

# **Pilaralisib**

**Jennifer R Brown, MD PhD**  
**Director, CLL Center**  
**Dana-Farber Cancer Institute**  
**Associate Professor**  
**Harvard Medical School**  
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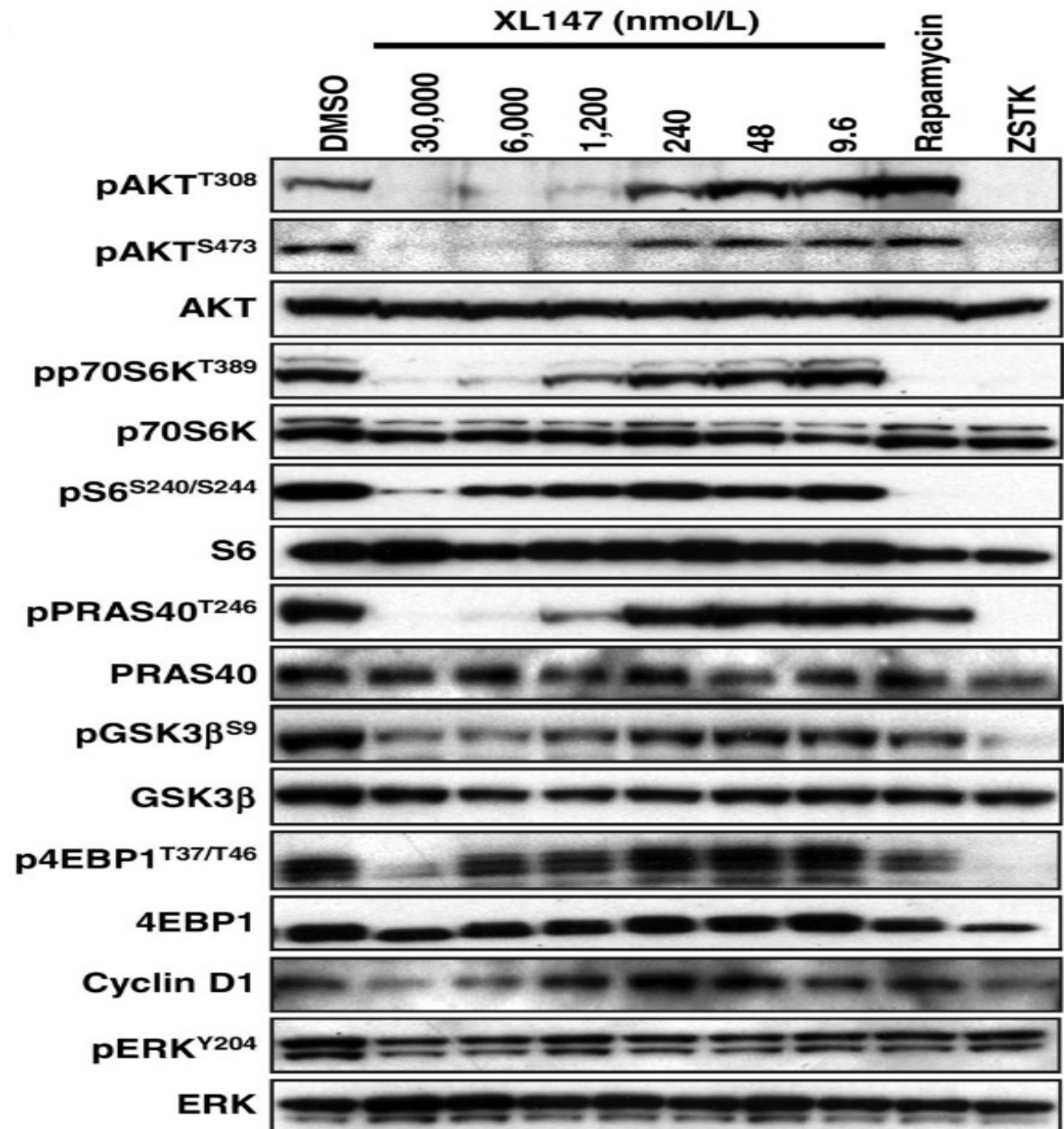
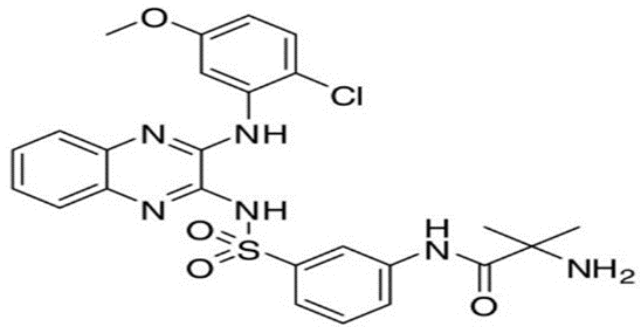
# IC<sub>50</sub> Values (nM) of Selected PI3K Inhibitors Against Recombinant Enzymes

| Drug Name   | p110 $\alpha$ | p110 $\beta$ | p110 $\delta$ | p110 $\gamma$ |
|-------------|---------------|--------------|---------------|---------------|
| Idelalisib  | 820           | 565          | 2.5           | 89            |
| Duvelisib   | 1602          | 85           | 2.5           | 27            |
| Umbralisib  | >10000        | 1116         | 22            | 1065          |
| Copanlisib  | 0.5           | 3.7          | 0.7           | 6.4           |
| INCB050465  | >20000        | >20000       | 1             | >20000        |
| ACP-319     | 33000         | 270          | 18            | 85            |
| Pilaralisib | 39            | 383          | 36            | 23            |
| Voxtalisib  | 39            | 110          | 43            | 9             |

# Kinase Activity of Pilaralisib

| Family               | Kinase        | XL147, IC <sub>50</sub> ± SEM (nM) |
|----------------------|---------------|------------------------------------|
| <b>PI3K</b>          |               |                                    |
| Class I <sub>A</sub> | PI3K $\alpha$ | <b>39 ± 10 / 48</b>                |
|                      | PI3K $\beta$  | <b>383 ± 78 / 617</b>              |
|                      | PI3K $\delta$ | <b>36 ± 8 / 260</b>                |
| Class I <sub>B</sub> | PI3K $\gamma$ | <b>23 ± 8 / 10</b>                 |
| Class III            | VPS34         | 6,974                              |
| PI3K related         | DNA-PK        | 4,750 ± 2,000                      |
|                      | mTOR          | >15,000                            |

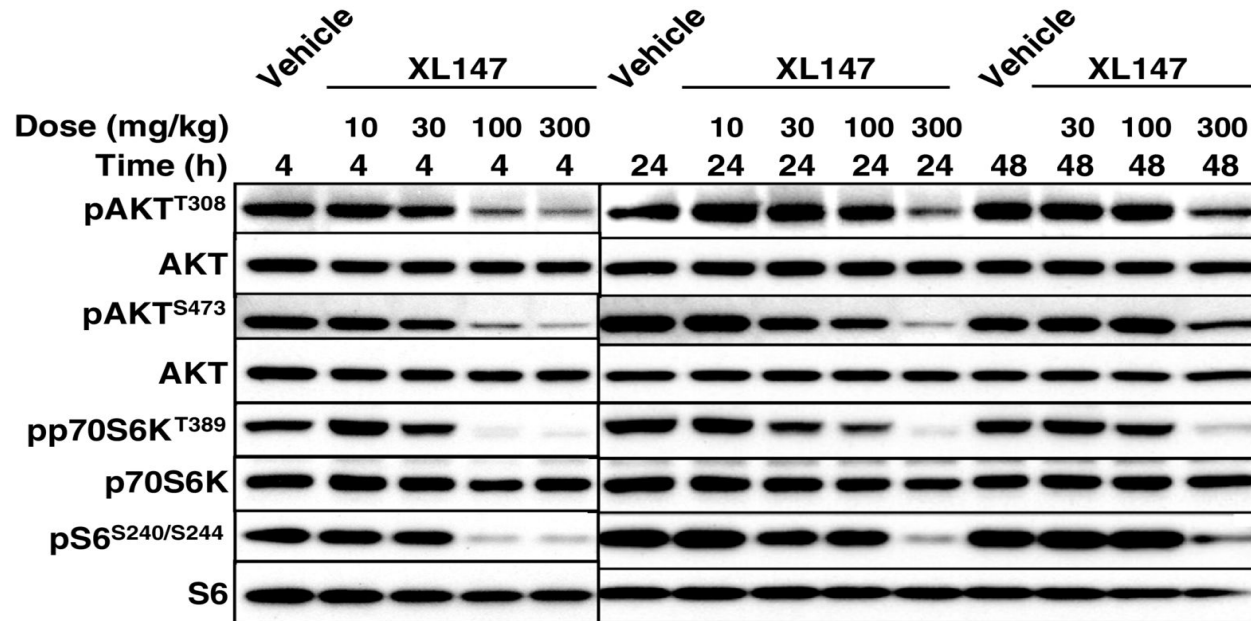
# Structure & Activity of XL147 (SAR245408)



# XL147 Inhibits PI3K Signaling in MCF7 and PC-3 Tumors

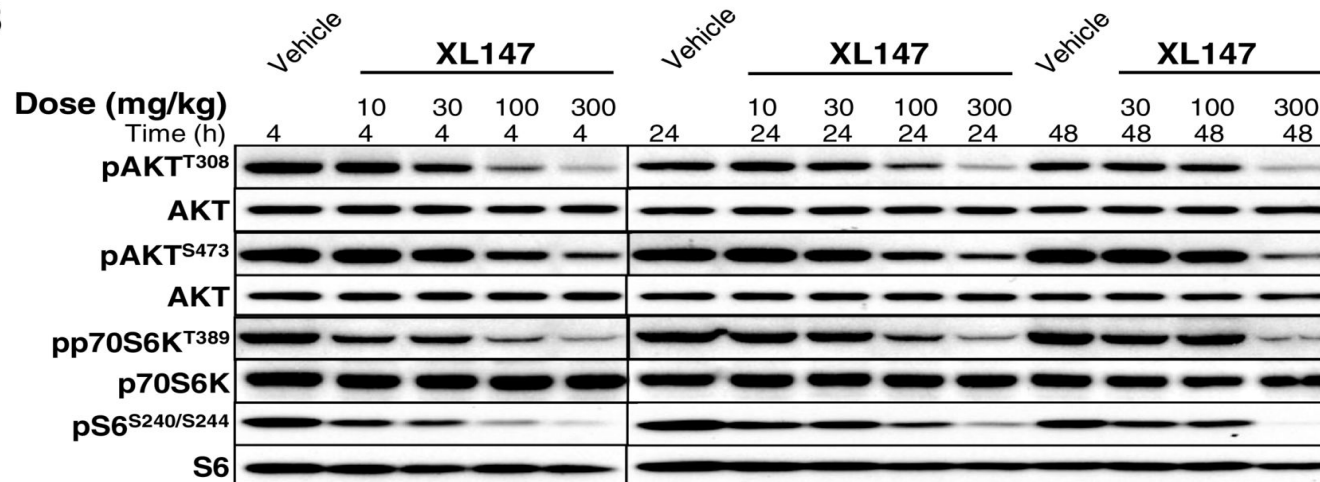
MCF7

**A**

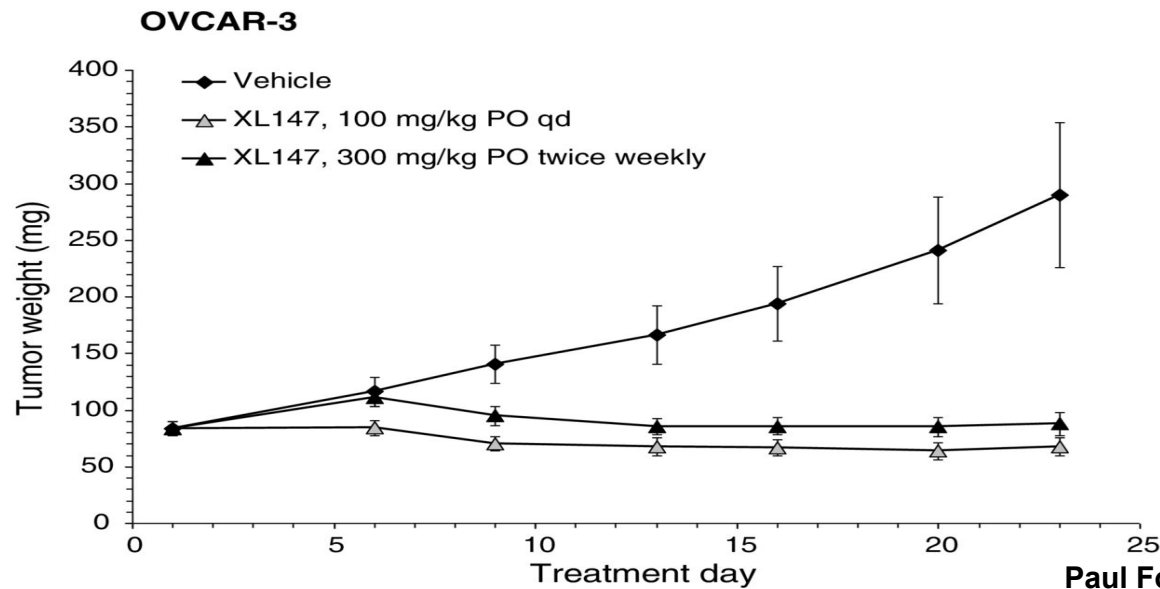
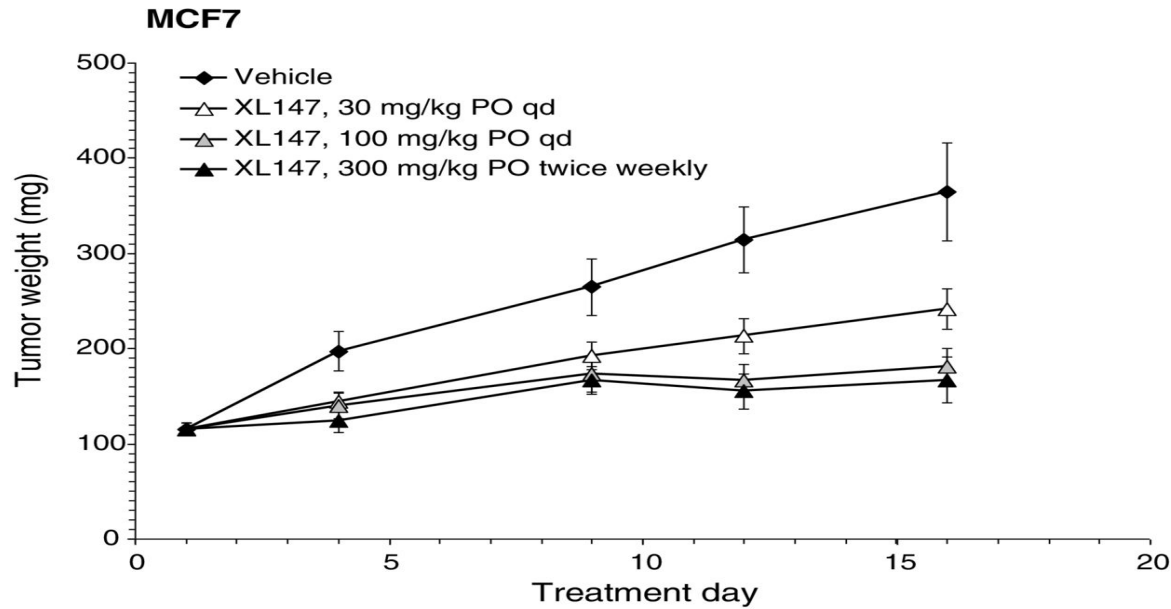


PC-3

**B**



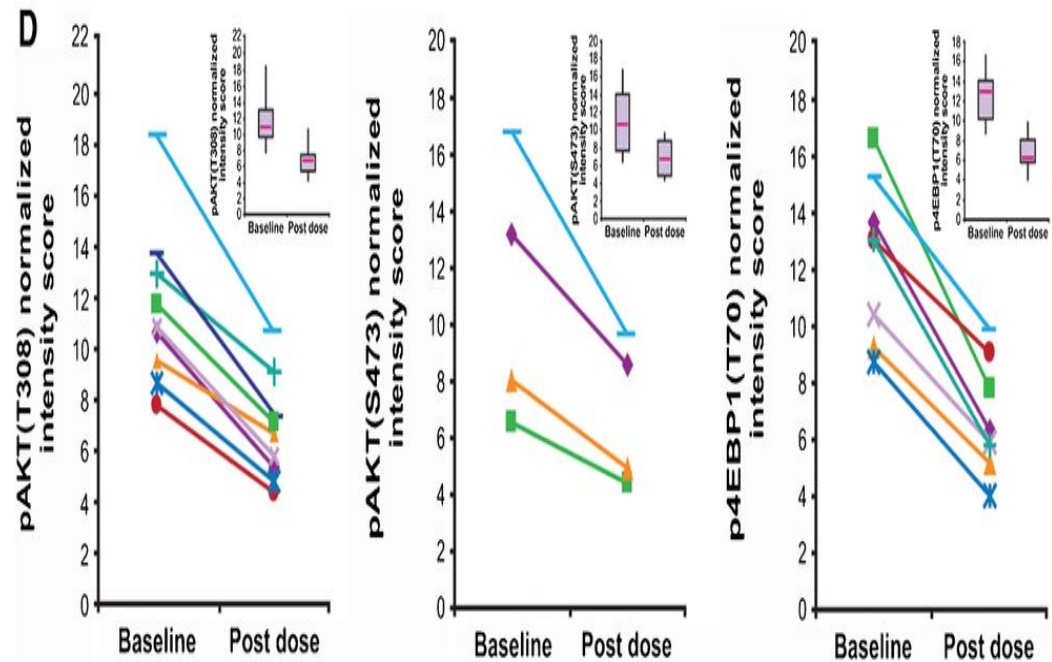
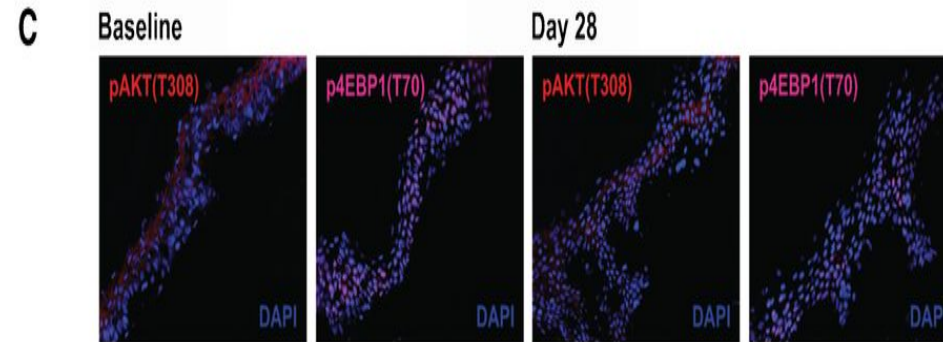
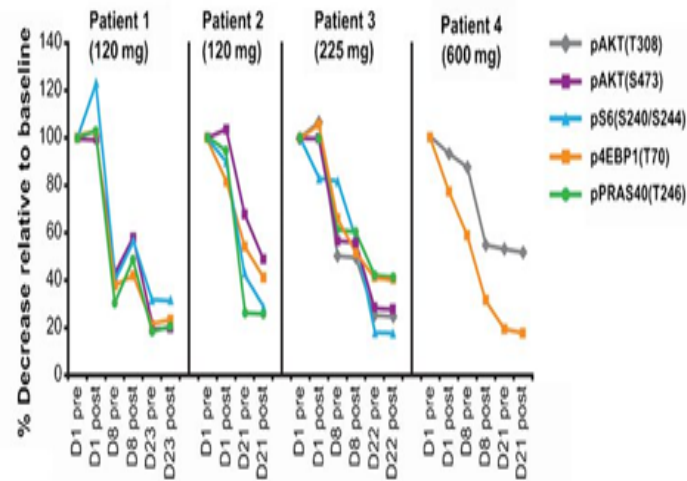
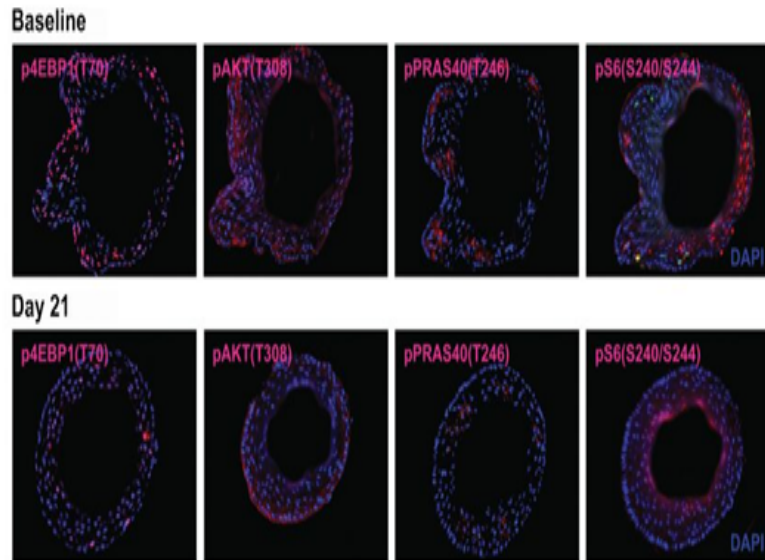
# XL147 Inhibits Tumor Growth and/or Causes Regression of Established Xenograft Tumors



# **Solid Tumor Studies**

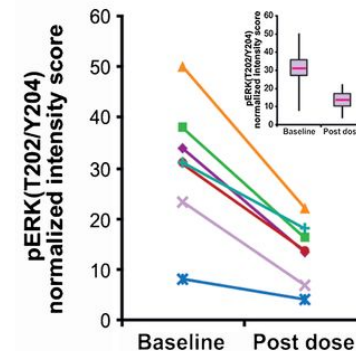
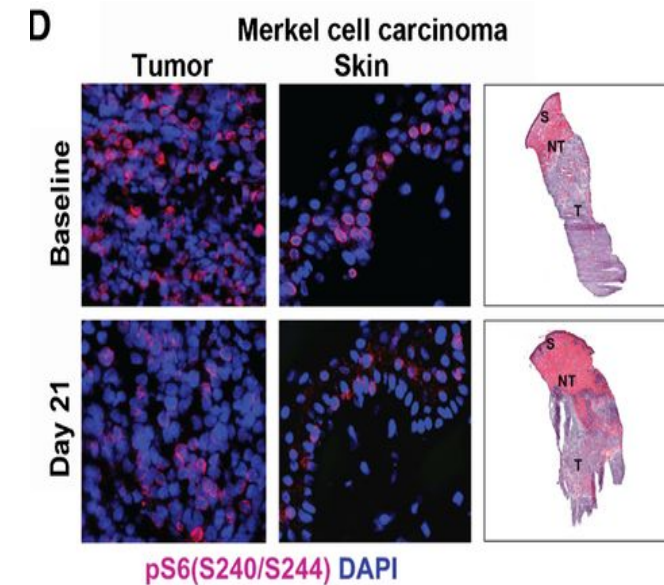
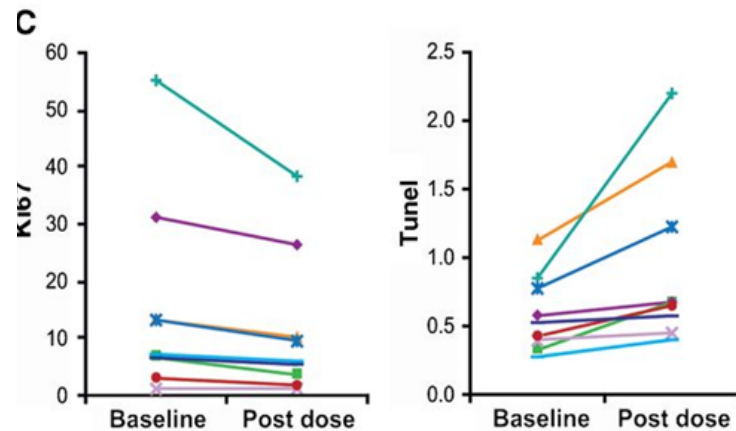
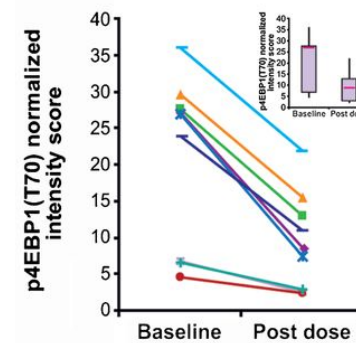
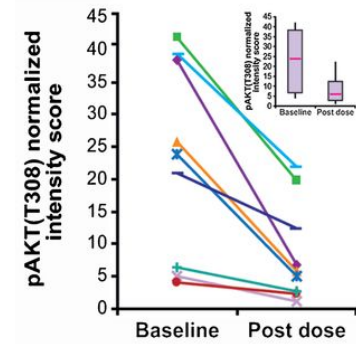
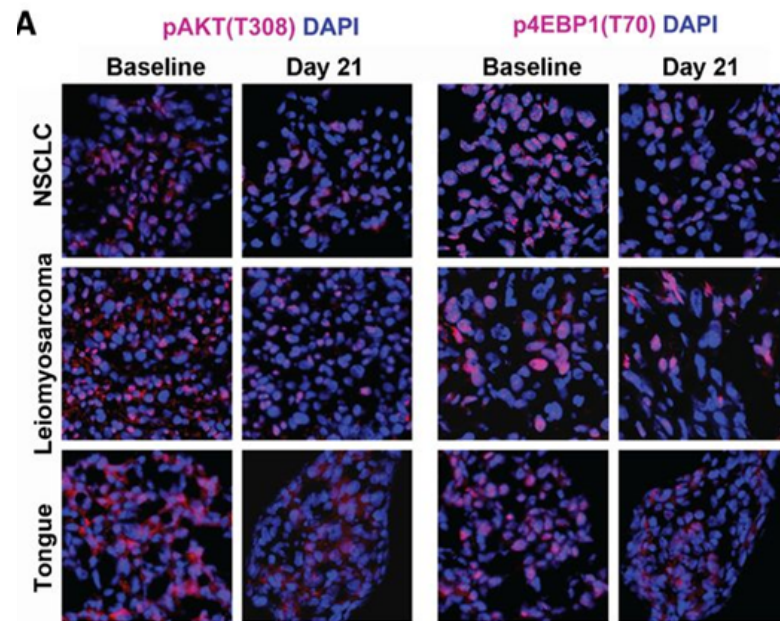
- **Phase 1 open label dose escalation study using capsule formulation, with std 3+3 escalation in two cohorts:**
  - **Continuous daily dosing**
  - **1<sup>st</sup> 21 out of 28 days**
- **68 patients were treated**
  - **In the 21/7 cohort, 1 gr 3 rash at 600 mg, 2 gr 3 rash at 900 mg, defining 600 mg as the MTD**
  - **With CDD, one potential DLT of gr 3 hypersensitivity at 600 mg, leading to 600 mg as selected dose**
  - **Best response was 44% SD; 8 lasted > 6 mos**

# Reduction of PI3K Signaling by SAR245408 in Serial Hair Cells and Skin Biopsies





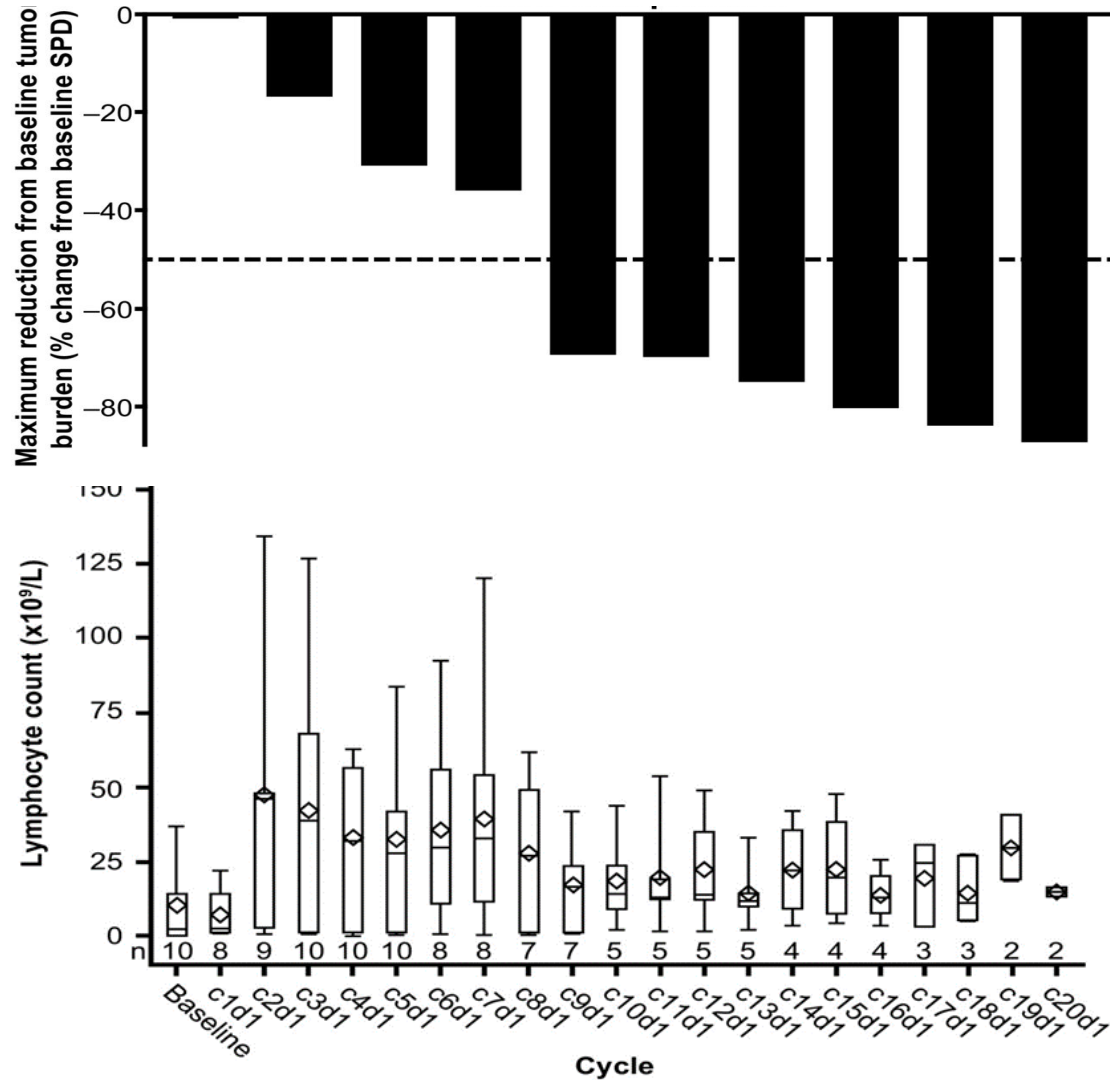
# Reduction in PI3K Signaling by SAR245408 in Paired Tumor Biopsies



# Phase 1b Study in CLL / Lymphoma

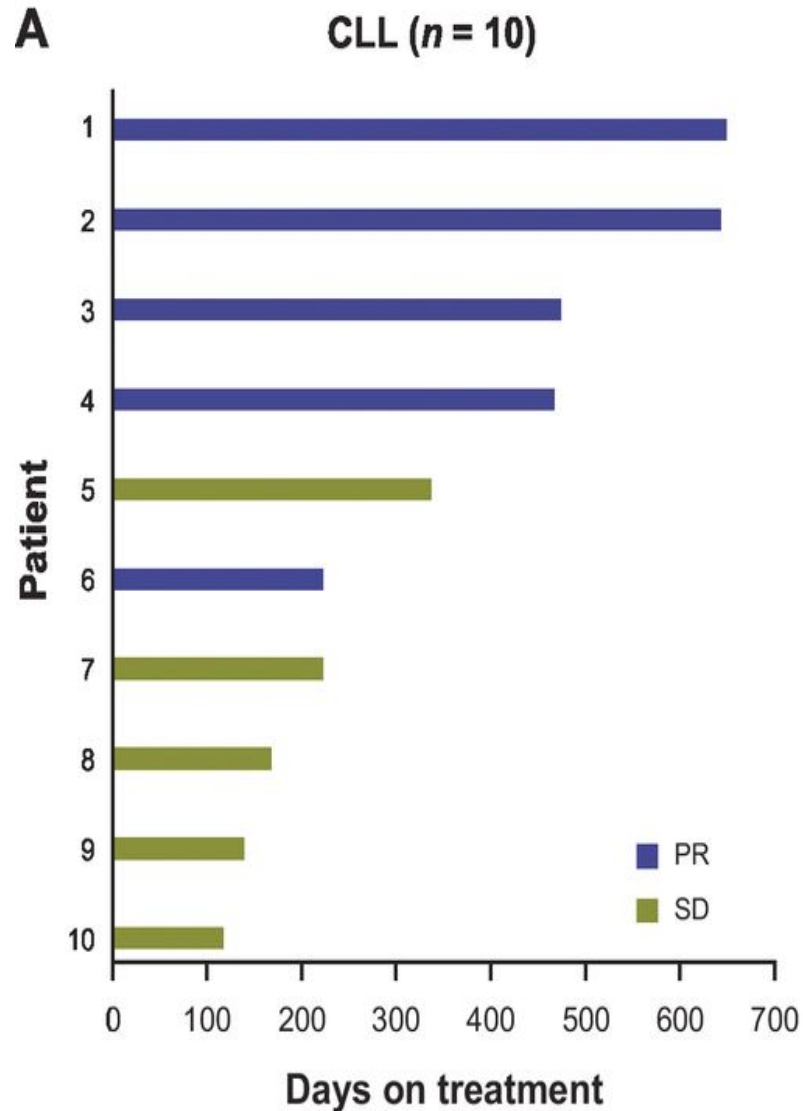
- **Pilaralisib (SAR245408, XL147) at its solid tumor MTD 600 mg daily**
- **N=25: 10 CLL, 15 relapsed/refractory lymphoma**
  - **Median age 66**
  - **Refractory: 40% CLL, 47% lymphoma**
  - **CLL: 80% bulky**
  - **2 with 17p deln, 5 with 11q deln**

# Effect of Pilaralisib 600 mg Once Daily on Nodes and Lymphocyte Counts in Patients with CLL



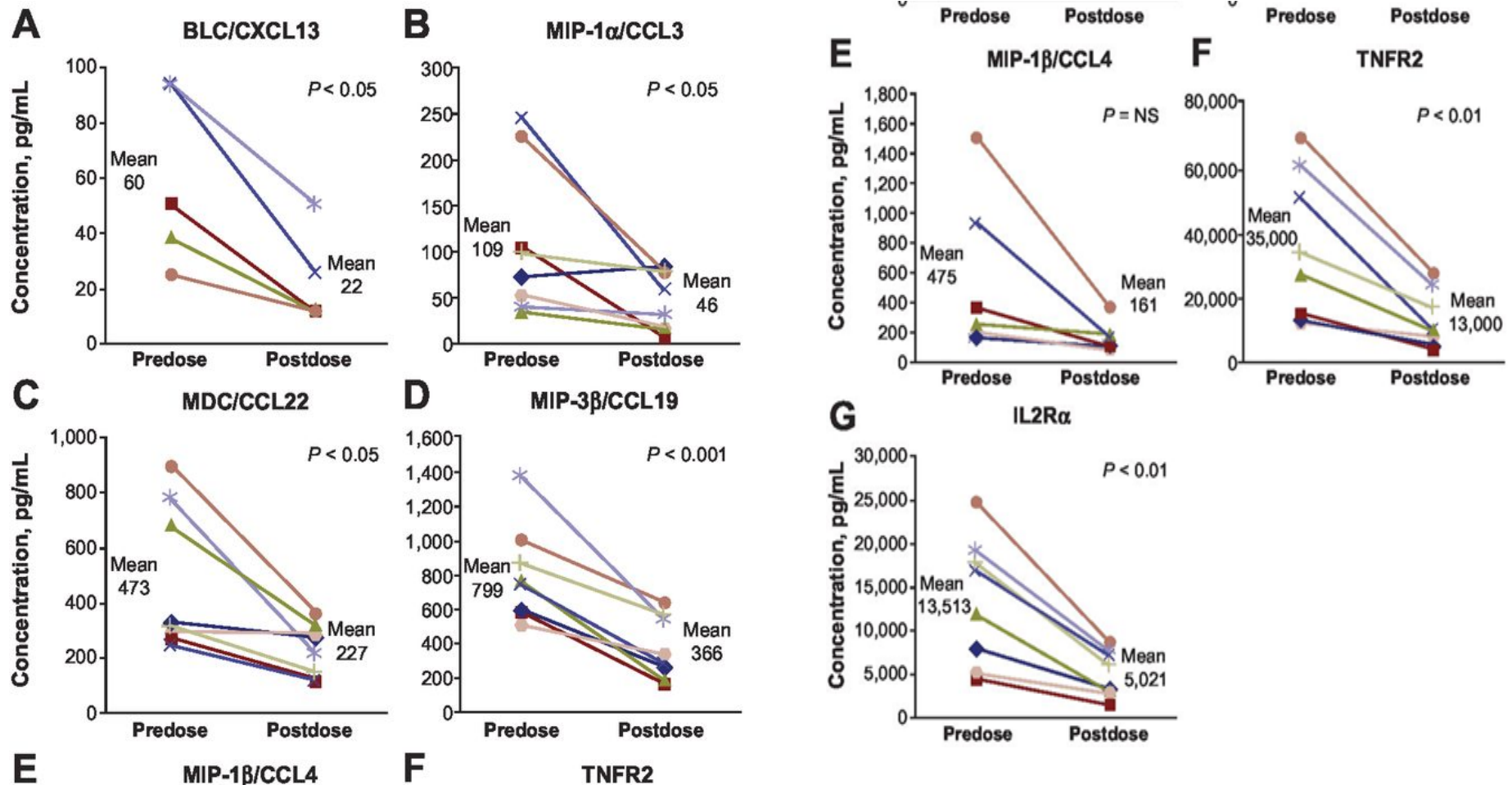
Jennifer R. Brown et al.  
 Clin Cancer Res 2015;  
 21:3160-3169

# Pilaralisib (SAR245408): CLL Efficacy



| Prior regimens, n | PFS, months       | Decrease in lymphadenopathy ≥50% | Lymphocytosis <sup>a</sup> | Prognostic markers                   | Additional therapy duration in extension trial, months <sup>b</sup> |
|-------------------|-------------------|----------------------------------|----------------------------|--------------------------------------|---|
| 1                 | 22.0 <sup>c</sup> | Y                                | Y                          | DEL13Q                               | -   |
| 1                 | 21.2 <sup>d</sup> | Y                                | Y                          | DEL6Q                                | Y (5.1)   |
| 7                 | 15.6 <sup>d</sup> | Y                                | Y                          | DEL11Q                               | Y (12.7)  |
| 1                 | 15.4 <sup>d</sup> | Y                                | Y                          | DEL17P                               | Y (12.0)  |
| 3                 | 12.5 <sup>c</sup> | N                                | N                          | DEL11Q, DEL13Q                       | -   |
| 1                 | 7.4               | Y                                | N                          | DEL11Q, DEL13Q, DEL17P, DEL3P, DEL3Q | -   |
| 1                 | 9.2 <sup>c</sup>  | Y                                | Y                          | DEL13Q                               | -   |
| 1                 | 5.6               | N                                | N                          | DEL11Q, DEL13Q                       | -   |
| 5                 | 4.6               | N                                | N                          | DEL11Q, DEL13Q                       | -   |
| 4                 | 3.6               | N                                | N                          | INV9                                 | -   |

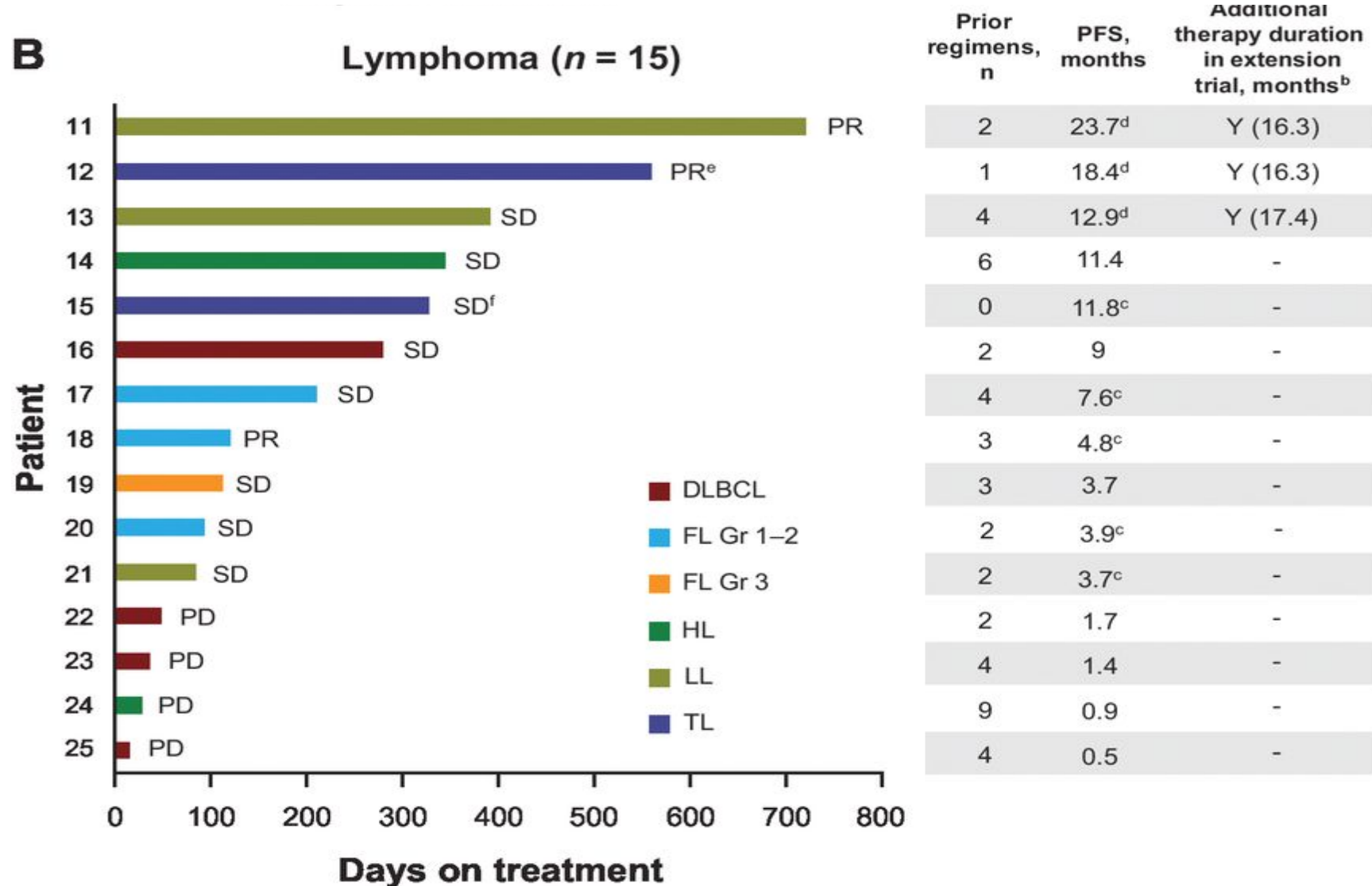
# Effect of Pilaralisib on Chemokines Involved in B-Cell Trafficking and Cytokine Receptors in Patients with CLL



# Pilaralisib (SAR245408): Lymphoma Efficacy

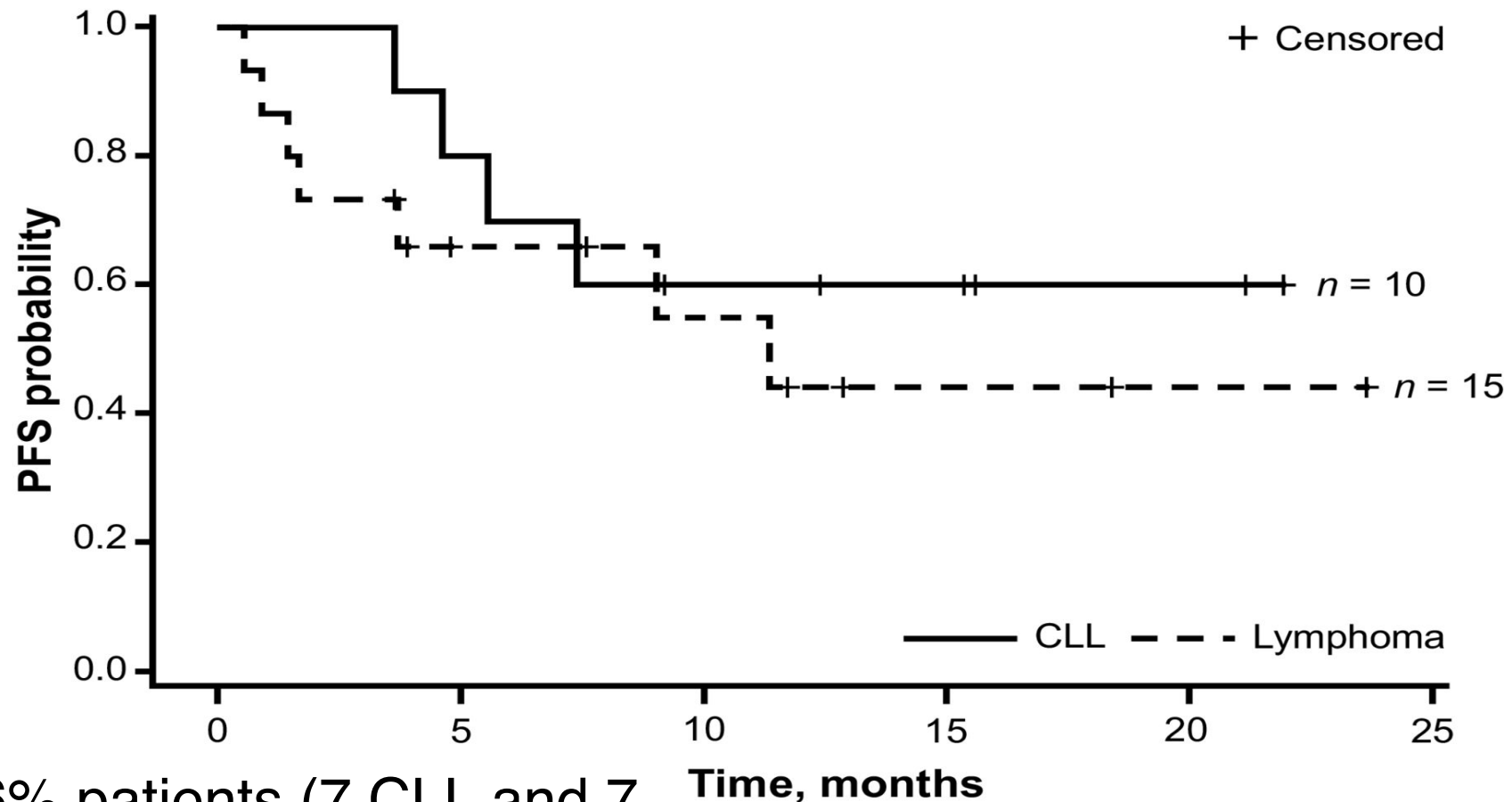
**B**

Lymphoma (n = 15)



| Prior regimens, n | PFS, months       | Additional therapy duration in extension trial, months <sup>b</sup> |
|-------------------|-------------------|---|
| 2                 | 23.7 <sup>d</sup> | Y (16.3)  |
| 1                 | 18.4 <sup>d</sup> | Y (16.3)  |
| 4                 | 12.9 <sup>d</sup> | Y (17.4)  |
| 6                 | 11.4              | -   |
| 0                 | 11.8 <sup>c</sup> | -   |
| 2                 | 9                 | -   |
| 4                 | 7.6 <sup>c</sup>  | -   |
| 3                 | 4.8 <sup>c</sup>  | -   |
| 3                 | 3.7               | -   |
| 2                 | 3.9 <sup>c</sup>  | -   |
| 2                 | 3.7 <sup>c</sup>  | -   |
| 2                 | 1.7               | -   |
| 4                 | 1.4               | -   |
| 9                 | 0.9               | -   |
| 4                 | 0.5               | -   |

# Pilaralisib: PFS for CLL vs Lymphoma



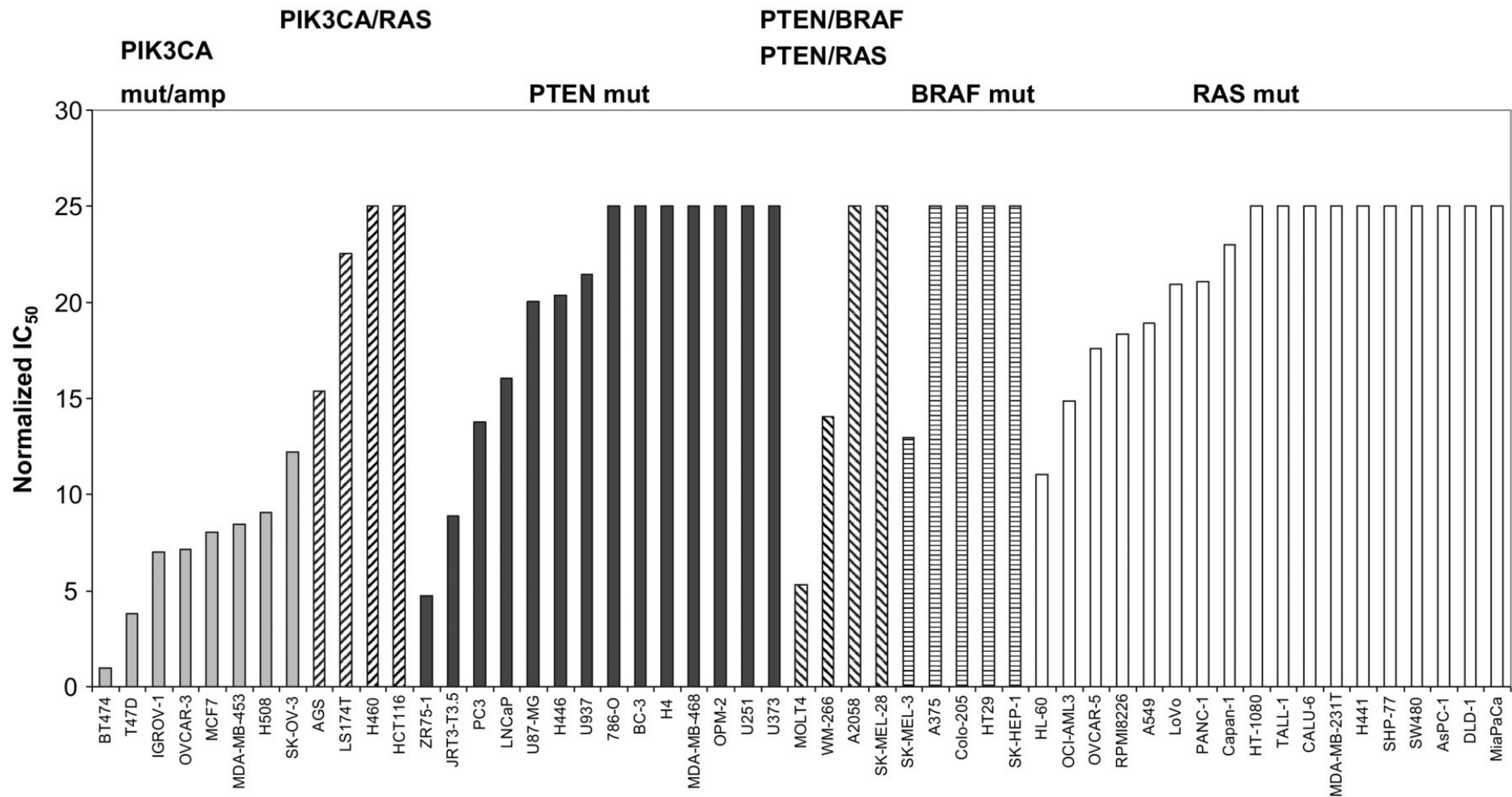
56% patients (7 CLL and 7 lymphoma) had PFS  $\geq$  6 months; 32% > 12 mos

# Adverse Events in CLL / Lymphoma

| Preferred term   | CLL (n = 10) | Lymphoma (n=15) | Total (N = 25) |
|--|--------------|-----------------|----------------|
| <b>All-grade AEs, regardless of causality, n (%)</b>                 |              |                 |                |
| Patients with any AE   | 10 (100)     | 15 (100)        | 25 (100)       |
| Diarrhea   | 8 (80.0)     | 15 (100)        | 23 (92.0)      |
| Pyrexia  | 6 (60.0)     | 7 (46.7)        | 13 (52.0)      |
| Fatigue  | 4 (40.0)     | 7 (46.7)        | 11 (44.0)      |
| Anemia   | 3 (30.0)     | 7 (46.7)        | 10 (40.0)      |
| Cough  | 3 (30.0)     | 7 (46.7)        | 10 (40.0)      |
| Nausea   | 4 (40.0)     | 6 (40.0)        | 10 (40.0)      |
| Back pain  | 3 (30.0)     | 5 (33.3)        | 8 (32.0)       |
| Dyspnea  | 3 (30.0)     | 5 (33.3)        | 8 (32.0)       |
| Neutropenia  | 5 (50.0)     | 3 (20.0)        | 8 (32.0)       |
| Rash   | 2 (20.0)     | 6 (40.0)        | 8 (32.0)       |
| Upper respiratory tract Infection                                    | 6 (60.0)     | 2 (13.3)        | 8 (32.0)       |
| Hyperglycemia  | 4 (40.0)     | 3 (20.0)        | 7 (28.0)       |
| Vomiting   | 2 (20.0)     | 5 (33.3)        | 7 (28.0)       |
| <b>Grade <math>\geq</math> 3 AEs, regardless of causality, n (%)</b> |              |                 |                |
| Patients with any grade $\geq$ 3 AE                                  | 10 (100)     | 12 (80.0)       | 22 (88.0)      |
| Neutropenia  | 5 (50.0)     | 3 (20.0)        | 8 (32.0)       |
| Diarrhea   | 3 (30.0)     | 2 (13.3)        | 5 (20.0)       |
| Hypotension  | 2 (20.0)     | 1 (6.7)         | 3 (12.0)       |



# Response of Cell Lines by PI3K Pathway Mutation



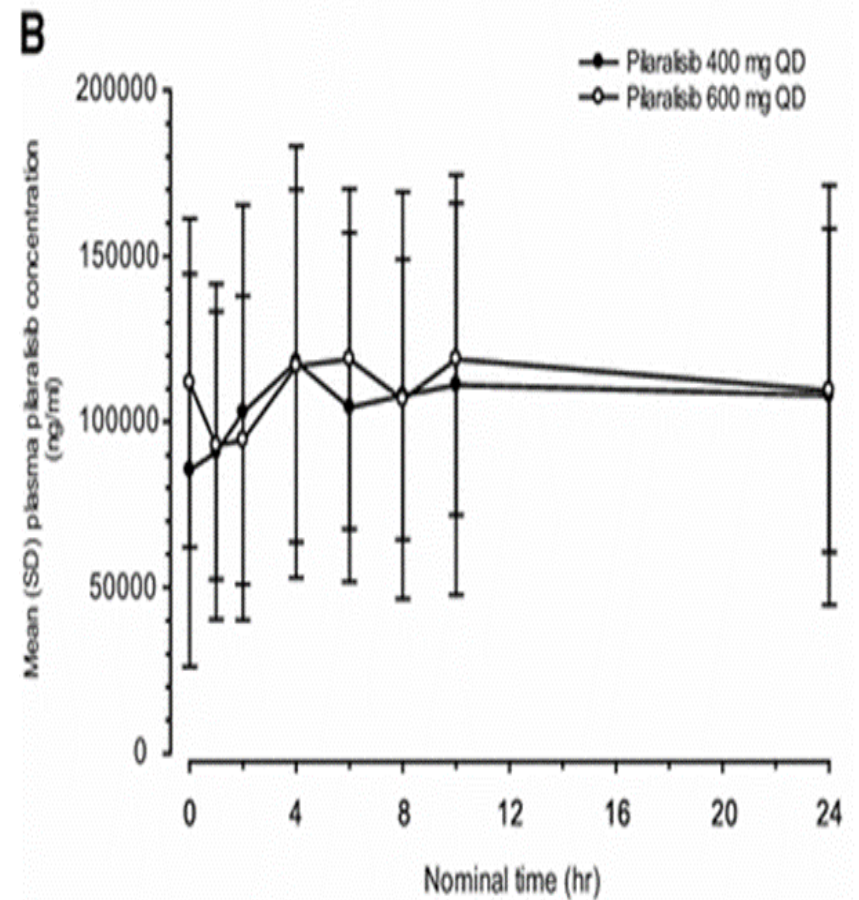
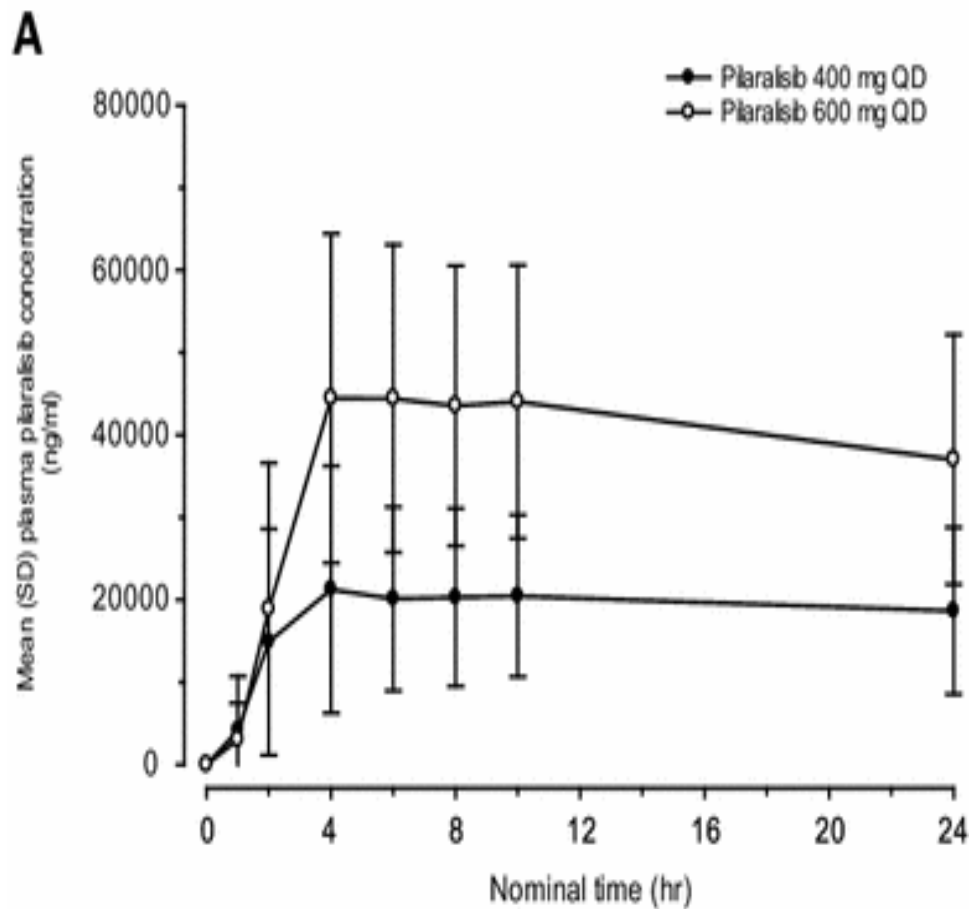
# Mutations by Patient: CLL, NHL

| Disease type | Patient (see Fig. 3) | Gene          | Functional impact | Protein change | Codon change   | PFS, months | Best overall response |
|--------------|----------------------|---------------|-------------------|----------------|----------------|-------------|-----------------------|
| CLL          | 1                    | <i>SF3B1</i>  | known             | K700E          | 2098A>G        | 22          | PR                    |
|              |                      | <i>MTOR</i>   | known             | V2006L         | 6016G>C        |             |                       |
|              |                      | <i>SYK</i>    | likely            | R434Q          | 1301G>A        |             |                       |
| CLL          | 2                    | <i>NFATC1</i> | known             | G446R          | 1336G>C        | 21.2        | PR                    |
|              |                      | <i>POT1</i>   | known             | Y324S          | 971A>C         |             |                       |
|              |                      | <i>DIRAS3</i> | known             | R103H          | 308G>A         |             |                       |
|              |                      | <i>BIRC3</i>  | known             | EE430fs        | 1290_1291insCA |             |                       |
|              |                      | <i>MAX</i>    | known             | T59K           | 176C>A         |             |                       |
|              |                      | <i>NCOR1</i>  | likely            | QK684fs        | 2052_2053delGA |             |                       |
|              |                      | <i>AKAP9</i>  | unknown           | K1052E         | 3154A>G        |             |                       |
| CLL          | 3                    | <i>CAMTA1</i> | unknown           | G1175R         | 3523G>A        | 15.6        | PR                    |
| CLL          | 9                    | <i>DDX3X</i>  | known             | K342Splice     | 1026Splice     | 4.6         | SD                    |
|              |                      | <i>SF3B1</i>  | known             | N626H          | 1876A>C        |             |                       |
| DLBCL        | 16                   | <i>MLL2</i>   | likely            | A221fs*40      | 657_657delC    | 9           | SD                    |
|              |                      | <i>ARID1A</i> | likely            | P1175fs*5      | 3524_3524delC  |             |                       |
|              |                      | <i>CREBBP</i> | likely            | P1947fs*19     | 5830_5831insG  |             |                       |
|              |                      | <i>EZH2</i>   | known             | Y646H          | 1936T>C        |             |                       |
|              |                      | <i>PIK3R1</i> | known             | N564D          | 1690A>G        |             |                       |
|              |                      | <i>PTCH1</i>  | unknown           | V1100A         | 3299T>C        |             |                       |
|              |                      | <i>RAD50</i>  | likely            | V683fs*11      | 2046_2047insC  |             |                       |
|              |                      | <i>TET2</i>   | known             | R1516*         | 4546C>T        |             |                       |
|              |                      | <i>TP53</i>   | known             | Y236C          | 707A>G         |             |                       |
|              |                      | <i>TP53</i>   | known             | Y234C          | 701A>G         |             |                       |
| FL           | 17                   | <i>CREBBP</i> | likely            | R1173*         | 3517C>T        | 7.6         | SD                    |
|              |                      | <i>MLL2</i>   | likely            | S3378*         | 10133C>G       |             |                       |
|              |                      | <i>MLL2</i>   | likely            | A1390fs*42     | 4162_4163insC  |             |                       |

# Mutations by Patient: Lymphoma

|       |    |                               |         |               |                  |      |    |
|-------|----|-------------------------------|---------|---------------|------------------|------|----|
| FL    | 18 | <i>ARID1A</i>                 | likely  | Q1579*        | 4735C>T          | 4.8  | PR |
|       |    | <i>CREBBP</i>                 | known   | S1679del      | 5034_5036delGAG  |      |    |
|       |    | <i>MED12</i>                  | known   | G44S          | 130G>A           |      |    |
|       |    | <i>MEF2B</i>                  | known   | E77K          | 229G>A           |      |    |
| FL    | 20 | <i>MLL2</i>                   | likely  | E5458fs*4     | 16370_16371insCA | 3.9  | SD |
|       |    | <i>MLL2</i>                   | likely  | A1390fs*42    | 4162_4163insC    |      |    |
|       |    | <i>REL</i>                    | known   | Amplification | -                |      |    |
|       |    | <i>TP53</i>                   | known   | C176F         | 527G>T           |      |    |
| DLBCL | 22 | <i>No alteration detected</i> |         |               |                  | 1.7  | PD |
| DLBCL | 23 | <i>CD79B</i>                  | known   | Y196D         | 586T>G           | 1.4  | PD |
|       |    | <i>MYD88</i>                  | known   | L265P         | 794T>C           |      |    |
|       |    | <i>RAD50</i>                  | unknown | R1256C        | 3766C>T          |      |    |
| HL    | 24 | <i>CDKN2A</i>                 | known   | A68T          | 202G>A           | 11.4 | SD |

# Reformulation Attempt to Increase Exposure?



# Summary: Pilaralisib

- **Pan-PI3K inhibitor, less potent with exposure plateau**
- **50% PR in CLL, 20% PR in lymphoma albeit with some durable remissions**
- **Insufficient representation of PI3K pathway mutations to associate with response**

