LUNG CANCER UPDATES

AACR HIGHLIGHTS

14-18 ABRIL 2018, CHICAGO

CPCP y biopsia líquida

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Hospital Clínic de Barcelona

Con el patrocinio de

Bristol-Myers Squibb

Iniciativa científica de:

GECP

Grupo Español de Cáncer de Pulmón

Spanish Lung Cancer Group

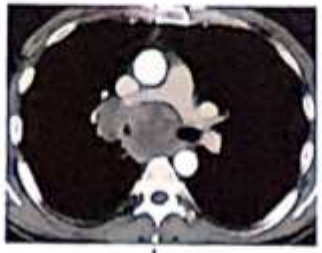
Combined inhibition of MEK and mTOR pathways is effective in NRAS Q61K mutant small cell lung cáncer (Ogino A *et al*)

Patient clinical course

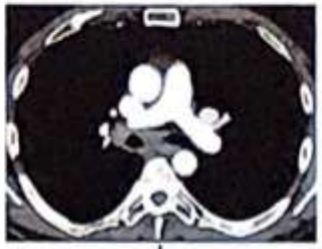
DANA-FARBER CANCER INSTITUTE

49 year-old, male, a never-smoker

- Diagnosis of limited stage SCLC:

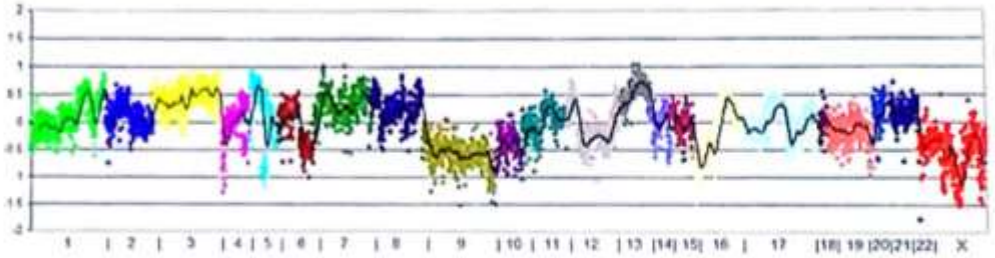


- Response to chemoRT:



- Systematic recurrence

- Targeted NGS was performed on the autopsy specimen
  - NRAS Q61K in 62% of 161 reads
  - CDKN2A R80* in 85% of 27 reads
  - No mutations in TP53 or RB1



Combined inhibition of MEK and mTOR pathways is effective in NRAS Q61K mutant small cell lung cáncer (Ogino A *et al*)

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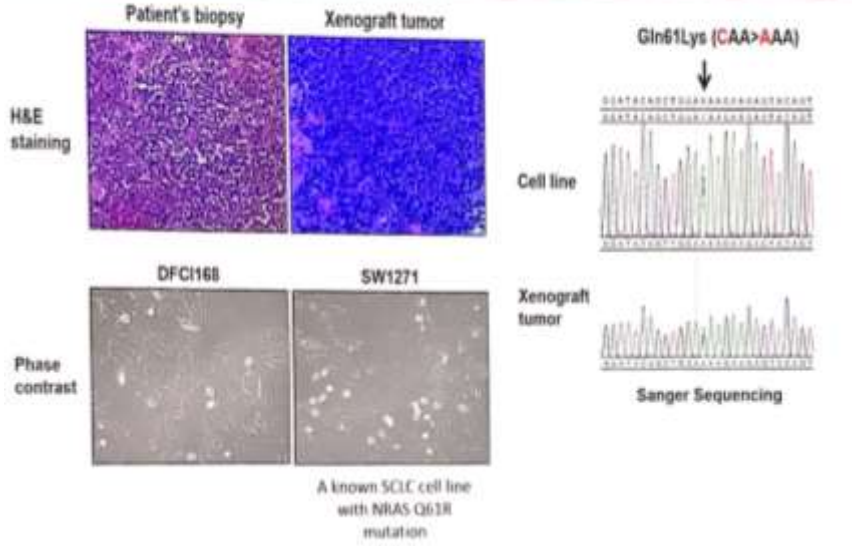
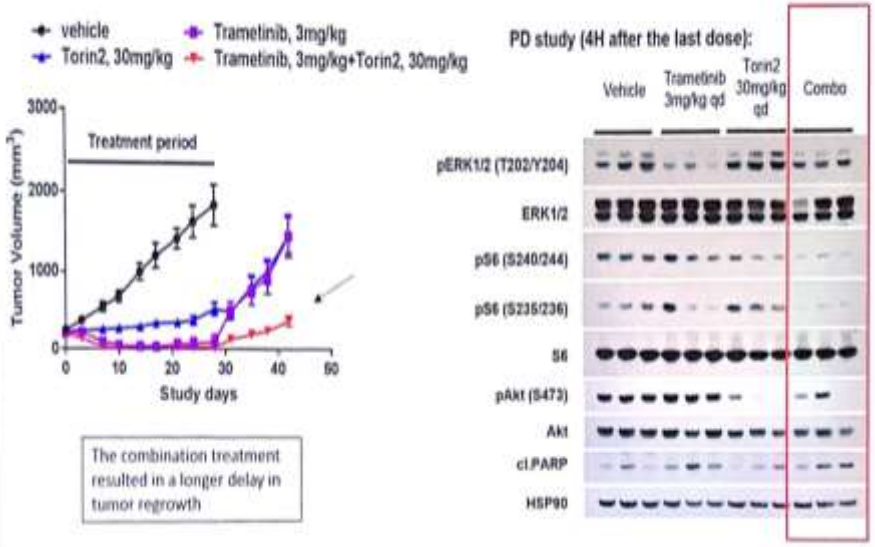
Successful establishment of a SCLC cell line and a PDX model with *NRAS*^{Q61K} mutation

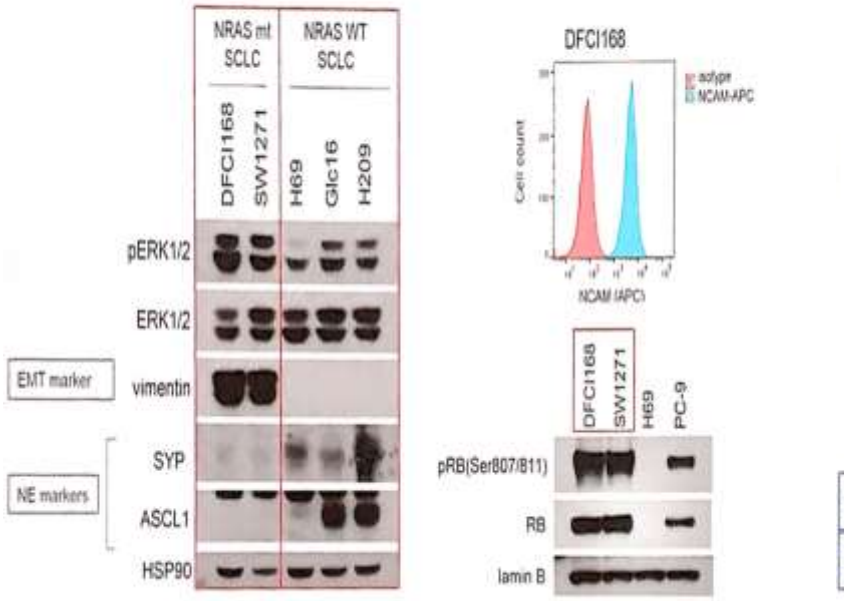


In vivo anti-tumor effect of combination therapy with MEK and mTORC1/2 inhibitors in DFCI168

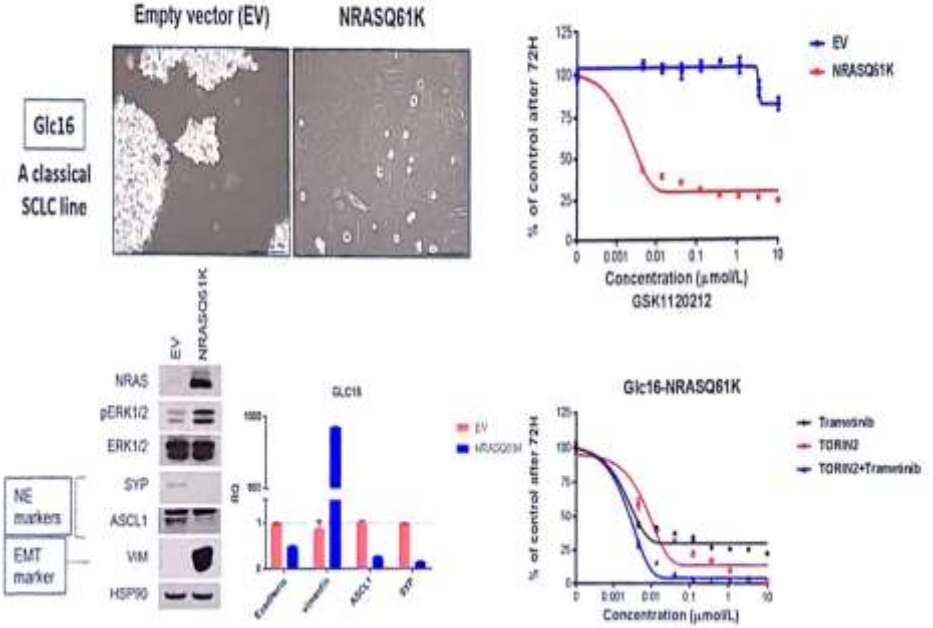


Combined inhibition of MEK and mTOR pathways is effective in NRAS Q61K mutant small cell lung cáncer (Ogino A *et al*)

DFCI168 lacks the expression of the classical NE markers and expresses EMT markers



Transition from NE to non-NE is mediated by *NRAS*^{Q61K} introduction

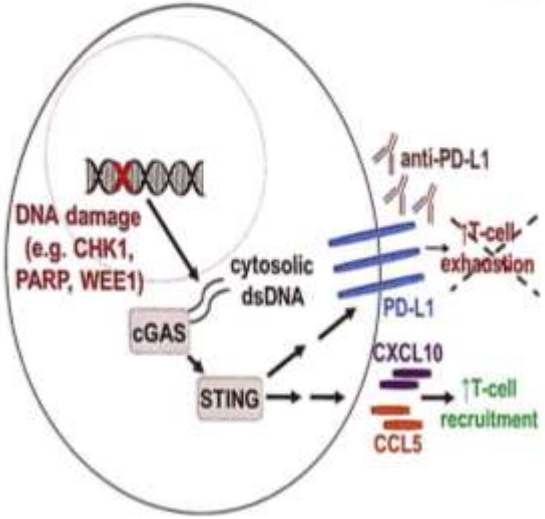


Summary

- We successfully established a cell line (DFCI168) from a SCLC never-smoker with NRASQ61K mutation.
- DFCI168 lacks classical neuroendocrine markers and presents mesenchymal features.
- NRAS mutant lung cancer model showed sensitivity to combination of MEK and mTOR inhibitors *in vitro*, and *in vivo* (DFCI168).
- Introduction of NRASQ61K into a classical SCLC cell line Glc16 lead to the transition from NE to non-NE/mesenchymal phenotype (EMT).

Como potenciar la respuesta inmunológica en CPCP?

Activation of innate immune system (e.g., STING pathway) by DNA damage



Hypothesis:

If DNA repair deficiency and genomic instability promote response to immunotherapy

(e.g., BRCA mutations, MSI high, high tumor mutation burden),

Then DNA damage response inhibitors (e.g. PARPi, Chk1i) may enhance response to Immunotherapy.

Mouw et al, DNA damage and repair biomarkers of immunotherapy response, Cancer Discovery 2017

DDR inhibition increases PDL1 expression in SCLC models

Cancer Therapy: Preclinical

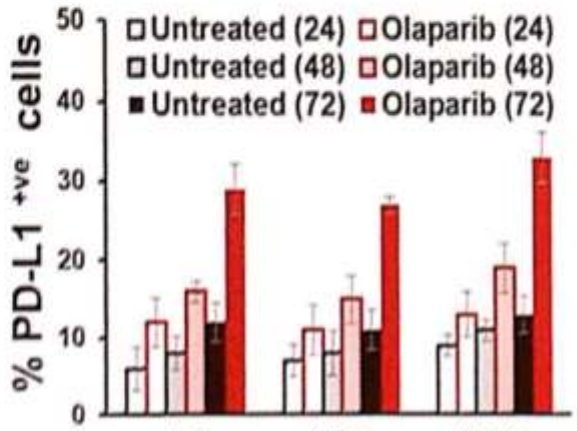
Clinical Cancer Research

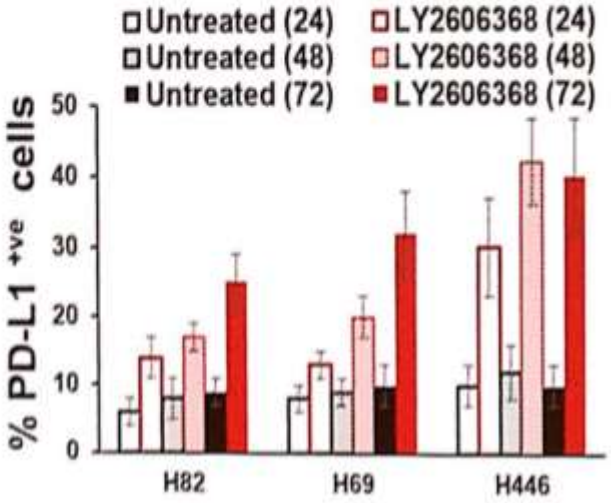
PARP Inhibitor Upregulates PD-L1 Expression and Enhances Cancer-Associated Immunosuppression

Shiping Jiao[1,2], Wenya Xia[1], Hirohito Yamaguchi[1], Yongkun Wei[1], Mei-Kuang Chen[1,2], Jung-Mao Hsu[1], Jennifer L. Hsu[1,4], Wen-Hsuan Yu[1,2], Yi Du[1], Heng-Huan Lee[1], Chia-Wei Li[1], Chiao-Kai Chou[1], Seung-Oe Lim[1], Shih-Shin Chang[1], Jennifer Litton[5], Banu Arun[5], Gabriel N. Hortobagyi[5], and Mien-Chie Hung[1,2,3,4]

Jiao et al, CCR 2017

PARPi and Chk1i increase PDL1 expression in SCLC cell lines





Triparna Sen, Byers lab, unpublished data

Current PARP inhibitor + anti-PD1/PDL1 combination trials in small cell lung cancer

OLAPARIB	
NCT02484404	Phase I/II – anti-PDL1 (MEDI4736) in Combination With Olaparib and/or Cediranib for SCLC and other Advanced Solid Tumors (MEDIOLA)
NCT03334617	Phase II Umbrella Study of Novel Anti-cancer Agents in NSCLC patients after progression on Anti-PD-1/PD-L1 (HUDSON; includes olaparib + durvalulab)
TALAZOPARIB	
NCT03330405	Avelumab Plus Talazoparib In Locally Advanced Or Metastatic Solid Tumors (Javelin)
NIRAPARIB	
NCT03308942	Niraparib +/- PD-1 Inhibitor in NSCLC
NCT03307785	Niraparib or Carboplatin-Paclitaxel in Combination With TSR-042 +/- Bevacizumab
VELIPARIB	
NCT02944396	Study of Veliparib in Combination With Nivolumab and Platinum Doublet Chemotherapy in Participants With Metastatic or Advanced Non-Small Cell Lung Cancer (NSCLC)

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

ClinicalTrials.gov

LB-143 /10: Th1/Th2 and inflammatory cytokines as biomarkers of response to ipilimumab in small cell lung cancer (SCLC) patients.

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By M. Hardy-Werbin, P. Rocha O. Arpí, Á. Taus, X. Durán Jordà, D. Joseph-Pietras, A. Rovira, J. Albanell, C. Ottensmeier, E. Arriola

Abstract: Cytokine levels and changes during treatment as biomarkers of outcome with ipilimumab in SCLC

Methods: serum samples of pts diagnosed SCLC, treated with CP or CP+ IPI within the ICE trial. Serum concentrations of Th1 (IL-2, IFN-γ), Th2 (IL-4, -5, -6, -10) and inflammatory (IL-1β, IL-8, GM-CSF, TNF-α, MIP1-α) cytokines evaluated.

Results: increased baseline levels of IL-2 (>1.67 pg/mL) showed a better OS with CP+IPI (24 m vs. 7.9 m p=0.030]. Higher levels of IL-6 had worse OS (9.5m vs. 18.5m; p=0.019). IL-8 levels decreased from baseline to the on-treatment time-point (ICE) by more than 28.3%, had a worse OS [7.9m (3.9-17) vs. 18.46m (9.5-30.5); p=0.008].

Cytokines could be explored as biomarkers of sensitivity (IL-2) or resistance (IL-6 and TNF-α) to ICP in SCLC

Issue of interest: 6 sections on AACR 2018 !!!!!!

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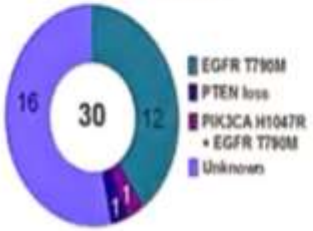
- Blood Tumor Mutational Burden (bTMB)
- Circulating Tumor Cells (CTC) and PDL-1 expression
- Dynamics ctDNA and TCR to predict response to IO
- Quantification ctDNA as prognostic
- Bioinformatics
- Other liquids: CSF, urine,
- Updates on efficiency of several technologies: novel amplicon-based Firefly NGS assay, InvisionFirst, IDYLLA….

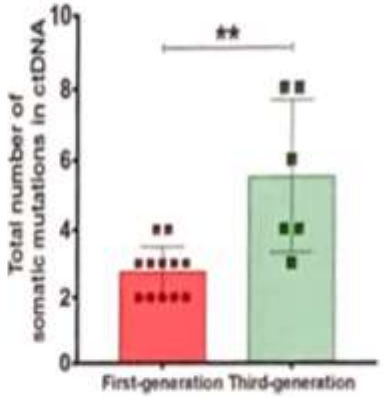
Longitudinal circulating-tumor DNA profiling of EGFR-mutated NSCLC treated with TKI. (Ortiz-Cuaran S. *et al.*)

Increased heterogeneity in 3rd Vs 1st generation EGFR inhibitors

First - generation



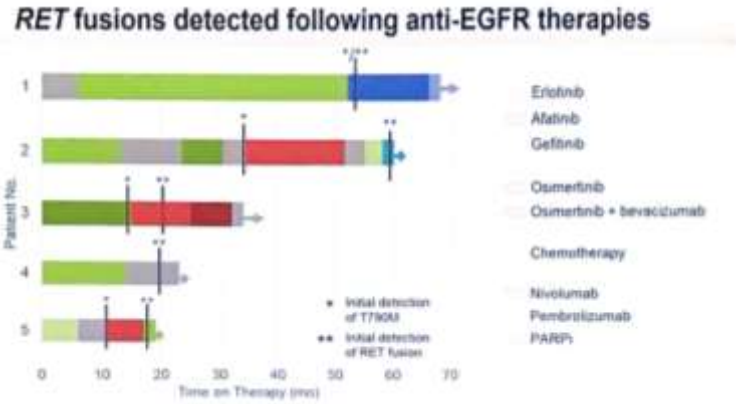
Third - generation

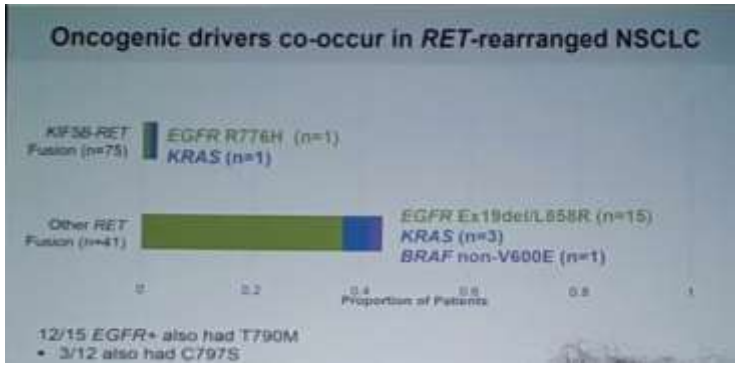


Conclusions & Perspectives

- Type of progression and number of metastatic sites impact the detection of mutation of ctDNA
- Increased number of mutations at progression disease under osimertinib in the second-line setting
- ctDNA sequencing is a promising complementary, non-invasive tool, to monitor response to treatment and heterogeneous mechanisms of resistance in NSCLC patients treated with TK inhibitors
- Detection of co-existent resistance mechanisms → potential of established PCR-based assays for ctDNA profiling at resistance
- Analyses of CTCs for EMT, phenotypic changes and expression profiles

Analysis of cell-free DNA from 32.991 advanced cancers revelals co-ocurring activating RET alterations (Reckamp K.L *et al.*)





Summary

- Largest patient cohort of activating *RET* alts in advanced cancers
- Alts in MAPK pathway genes and other RTKs are common in *RET*+ cancers, but frequency varies by *RET* fusion partner:
  - *KIF5B-RET* may only occur in NSCLC, and is only rarely found with *bona fide* NSCLC drivers
  - Drivers frequently co-occurred in NSCLC with *RET* fusions involving other partners (e.g. *CCDC6*, *NCOA4*), particularly *EGFR*
  - Acquired *RET* fusions may contribute to anti-EGFR therapy resistance in patients with NSCLC, but none of these were *KIF5B-RET*
- The *RET* fusion partner may have important clinical implications, and can be obtained with plasma-based cfDNA NGS (vs. IHC and FISH)