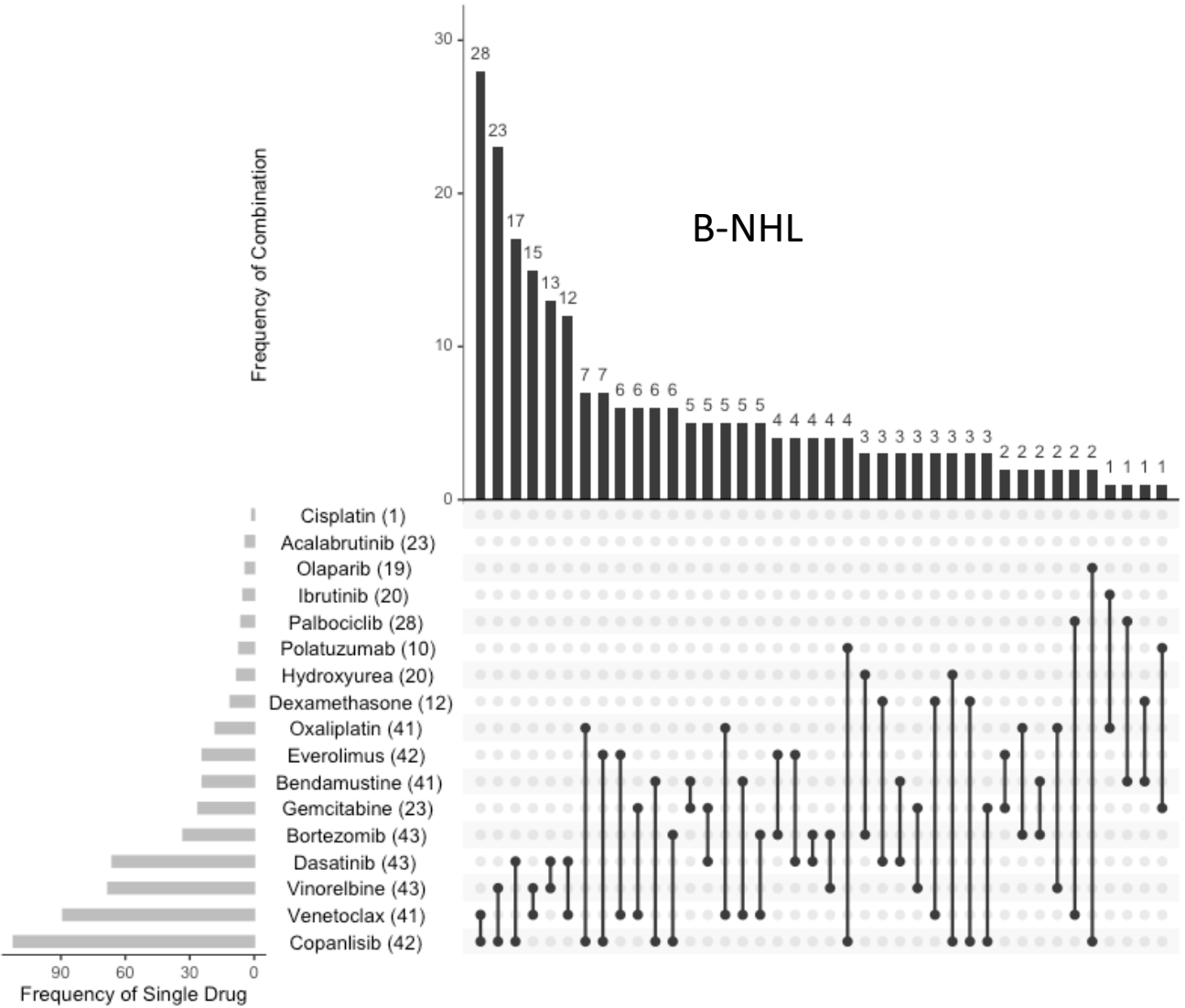
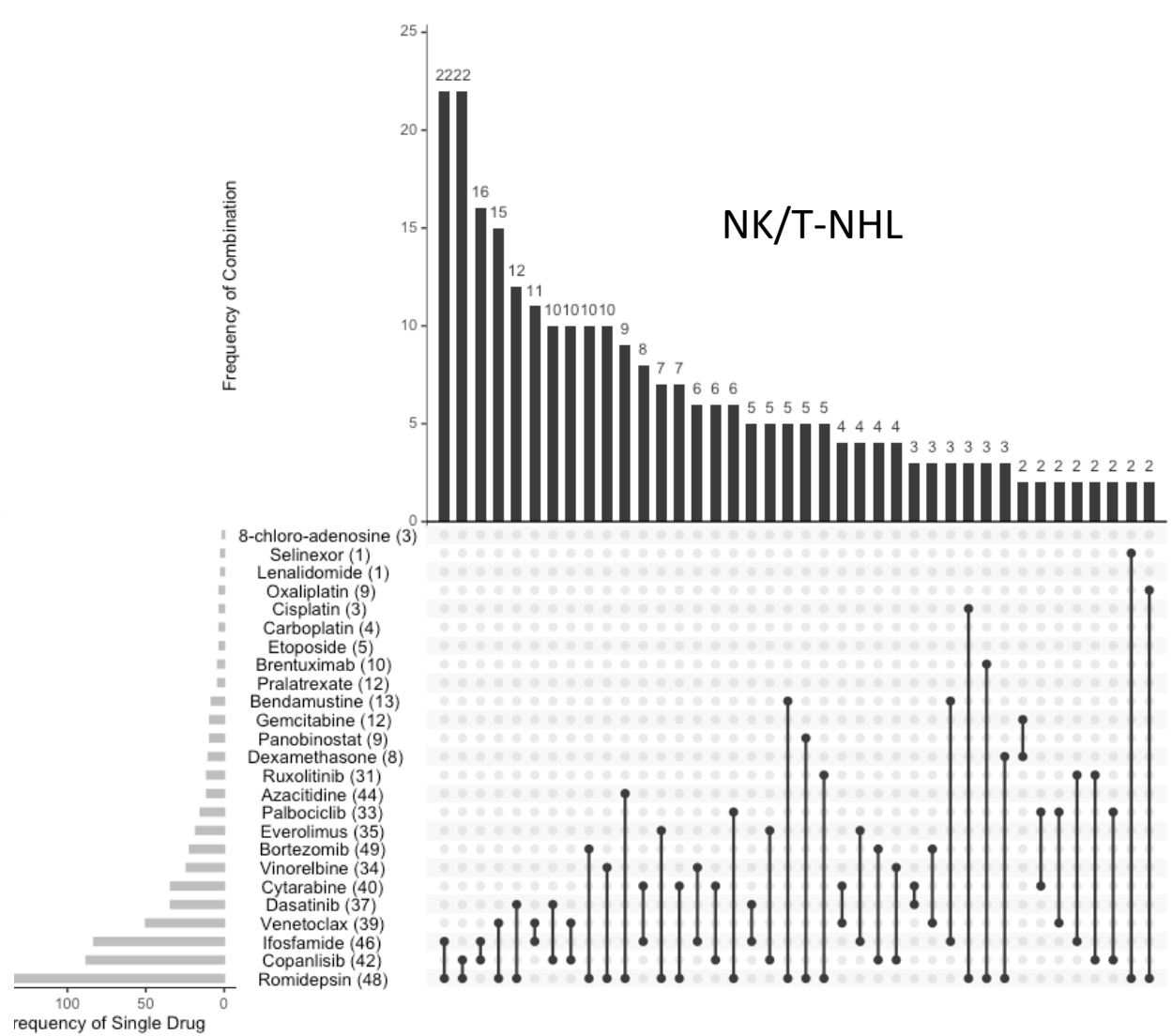
Bortezomib
Carboplatin
Cyclophosphamide
Cytarabine
Dexamethasone
Doxorubicin
Etoposide
Gemcitabine
Ifosfamide
Panobinostat
Pralatrexate
Selinexor
Brentuximab
Fludarabine
L-asparaginase
Methotrexate
Oxaliplatin
Bendamustine
Cisplatin
Procarbazine
Sorafenib
Azacitidine
Dabrafenib
Selumetinib
Romidepsin
Ibrutinib
Lenalidomide
Venetoclax
Copanlisib
Ruxolitinib
Dasatinib
Everolimus
Palbociclib
Vinorelbine
8-Cl-Ado

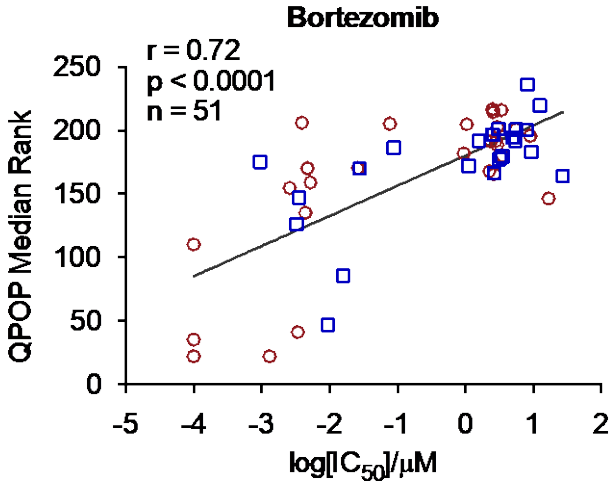
Copanlisib-based combination still most frequent in B-NHL
Romidepsin-based combination still most frequent in NK/T-NHL

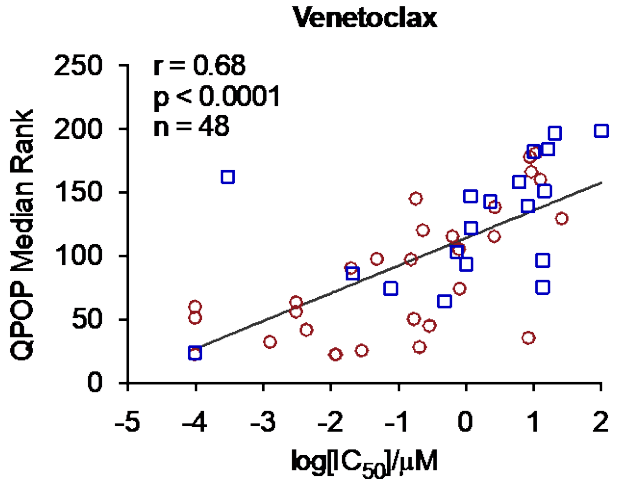


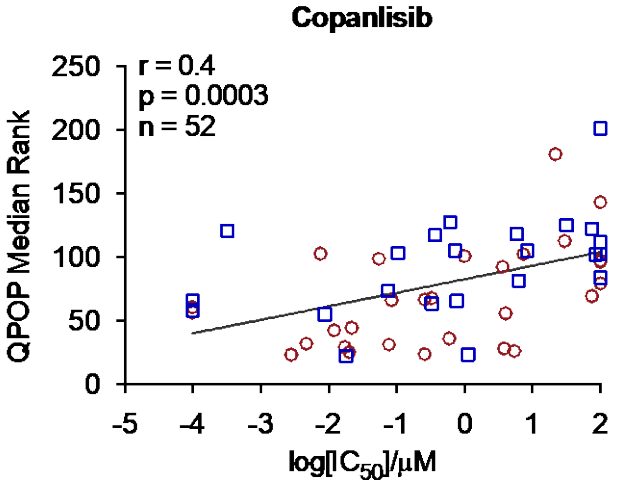
n = 43

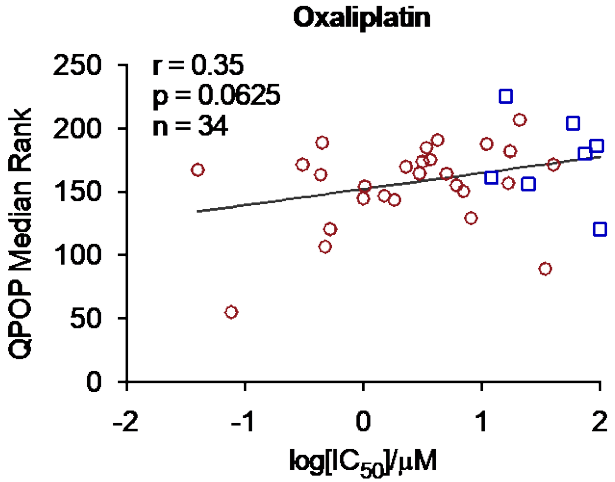


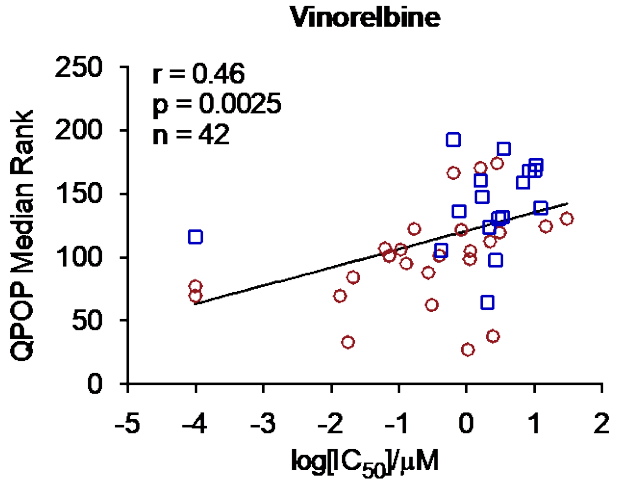
n = 49

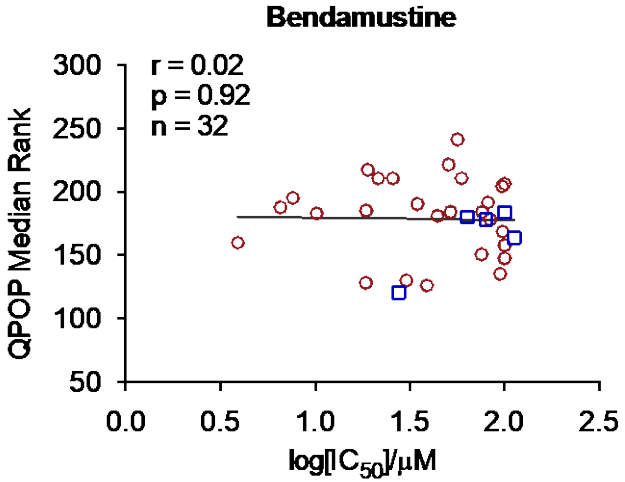

Bortezomib
r = 0.72
p < 0.0001
n = 51
QPOP Median Rank
log[IC50]/μM


Venetoclax
r = 0.68
p < 0.0001
n = 48
QPOP Median Rank
log[IC50]/μM

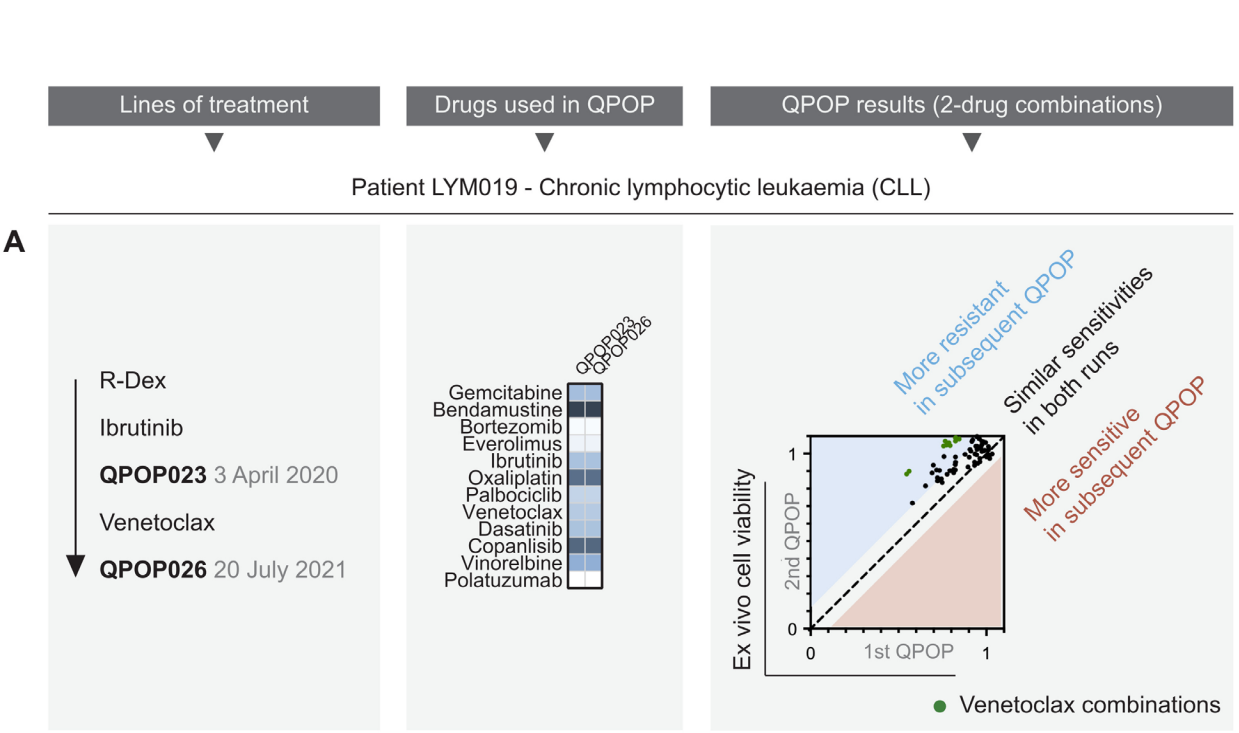

Copanlisib
r = 0.4
p = 0.0003
n = 52
QPOP Median Rank
log[IC50]/μM

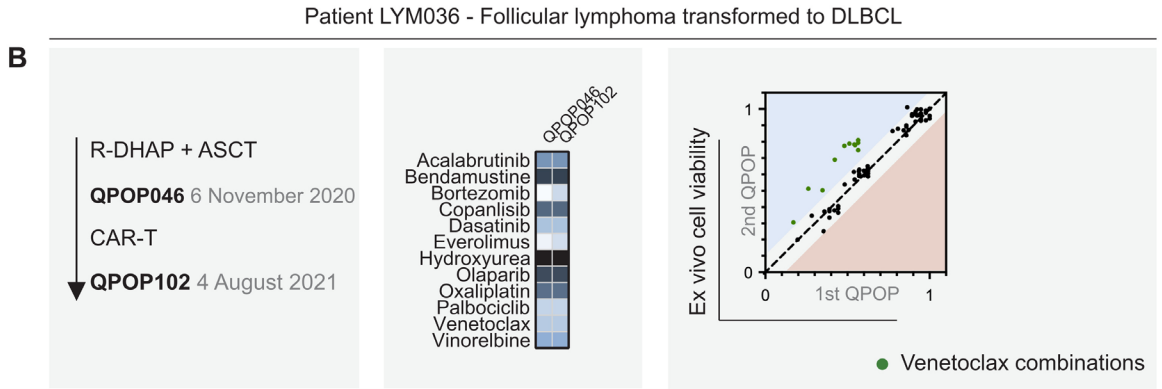

Oxaliplatin
r = 0.35
p = 0.0625
n = 34
QPOP Median Rank
log[IC50]/μM

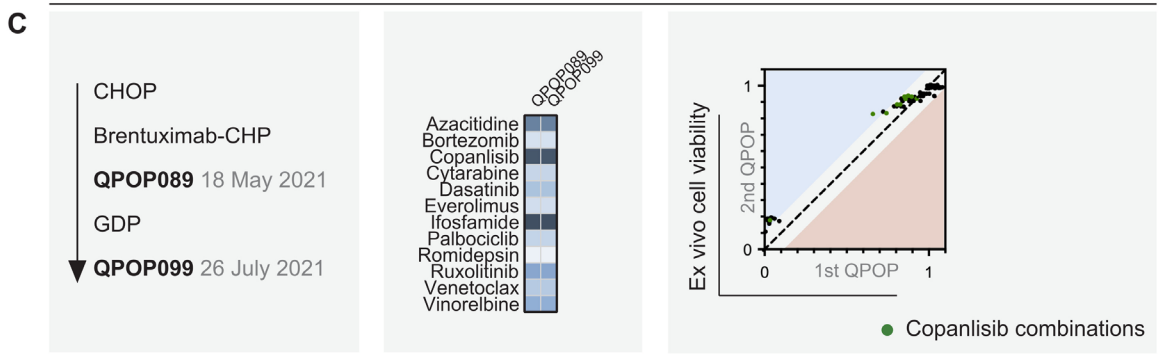

Vinorelbine
r = 0.46
p = 0.0025
n = 42
QPOP Median Rank
log[IC50]/μM

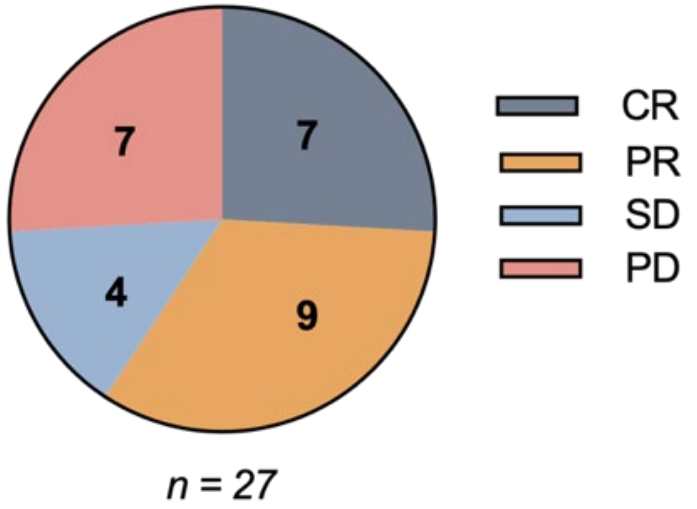

Bendamustine
r = 0.02
p = 0.92
n = 32
QPOP Median Rank
log[IC50]/μM

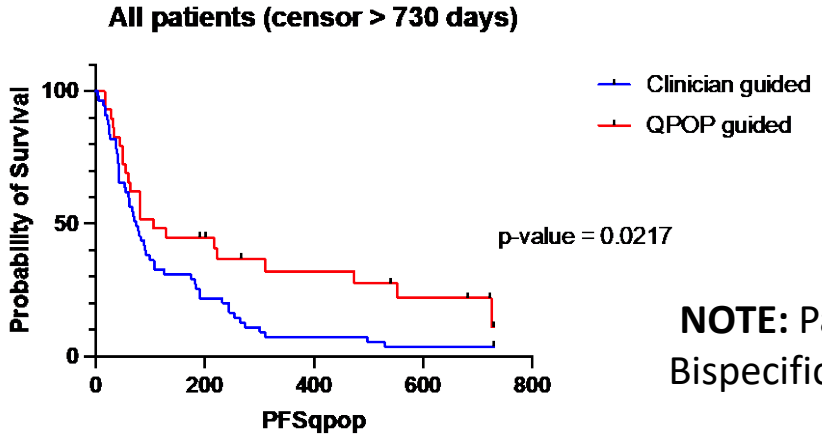
Concordance between distinct time points





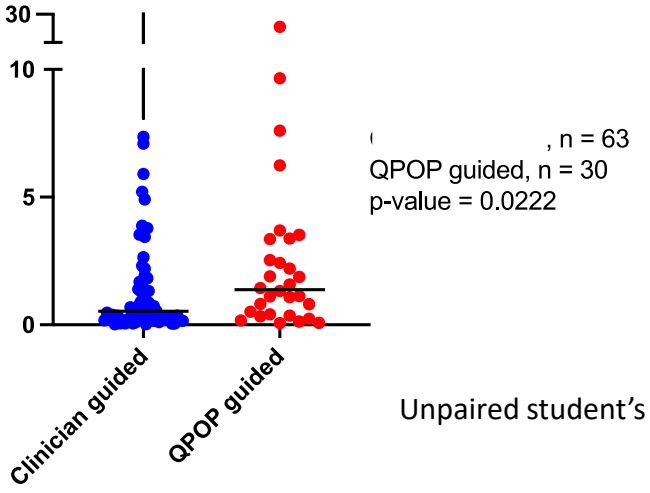






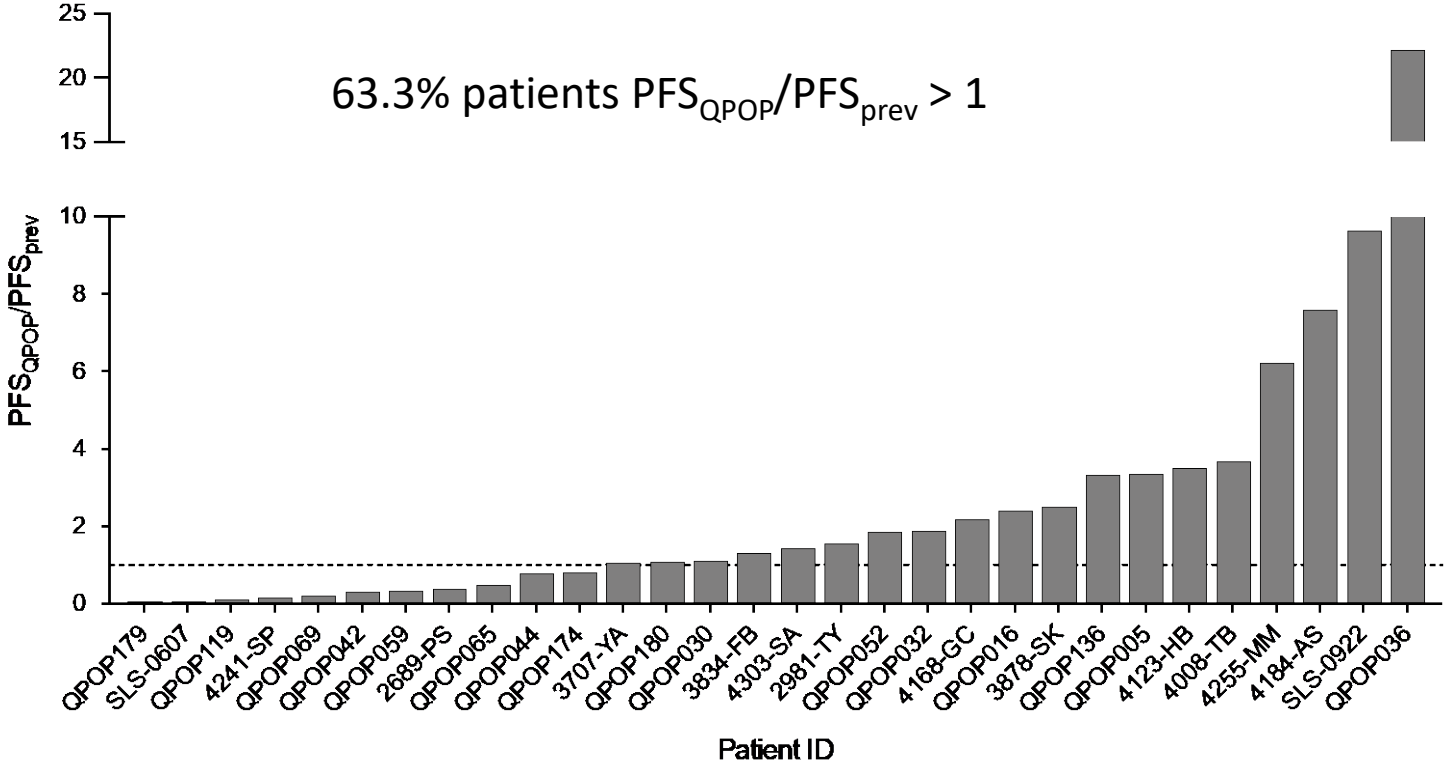
NOTE: Patients who received AlloSCT or Bispecifics/BiTEs were removed from the survival analysis

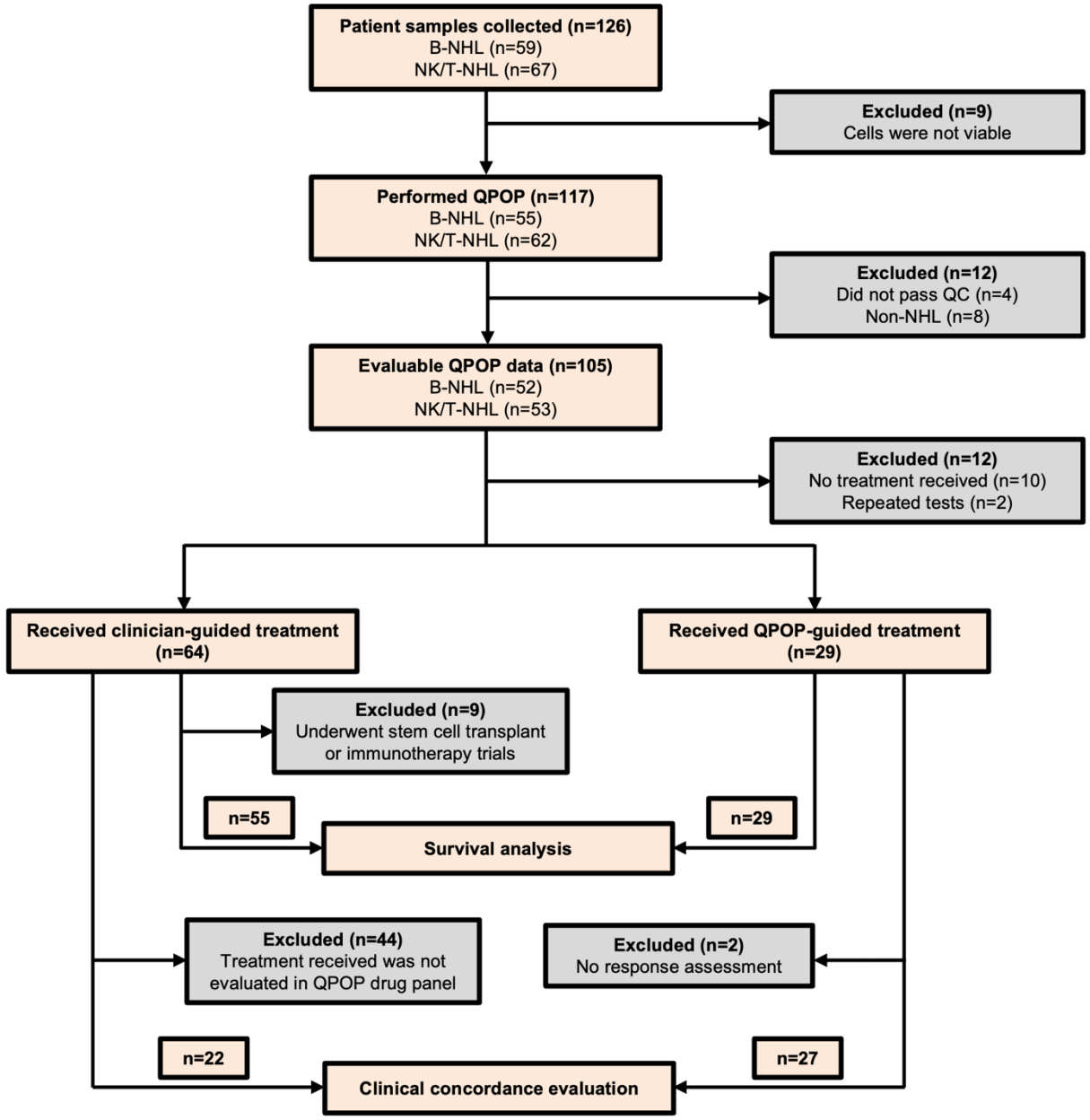
Improved PFS ratios in QPOP guided patients



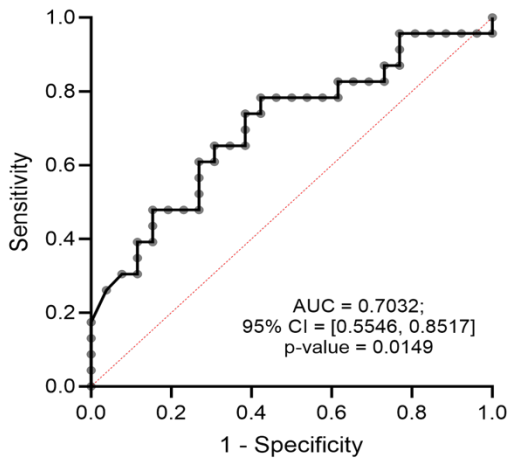
Unpaired student's t-test

63.3% patients $PFS_{QPOP}/PFS_{prev} > 1$





A



B

	Clinical Responder	Clinical Non-Responder	Total
QPOP Responder	20	7	27
QPOP Non-Responder	4	18	22
Total	24	25	p-value = 0.0001

Sensitivity	83.3%
Specificity	72.0%
Positive Predictive Value	74.1%
Negative Predictive Value	81.8%
Accuracy	77.6%

National University Cancer Institute Singapore

Considerations

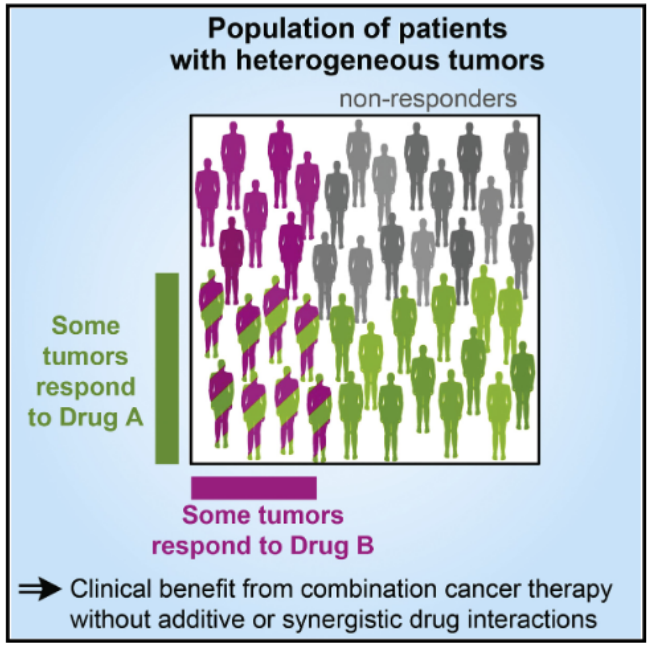
- Limitations
  - Is the response related to single agent activity?
  - Heterogeneity in samples
  - Need for “normal” controls
  - Cell-extrinsic factors influencing outcome
  - Scalability

Theory

Cell

Combination Cancer Therapy Can Confer Benefit via Patient-to-Patient Variability without Drug Additivity or Synergy

Graphical Abstract



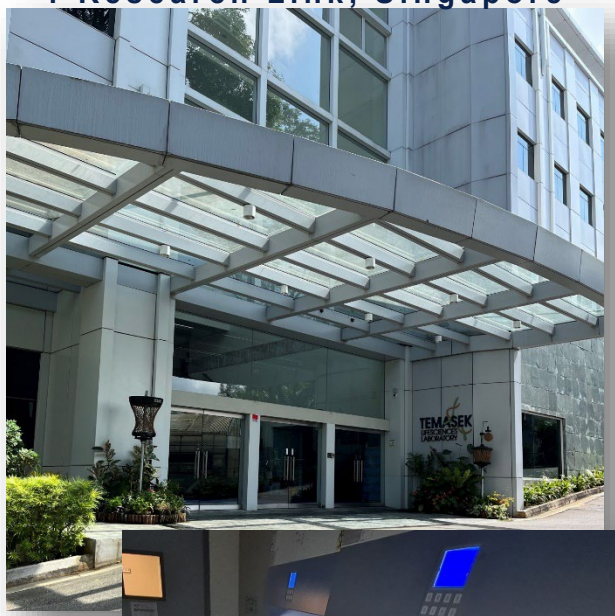
Authors
Adam C. Palmer, Peter K. Sorger

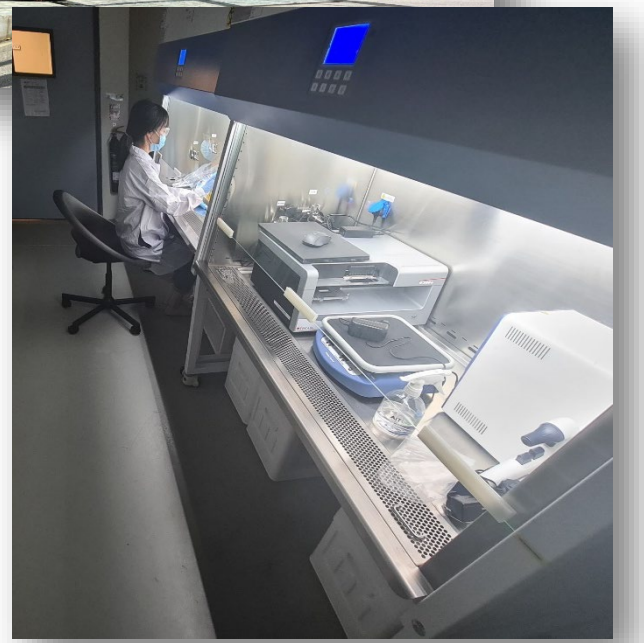
Correspondence
peter_sorger@hms.harvard.edu

In Brief
Patient-to-patient variability in response to single drugs is sufficient to explain the efficacy of a large number of combination cancer therapies without pharmacologically additive or synergistic effect in individual patients.

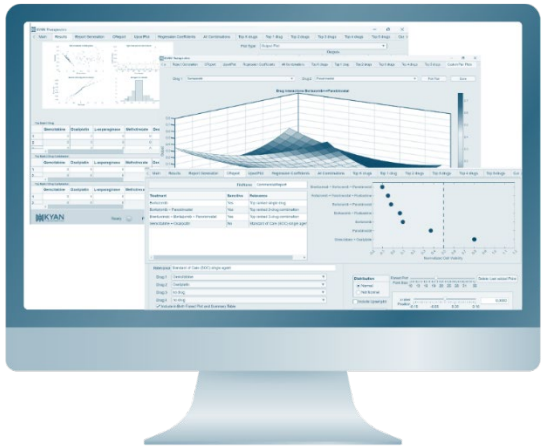
Commercialisation of QPOP Platform

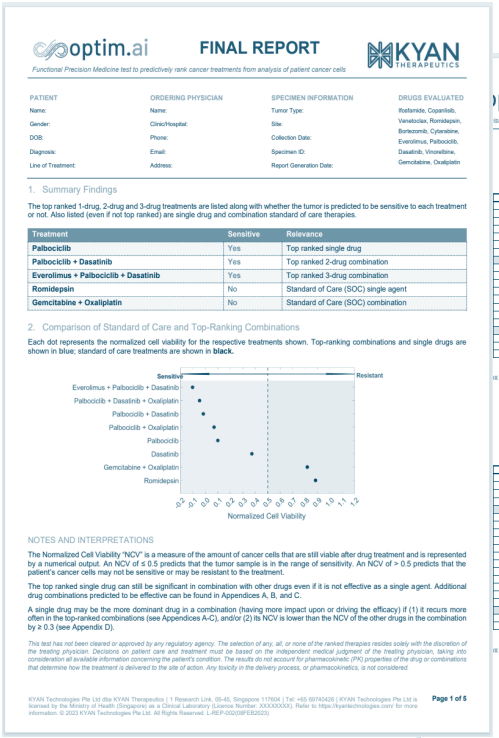
KYAN Technologies Clinical Lab
Temasek Lifesciences Laboratory
1 Research Link, Singapore





MOH Clinical Licence Approval to offer LDT on May 26, 2023 (KYAN Technologies/Optim.AI)





optim.ai **FINAL REPORT** KYAN THERAPEUTICS

Functional Precision Medicine test to predictively rank cancer treatments from analysis of patient cancer cells

PATIENT	ORDERING PHYSICIAN	SPECIMEN INFORMATION	DRUGS EVALUATED
Name:	Name:	Tumor Type:	Ifosfamide, Copanlisib, Venetoclax, Romidepsin, Bortezomib, Cytarabine, Everolimus, Palbociclib, Dasatinib, Vinorelbine, Gemcitabine, Oxaliplatin
Gender:	Clinic/Hospital:	Site:	
DOB:	Phone:	Collection Date:	
Diagnosis:	Email:	Specimen ID:	
Line of Treatment:	Address:	Report Generation Date:	

1. Summary Findings

The top ranked 1-drug, 2-drug and 3-drug treatments are listed along with whether the tumor is predicted to be sensitive to each treatment or not. Also listed (even if not top ranked) are single drug and combination standard of care therapies.

Treatment	Sensitive	Relevance
Palbociclib	Yes	Top ranked single drug
Palbociclib + Dasatinib	Yes	Top ranked 2-drug combination
Everolimus + Palbociclib + Dasatinib	Yes	Top ranked 3-drug combination
Romidepsin	No	Standard of Care (SOC) single agent
Gemcitabine + Oxaliplatin	No	Standard of Care (SOC) combination

2. Comparison of Standard of Care and Top-Ranking Combinations

Each dot represents the normalized cell viability for the respective treatments shown. Top-ranking combinations and single drugs are shown in blue; standard of care treatments are shown in **black.**

NOTES AND INTERPRETATIONS

The Normalized Cell Viability "NCV" is a measure of the amount of cancer cells that are still viable after drug treatment and is represented by a numerical output. An NCV of ≤ 0.5 predicts that the tumor sample is in the range of sensitivity. An NCV of > 0.5 predicts that the patient's cancer cells may not be sensitive or may be resistant to the treatment.

The top ranked single drug can still be significant in combination with other drugs even if it is not effective as a single agent. Additional drug combinations predicted to be effective can be found in Appendices A, B, and C.

A single drug may be the more dominant drug in a combination (having more impact upon or driving the efficacy) if (1) it recurs more often in the top-ranked combinations (see Appendices A-C), and/or (2) its NCV is lower than the NCV of the other drugs in the combination by ≥ 0.3 (see Appendix D).

This test has not been cleared or approved by any regulatory agency. The selection of any, all, or none of the ranked therapies resides solely with the discretion of the treating physician. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all available information concerning the patient's condition. The results do not account for pharmacokinetic (PK) properties of the drug or combinations that determine how the treatment is delivered to the site of action. Any toxicity in the delivery process, or pharmacokinetics, is not considered

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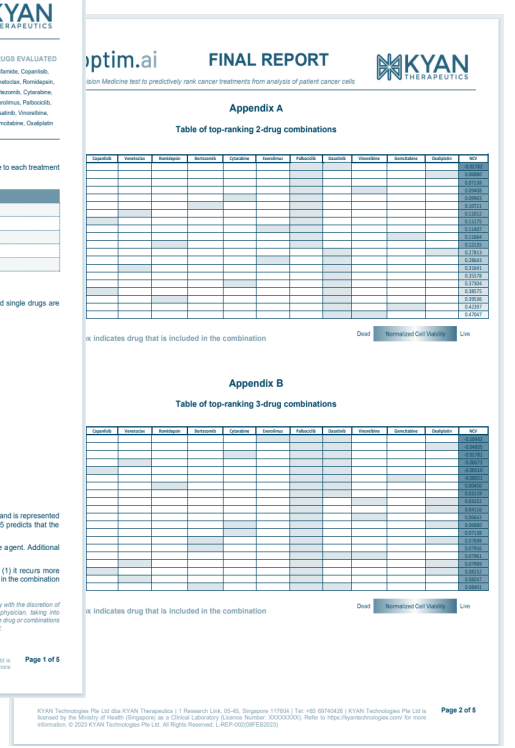

optim.ai **FINAL REPORT** KYAN THERAPEUTICS

ision Medicine test to predictively rank cancer treatments from analysis of patient cancer cells

Appendix A

Table of top-ranking 2-drug combinations

α indicates drug that is included in the combination

Dead — Normalized Cell Viability — Live

Appendix B

Table of top-ranking 3-drug combinations

α indicates drug that is included in the combination

Dead — Normalized Cell Viability — Live

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Page 2 of 5

First MOH approved ex vivo drug sensitivity LDT for oncology

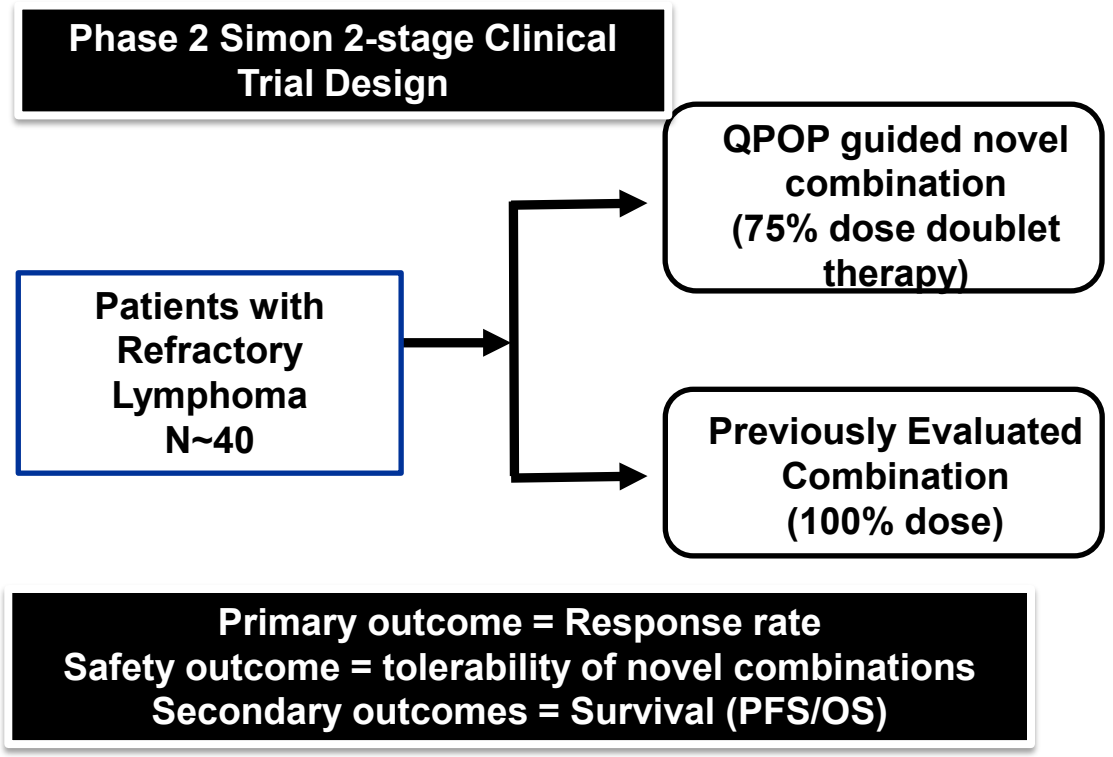
103 samples run to date

98% LDT report generation success rate

Clinical trial considerations

- What drugs, and who will fund?
- Focus on single company assets?
- Truly individualized vs choose from top 5 combinations?
- Primary end-point?
- Intra-patient comparisons?

- Possible strategy:



Engagements with Pharma, STCC, MOH/HSA to continue to bring individualized treatment to patients

Novel doublet for PTCL, but not fundable

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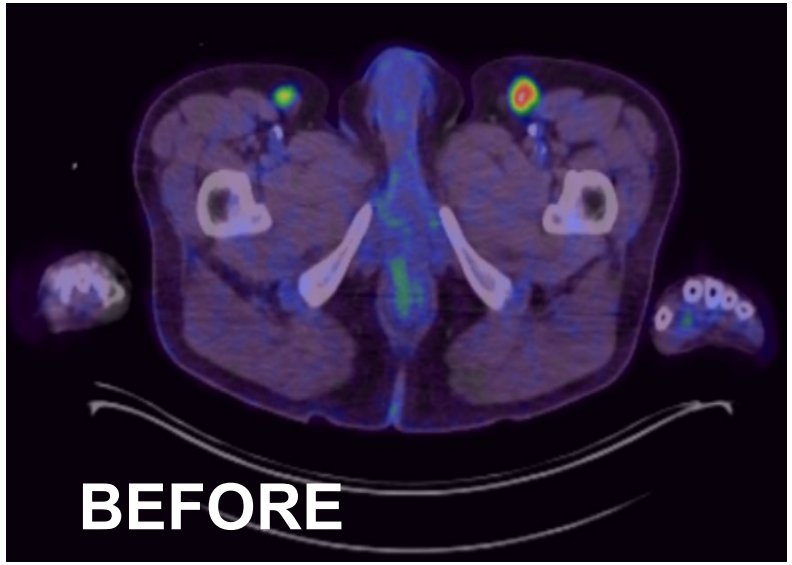
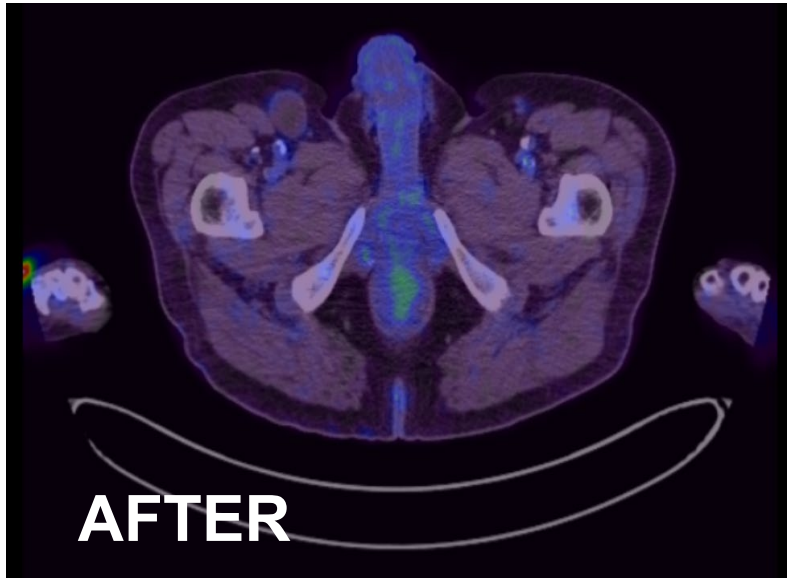
75yM with PTCL-NOS

- Relapsed after CHOPx6 (transplant ineligible), CD30 negative
- QPOP done at patient request
- Treated with Venetoclax-Ifosfamide based on QPOP (no data in PTCL, but part of VIPOR regimen)
- Remains in CR





CURRENT AND REVISED MEDISHIELD LIFE AND MEDISAVE LIMITS

	Current	Revised
MediShield Life	**S$3,000** per month for all cancer drug treatments and services	Ranges from **S$200** to **S$9,600** per month for cancer drug treatments on the positive list Additional **S$1,200** per year for cancer drug services

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Conclusions

- **Ex-vivo drug combination testing through QPOP is feasible in a clinically actionable time frame with typical incision biopsies**
- **Not just IC50 dependent (for all drugs)**
- **Potential to uncover clinically usable combinations, requires phase 1 like monitoring**
- **Funding clinical trials is challenging in this space; T-cell lymphoma remains the key unmet need**
- **Potential for incorporation of ADCC and monoclonal antibodies**

Phenotypic Assays in Lymphoma (Spatial and Ex-vivo)

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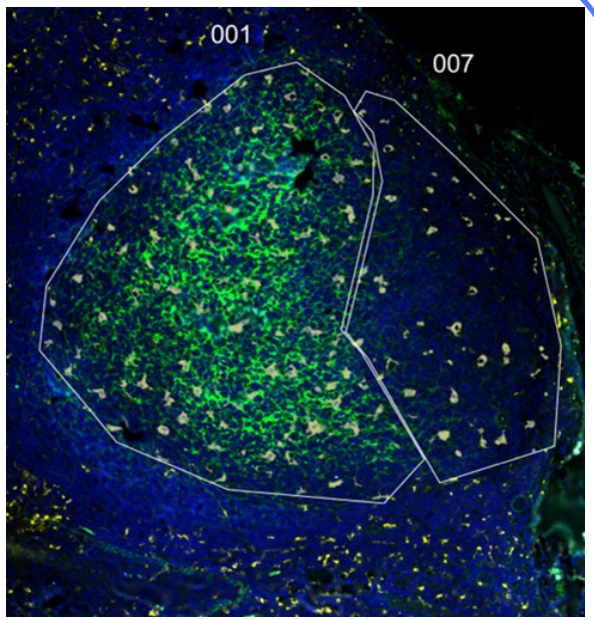
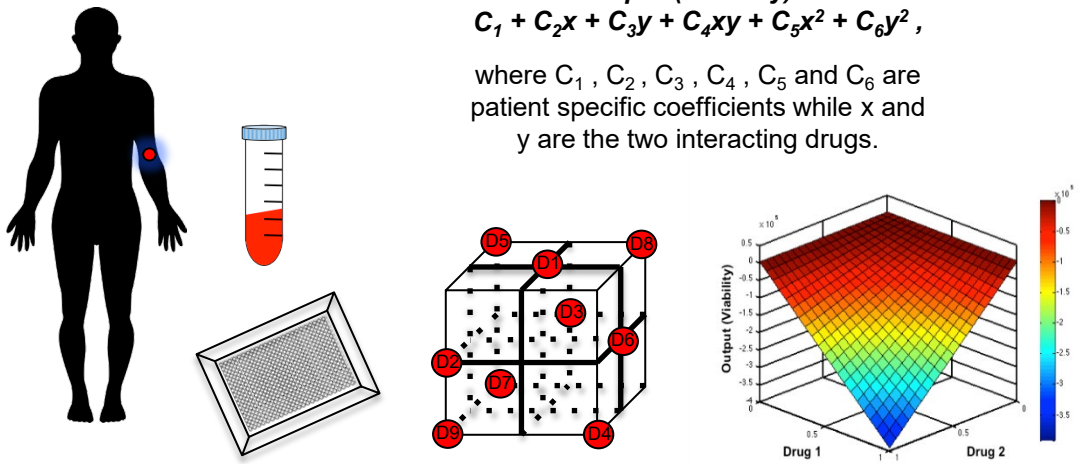


AACR JOURNALS

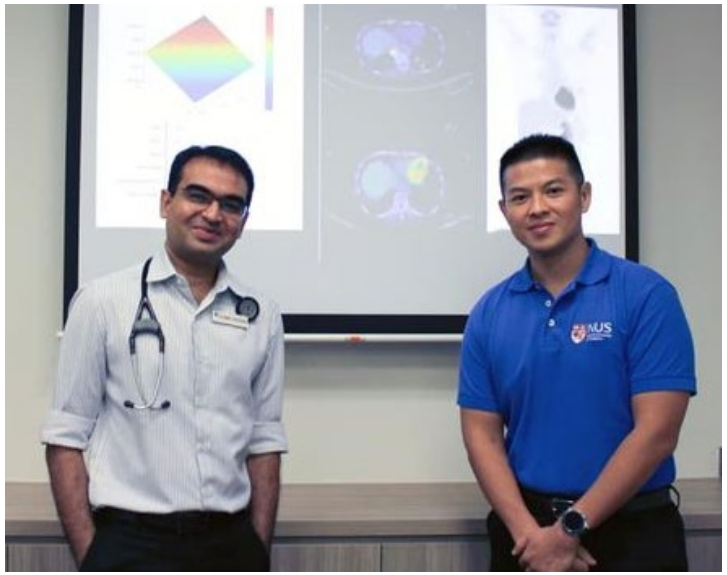
Output (Viability) =
$$C_1 + C_2x + C_3y + C_4xy + C_5x^2 + C_6y^2 ,$$

where C_1 , C_2 , C_3 , C_4 , C_5 and C_6 are patient specific coefficients while x and y are the two interacting drugs.



$Sf(PM)$

-CSI RCE Main Grant
-Ministry of Education AcRF
-NCIS Seed Funding Scheme
-NMRC Large-Collaborative Grant: Singapore lymphoma translational study (SYMPHONY)



Ed Chow

NCIS Lymphoma Team:
Sanjay de Mel
Michelle Poon
Yen Lin Chee
Esther Chan
Joanne Lee
Other Clinical Collaborators:
Chng Wee Joo (NCIS/ CSI)
Ng Siok Bian (Pathology)
Lim Soon Thye (NCCS)
Nagavalli Somasundaram (NCCS)
Tiffany Tang (NCCS)
Nick Grigoropoulos (SGH)
Ong Shin Yeu (SGH)
Eugene Fan (TTSH)

Laboratory Collaborators
CSI lab team:
Jasmine Goh (Ed Chow lab)
Lee Rui Xue (EC/ ADJ)
Masturah Rashid (KYAN Technologies)

Michal Hoppe (ADJ lab)
Patrick Jaynes (ADJ lab)

NCCS laboratory team:
Ong Choon Kiat
Daryl Tan
Daryl Ming Zhe Cheah
Wan Lu Pang
Dachuan Huang

Lymphoma patients and their families

National University Cancer Institute Singapore

csiadj@nus.edu.sg

adj_23