Oncology Phase I Trials: The Critical Step of Drug Development

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Oncology Phase I Trials Traditional

Primary endpoints

- Dose limiting toxicity (DLT)
- Maximum tolerated dose (MTD)
- Recommended phase II dose (RP2D)

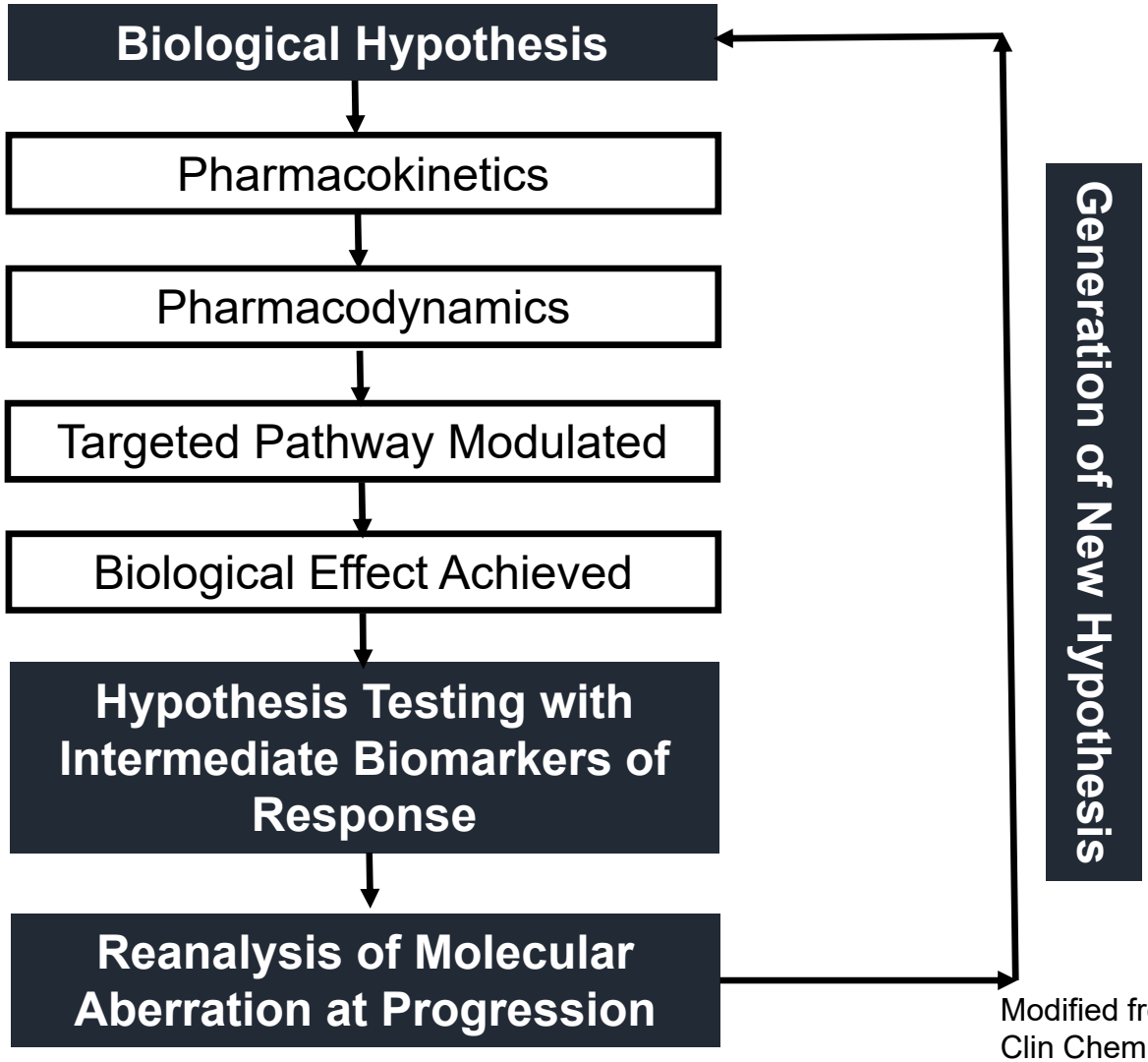
Secondary endpoints

- Pharmacokinetics (PK)
- Pharmacodynamics (PD)
- Preliminary antitumor activity

Eligibility

- Patients with refractory cancers of any type

Oncology Phase I Trials Modern



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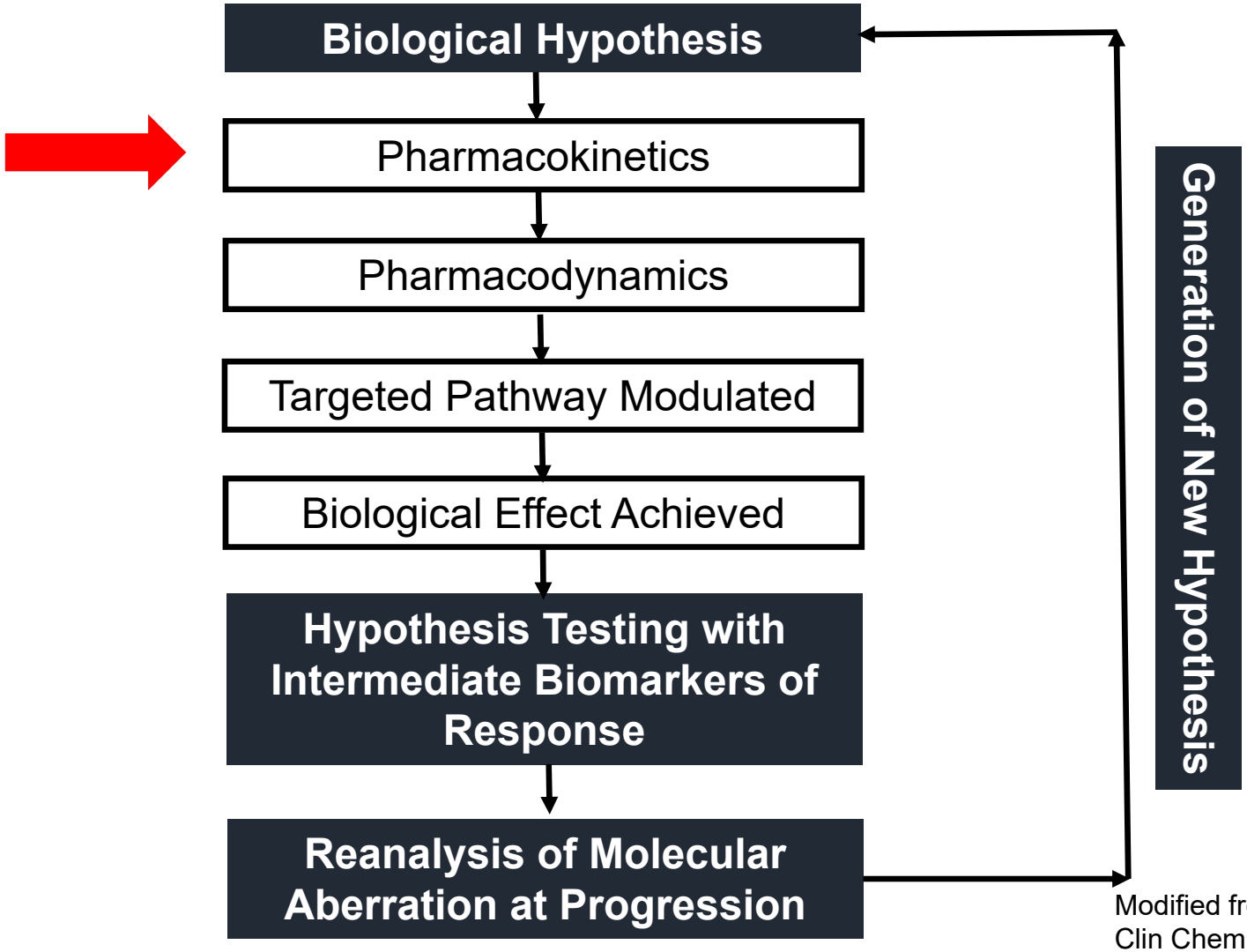

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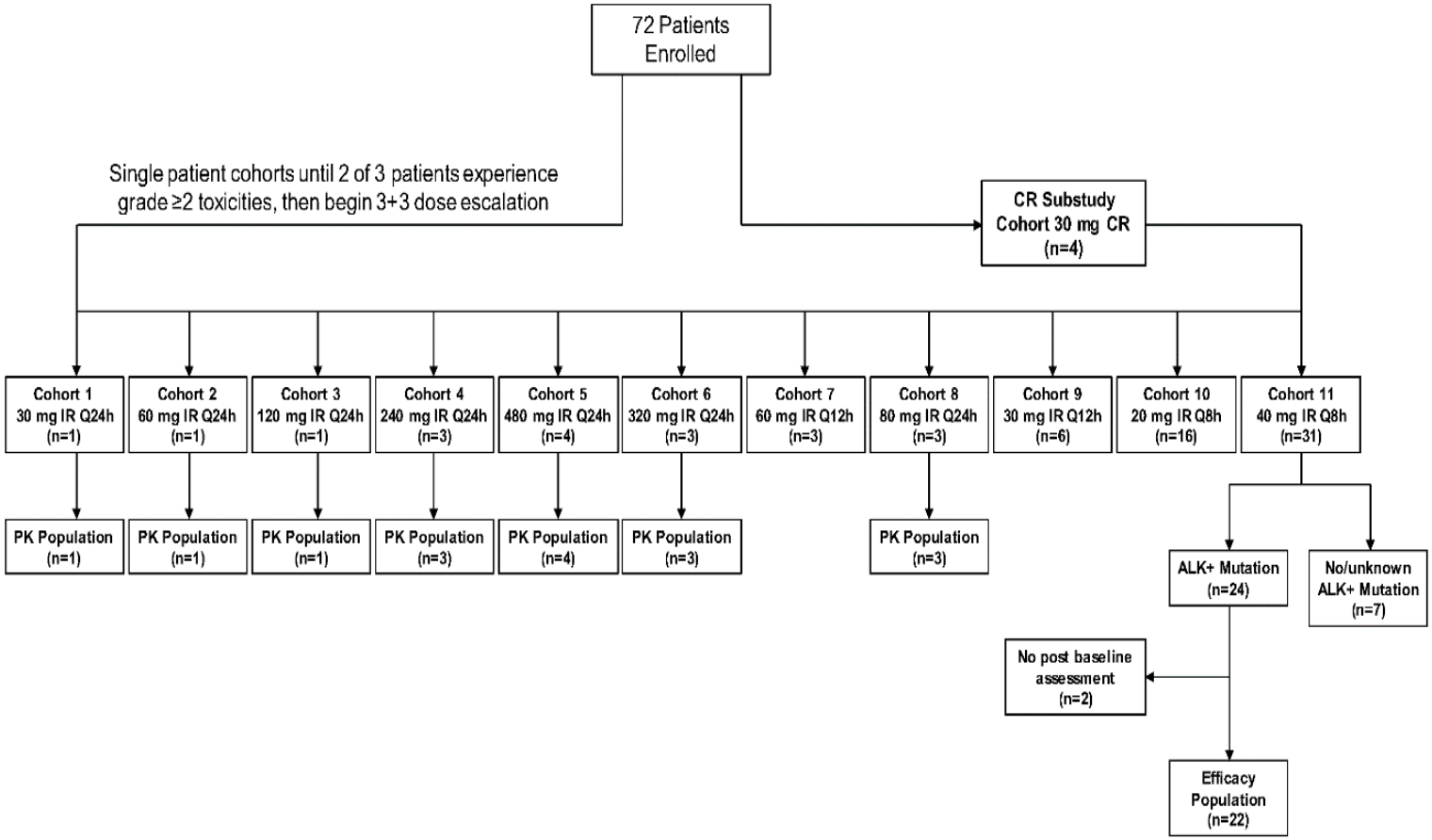
ALK Inhibitors Beyond Crizotinib

IC_{50} ≤50 nM IC_{50} >50–<200 nM IC_{50} ≥200 nM

	Molecular Targets Other Than ALK	Activity Against C1156Y	Activity Against L1196M	Activity Against G1202R	Activity Against G1269A
Ceritinib	ROS1, IGF1R, InsR	Yes	Yes	Intermediate	Yes
Alectinib		Yes	Intermediate	No	Yes
Brigatinib	ROS1, $EGFR^{del19/T790M}$	Yes	Yes	Intermediate	NA
Lorlatinib	ROS1	Yes	Yes	Yes	Yes
Belizatinib	**NTRK**	**NA**	**Yes**	**NA**	**NA**
Entrectinib	ROS1, NTRK	Yes	Yes	NA	NA

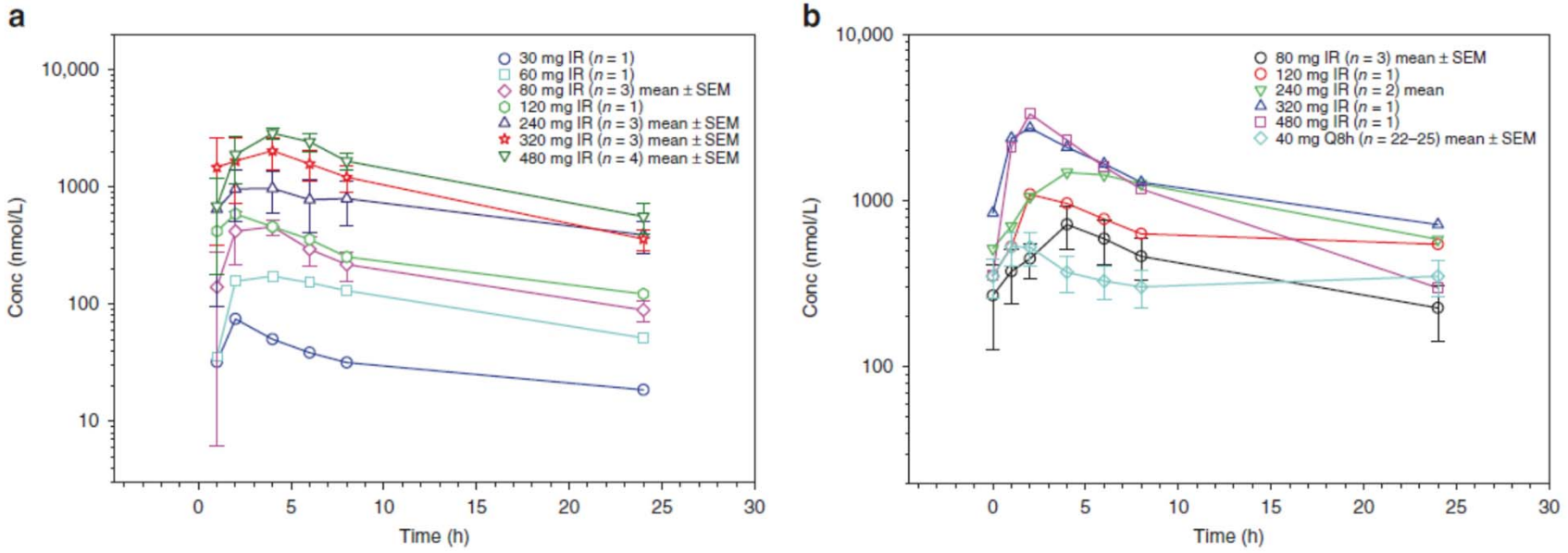
Modified from Liao B-C, Lin C-C, et al. Ther Adv Med Oncol 7:274-90, 2015 (review)

Belizatinib (TSR011) Phase I Trial



Lin C-C, et al. Br J Cancer 121:131-8, 2019

Belizatinib (TSR011) Phase I Trial



Lin C-C, et al. Br J Cancer 121:131-8, 2019

Belizatinib (TSR011) Phase I Trial

	ALK inhibitor-naïve (n = 14)	Prior ALK inhibitor-treated (n = 8)	All patients (n = 22)
Best overall response, n (%)			
Complete response	0	0	0
Partial response	6 (42.9)	1 (12.5)	7 (31.8)
Stable disease	8 (57.1)	6 (75.0)	14 (63.6)
Progressive disease	0	1 (12.5)	1 (4.5)
Objective response, n (%)			
Complete response + partial response	6 (42.9)	1 (12.5)	7 (31.8)

Lin C-C, et al. Br J Cancer 121:131-8, 2019

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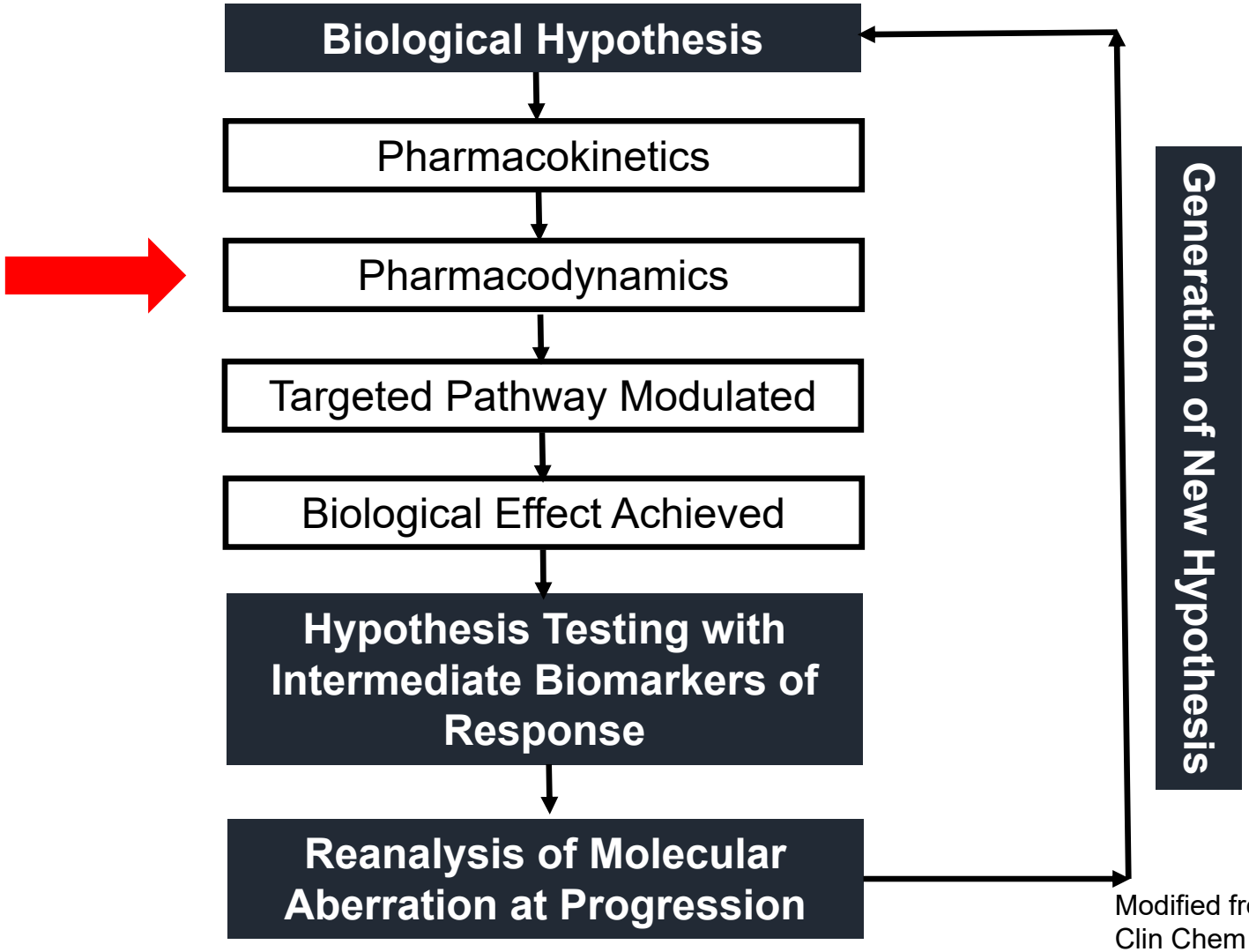

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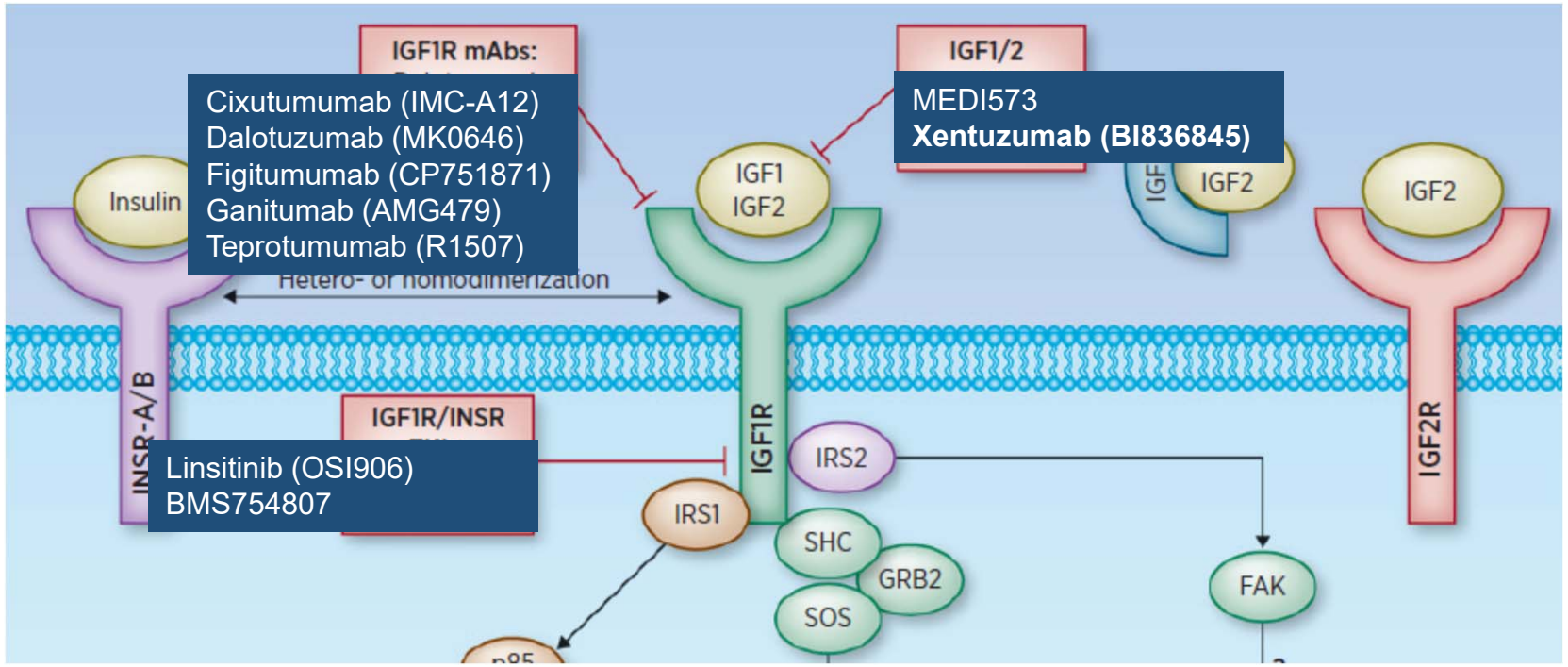
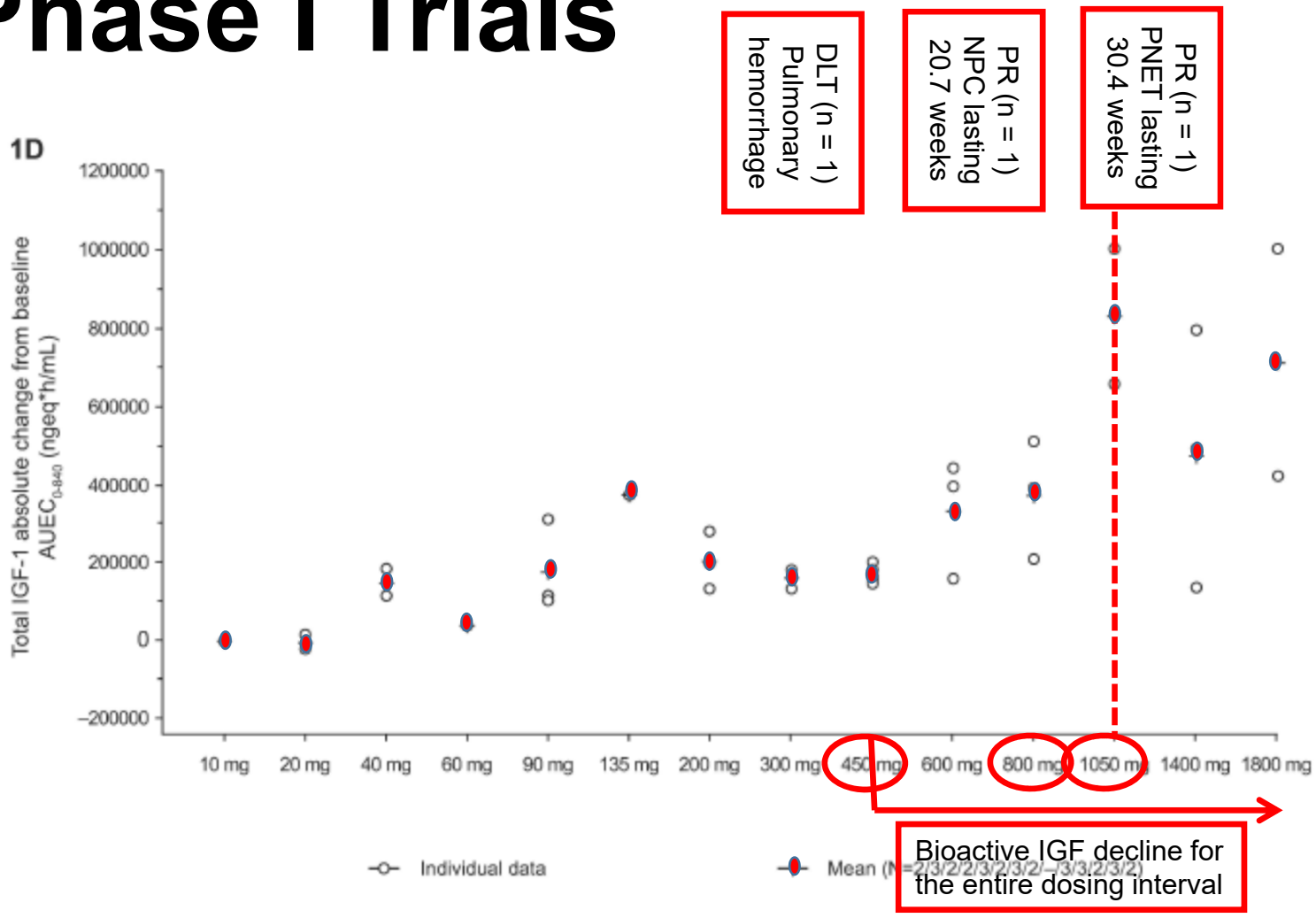
Anti-IGF / IGF1R Antibodies



Modified from Iams WT, et al. Clin Cancer Res 21:4270-7, 2015 (review)

Xentuzumab (BI836845) Phase I Trials



de Bono J*, Lin C-C*, et al. Br J Cancer Br J Cancer 122:1324-32, 2020 (*equal contribution)

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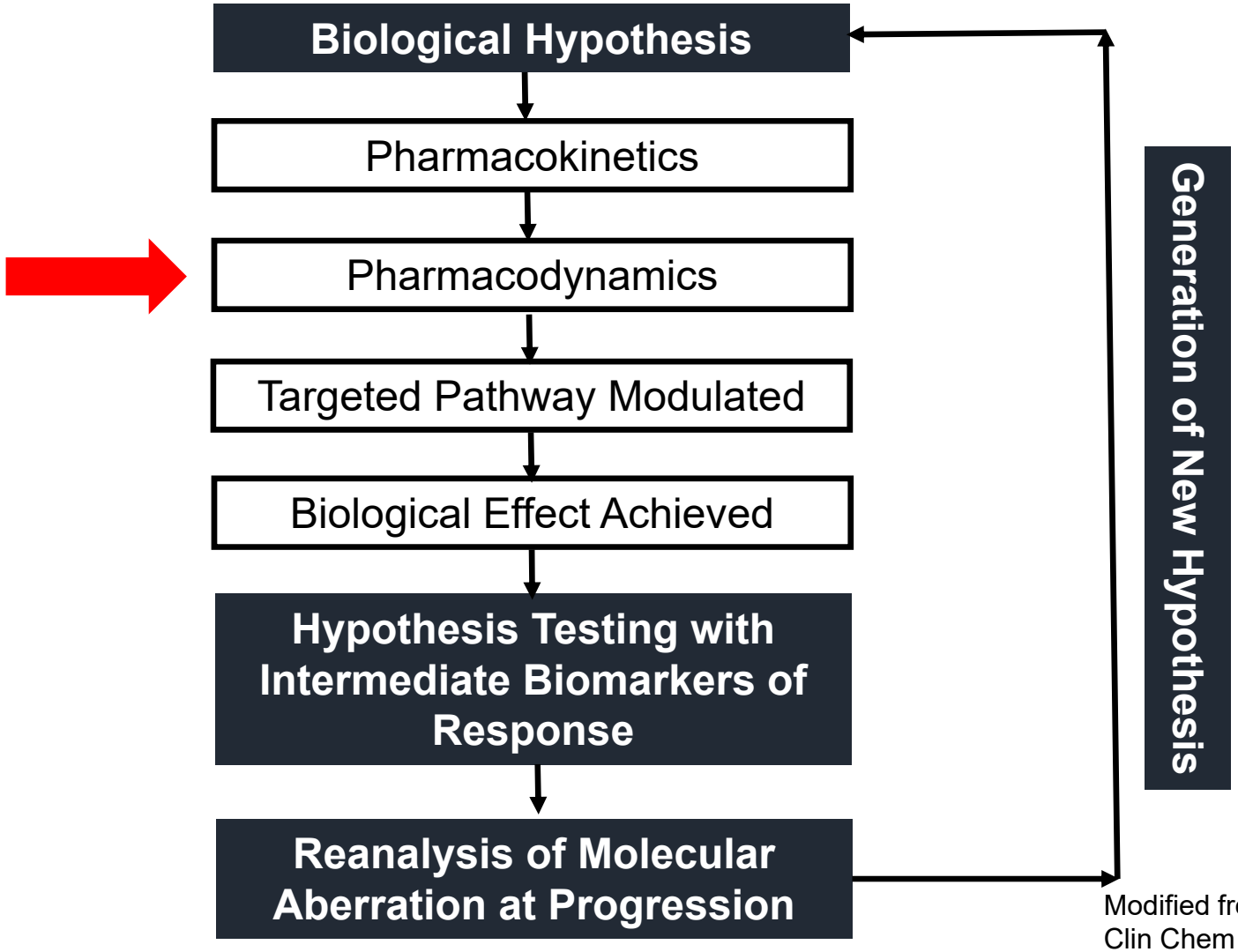
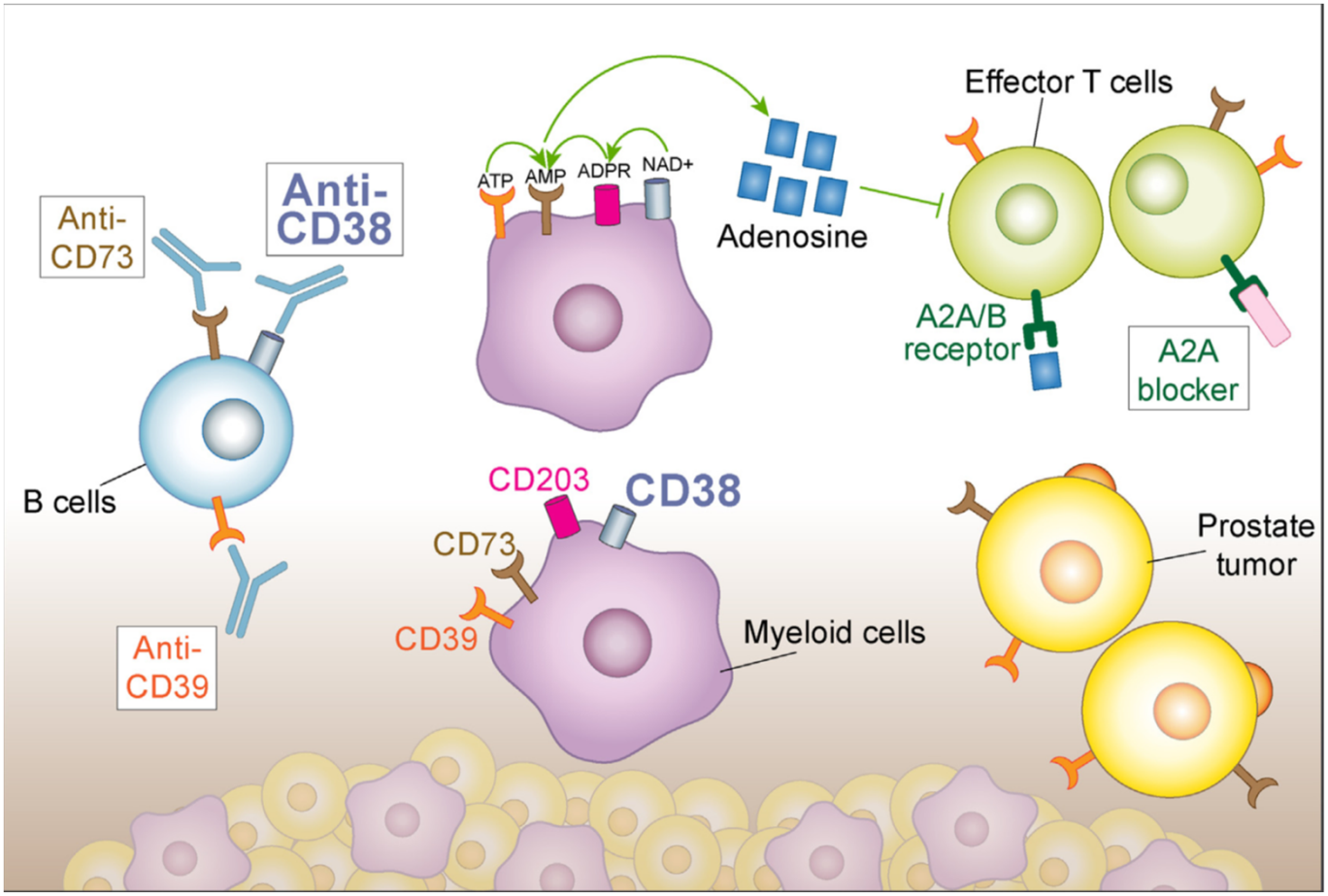


Modified from Ferraldeschi R, et al. Clin Chem 59:75-84, 2013

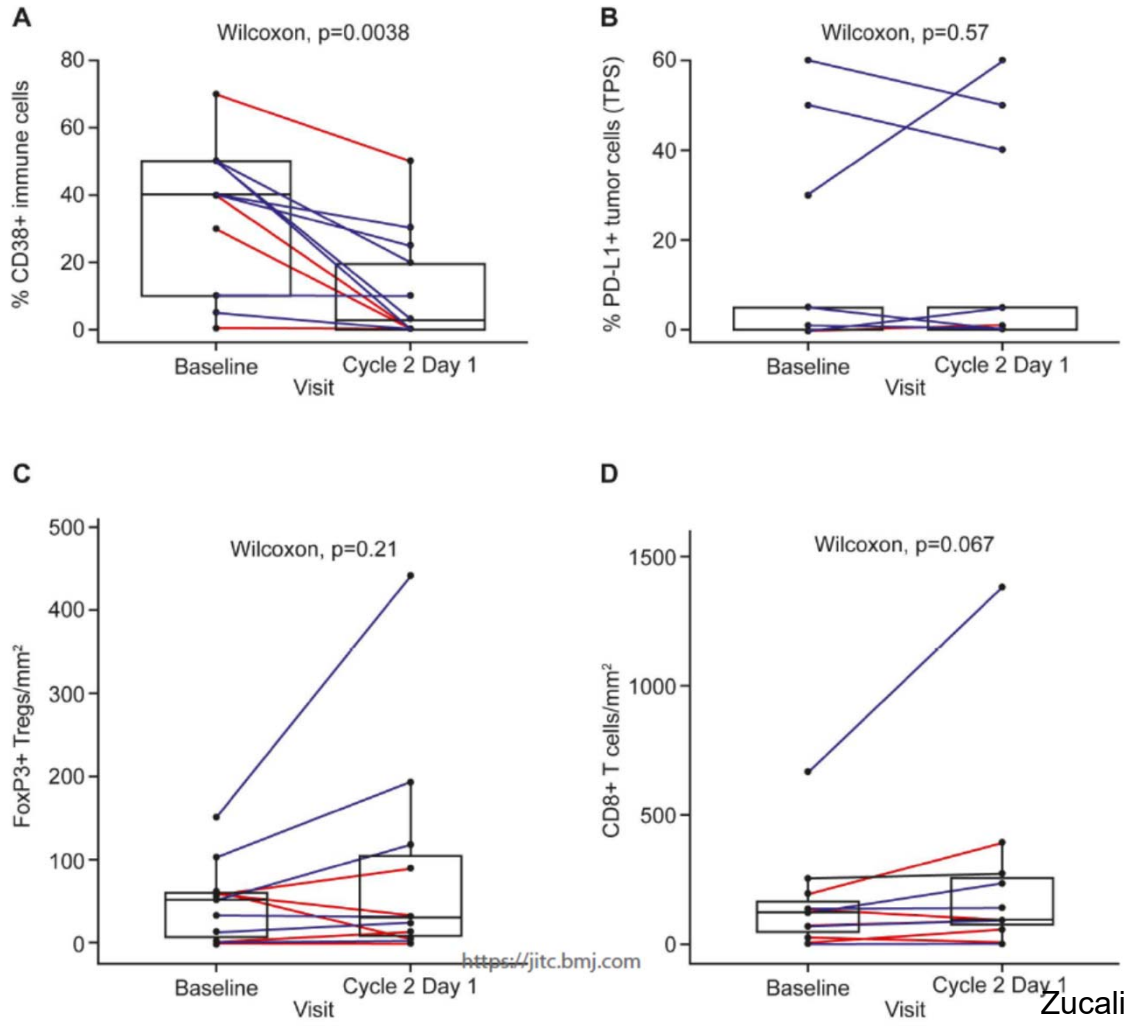
REGN2810 + SAR650984 Rationale



Yver A. Eur Urol 79:747-9, 2021

REGN2810 + SAR650984
Tumor Biopsies

CRPC
NSCLC



A. Decrease of CD38+ immune cells

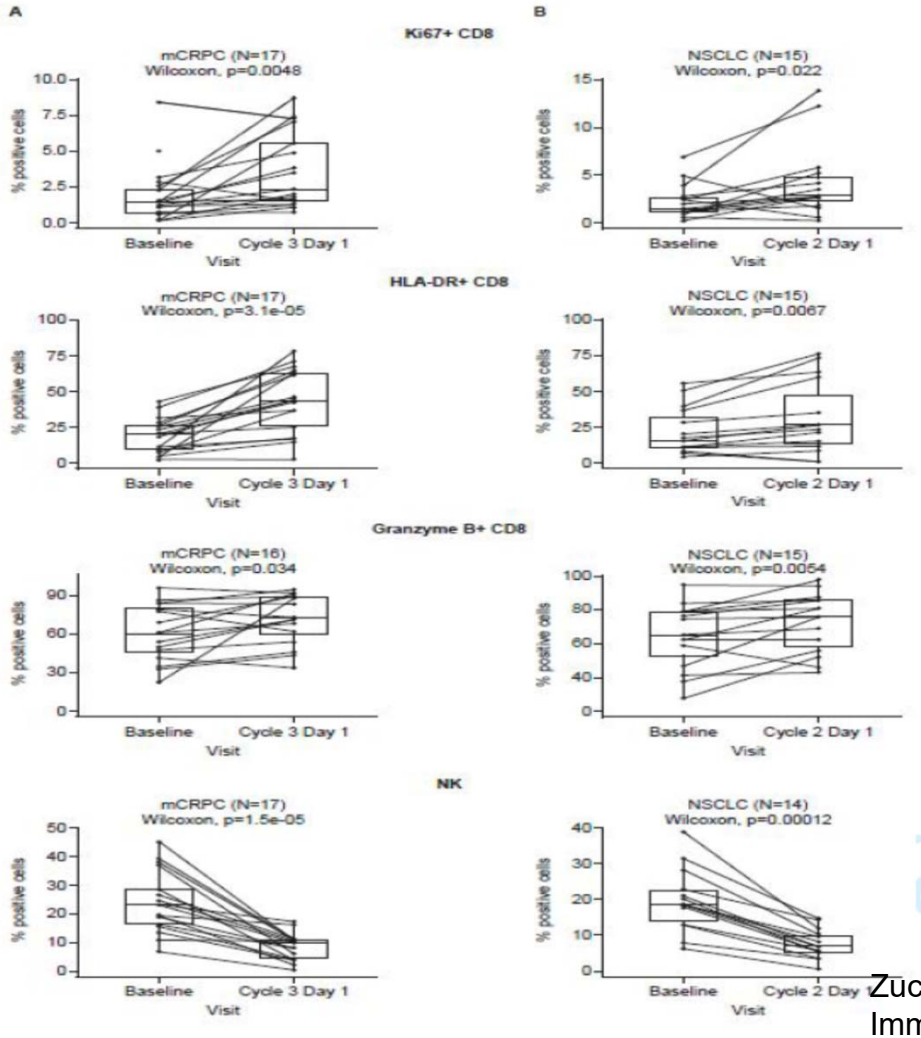
B. No increase of PD-L1+ tumor cells

C. No decrease of regulatory T cells

Zucali PA,* Lin C-C,* et al. J Immunother Cancer 9, 2021 (in press)

REGN2810 + SAR650984
Peripheral Blood Immune Cells

A: CRPC
B: NSCLC



Increase of Activated T Cells

Increase of Cytolytic T Cells

Decrease of NK Cells

Zucali PA,* Lin C-C,* et al. J Immunother Cancer 9, 2021 (in press)

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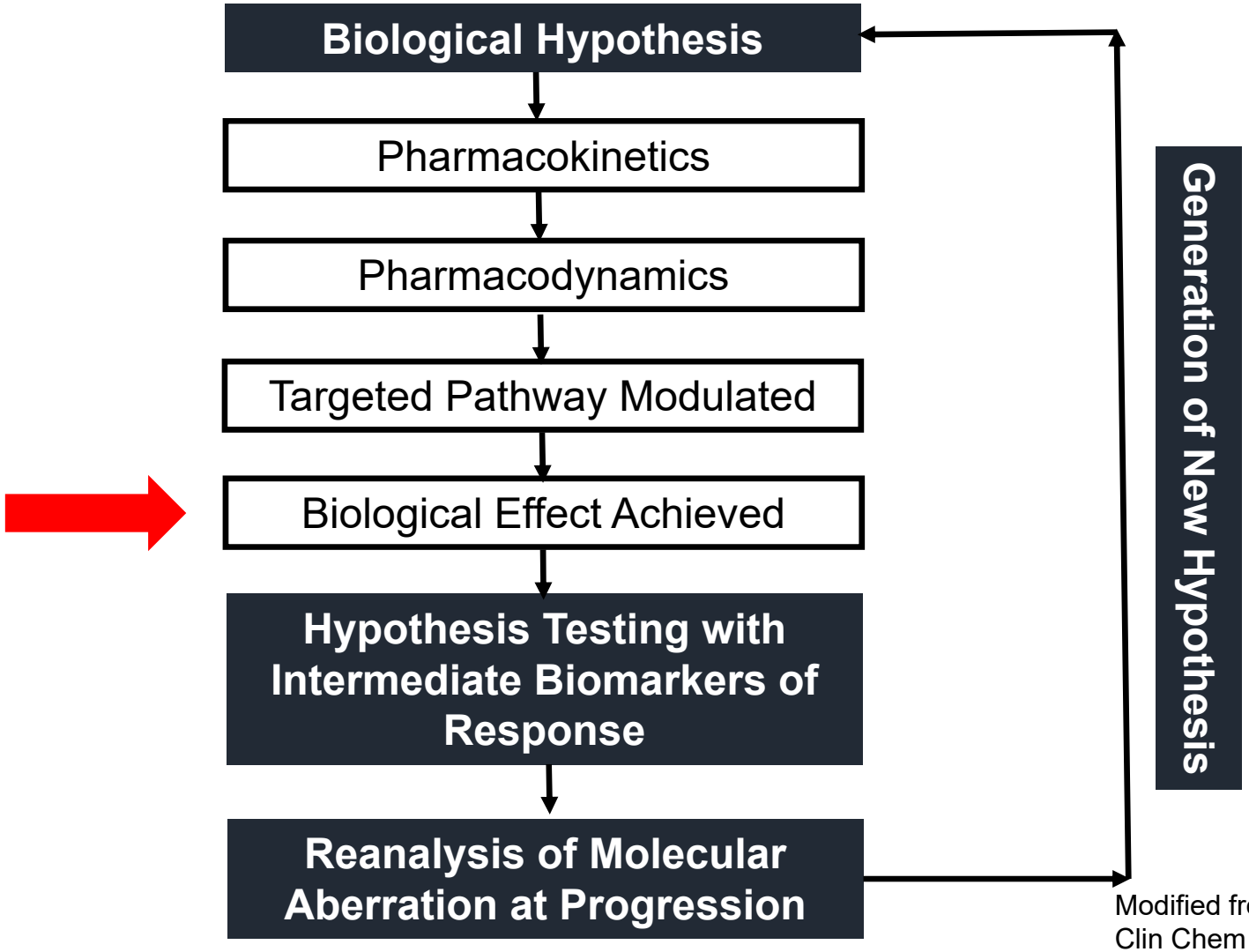

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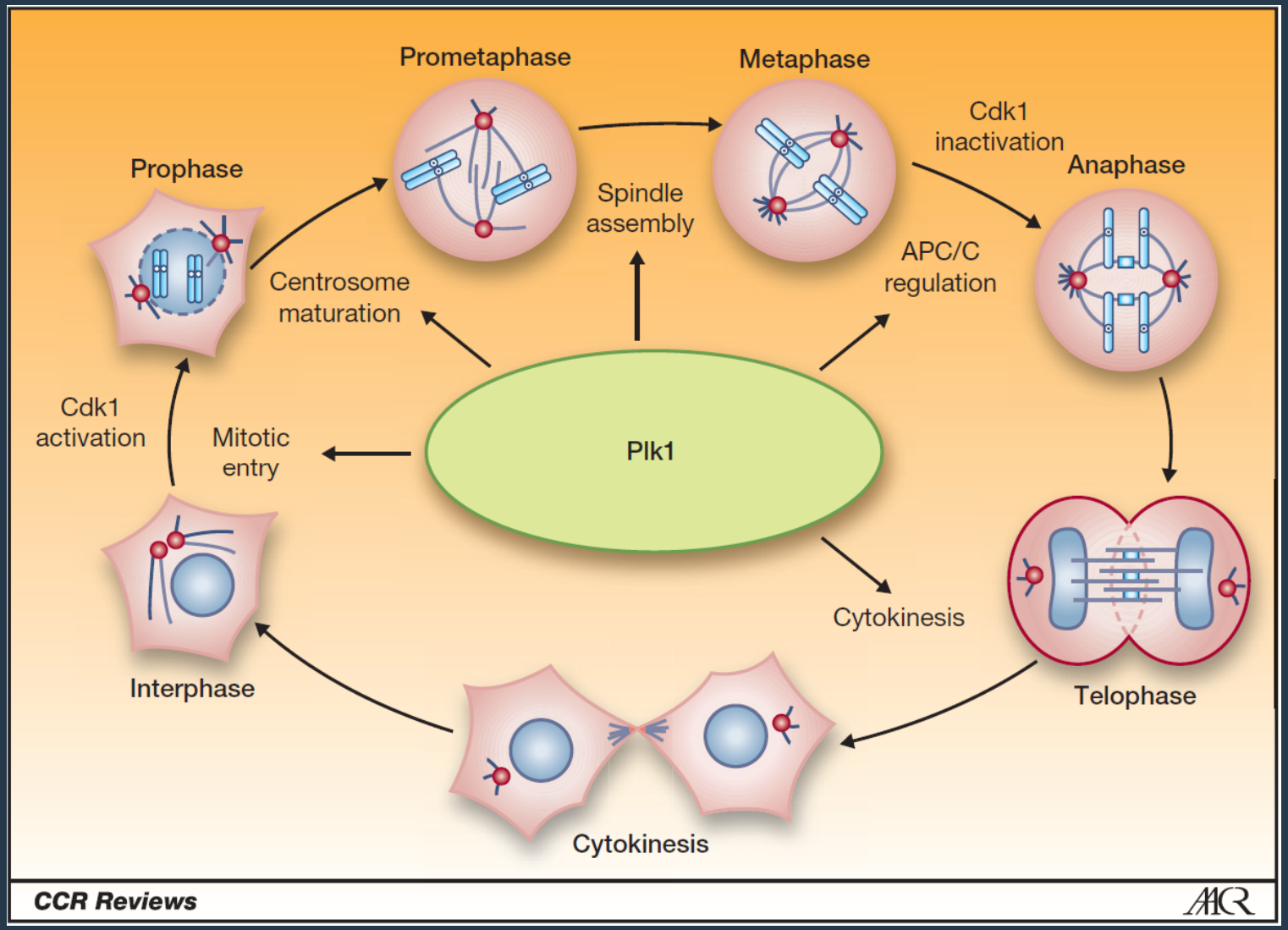
Polo-Like Kinases



Medema RH, Lin C-C, Yang C-H. Clin Cancer Res 17:6459-66, 2011 (review)

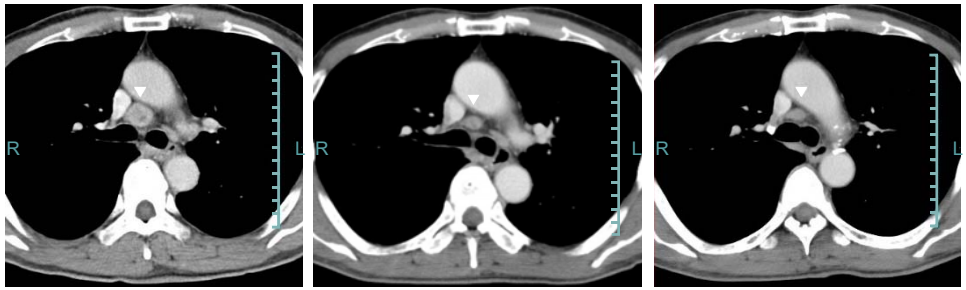
Volasertib (BI6727) Phase I Trials

Study	1230.1[1]	1230.16[2]	
Region	Europe	Asia	
Schedule(s)	D1, Q21D	D1, Q21D	D1 & 8, Q21D
Dose levels, mg	12 - 450	100 - 350	50 - 200
Total, n	65	32	27
DLT	G4 ANC G4 platelets	G4 platelets	G4 ANC
MTD, mg	400	300	150
RP2D, mg	300	300 (tbc)	150 (tbc)
PR, n	3	1	1
Tumors (dose)	Melanoma (300) Ovarian (400) Urothelial (450)	Urothelial (350)	Melanoma (150)

1. Schoffski P, et al. Eur J Cancer 48:179-186, 2012
2. Lin C-C, et al. Br J Cancer 110:2434-40, 2014

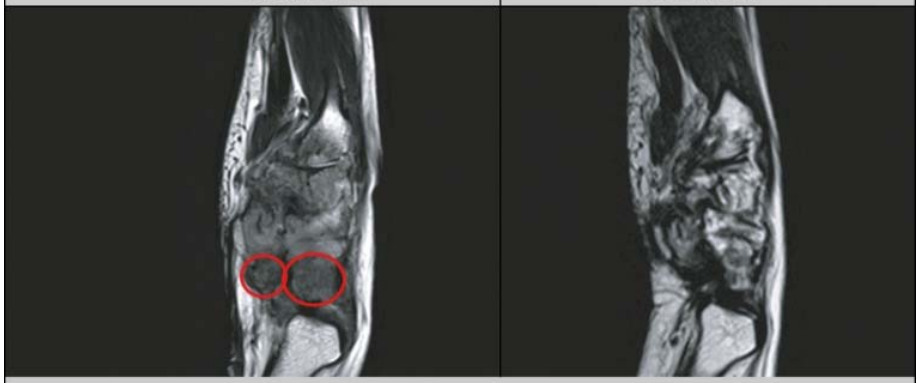
BI853520, Pexidartinib (PLX3397) Phase I Trials

BI853520: FAK inhibitor
Gastric cancer



Baseline Cycle 4: PR Cycle 6: PR Confirmed

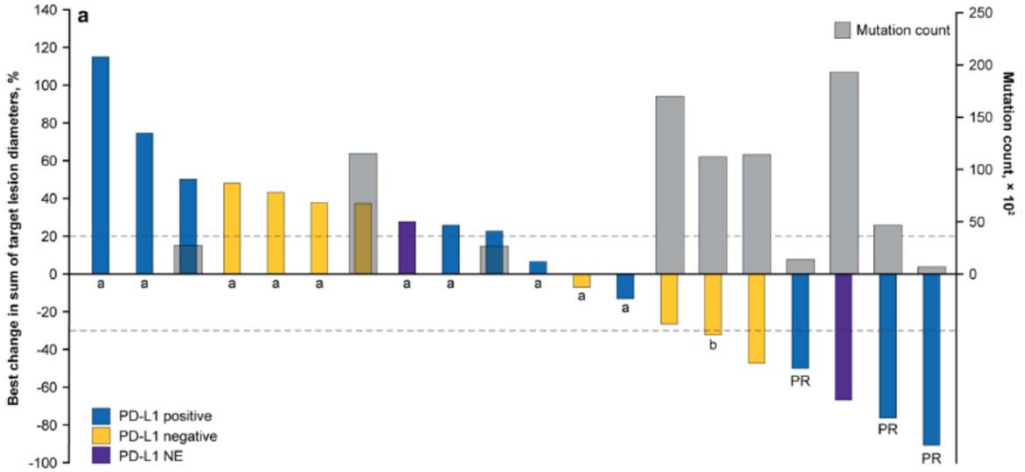
Pexidartinib: CSF1R inhibitor
TGCT

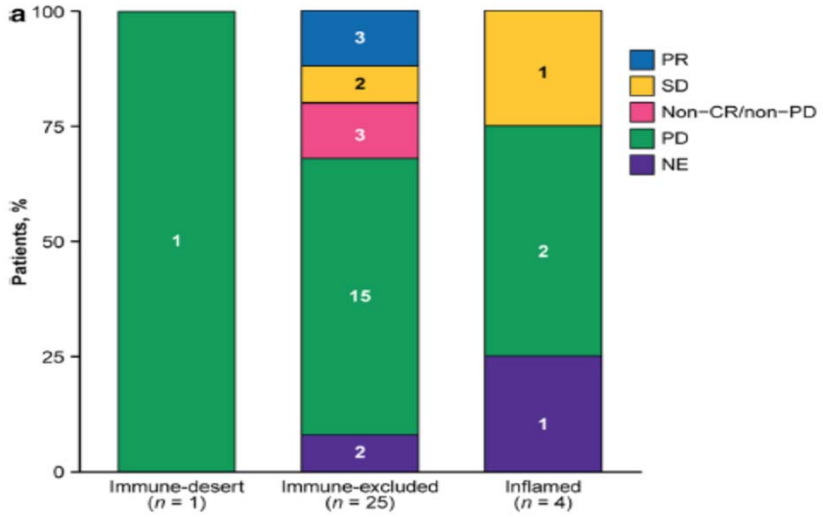


Longest diameter (mm)		
Lesion 1	26.0	13.6
Lesion 2	18.1	7.8
Administration period (days)		
	0	207

Doi T, … Lin C-C.* Target Oncol 14:57-65, 2019 (*corresponding author)
Lee J-H, … Lin C-C.* Invest New Drugs 38:99-110, 2020 (*corresponding author)

Bintrafusp Alfa (M7824) Phase I Trials





- Bintrafusp alfa: anti-PD-L1 antibody + TGFβ trap
- ESCC

C-C, et al. Target Oncol 16:447-59, 2021

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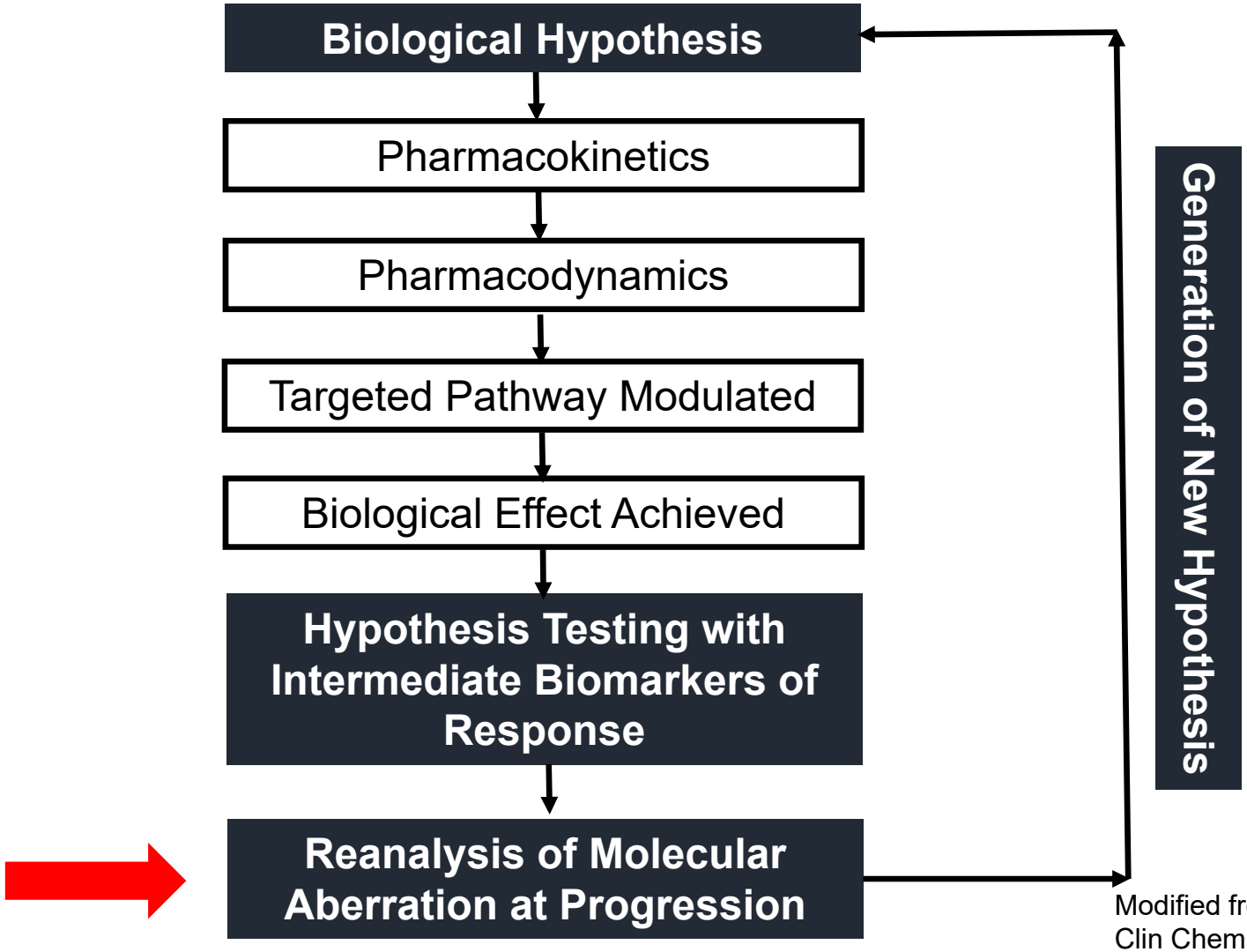

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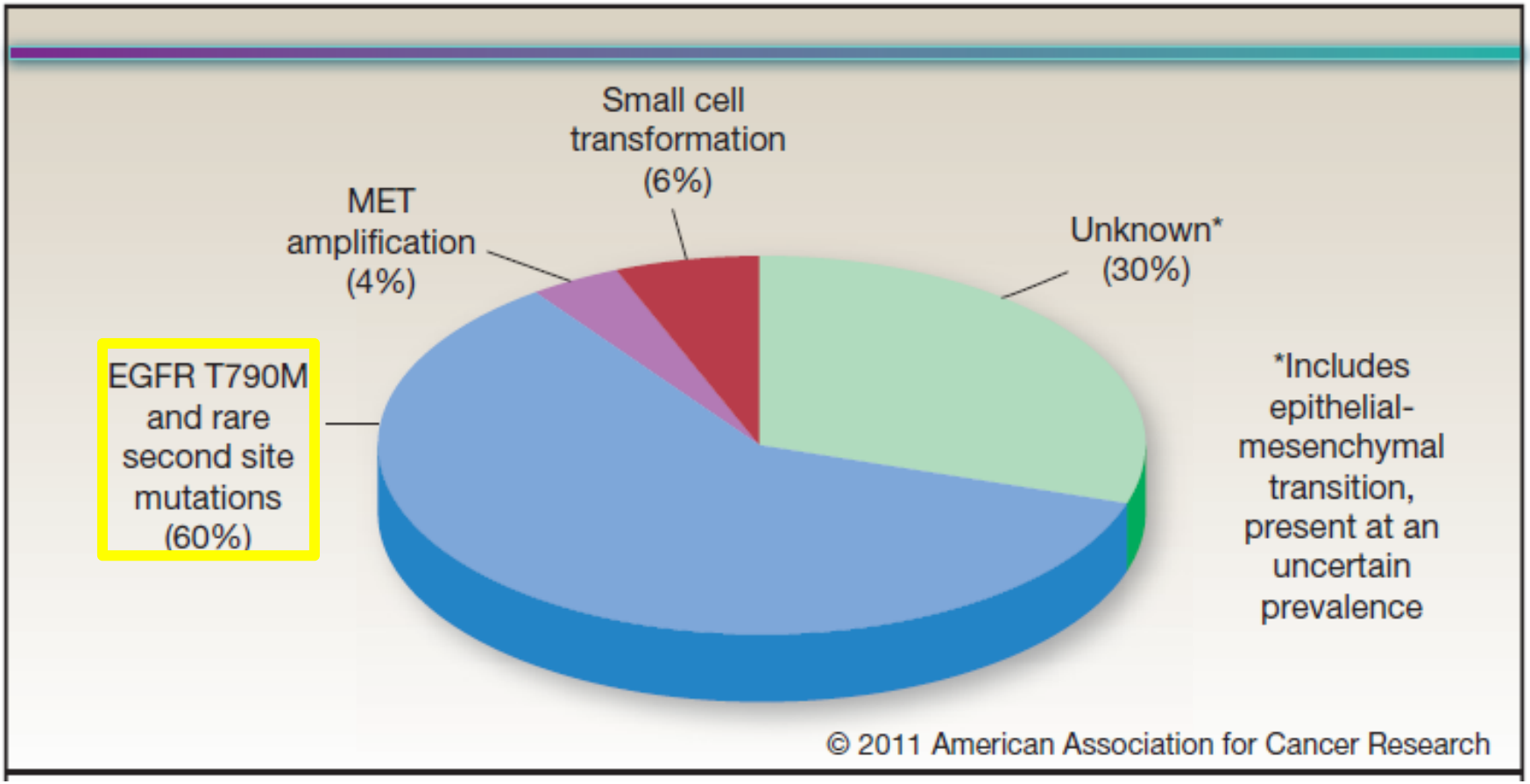
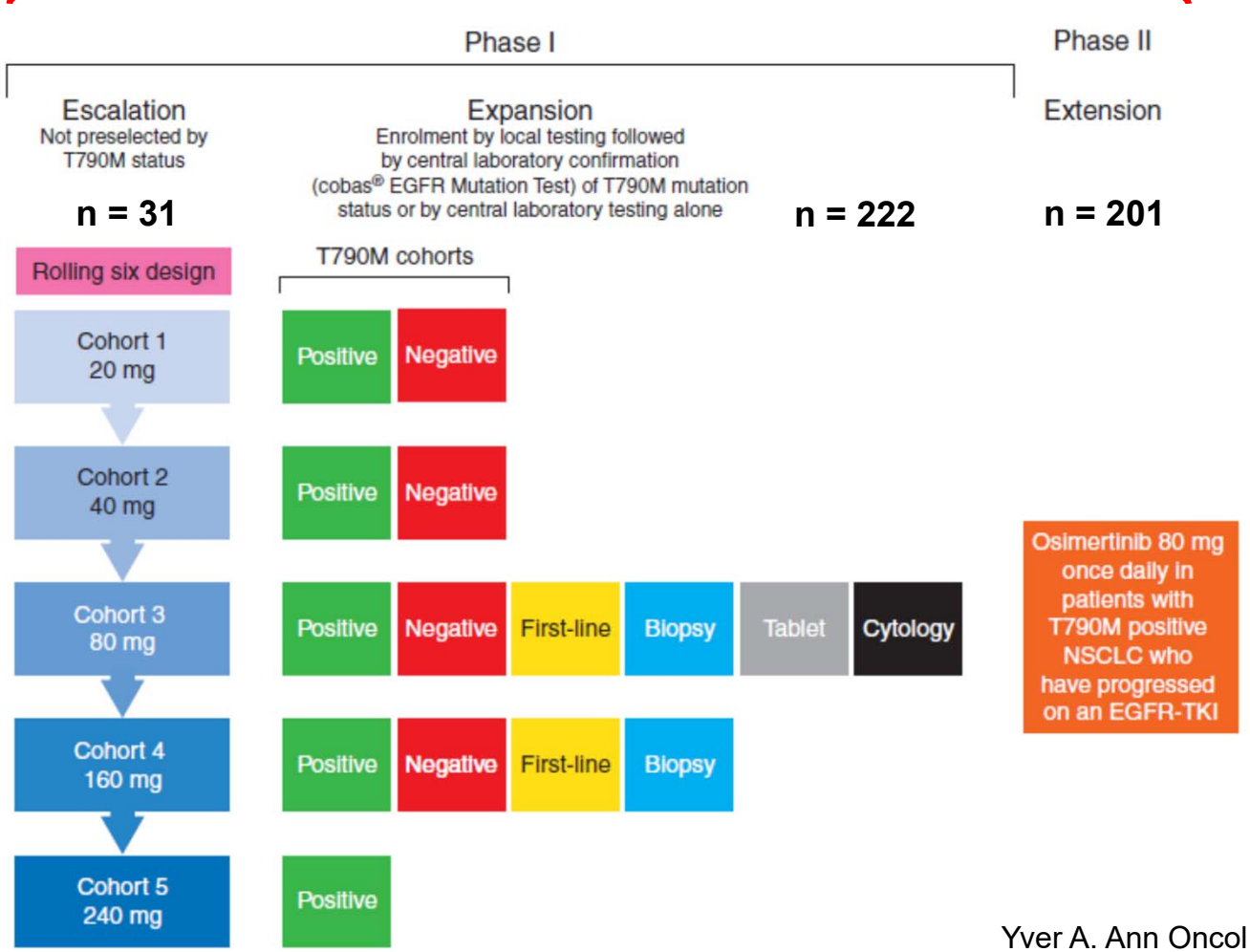
EGFR TKI
Acquired Resistance



Clin Cancer Res 2011;17:5530-7

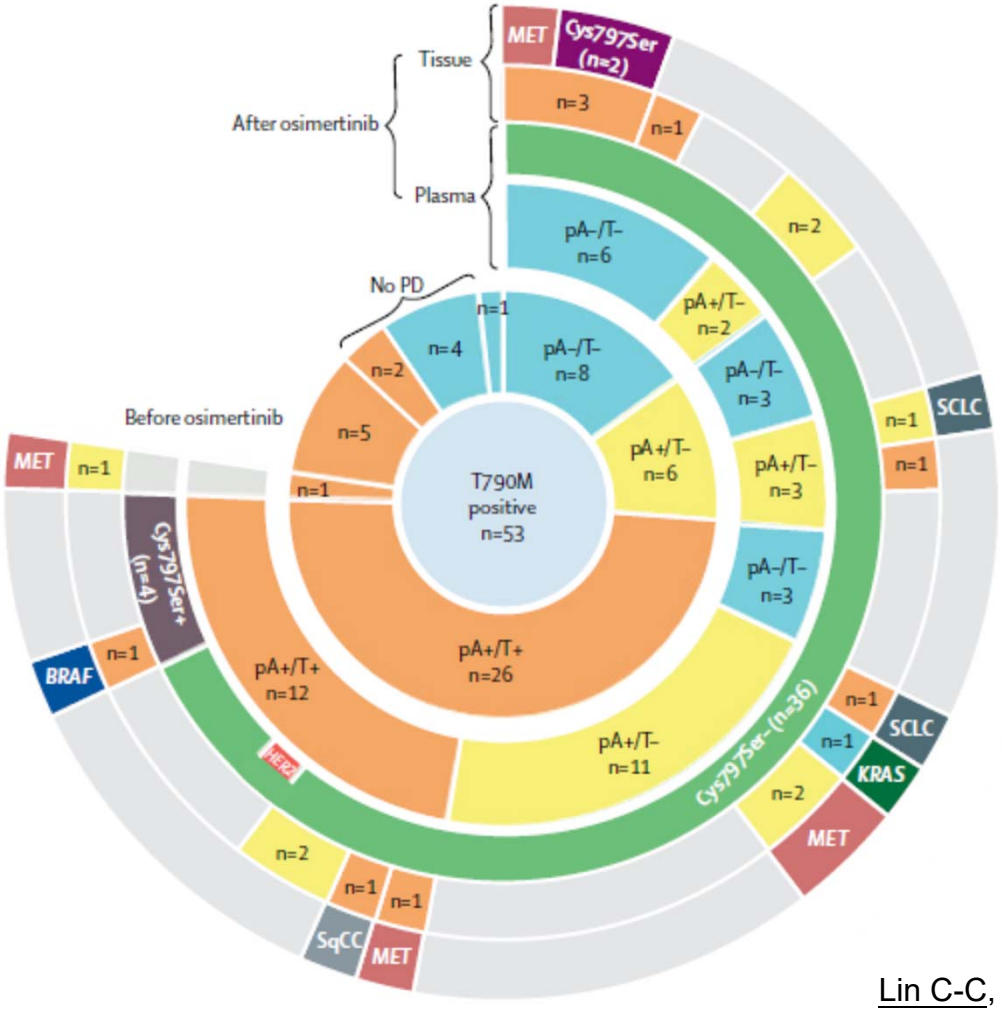
Osimertinib (AZD9291) Phase I Trial

n = 71
NTUH



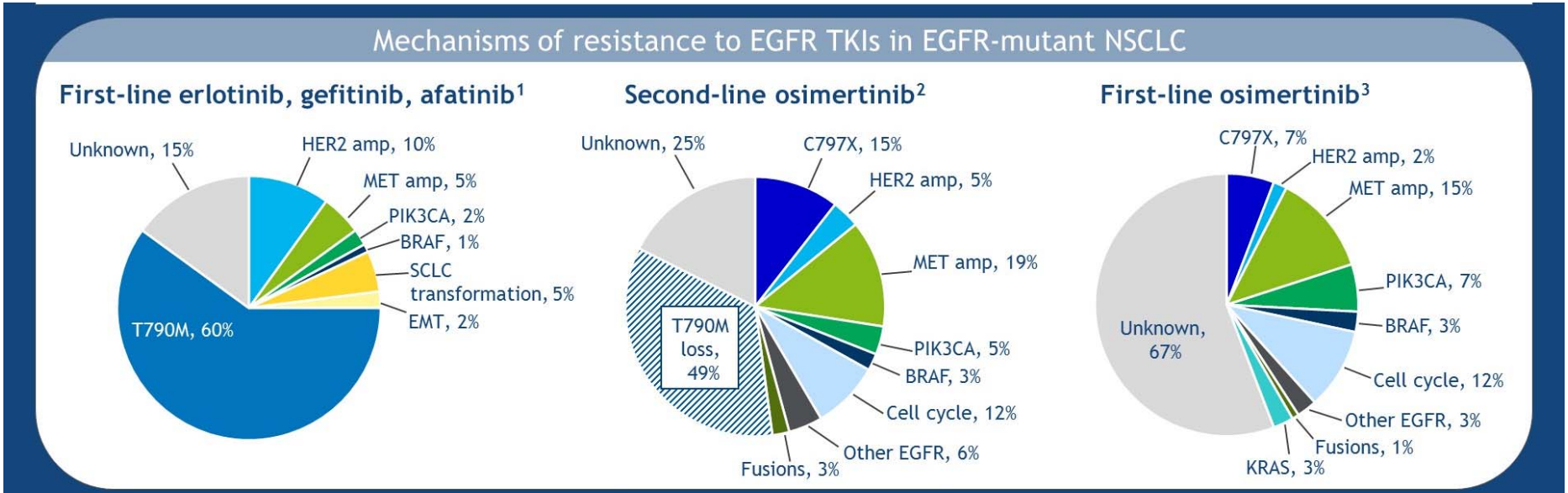
Yver A. Ann Oncol 27:1165-70, 2016

Osimertinib (AZD9291) Phase I Trial



Lin C-C, et al. Lancet Respir Med 6:107-16, 2018

Osimertinib (AZD9291) Resistance Mechanisms



- Developing therapies to combat all individual resistance mechanisms is likely impractical
- Resistance mechanisms may overlap in an individual patient

1. Wu, et al. *Mol Cancer*. 2018;17:38. 2. Papadimitrakopoulou, et al. *Ann Oncol*. 2018;29. 3. Ramalingam, et al. *Ann Oncol*. 2018;29. 4. Yi, et al. *Mod Pathol*. 1997;10:142-148. 5. Kawano, et al. *J Surg Res*. 2008;146:43-48.

Study Design of Sonidegib Phase I Studies

	Western study	Asian study
Dose (mg)	100, 200, 400, 800, 1000, 1500, 3000 (qd) 150, 400, 750 (bid)	400, 600, 800 (qd)
DLT	grade 3 or 4 significant AE or abnormal laboratory parameters	
MTD evaluatiom	cycle 1	
MTD estimation	Bayesian logistic regression model (BLRM)	
MTD definition (the highest dose with)	P(DLT rate of ≥33%) < 25%	and P(DLT) = 16-33%
Number of patients at MTD	≥ 22*	≥ 6

*to provide a 90% probability of detecting adverse events with an incidence of 10%)

Common Toxicities of Sonidegib (Western Phase I Study)

	400 mg QD (n = 5)		800 mg QD (n = 26)		1000 mg QD (n = 11)		1500 mg QD (n = 9)		3000 mg QD (n = 10)	
	Grade		Grade		Grade		Grade		Grade	
	All	3/4	All	3/4	All	3/4	All	3/4	All	3/4
CK increased	0	0	7	2 (8%)	4	2 (18%)	3	3 (33%)	4	3 (30%)
ALT/AST increased	0	0	2	0	0	0	2	0	2	2
Myalgia	0	0	4	0	3	1	2	0	2	0
Muscular spasm	0	0	9	0	3	0	4	0	0	1
Alopecia	0	0	4	0	1	0	2	0	1	0
Dysgeusia	0	0	5	0	3	0	3	0	5	0
Fatigue	0	0	3	0	1	0	0	0	1	0

Rodon J, et al. Clin Cancer Res 20: 1900-9, 2014

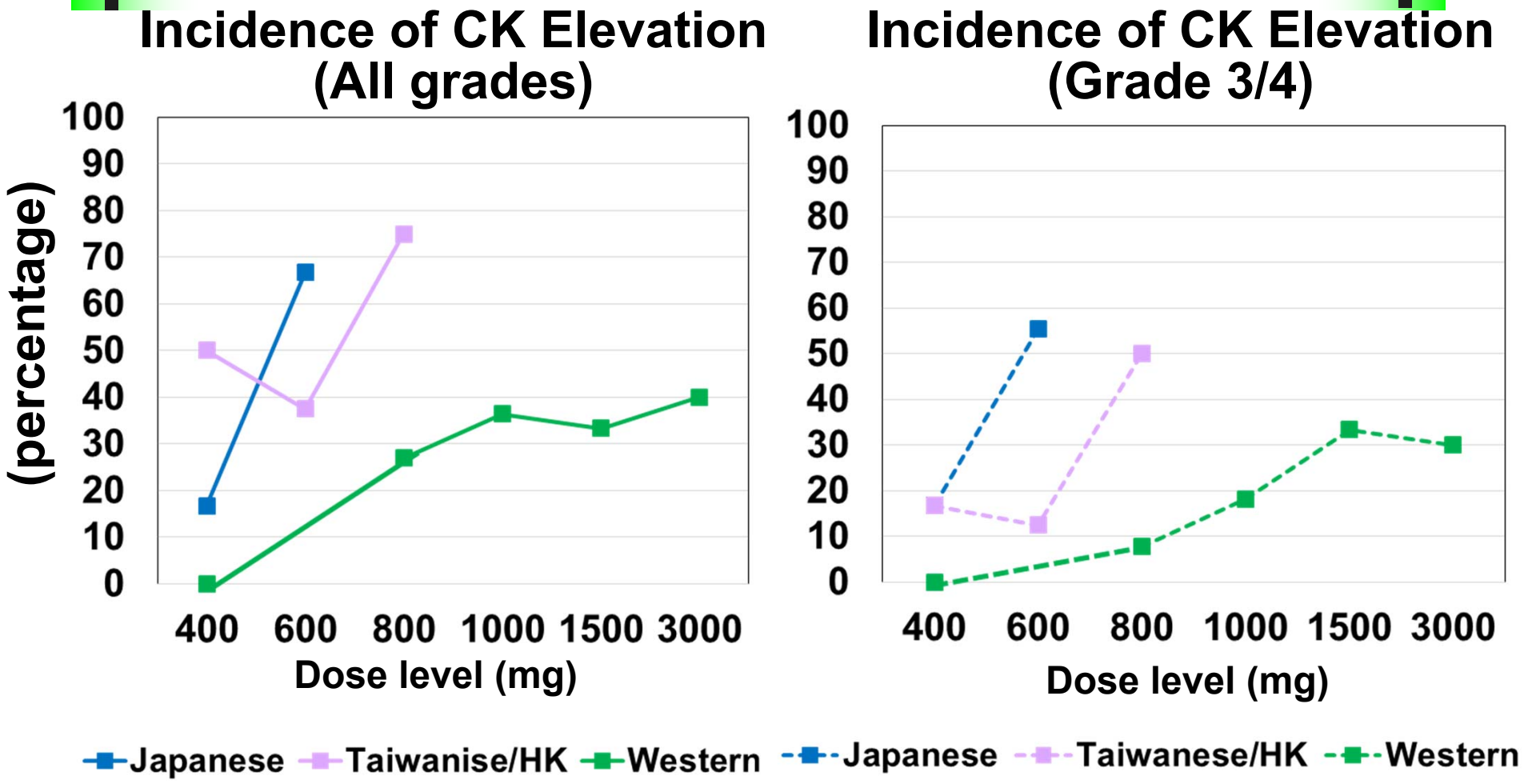
Common Toxicities of Sonidegib (Taiwanese / Hong Konger)

Toxicities, n	400 mg QD (n = 12)			600 mg QD (n = 8)			800 mg QD (n = 4)		
	Grade			Grade			Grade		
	All	3	4	All	3	4	All	3	4
CK increased	6	1	1	3	0	1	3	0	2
ALT increased	1	0	0	2	1	0	3	1	0
AST increased	1	0	0	2	1	0	3	2	0
Myoglobin increased	1	0	0	0	0	0	0	0	0
Myalgia	2	0	0	3	1	0	3	1	0
Muscular weakness	0	0	0	1	0	0	3	2	0
Alopecia	1	0	0	0	0	0	0	0	0
Dysgeusia	2	0	0	3	0	0	1	0	0
Fatigue	4	0	0	1	0	0	3	2	0

- A single DLT of CK elevation was observed at 800 mg in cycle 1, but one additional patient experienced grade 4 CK elevation after cycle 1 (50% in total).
- Grade 3 or 4 CK elevation was also observed at 400 and 600 mg after cycle 1.
- Grade 2 or 3 myalgia and muscle weakness was observed at 600 mg.
- Taking into consideration the muscle-related toxicities and similar pharmacokinetics to Japanese patients, 400 mg was also recommended.

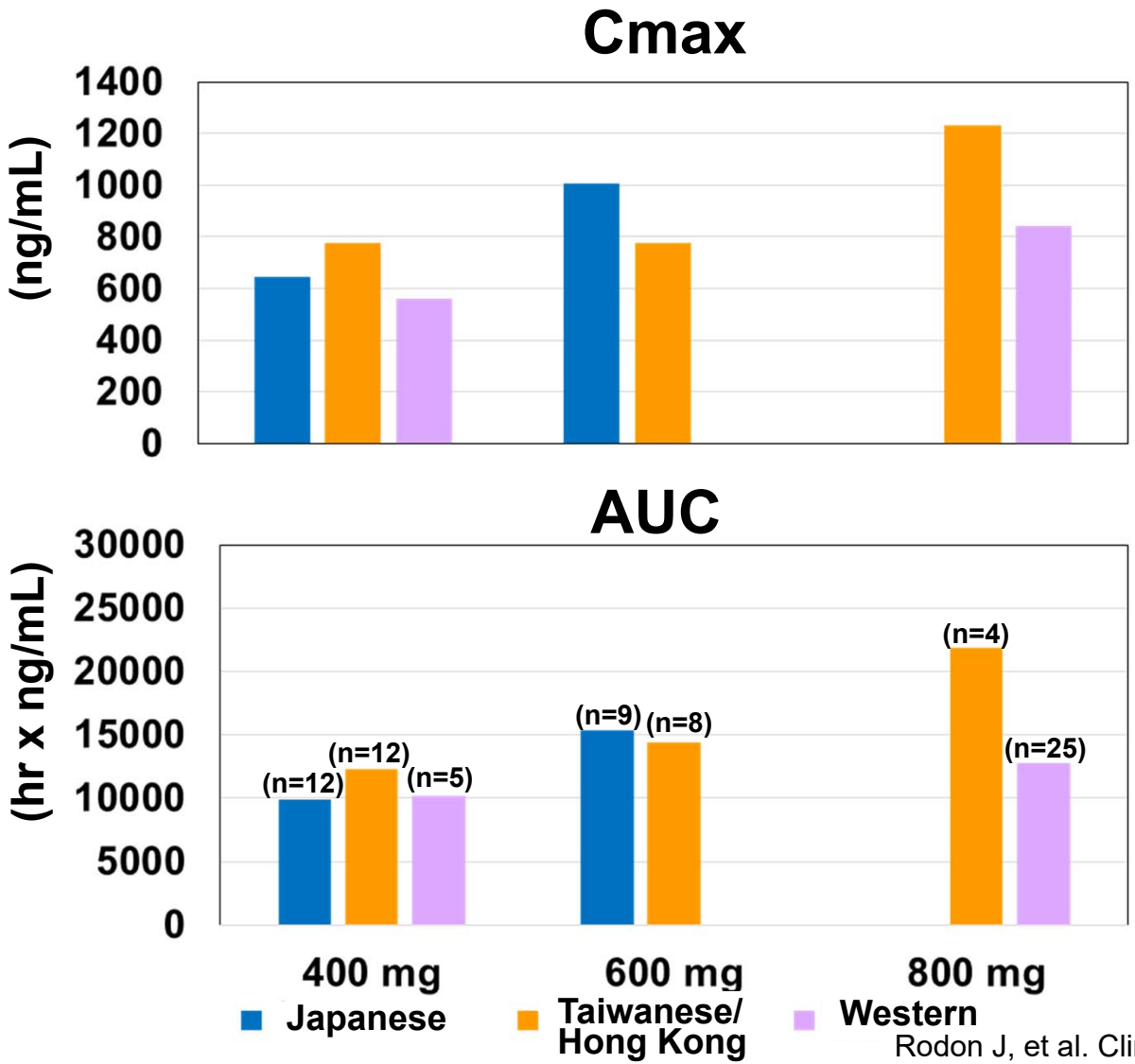
Minami H*, …, Lin, C-C*. Cancer Sci 107: 1477-83, 2016

Incidence of CK Elevation in Phase I Studies of Sonidegib



Rodon J, et al. Clin Cancer Res 20: 1900-9, 2014
Minami H*, …, Lin, C-C*. Cancer Sci 107: 1477-83, 2016

Pharmacokinetics of Sonidegib on C1D15



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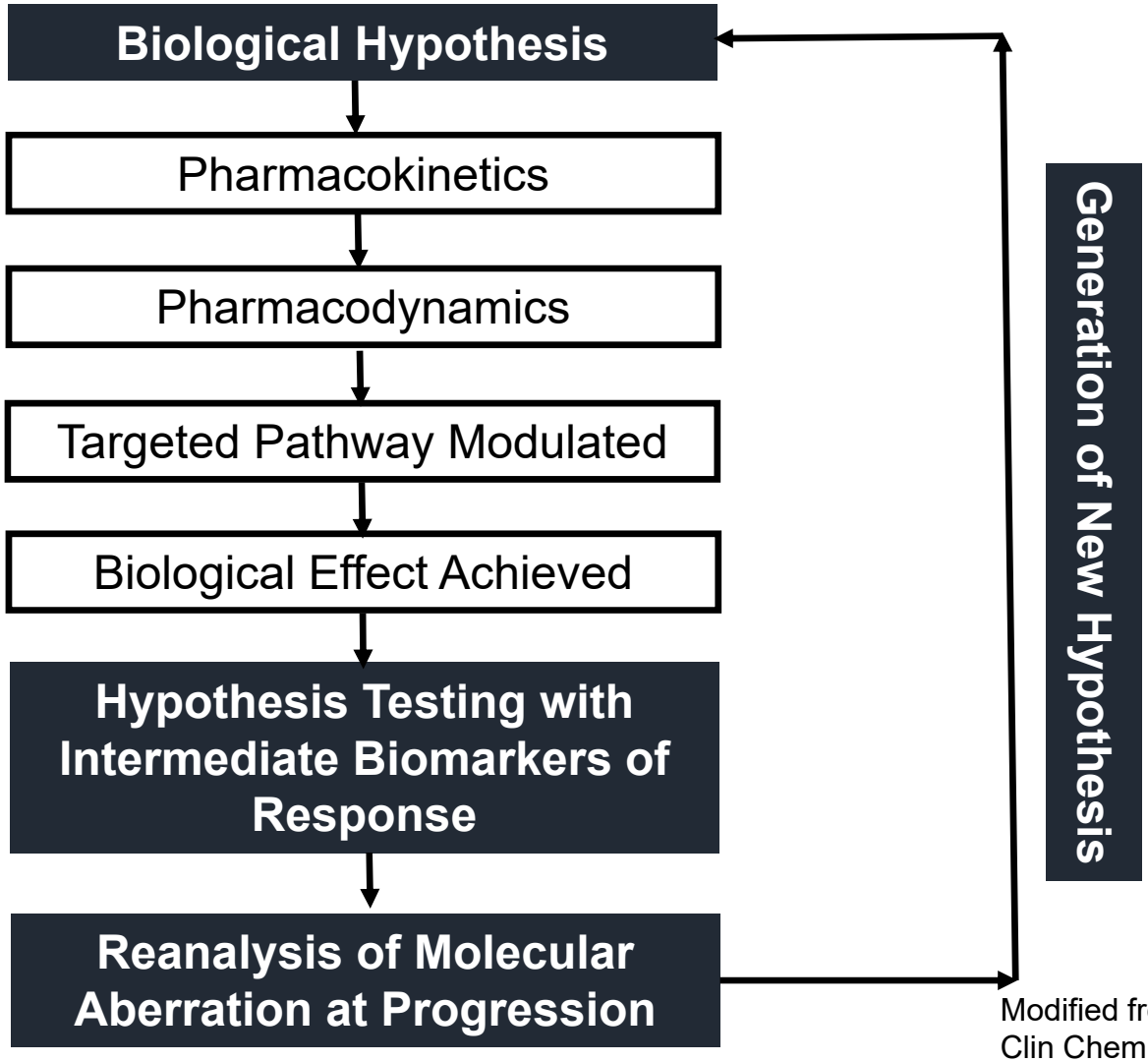

Modified from Ferraldeschi R, et al. Clin Chem 59:75-84, 2013

Conclusion

- QTc prolongation correlated with C_{max} of belizatinib (TSR011, ALK inhibitor)
- Integration of biomarker (total plasma IGF-1) and response data to confirm PR2D of xentuzumab (BI836845, anti-IGF antibody)
- Molecular aberrations of tumors reanalyzed at PD to reveal the resistance mechanisms of osimertinib (AZD9291, EGFR inhibitor)
- Difference in tolerability of sonidegib (LDE225, SMO inhibitor) between populations

Acknowledgement

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Data Management

PK Sampling

Translational Research

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