Other Immunotherapy Targets and Agents (Advanced PD-L1)

Jonathan Riess, MD
Associate Professor
UC Davis Comprehensive Cancer Center
USA

IASLC 2020 World Conference on Lung Cancer Singapore
JANUARY 28-31, 2021 | WORLDWIDE VIRTUAL EVENT

DISCLOSURES

Commercial Interest	Relationship(s)
Advisory Board	Daichi-Sankyo, Blueprint, EMD Serano
Consulting	Novartis, Boehringer Ingelheim
Research (to institution)	AstraZeneca, Merck, Spectrum, Novartis, Revolution Medicines

CD47 Agonist Peptide PKHB1 Induced Cell Death in NSCLC via Triggering Endoplasmic Reticulum Stress

Jiani Ye
Department of Respiratory Medicine, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China.

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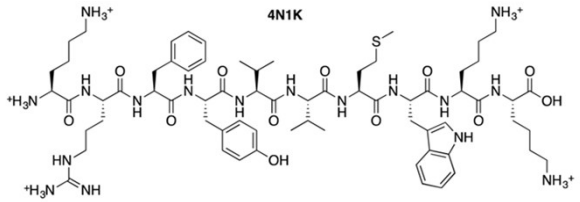
Background

CD47, a transmembrane glycoprotein highly expressed on the surface of tumor cells, and inhibiting its binding to macrophage **SIRPα** promotes phagocytosis of tumor cells and engagement of the adaptive immune response[1].

TSP-1, a natural ligand of CD47, its binding to CD47 can alter a variety of processes, including cell adhesion, growth, differentiation, and survival [2].

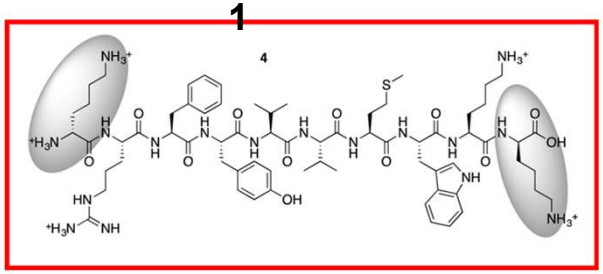
4N1K (KRFYVVMWKK), a functional decapeptide derived from the C-terminus globular domain of TSP-1[3].

4N1K
（KRFYVVMWKK）



The VVM motif was identified as TSP-1/CD47 binding epitope

PKHB 1



the first- described serumstable soluble CD47- agonist peptide[3]

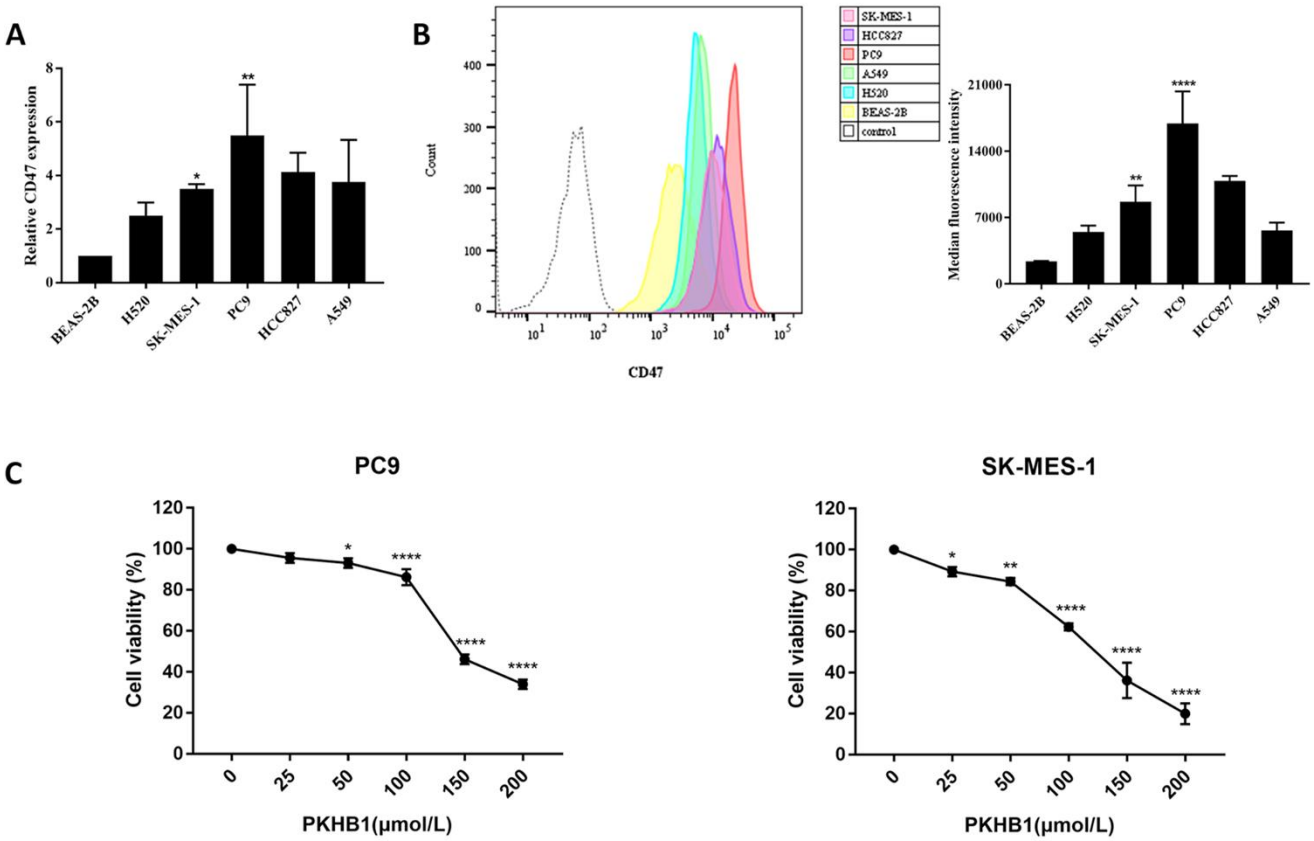
1. Zhang, W., et al., *Advances in Anti-Tumor Treatments Targeting the CD47/SIRPα Axis.* Front Immunol, 2020. 11: p. 18.
2. Kaur, S. and D.D. Roberts, Divergent modulation of normal and neoplastic stem cells by thrombospondin-1 and CD47 signaling. Int J Biochem Cell Biol, 2016. 3. 81(Pt A): p. 184-194.
3. *Denefle, T., et al., Thrombospondin-1 Mimetic Agonist Peptides Induce Selective Death in Tumor Cells: Design, Synthesis, and Structure-Activity Relationship Studies. J Med Chem, 2016. 59(18): p. 8412-21.*

Results

(A) qPCR on CD47 mRNA level in indicated NSCLC cell lines

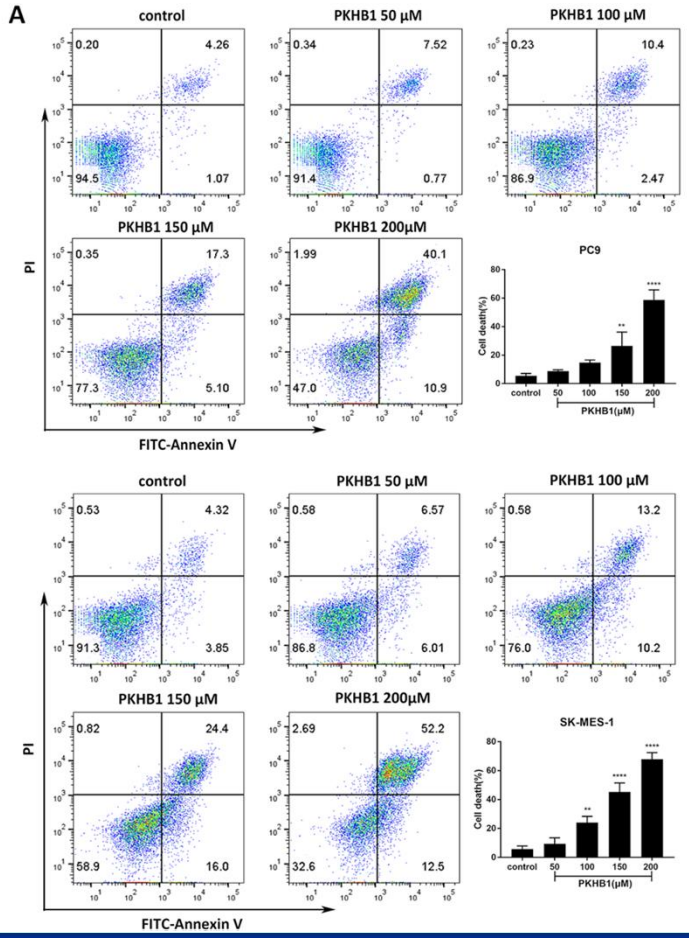
(B) Flow cytometry analysis of the expression of CD47 protein in indicated NSCLC cell lines

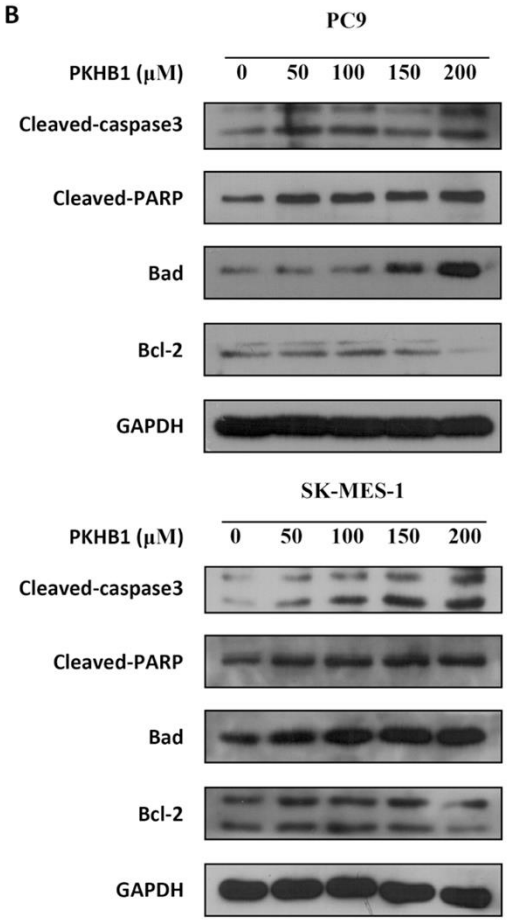
(C) PKHB1 inhibited the NSCLC cells viability in dose-dependent manner (2h）



Results

PKHB1 induced cell apoptosis in NSCLC cell lines (2h)

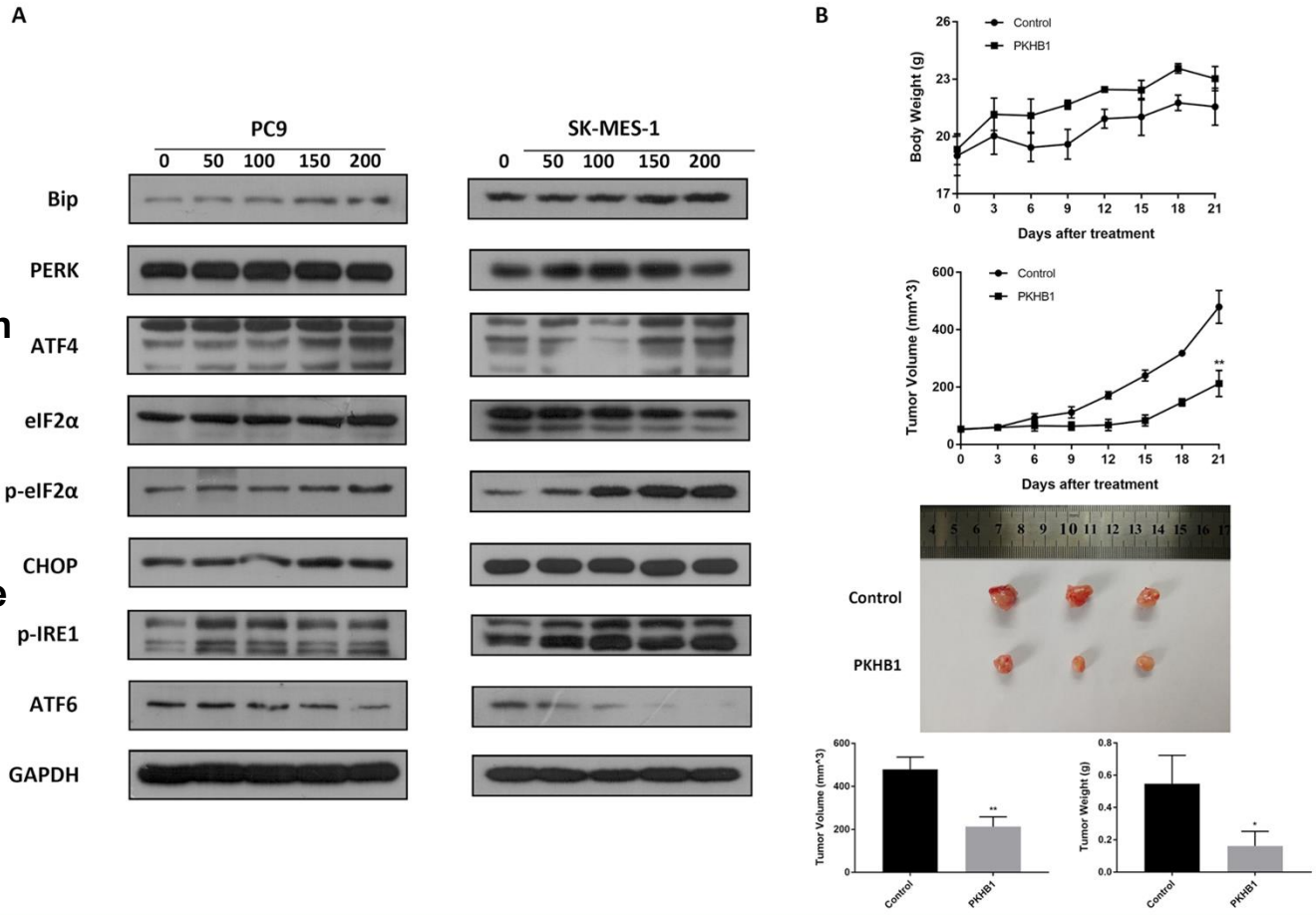




Results

(A) PKHB1 provoked apoptosis in NSCLC cells through triggering endoplasmic reticulum stress

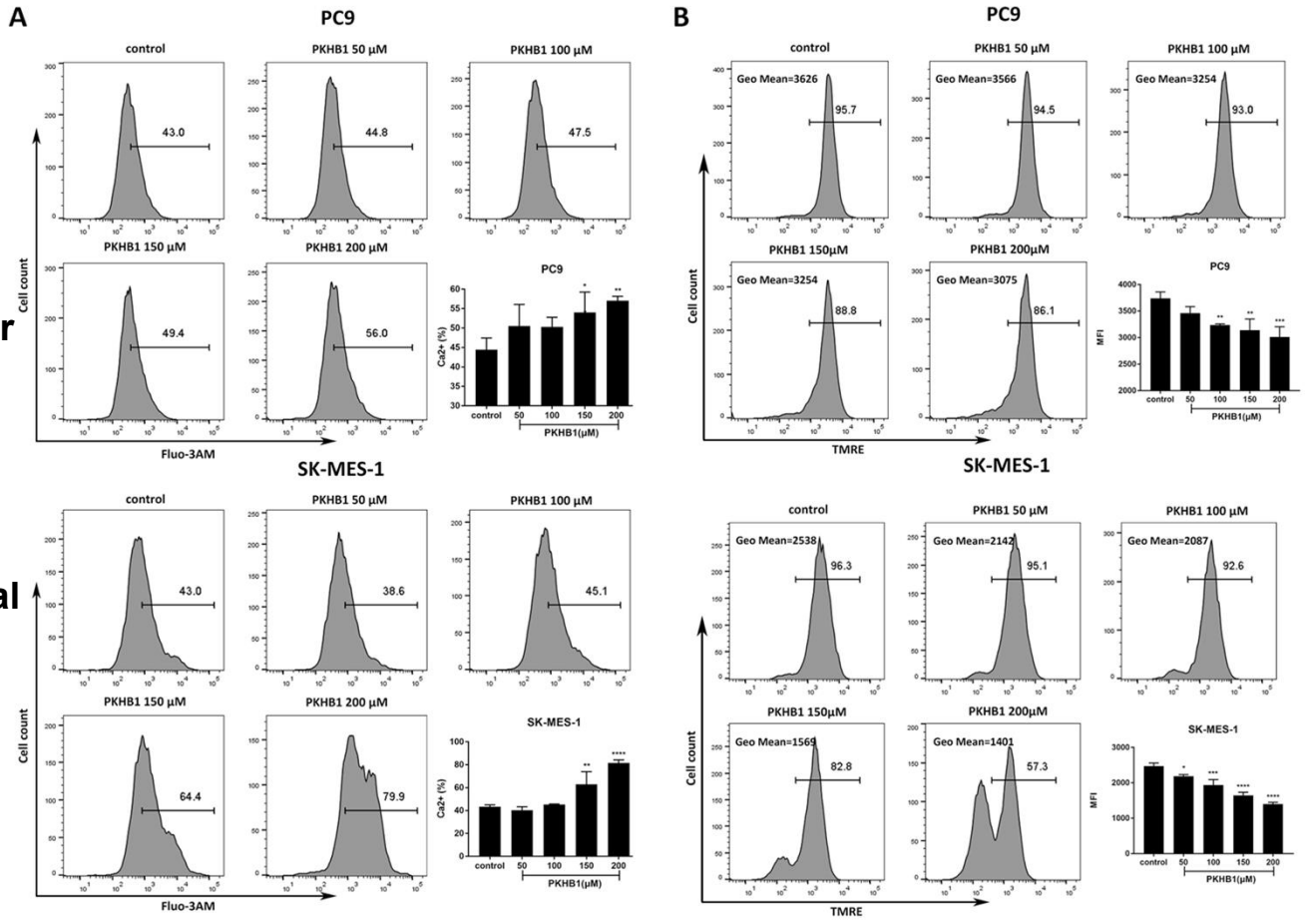
(B) PKHB1 exerted antitumor effects in the PC9 xenograft nude mouse model



Results

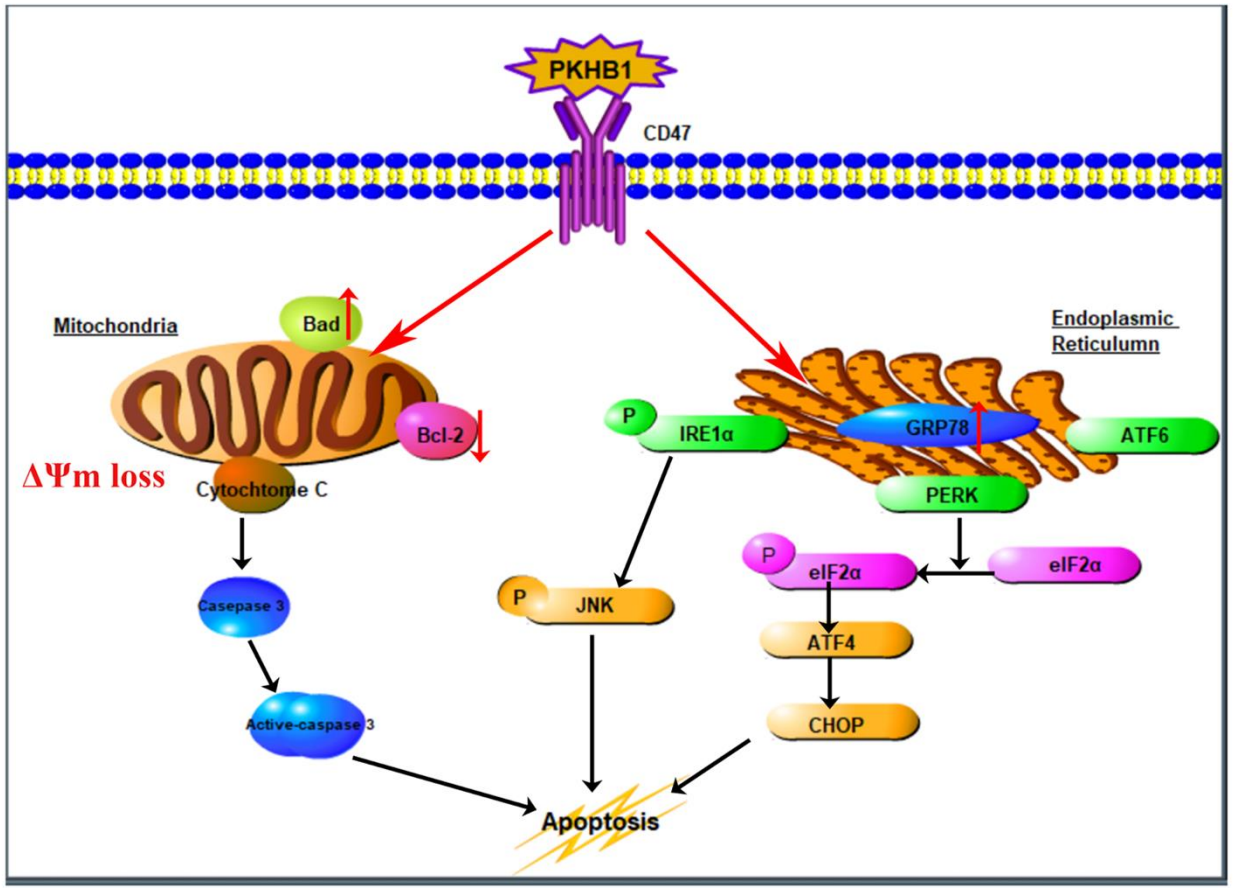
(A) PKHB1 increased intracellular Ca2+ level in NSCLC cell lines

(B) PKHB1 induced mitochondrialmembrane potential (ΔΨm) loss in NSCLC cell lines

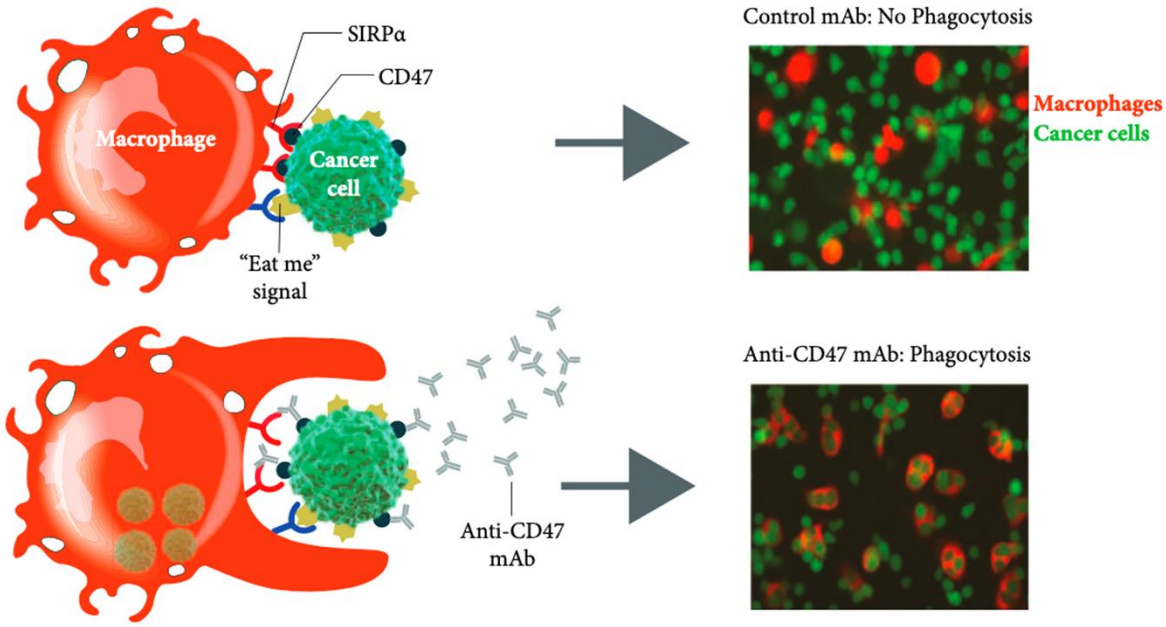


Conclusion

CD47 agonist peptide PKHB1 induced cell death in NSCLC via triggering endoplasmic reticulum stress, and may be a promising peptide-based therapeutic target for NSCLC.



Blocking CD47-SIRPa signaling with an anti-CD47 monoclonal antibody enhances macrophage-mediated phagocytosis of Cancer cells



Takimoto et al. Annals of Oncology 2019.

Table 1. Agents targeting CD47 in clinical development

Class	Anti-CD47 monoclonal antibodies				SIRPα fusion proteins		
Compound	**Hu5F9-G4**	**CC-90002**	**Ti-061**	**SRF231**	**TTI-621**	**TTI-622**	**ALX148**
Molecule	IgG4 mAb	IgG4 mAb	IgG4 mAb	IgG4 mAb	Wild-type SIRPα-IgG1 Fc fusion	Wild-type SIRPα-IgG4 Fc fusion	High-affinity SIRPα-IgG1 fusion with inactive Fc
Clinical development start date	August 2014	March 2015	March 2017	March 2018	January 2016	May 2018	February 2017
Study phase	Phase II	Phase I	Phase I	Phase I	Phase I	Phase I	Phase I
Number of clinical trials	6	2	1	1	2	1	1
Sponsor	Forty Seven Inc.	Celgene	Arch Oncology	Surface Oncology	Trillium Therapeutics	Trillium Therapeutics	ALX Oncology

Takimoto et al. Annals of Oncology 2019.

PARP1 inhibitors enhanced IFNγ-induced PD-L1 expression in LKB1-mutant lung cancer

Presenter: Xue Bai

Xue Bai, Zeqin Guo, Lili Long, Yanpei Zhang, Zhongyi Dong

Department of radiotherapy, Nanfang Hospital.

Guangzhou, China

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Background

LKB1

- is a tumor suppressor encodes a serine/threonine kinase which coordinates cell growth, polarity, motility, and metabolism.
- exhibits a distinct T cell-excluded tumor immune microenvironment.
- negatively impacts PDL1 expression on tumor cells

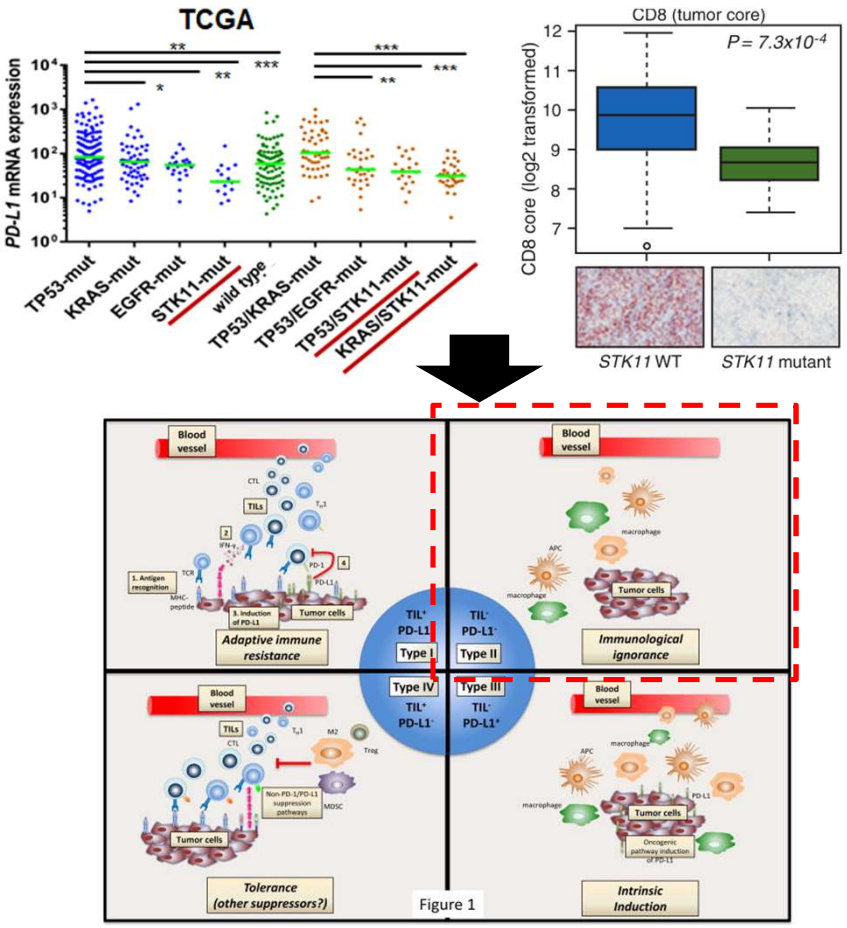
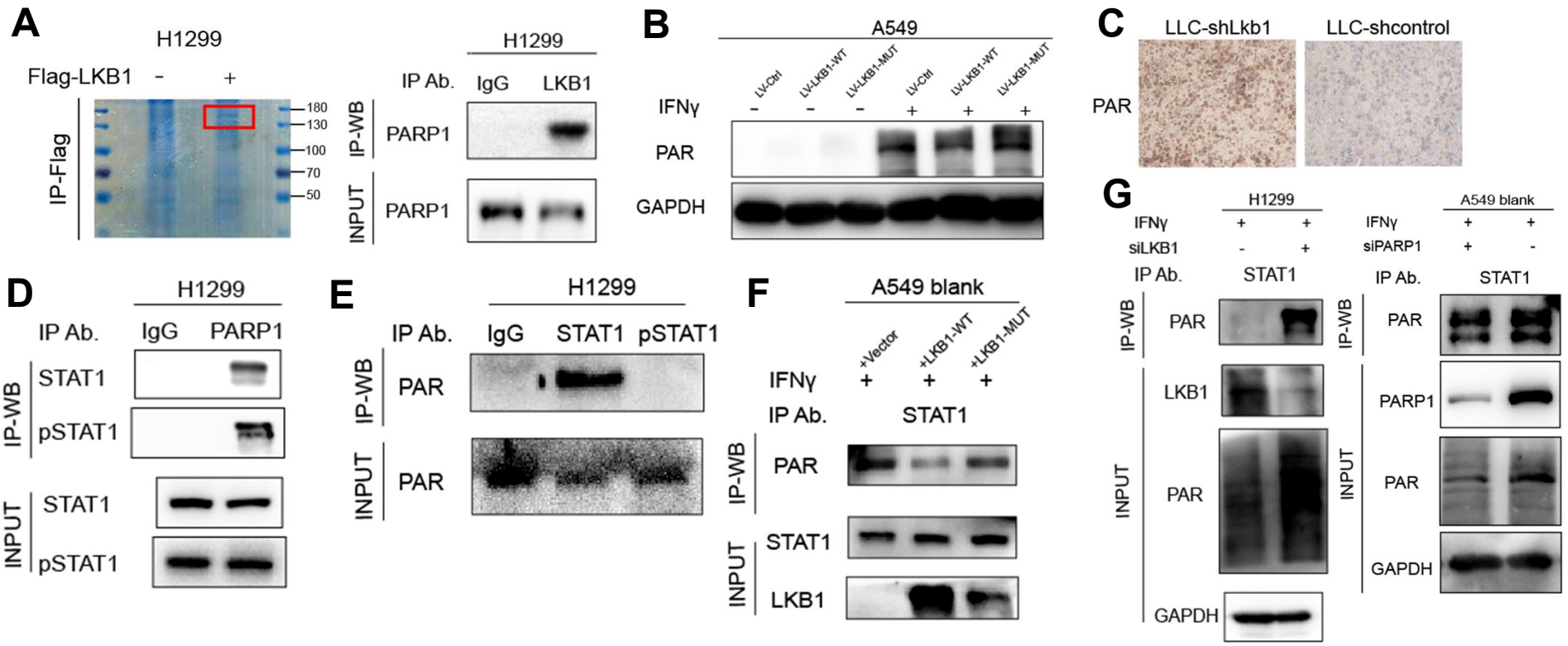


Figure 1

→ “Cold” tumor

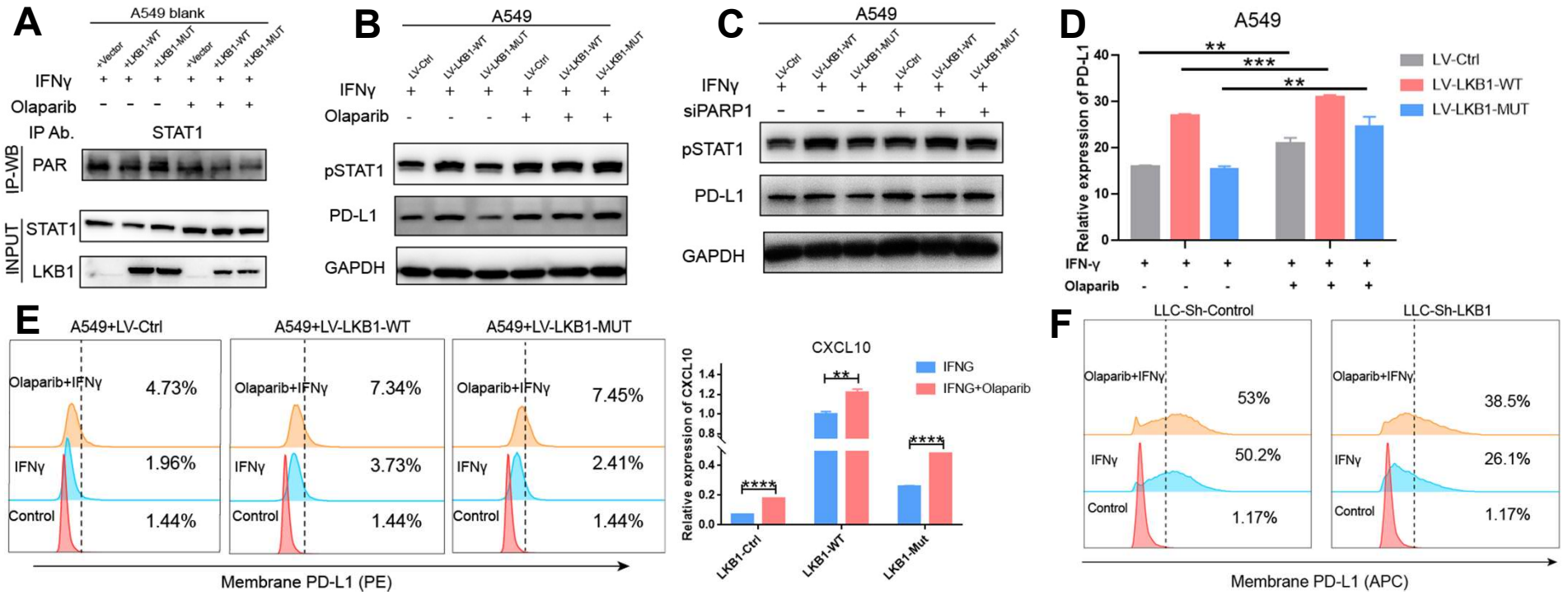
Results

Figure 2 LKB1 increased IFNγ-induced pSTAT1 by decreasing the catalytic activity of PARP1



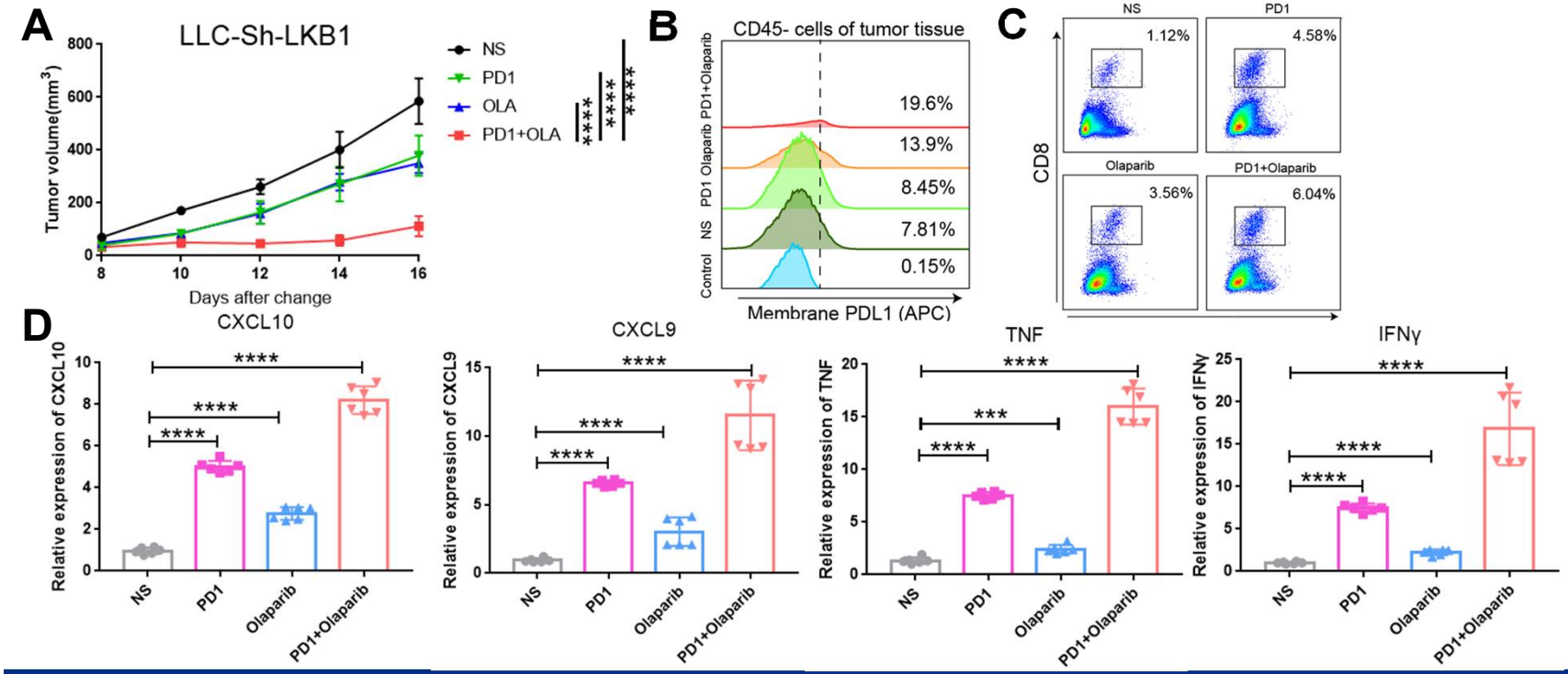
Results

Figure 3 PARP1 knockdown or inhibitors decreased poly(ADP-ribosyl)ation of STAT1 and enhanced its phosphorylated level in an IFNγ-dependent manner



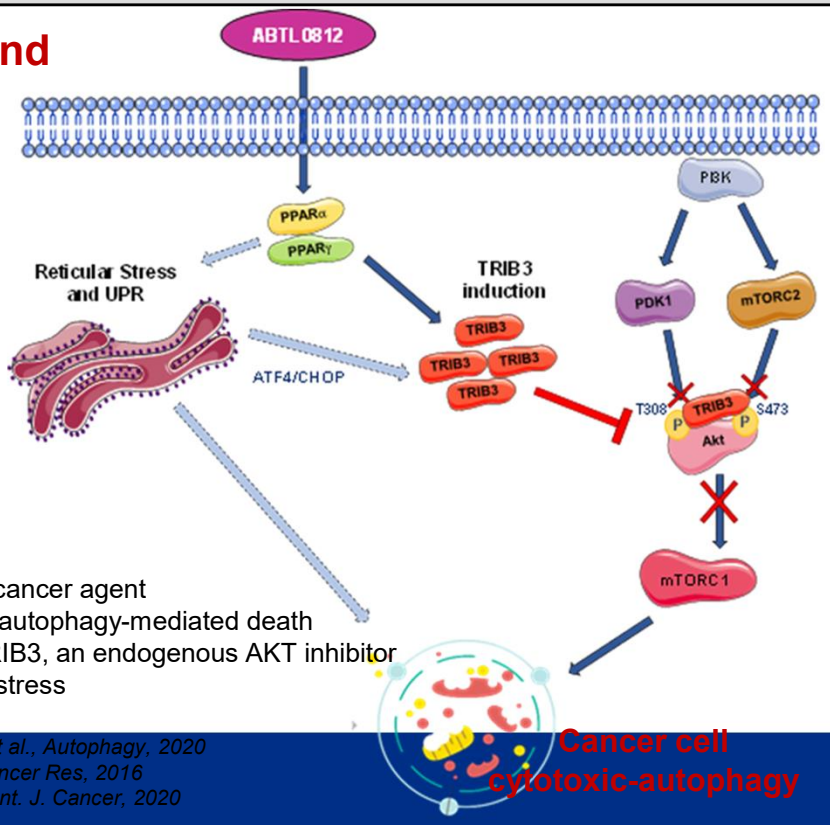
Results

Figure 4 PARP1 inhibitors combined with PD1 immunotherapy induced a “hot” tumor microenvironment



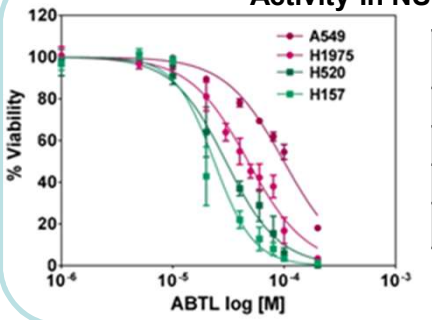
MA01.06 Phase 2 of Pro-Autophagic Drug ABTL-0812 in Combination with First-Line Paclitaxel and Carboplatin in Squamous NSCLC

Background



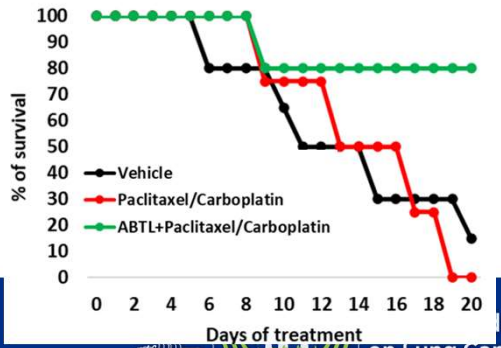
ABTL-0812
- Novel oral anti cancer agent
- Induced strong autophagy-mediated death
- Upregulates TRIB3, an endogenous AKT inhibitor
- Elicits reticular stress

Activity in NSCLC cell lines



Cells	Hist	Mutation	IC_{50} (μM)
H157	Squam	PTEN	19
H520	Squam	WT	21
A549	Adeno	KRAS	45
H1975	Adeno	PI3K/EGFR	63

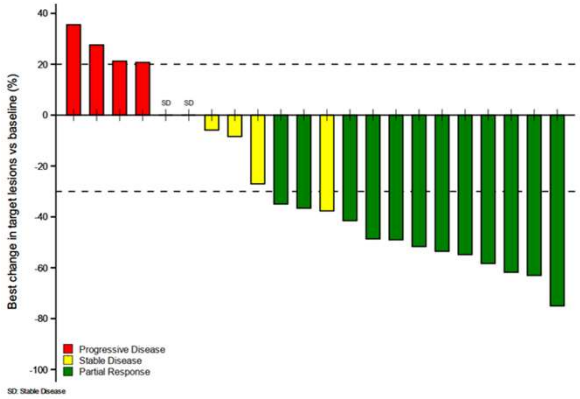
Efficacy in H157 xenograft model



[1] Muñoz-Guardiola P et al., Autophagy, 2020
[2] Erazo T et al. Clin Cancer Res, 2016
[3] Lopez-Plana A et al. Int. J. Cancer, 2020

Efficacy Results

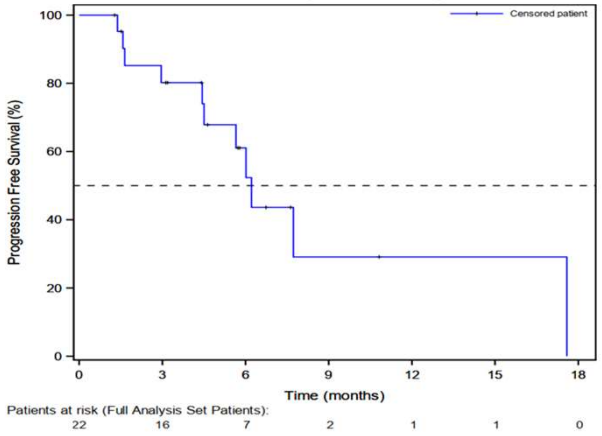
Overall Response Rate



Parameter	ABTL0812+ P/C n=22	Historical data*, n=281
ORR, % (n)	54.5 (12)	31.7 (89)
SD, % (n)	27.3 (6)	44.1 (124)
PD, % (n)	18.2 (4)	13.9 (39)
DOR, median (95% CI)	4.9 (1.4-14.5)	4.9
Chemo cycles, median (95% CI)	4.0 (2.8-4.5)	N.R.

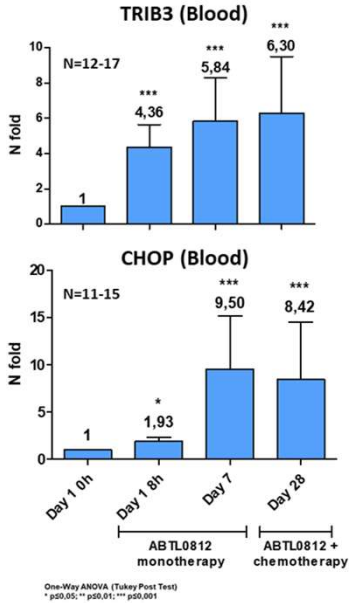
**Paz-Ares, NEJM 2018*

Progression Free Survival



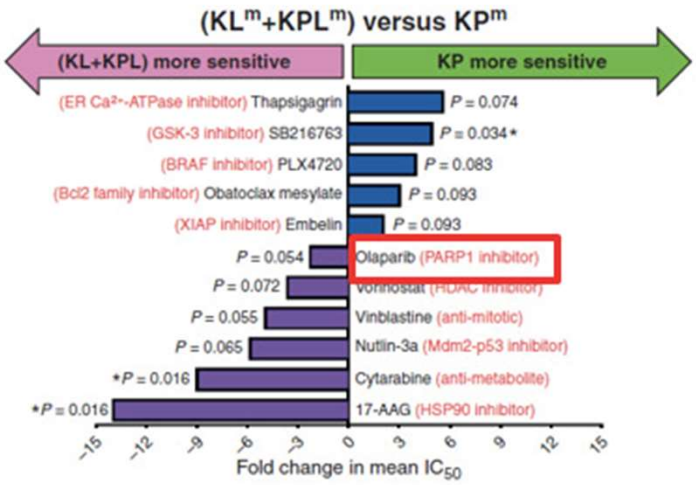
Parameter	ABTL0812+ P/C n=22	Historical data, n=281*
Median PFS (months), 95% CI	6.2 (4.4-17.6)	4.8* (4.3-5.7)
6-month event free rate (%), 95% CI	61.1 (34.5-79.6)	N.R.
12-month event free rate (%), 95% CI	29.1 (6.2-57.8)	N.R.

PD Biomarkers

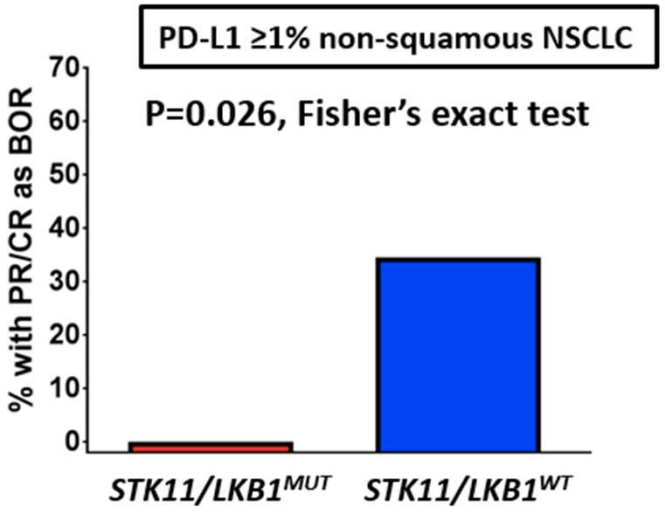


PARPi in Combination with IO in NSCLC and LKB1/STK11 mutation

L
K



Skoulidis et al., *Cancer Discovery*, 2015

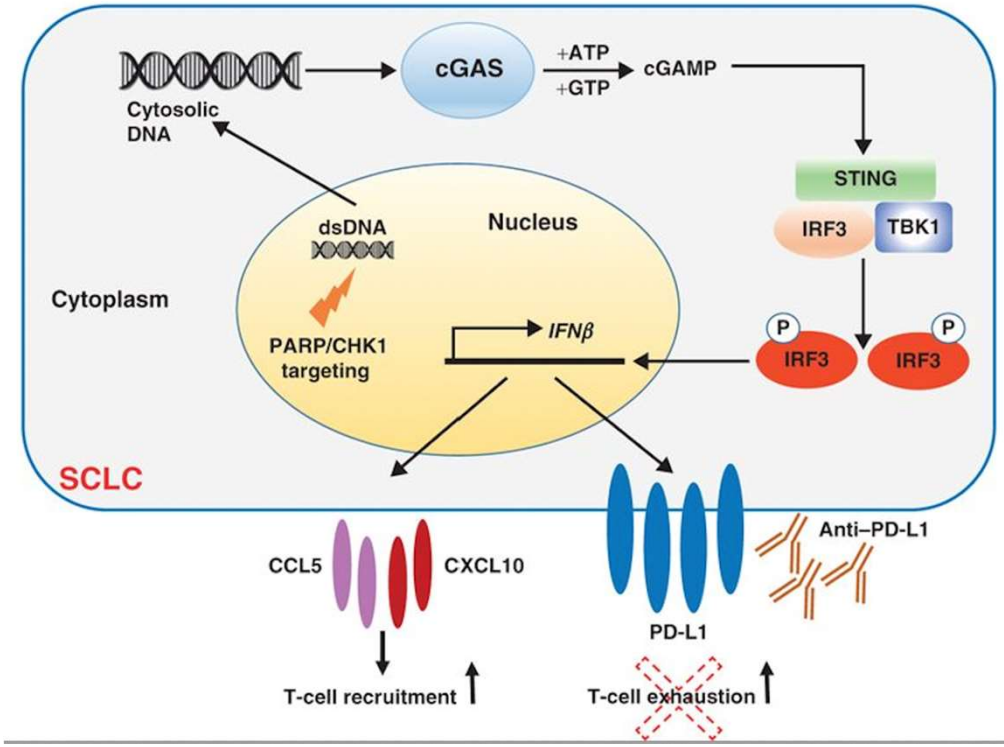


Group	*STK11/LKB1*^{MUT}	*STK11/LKB1*^{WT}
ORR	0% (0/11)	34.5% (19/55)

Skoulidis F et al, Cancer Discovery, 2018

Trial	Phase	Population	PARPi	Combo
NCT02944396	1/2	1st line NSCLC	veliparib	platinum-double/nivolumab
Javelin Parp Medley	1/2	Solid Tumors/NSCLC	talazoparib	avelumab
NCT03308942	2	NSCLC	niraparib	PD-1
S1900C/Lung MAP	2	NSCLC	talazoparib	avelumab

Model for STING pathway activation in response to DDR targeting in SCLC



Sen et al.
Cancer Discovery 2019

TAKE HOME MESSAGE

- CD47-SIRP-alpha antibodies have potential acitivity in cancer including in lung cancer
- PARPi may potential immunotherapy in LKB1 mutant NSCLC via increase in IFN-alpha (currently being studies in mSWOG Lung MAP substudy with PD-L1+ PARPi combination
- PARPi may potentiate IO in SCLC via STING pathway activation in response to DDR targeting in SCLC