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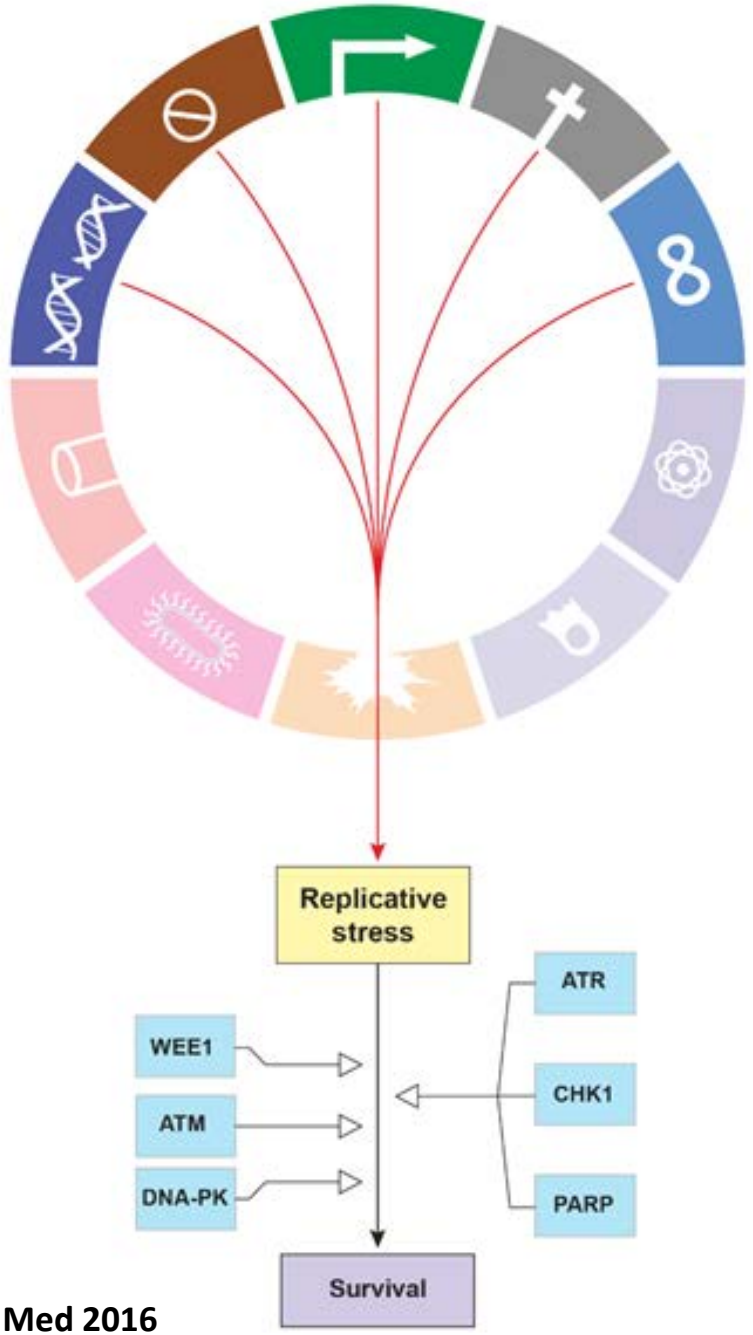
# Targeting ATR and other DNA repair proteins

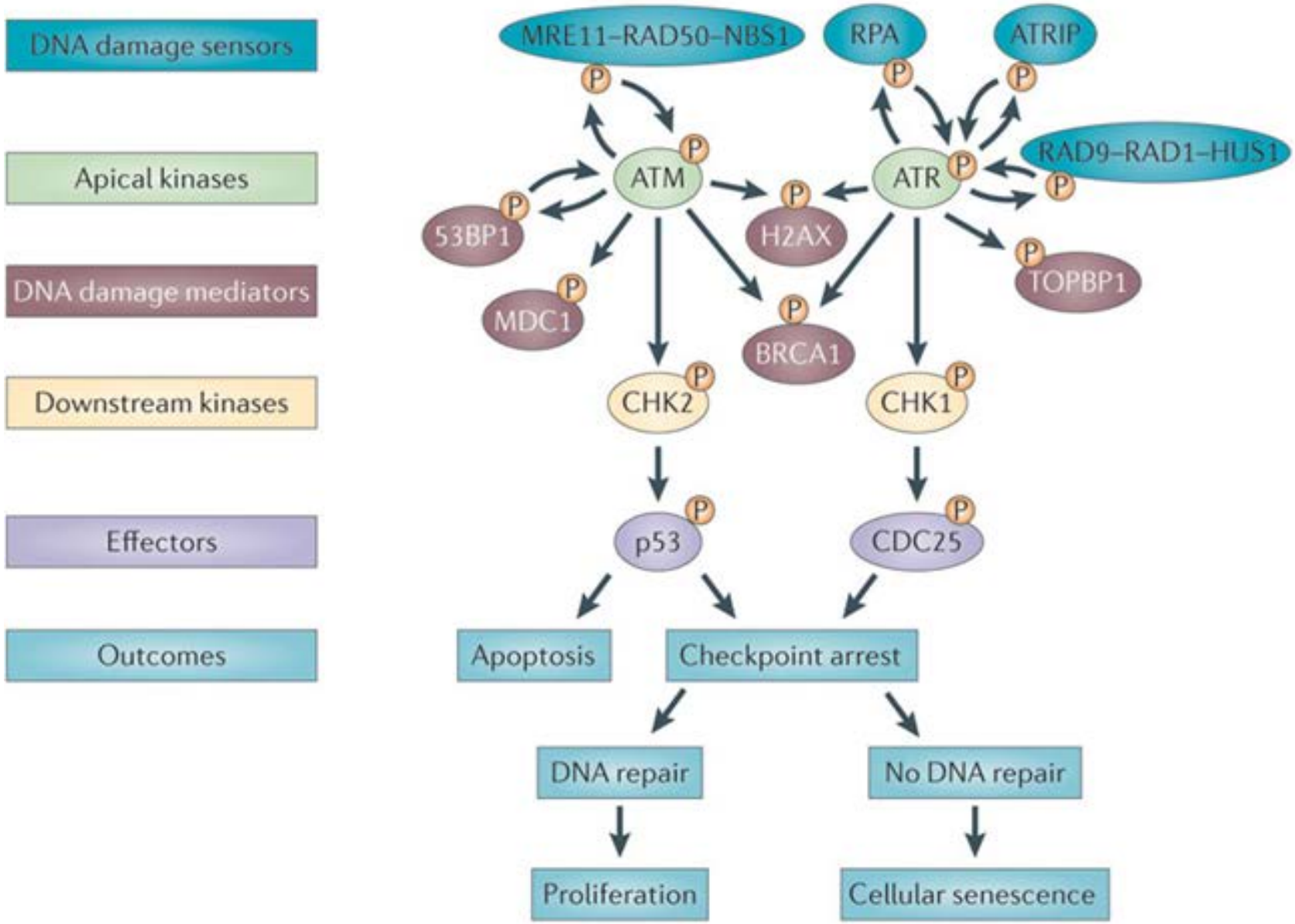
# Replicative stress is a SCLC hallmark

1. Loss of growth suppressors (TP53 and RB1 ~100%)
2. Sustained proliferation (e.g. MYC amplification)
3. Genomic instability (↑↑ mutations, ↑PARP)




Thomas and Pommier. Sci Transl Med 2016

# DNA damage response




Sulli et al. Nature Reviews Cancer 2012

*Therapeutics, Targets, and Chemical Biology*

Cancer Research

# ATR Inhibitors VE-821 and VX-970 Sensitize Cancer Cells to Topoisomerase I Inhibitors by Disabling DNA Replication Initiation and Fork Elongation Responses

Rozenn Jossé[1], Scott E. Martin[2], Rajarshi Guha[2], Pinar Ormanoglu[2], Thomas D. Pfister[3], Philip M. Reaper[4], Christopher S. Barnes[4], Julie Jones[4], Peter Charlton[4], John R. Pollard[4], Joel Morris[5], James H. Doroshow[1,5], and Yves Pommier[1]

**Synthetic lethal siRNA screen→Depletion of ATR was a top candidate gene for camptothecin synthetic lethality**

**ATR inhibition abrogated the S-phase replication elongation checkpoint and the replication origin-firing checkpoint induced by camptothecin**

**Jossé, Pommier. Can Res 2014**
**Martin, Pommier, Caplen. Curr Can Drug Tar 2011**

# ATR inhibition disrupts rewired homologous recombination and fork protection pathways in PARP inhibitor-resistant BRCA-deficient cancer cells

Stephanie A. Yazinski,[1] Valentine Comaills,[1,6] Rémi Buisson,[1,6] Marie-Michelle Genois,[1,6] Hai Dang Nguyen,[1] Chu Kwen Ho,[1] Tanya Todorova Kwan,[1,2] Robert Morris,[1] Sam Lauffer,[1,3] André Nussenzweig,[4] Sridhar Ramaswamy,[1] Cyril H. Benes,[1] Daniel A. Haber,[1,2] Shyamala Maheswaran,[1] Michael J. Birrer,[1,3] and Lee Zou[1,5]

**PARPi-resistant BRCA1-deficient cells**

**Gene profiling and inhibitor screening → ATR promotes RAD51 loading to DSBs and stalled forks → controls BRCA1-independent HR and fork protection**

**ATR inhibition disrupted the rewired HR and replication fork protection pathways-resensitizing resistant cells to PARPi**

**Yazinski. Genes & Development 2017**

# ATR inhibitors in clinical trials

- **Berzosertib (VX-970; M6620; VE-822)- Phase II**
- **AZD6738- Phase II**
- **BAY1895344- Phase I**

# ATR inhibitors- phase I trials

- **VX-970 (M6620; VE-822)- Phase I/II**
- AZD6738- Phase I
- BAY1895344- Phase I

**Well tolerated in patients**

**No dose-limiting toxicities**

**Limited anti-tumor activity as monotherapy**

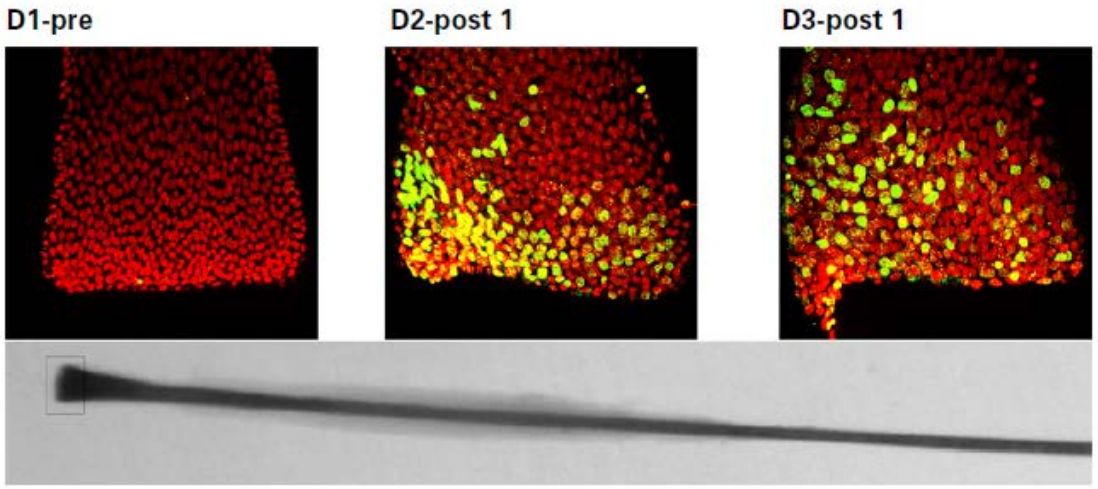
**O'Carrigan, ASCO Meeting 2016**
**Plummer, ASCO Meeting 2016**

# Phase I trial of VX-970 (M6620) and topotecan

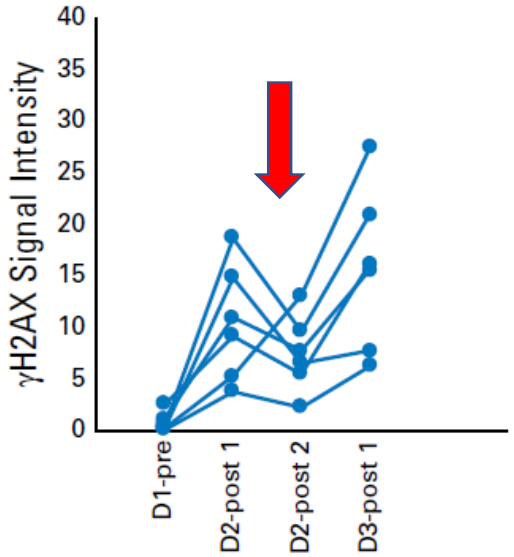

| Dose Level | Topotecan (days 1-5), mg/m$^2$ IV | M6620, mg/m$^2$ IV |
|---|---|---|
| 1 | 1 | 140 on day 5 |
| 2 | 1 | 140 on days 2 and 5 |
| 3 | 1.25 | 140 on days 2 and 5 |
| 4 | 1.25 | 210 on days 2 and 5 |
| 21-day cycles | | |

**Patients with advanced cancers and progressive disease after ≥ 1 chemotherapy**

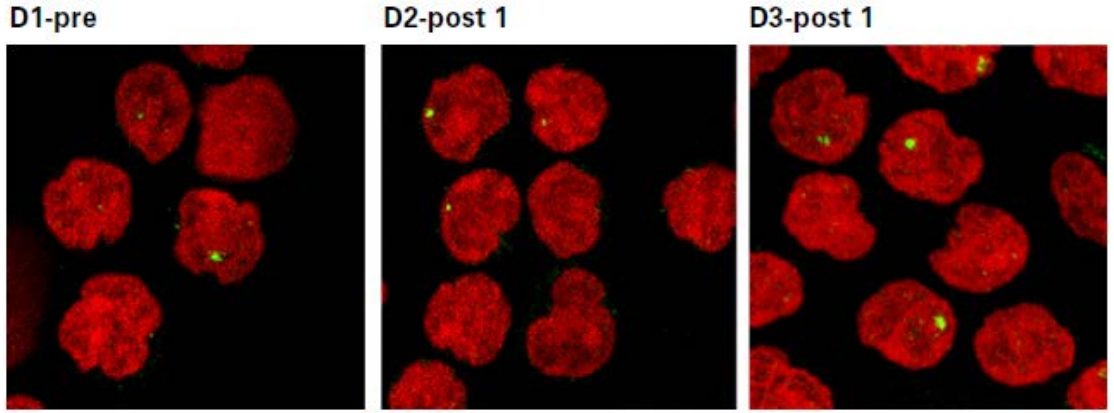
# γH2AX, a sensitive marker for DNA double-strand breaks




Increasing number and intensity of γH2AX foci in hair follicles




Reduced ATR-dependent phosphorylation of H2AX




Cytotoxicity related to replication

# Toxicities were predictable and manageable

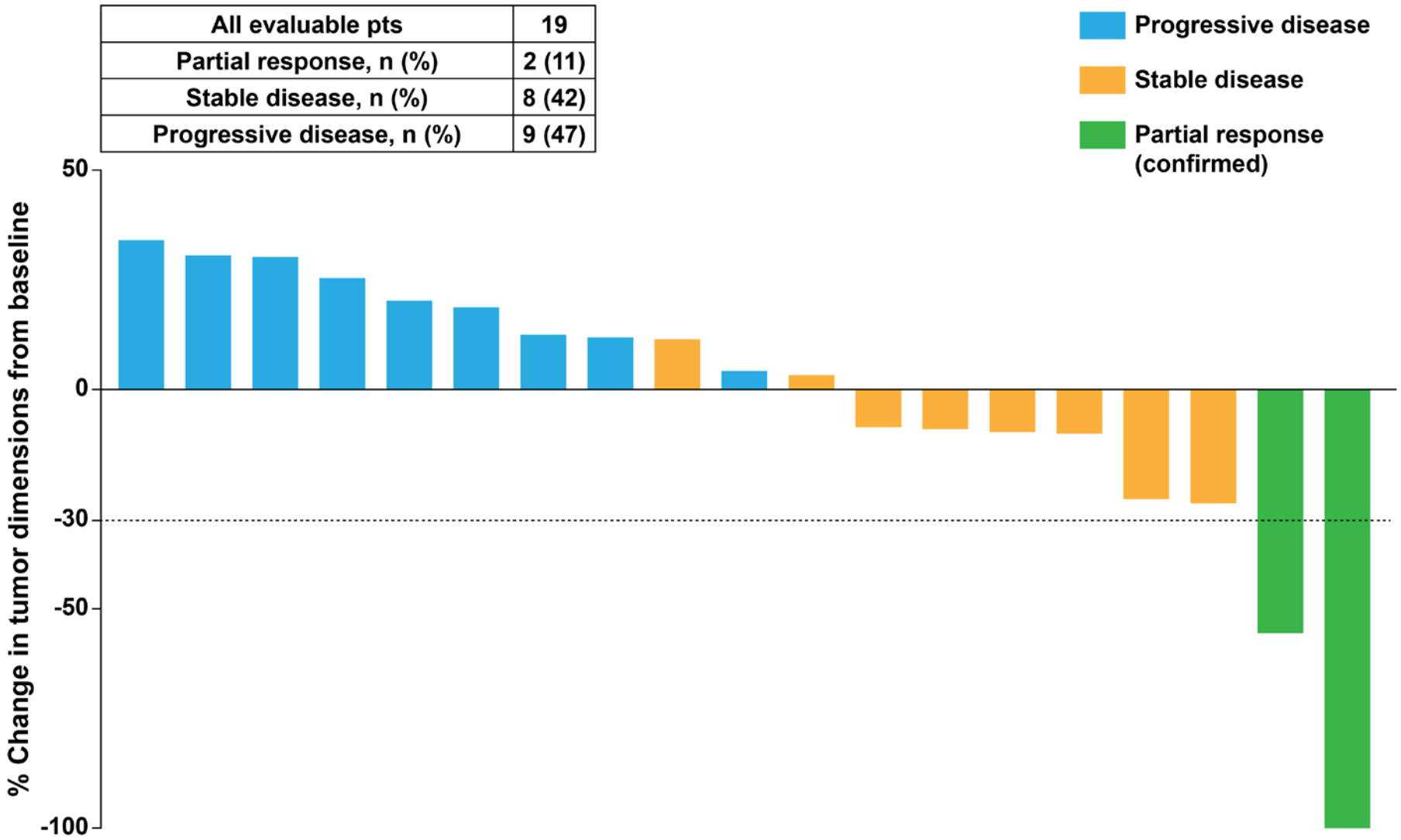
Most Common (≥ 10%) Treatment-Related Adverse Events (maximum grade, all cycles)

| | Dose Level and Adverse Event Grade, No. (%) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | All (N = 21) | | 1* (n = 6) | | 2† (n = 6) | | 3‡ (n = 3) | | 4§ (n =6) | |
| Adverse Event | All | ≥ Grade 3 | All | ≥ Grade 3 | All | ≥ Grade 3 | All | ≥ Grade 3 | All | ≥ Grade 3 |
| Anemia | 21 | 8 (38) | 6 | 0 | 6 | 2 (10) | 3 | 2 (10) | 5 | 4 (19) |
| Lymphopenia | 21 | 9 (43) | 4 | 3 (14) | 8 | 2 (10) | 3 | 1 (5) | 6 | 3 (14) |
| Leukopenia | 19 | 11 (52) | 6 | 2 (10) | 6 | 4 (19) | 2 | 1 (5) | 5 | 4 (19) |
| Neutropenia | 17 | 11 (52) | 5 | 2 (10) | 6 | 4 (19) | 1 | 1 (5) | 5 | 4 (19) |
| Thrombocytopenia | 16 | 5 (24) | 4 | 1 (5) | 5 | 1 (5) | 2 | 1 (5) | 5 | 2 (10) |
| Febrile neutropenia | 2 | 1 (5) | | | 1 | 1 (5) | | | | |
| Hyponatremia | 3 | 1 (5) | 1 | 1 (5) | 1 | | | | | |
| ALT increase | 3 | 1 (5) | 2 | 1 (5) | | | | | 1 | |
| AST increase | 4 | 1 (5) | 2 | 1 (5) | 1 | | | | 1 | |
| Nausea | 13 | 1 (5) | 4 | | 4 | | 2 | | 3 | 1 (5) |
| Vomiting | 8 | | 1 | | 3 | | 1 | | 3 | |
| Anorexia | 6 | | 1 | | 3 | | | | 2 | |
| Fatigue | 5 | 1 (5) | 1 | | 2 | | | | 2 | 1 (5) |
| Fever | 2 | | 1 | | 1 | | | | | |
| Mucositis oral | 2 | | 1 | | | | | | 1 | |
| Alopecia | 2 | | 1 | | | | | | 1 | |
| Diarrhea | 2 | | 2 | | | | | | | |
| Infusion-related reaction | 2 | | 2 | | | | | | | |

*Topotecan 1 mg/m$^2$ days 1 to 5; M6620 140 mg/m$^2$ day 5.
†Topotecan 1 mg/m$^2$ days 1 to 5; M6620 140 mg/m$^2$ days 2 and 5.
‡Topotecan 1.25 mg/m$^2$ days 1 to 5; M6620 140 mg/m$^2$ days 2 and 5.
§Topotecan 1.25 mg/m$^2$ days 1 to 5; M6620 210 mg/m$^2$ days 2 and 5.

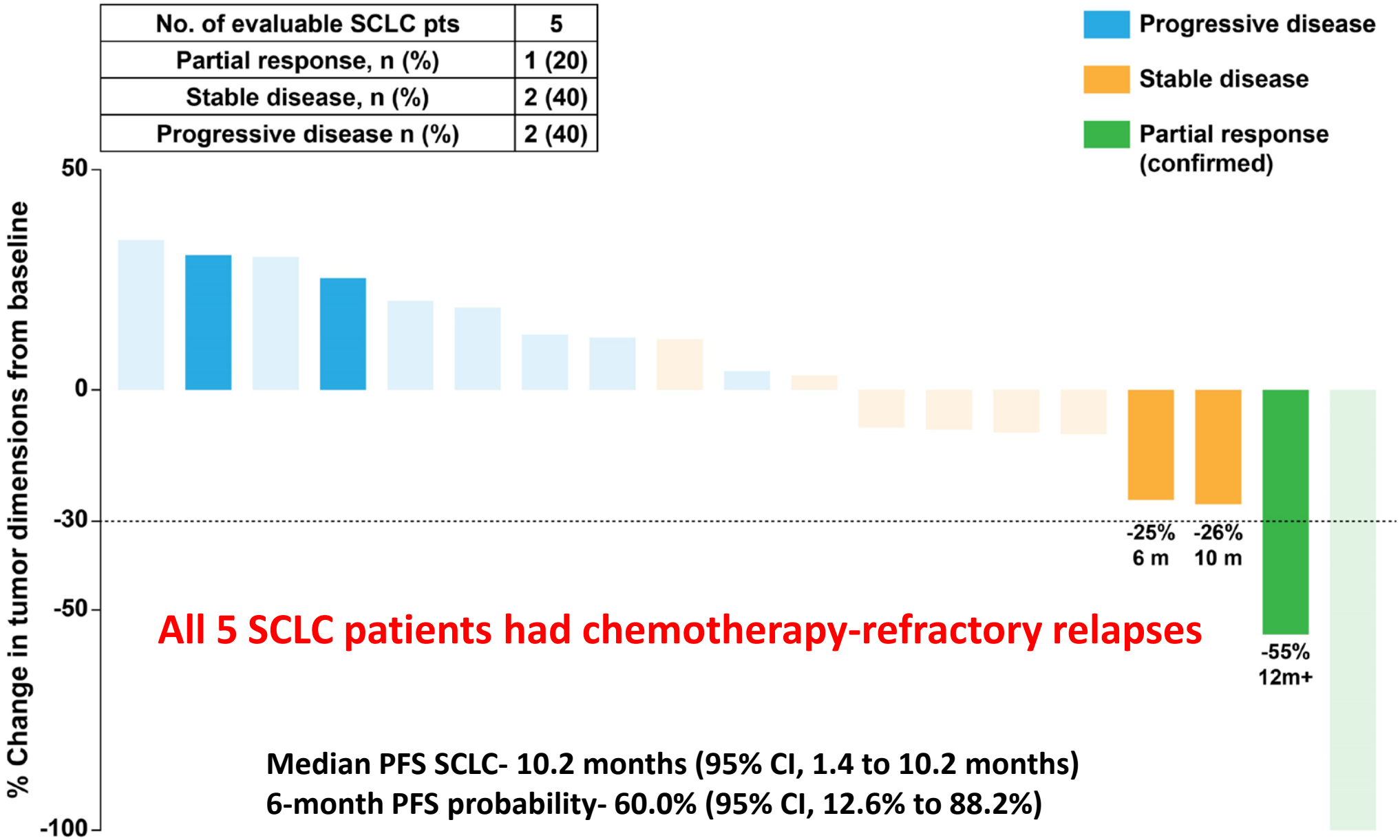
# Efficacy: VX-970 and topotecan

| All evaluable pts | 19 |
|---|---|
| Partial response, n (%) | 2 (11) |
| Stable disease, n (%) | 8 (42) |
| Progressive disease, n (%) | 9 (47) |



# Efficacy in SCLC: VX-970 and topotecan

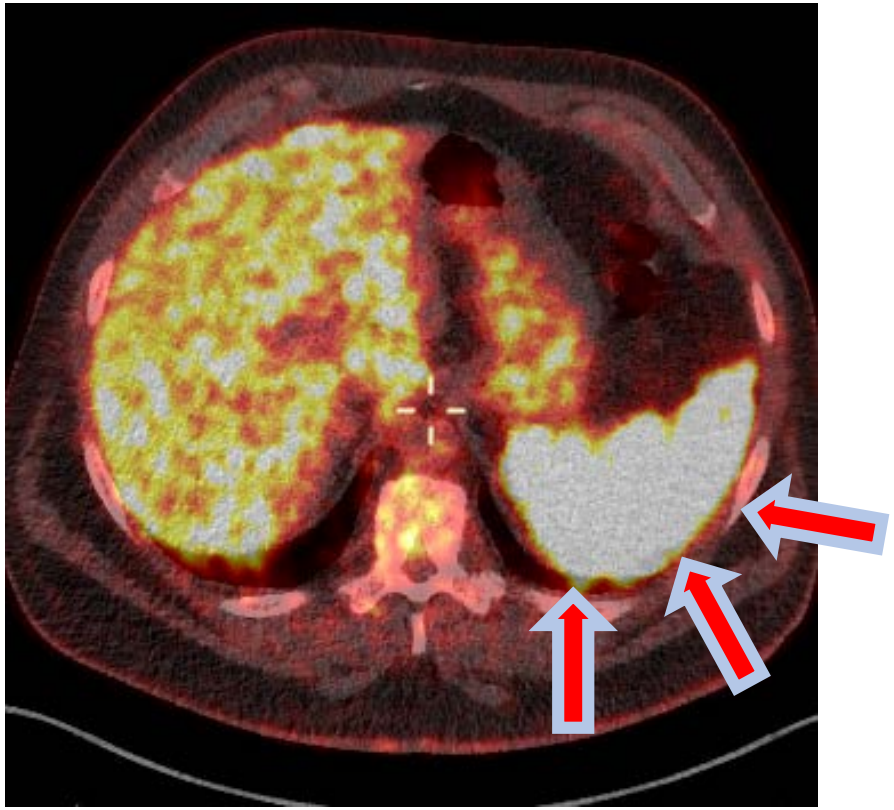
| No. of evaluable SCLC pts | 5 |
|---|---|
| Partial response, n (%) | 1 (20) |
| Stable disease, n (%) | 2 (40) |
| Progressive disease n (%) | 2 (40) |



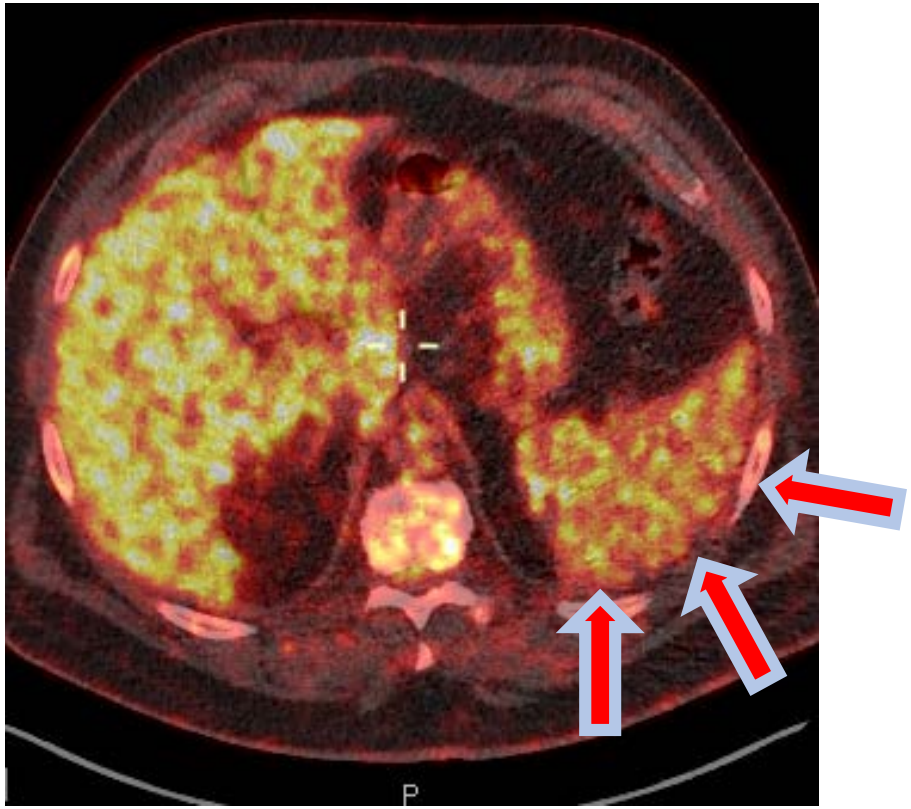

**All 5 SCLC patients had chemotherapy-refractory relapses**

**Median PFS SCLC- 10.2 months (95% CI, 1.4 to 10.2 months)**
**6-month PFS probability- 60.0% (95% CI, 12.6% to 88.2%)**

# Response to VX-970 and topotecan in refractory SCLC



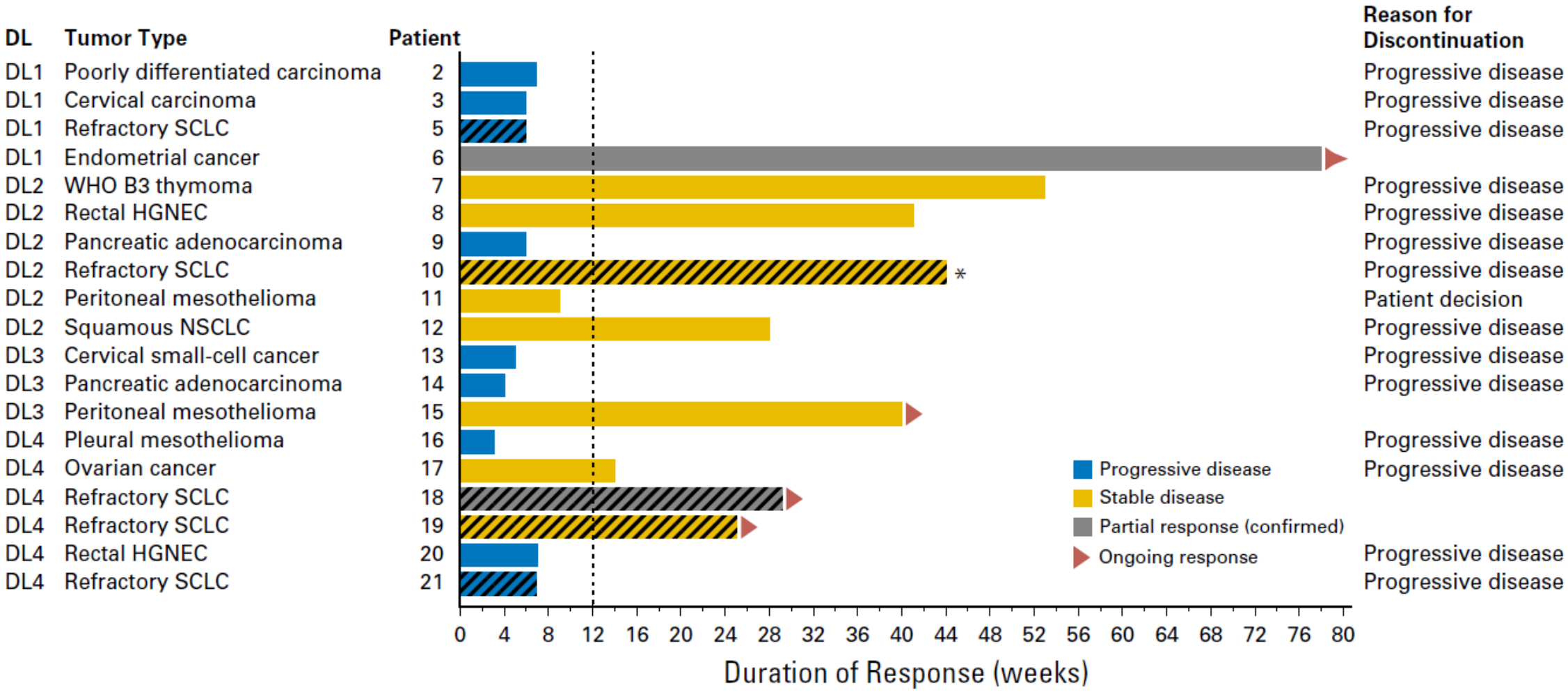
Before treatment



5 months after treatment

**Patient remains on treatment at 13 months**

# Prolonged stable disease




**Seven of the eight patients with SD had prolonged SD (≥3 months); Median, 9 months(3- 12)**

JOURNAL OF CLINICAL ONCOLOGY
Official Journal of the American Society of Clinical Oncology

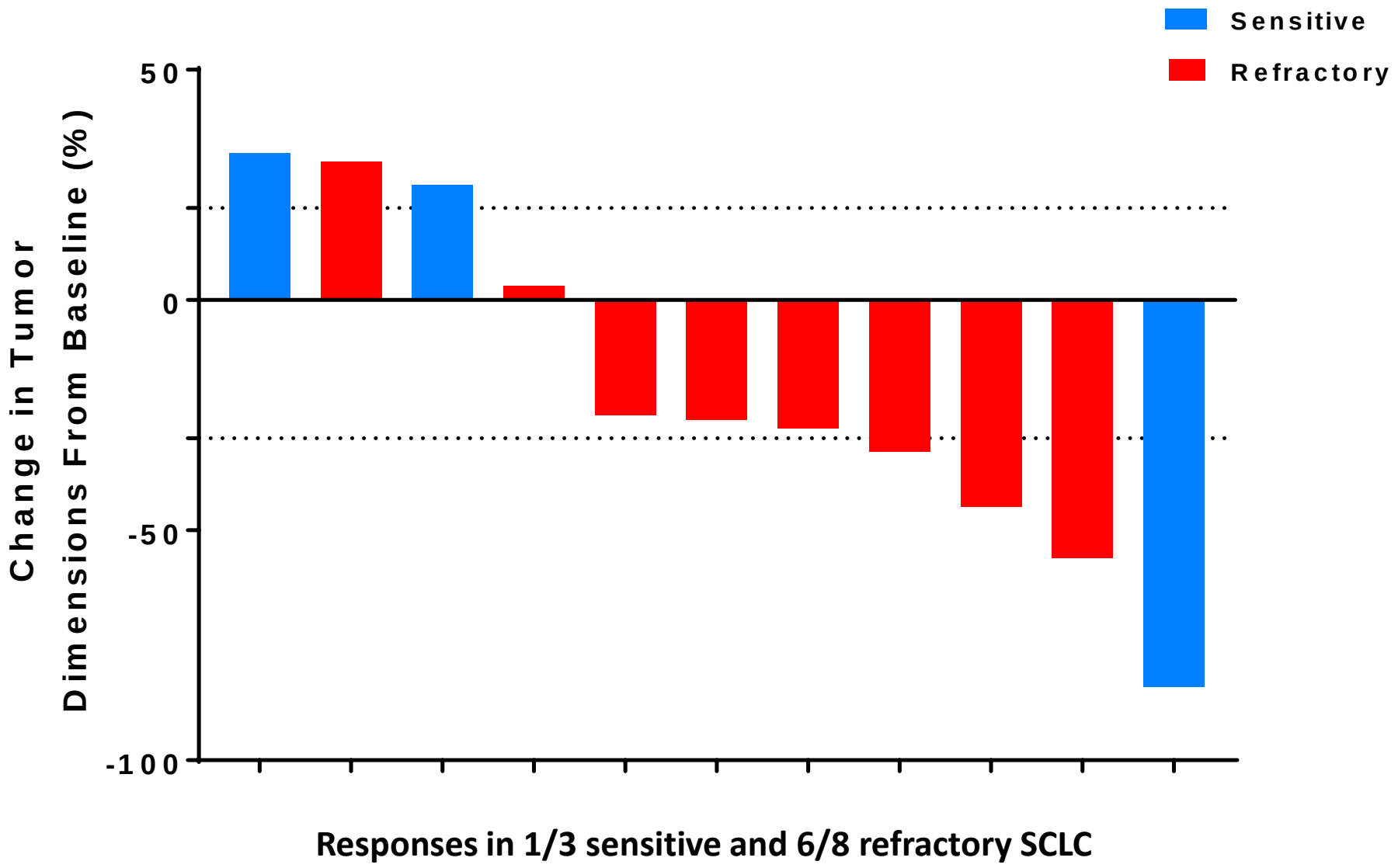
# Phase I Study of ATR Inhibitor M6620 in Combination With Topotecan in Patients With Advanced Solid Tumors

*Anish Thomas, Christophe E. Redon, Linda Sciuto, Emerson Padiernos, Jiuping Ji, Min-Jung Lee, Akira Yuno, Sunmin Lee, Yiping Zhang, Lan Tran, William Yutzy, Arun Rajan, Udayan Guha, Haobin Chen, Raffit Hassan, Christine C. Alewine, Eva Szabo, Susan E. Bates, Robert J. Kinders, Seth M. Steinberg, James H. Doroshow, Mirit I. Aladjem, Jane B. Trepel, and Yves Pommier*

**Phase II is enrolling SCLC patients**

Thomas. J Clin Oncol 2018

# Updated responses- Phase I/II




Responses in 1/3 sensitive and 6/8 refractory SCLC

Unpublished data

# Predictive biomarkers of response- MYC?

**In vivo, MYC-driven SCLC rapidly relapse following chemotherapy**

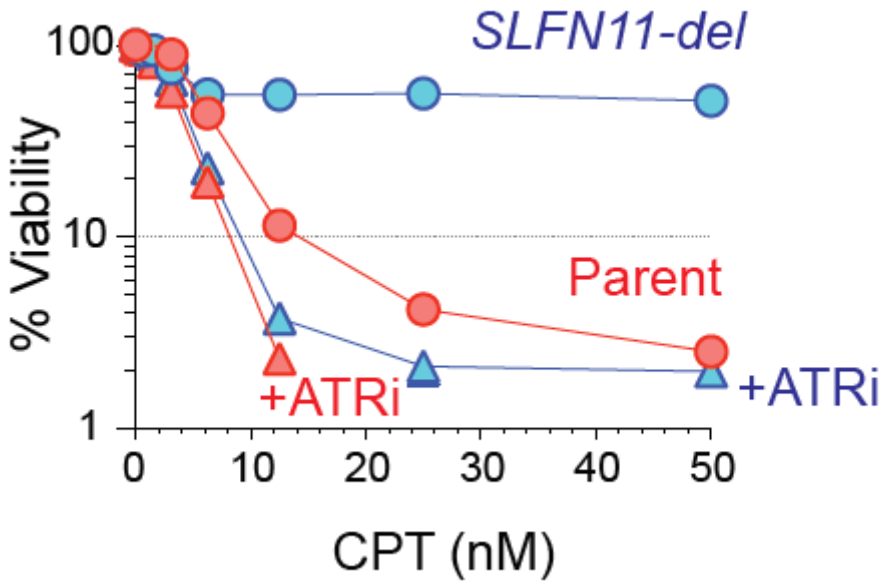
**Mollaoglu. Cancer Cell 2017**

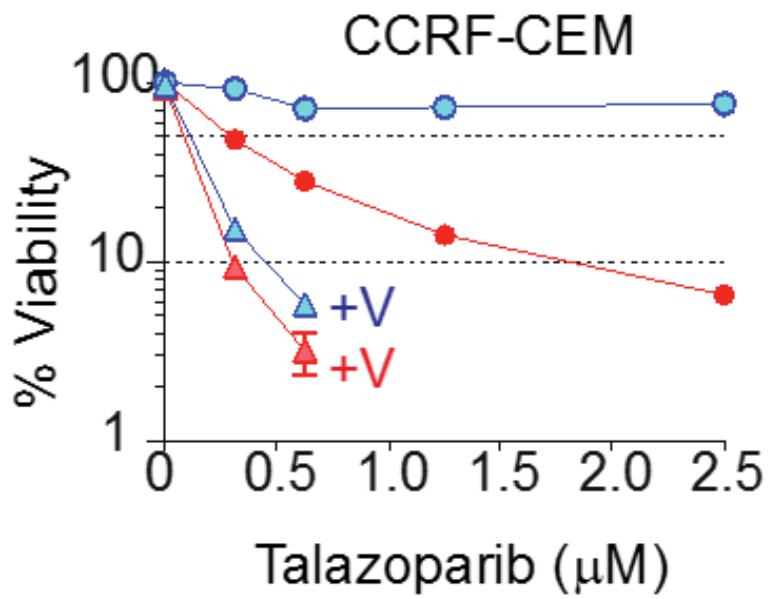
**Reduced levels of ATR completely prevented the development of MYC-induced lymphomas and pancreatic tumors**

**Murga. Nat Struct Mol Biol 2011**

**Are resistant SCLCs responding to ATRi/topotecan MYC amplified?**

# Predictive biomarkers of response- SLFN11- tumors?



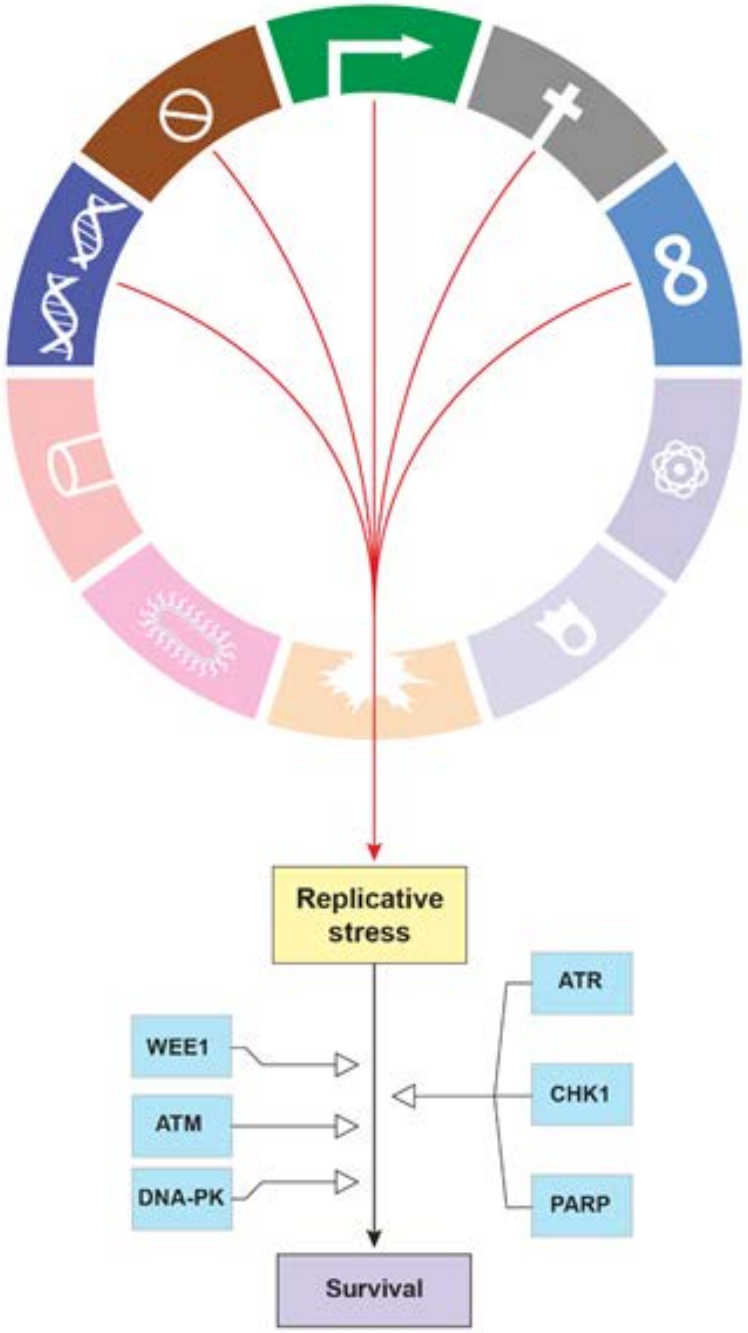

Parent
Parent + VE-821
*SLFN11*-del
*SLFN11*-del + VE-821

**Are resistant SCLCs responding to ATRi/topotecan SLFN11 negative?**

Murai, Pommier. Mol cell 2018

# Summary

- Chemotherapy resistance in SCLC may arise from multiple mechanisms- rewiring of HR, suppression of SLFN11, others…
- ATR inhibition may disrupt the rewired HR in platinum-refractory SCLC cell- could render them sensitive to topotecan
- ATR inhibition was tolerable in patients- no additive toxicities with topotecan
- Preliminary data indicates efficacy of the combination in refractory SCLC- are these tumors MYC driven/ SLFN11 negative ?




**WEE1**

- AZD1775 monotherapy (NCT02593019)
- AZD1775 in MYC Amplified or CDKN2A Mutated plus TP53 Mutated SCLC (NCT02688907)
- AZD1775 plus olaparib in MYC or CCNE1 amplified SCLC (NCT02511795)

**ATR**

- VX970 plus topotecan (NCT02487095)
- AZD6738 plus olaparib (NCT03428607)

**CHK1**

- Prexasertib monotherapy (NCT02735980)

**DNA-PK**

- M3814 plus cisplatin/ etoposide (NCT03116971)

# Acknowledgements

**Patients and Families**

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Christophe Redon

Yves Pommier

Jane Trepel