Sensitization to immunotherapy through manipulation of tumour transcription by Lurbinectedin

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Introduction

Despite recent advances in the use of immunotherapy, only a minority of aggressive cancers respond to immune checkpoint blockade (ICB). Current cytotoxic drugs and radiotherapy treatments for small cell lung cancer (SCLC) have long been known to act by induction of DNA damage. These notable results can be explained by the exceptionally high number of genomic aberrations observed in SCLC, combined with the characteristic rapid cellular proliferation resulting in accumulation of DNA damage and genomic instability. To flourish in this precarious genomic context, SCLC cells are reliant on functional DNA damage repair pathways, transcription proficiency and cell cycle checkpoints. Moreover, recent preclinical and clinical data have further shown that the DDR influences multiple aspects of tumor immunogenicity, including tumor cell– microenvironment interactions. We propose the concept of sensitize ICB-resistant tumors by generating transcriptional stress, by exposing them to the RNA polymerase II inhibitor Lurbinectedin (LUR).

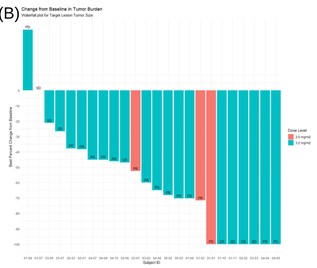
2SMALL: Lurbinectedin in combination with Atezolizumab Phase I/II Clinical Trial

Phase I-II study in SCLC patients who have failed one prior platinum-containing line (without anti-PD-1/PD-L1) and no re-challenge allowed. Phase I: dose-ranging with escalating doses of LUR in combination with a fixed dose of atezolizumab. Phase II: single-arm at the recommended dose determined during the phase I (3.2mg/m^2).

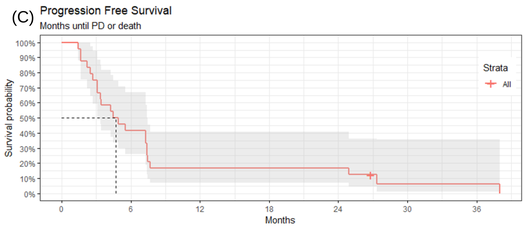
(A)

	2SMALL (NCT02454972)	Lurbinectedin as second-line treatment in SCLC (NCT02454972)
Best response	**N (%)**	
Complete Response	3 (12.5)	0 (0.0)
Partial Response	13 (54.17)	38 (36.2)
Stable Disease	5 (20.83)	34 (32.4)
Progression Disease	3 (12.5)	28 (26.7)
Total	24 (100)	105 (100)
Overall Response Rate	**N (%) [95% CI]**	
ORR	16 (66.67) [44.69-83.57]	38 (36.2) [27.0-46.1]
Total Patients	24 (100)	105 (100)
Progression Free Survival	**Median Months (95% CI)**	
PFS	4.7 (3.37 - 7.4)	3.7 (2.6 to 4.3)
Total Patients	23 (100%)	105 (100%)
Overall Survival	**Median Months (95% CI)**	
OS	14.5 (9.5 - 23.4)	8.1 (6.5 to 10.9)
Total Patients	18 (100%)	105 (100%)

(B)



(C)



(D)

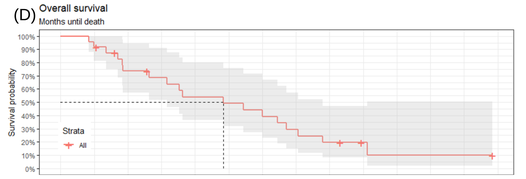


Figure 1.- (A) Summary table showing relevant endpoints from 2SMALL compared to clinical trial from which FDA granted accelerated approval for LUR in second-line treatment. (B) Waterfall plot showing change from baseline in tumour burden . (C) Progression Free Survival. (D) Overall Survival.

Conclusions

Phase I: the combination of LUR plus ATZ was well tolerated, without unexpected toxicities. The RD for further studies is LUR 3.2mg/m^2 on D1 + ATZ 1200 mg D1 with G-CSF. Phase II: anti-tumour activity is remarkable. Overall Response Rate was observed in 16 patients (66.67%), including complete responses in 3 patients (12.5%), partial response in 13 patients (54.17%). 5 patients had stable disease (20.83%) and 3 patients progressive disease (12.5%). With one patient censored, median PFS was 4.7 months (3.37 - 7.4). With 6 patients, OS was 14.5 months (9.5 - 23.4)

Synergy of Lurbinectedin with PD-L1 blockade in a SCLC mouse model

A syngeneic SCLC mouse model, RP1, recapitulated the clinical benefits shown by patients enrolled in 2SMALL clinical trial, proving its suitability for this treatment strategy. Although LUR treatment was able to stabilise tumour growth in monotherapy, only LUR plus anti-PD-L1combination achieved clearance of primary tumour site.
Cured mice were rechallenge with same RP1 SCLC model. Rejection of tumour rechallenge in the absence of therapy was observed in 2 out of 3 mice demonstrating long immunological memory.

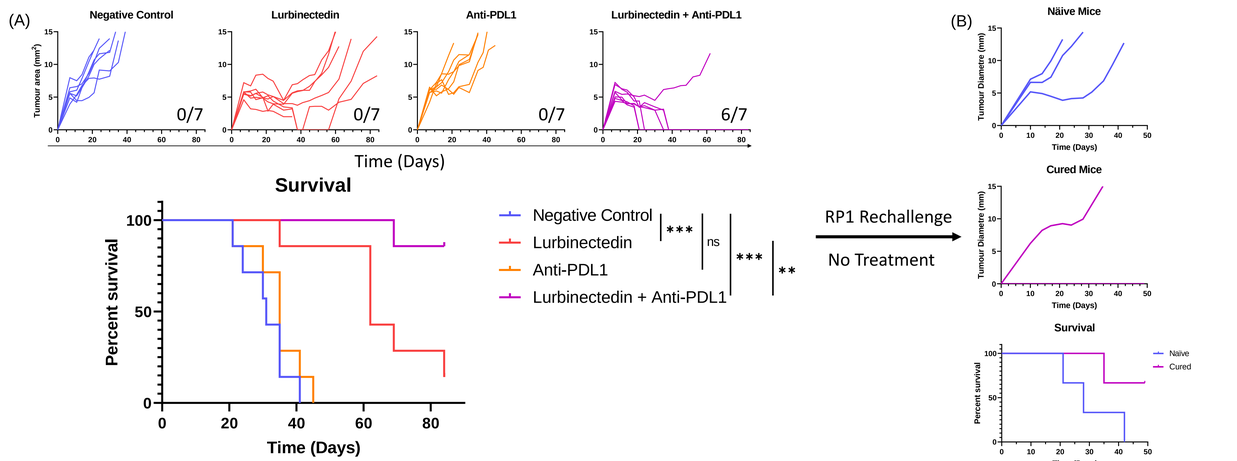


Figure 2.- (A) Lurbinectedin and anti-PD-L1 blockade, in monotherapy and in combination, in a syngeneic SCLC mouse model subcutaneously implanted in immunocompetent (C57BL/6x129/SvF1) mice. (B) Cured and näive, age-matched mice were rechallenge with same RP1 SCLC model at same flank. RP1 syngeneic SCLC mouse model was derived from a genetically engineered SCLC mouse with conditional loss of *Trp53* and *Rb1*.

Lurbinectedin increases MHCI expression in SCLC

Treatment of human SCLC cell lines (H82, H446 & H526) and a mouse SCLC cell line (RP1) with LUR at several time-points. LUR treatment significantly increased expression of MHCI in all cell lines in a progressive manner.

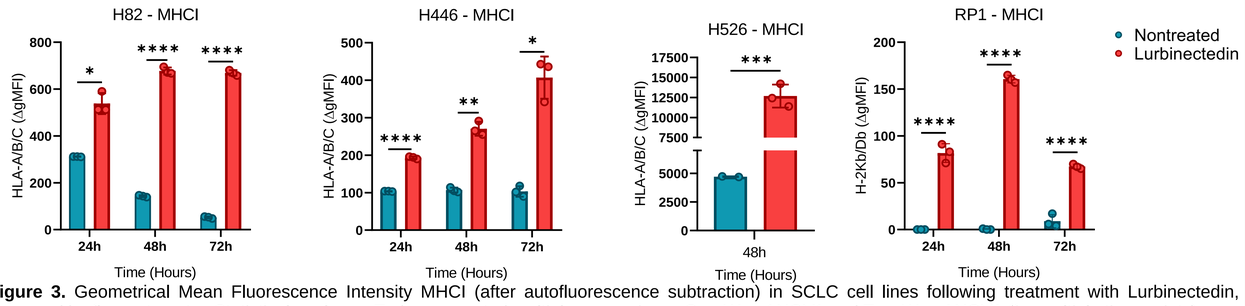


Figure 3. Geometrical Mean Fluorescence Intensity MHCI (after autofluorescence subtraction) in SCLC cell lines following treatment with Lurbinectedin, assessed by flow cytometry. Statistical analyses: Turkey-corrected multiple comparisons One-Way-ANOVA and Two-Way-ANOVA (for multiple time-points).

Lurbinectedin triggers type IFN-I in SCLC

Upregulation of IFNα and IFNβ expression after LUR treatment was observed in SCLC cell lines cultured *in vitro* as well as syngeneic RP1 mouse model.

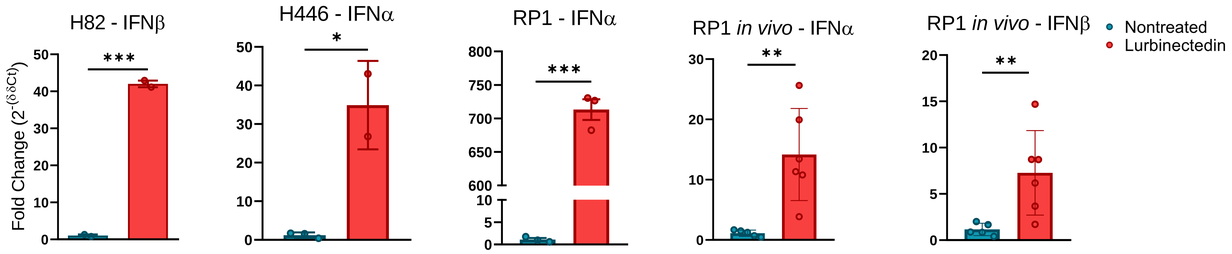


Figure 4. RT-qPCR measurement of IFNα and IFNβ mRNA extracted from RP1, H82 and H446 cultured *in vitro,* and RP1 tumours *in vivo* from engraftments in immunocompetent mice treated with/without LUR for 72 hours. Statistical analyses: Turkey-corrected multiple comparisons One-Way-ANOVA, Welch's t test or unpaired t test.

Conclusions

The combination of Lurbinectedin plus Atezolizumab was well tolerated and without unexpected toxicities. Anti-tumour activity was remarkable with complete response in 3 patients (12.5%) and 13 partial responses (54.17%), and improved PFS and OS from that in Lurbinectedin alone in second-line treatment. Our syngeneic SCLC mouse model was able to recapitulate clinical benefits seen in the clinical trial, showing a significant anti-tumour effect and acquisition of immunological memory, suggesting that such combinations might be further explored to overcome primary resistance to ICB in SCLC. Mechanistically, our results demonstrated that upon LUR treatment human and mouse SCLC cell line increase their MHCI levels in the surface and upregulate type-I IFN *in vitro* and *in vivo*. All these evidences indicate a clear interplay between transcriptional stress and anticancer immunity, providing the rational to combine transcriptional inhibitors with ICBs.