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# First-in-human results of STX-478, a mutant-selective PI3Kα inhibitor, in advanced solid tumor patients

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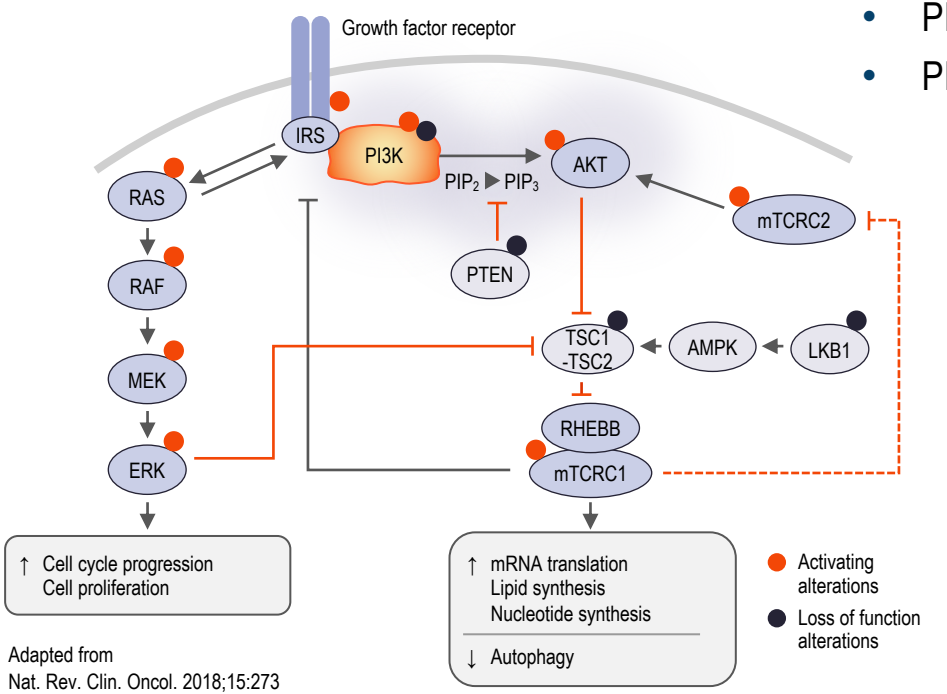
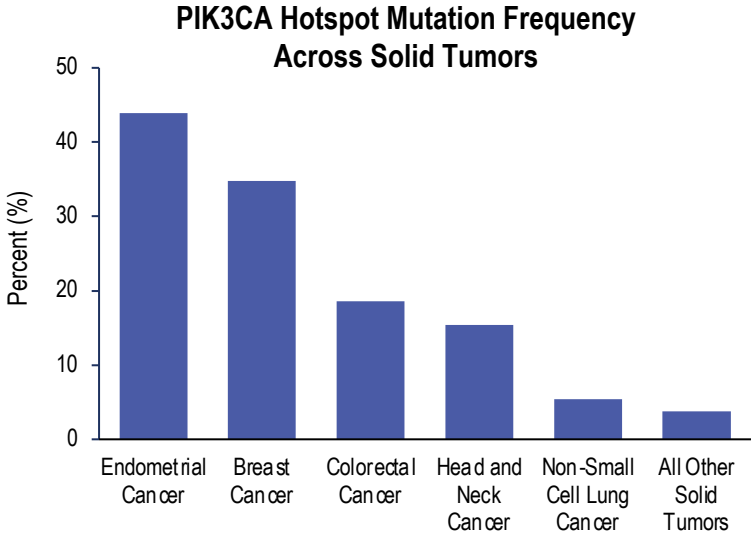
# The PI3K Pathway is Commonly Mutated in Cancer




Adapted from
Nat. Rev. Clin. Oncol. 2018;15:273

- PI3K pathway alterations are a major driver in cancer
- PI3Kα is mutated in 12.7% of all cancers[1]




[1]GENIE Cohort v16.0-public



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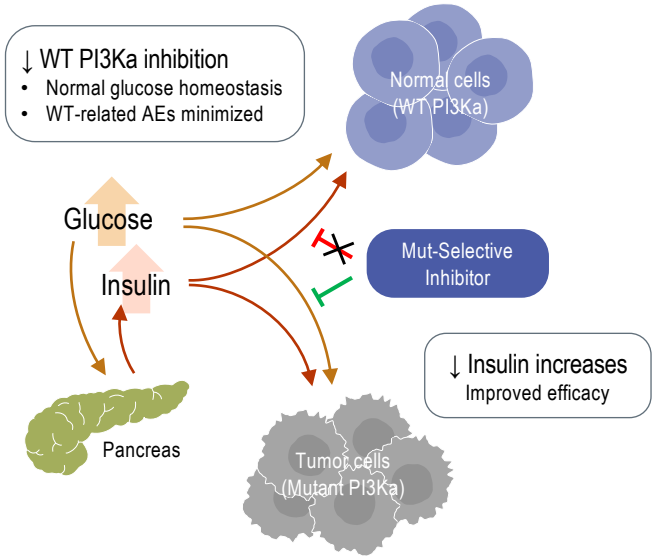
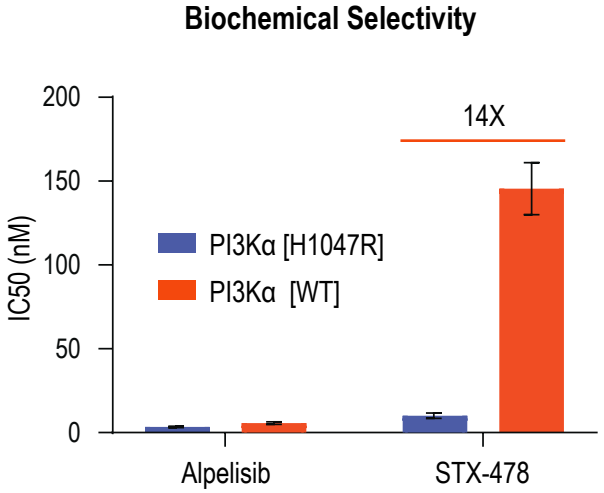
# STX-478 is an Oral, Allosteric, Mutant Selective PI3Kα Inhibitor




- STX-478 is an allosteric, mutant-selective inhibitor that selectively targets mutant PI3Kα and minimizes wildtype toxicities
- STX-478 is an oral, once-daily, low dose, CNS-penetrant molecule

WT: wildtype



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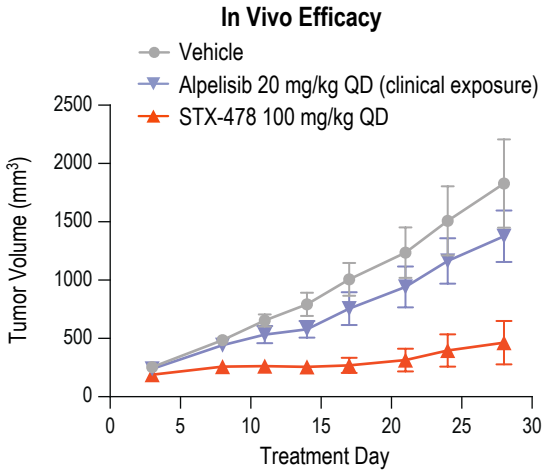
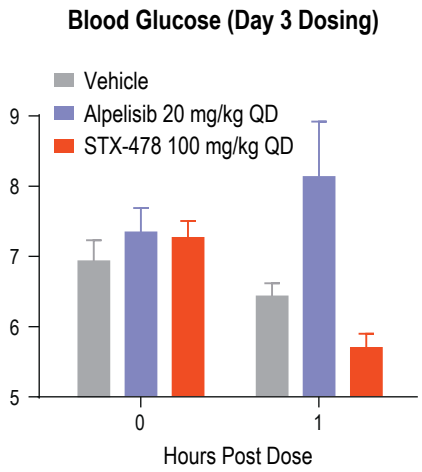
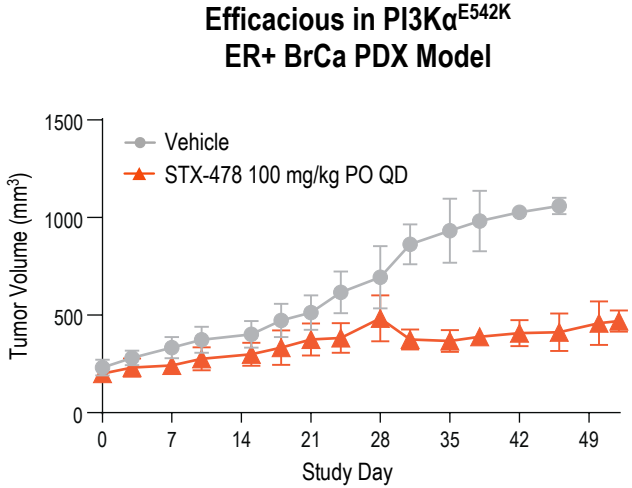
# STX-478 is Metabolically Safe and Efficacious in PI3Kα Kinase and Helical Domain Mutant Tumors

**Improved Efficacy & Selectivity vs Clinically-Relevant Dose of Alpelisib in PI3Kα$^{H1047R}$ Cal33 HNSCC CDX**




STX-478 demonstrated in vivo efficacy and safety in preclinical models superior to clinically-relevant doses of alpelisib, a non-mutant selective PI3Kα inhibitor

[1] Buckbinder, St. Jean, et al., 2023, BrCA: breast cancer, HNSCC: head and neck squamous cell carcinoma



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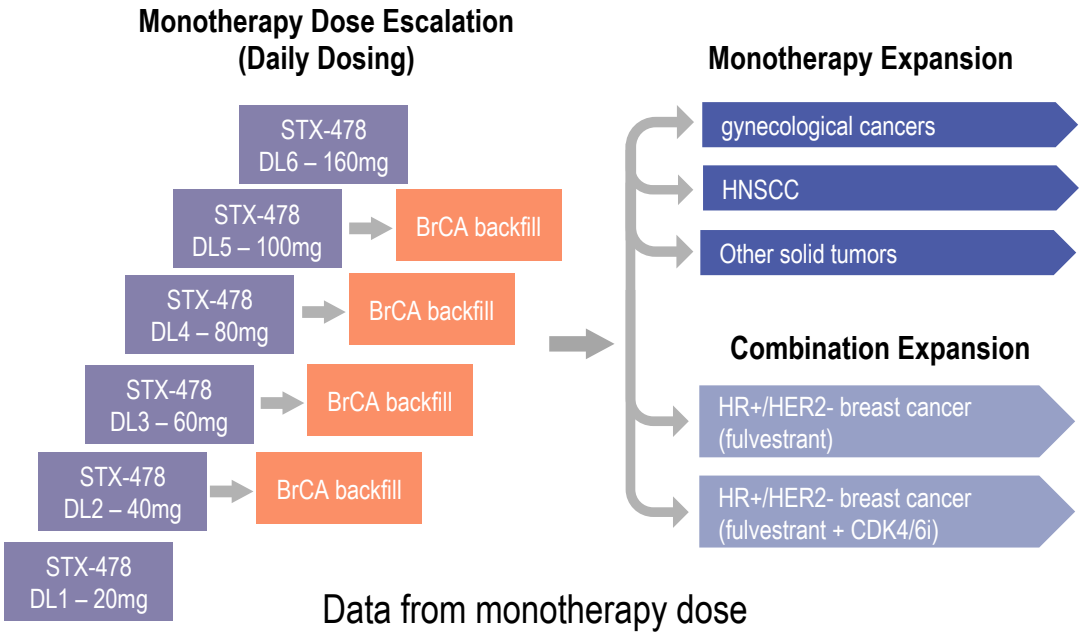
# First-in-Human Phase 1 Trial Design of STX-478 in Advanced Solid Tumors




Data from monotherapy dose escalation and initial monotherapy expansion are presented

**Key Eligibility Criteria**

- PIK3CA helical and kinase domain mutant advanced solid tumors who received prior SOC[1]
- ECOG 0-1
- Adequate organ function
- Fasting plasma glucose < 140 mg/dL and HbA1c < 7.0%
- Type 2 diabetics controlled on medications permitted
- Prior PI3K/AKT/mTOR inhibitor therapy permitted if stopped due to intolerance

**Key Endpoints**

- Safety and tolerability
- PK, PD, RP2D
- Anti-tumor activity assessed by ORR by RECIST v1.1, DOR, PFS, OS
- Patient reported outcomes via EORTC QLQ-C30 score

Data as of 21 June 2024

BrCA: breast cancer, DL: dose level, DOR: duration of response, HNSCC: head and neck squamous cell carcinoma, HR: hormone receptor, ORR: objective response rate, OS: overall survival, PD: pharmacodynamics, PFS: progression-free survival, PK: pharmacokinetics, RP2D: recommended Phase 2 dose, SOC: standard of care, [1]monotherapy cohorts



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# Patient Demographics and Baseline Characteristics

| | All Tumors[1] (n=61) | HR+/HER2-Breast Cancer (n=29) | Other Solid Tumors (n=32) |
|---|---|---|---|
| Age, median (range), yr | 64 (32–82) | 64 (37 – 81) | 65 (32 – 82) |
| Female, n (%) | 50 (82) | 29 (100) | 21 (66) |
| Male, n (%) | 11 (18) | 0 (0) | 11 (34) |
| ECOG, n (%) | | | |
| 0 | 25 (41) | 13 (45) | 12 (38) |
| 1 | 36 (59) | 16 (55) | 20 (63) |
| Glucose metabolism, n (%) | | | |
| Pre-diabetic | 23 (38) | 11 (38) | 12 (38) |
| Type 2 Diabetic | 10 (16) | 4 (14) | 6 (19) |
| PI3Kα-mutation, n (%) | | | |
| Kinase domain | 33 (54) | 17 (59) | 16 (50) |
| Helical domain | 22 (36) | 8 (28) | 14 (44) |
| Double mutant | 5 (8) | 3 (10) | 2 (6) |
| Not available | 1 (2) | 1 (3) | 0 (0) |
| Visceral disease (%) | 46 (75) | 25 (86) | 21 (66) |
| Median prior metastatic therapies (range) | 3 (1 – 7) | 3 (1 – 7) | 4 (1 – 7) |
| Prior CDK inhibitor, n (%) | 28 (46) | 28 (97) | 0 (0) |
| Prior PI3Kα- or mTOR or AKT-inhibitor, n (%) | 13 (21) | 12 (41) | 1 (3) |

- Most common solid tumors enrolled include breast cancer (54%), endometrial cancer (11%), urothelial cancer (8%), HNSCC (5%), and CRC (5%)
- 54% of patients are prediabetic or have Type 2 diabetes, typically excluded from other PI3K inhibitor trials
- Patients are heavily pre-treated, including 41% of HR+/HER2- breast cancer patients receiving prior PI3K pathway inhibitors

[1] Data as of 21 June 2024, [2]definition based on HbA1c/fasting glucose levels, medical history and diabetic medication use
CRC: colorectal cancer, HR: hormone receptor, HNSCC: head and neck squamous cell



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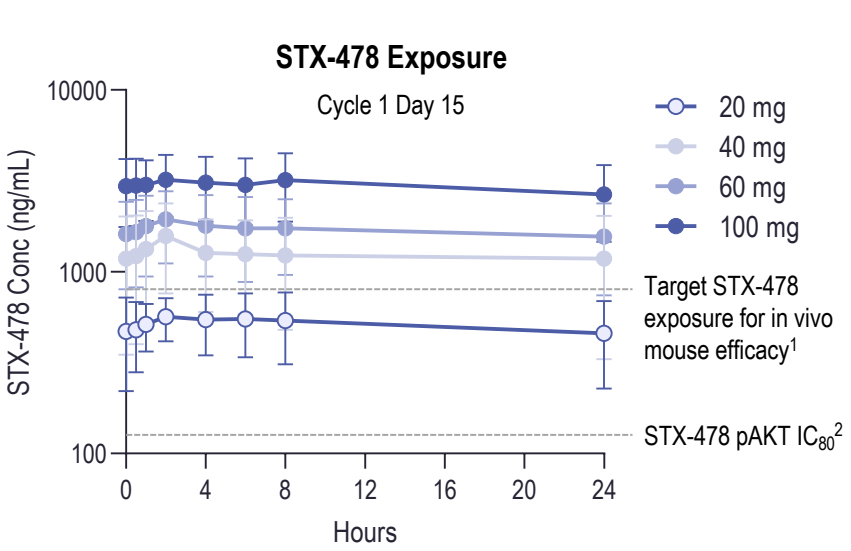
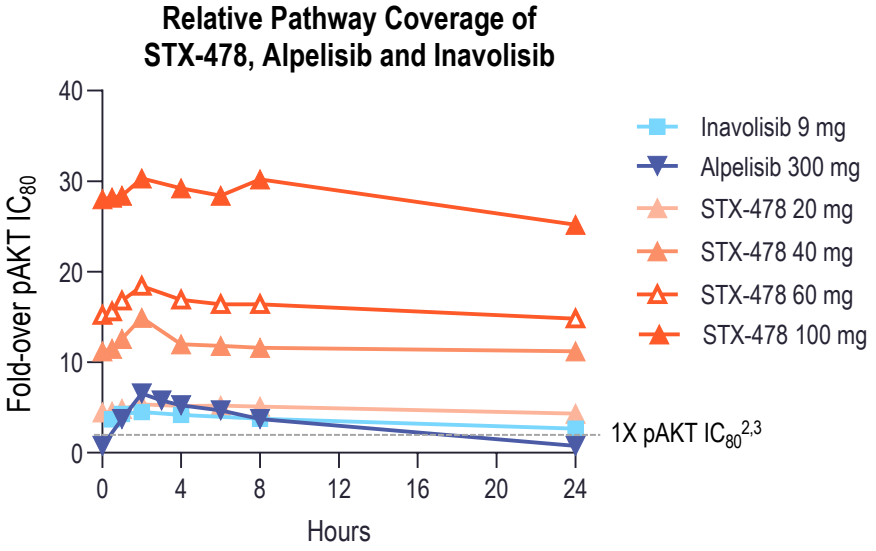
# STX-478 Pharmacokinetic and Target Coverage Profile




- STX-478 exposure is dose proportional and linear, with an estimated half-life of around 60 hours
- At doses ≥ 40mg QD, STX-478 exceeded the average exposures needed for mouse in vivo efficacy
- STX-478 achieved target coverage significantly higher than other PI3K inhibitors at their RP2D

[1] Based on mouse efficacious exposure 100mg/kg in 3 CDX models
[2] Based on in vitro T47D (H1047R) cell pAkt assay
[3] Matched unbound pAkt suppression in head-to-head benchmarked T47D in vitro assays



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# Summary of STX-478 Safety

**Treatment-Related AEs (TRAEs), N=61 Patients**

| Adverse Event[1] | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Any Grade |
|---|---|---|---|---|---|
| **TRAEs occurring in ≥ 15%, n (%)** | | | | | |
| Fatigue | 5 (8) | 8 (13) | 5 (8) | 0 | 18 (30) |
| Hyperglycemia | 8 (13) | 6 (10) | 0 | 0 | 14 (23) |
| Nausea | 11 (18) | 1 (2) | 0 | 0 | 12 (20) |
| Diarrhea | 6 (10) | 3 (5) | 0 | 0 | 9 (15) |
| **Other TRAEs of Interest, n (%)** | | | | | |
| Rash[2] | 5 (8) | 1 (2) | 0 | 0 | 6 (10) |
| AST/ALT increased[3] | 2 (3) | 0 | 5 (8)[4] | 1 (2)[4] | 8 (13) |
| Blood bilirubin increased | 1 (2) | 0 | 0 | 0 | 1 (2) |
| Neutropenia[5] | 0 | 0 | 0 | 0 | 0 |
| Anemia | 1 (2) | 0 | 0 | 0 | 1 (2) |
| Thrombocytopenia[6] | 1 (2) | 1 (2) | 0 | 0 | 2 (3) |
| Creatinine increase | 0 | 0 | 0 | 0 | 0 |
| **AEs leading to discontinuation** | **0** | **0** | **0** | **0** | **0** |

- STX-478 was well-tolerated with most toxicities mild/moderate and transient
- No Grade ≥ 3 PI3Kα wildtype toxicities (hyperglycemia, diarrhea and rash) seen
- MTD was reached at 100mg
  - 2 DLTs (Grade 3 myalgia and paresthesia) observed at 160mg and were transient, resolving rapidly after brief dose interruption
- AST/ALT elevations were asymptomatic, transient and reversible, with no Hy's Law criteria met
- No patient discontinued STX-478 due to an AE

No Grade 5 TRAEs were observed

[1]Per CTCAE v5.0, [2]includes all rash-related terms, [3]includes patients with either AST or ALT elevation, [4]one each occurred at 160mg dose, which exceeded the MTD of 100mg, [5]includes neutropenia and neutrophil count decreased, [6]includes thrombocytopenia and platelet count decreased



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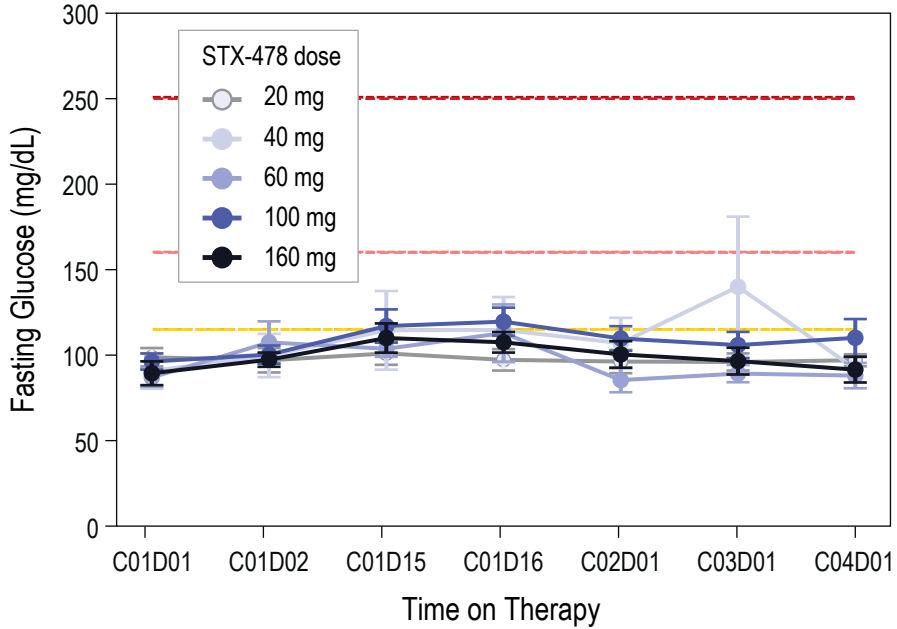
# Impact of STX-478 on Fasting Glucose Levels




**Alpelisib label management**

Grade 3 (250-500 mg/dL)

Grade 2 (160-250 mg/dL)

Grade 1 (115-160 mg/dL)

Mean and standard error is shown

- Minimal changes in fasting glucose have been observed at all STX-478 dose levels
- No CTCAE v5.0 Grade 3 or higher hyperglycemia has been observed at any dose level



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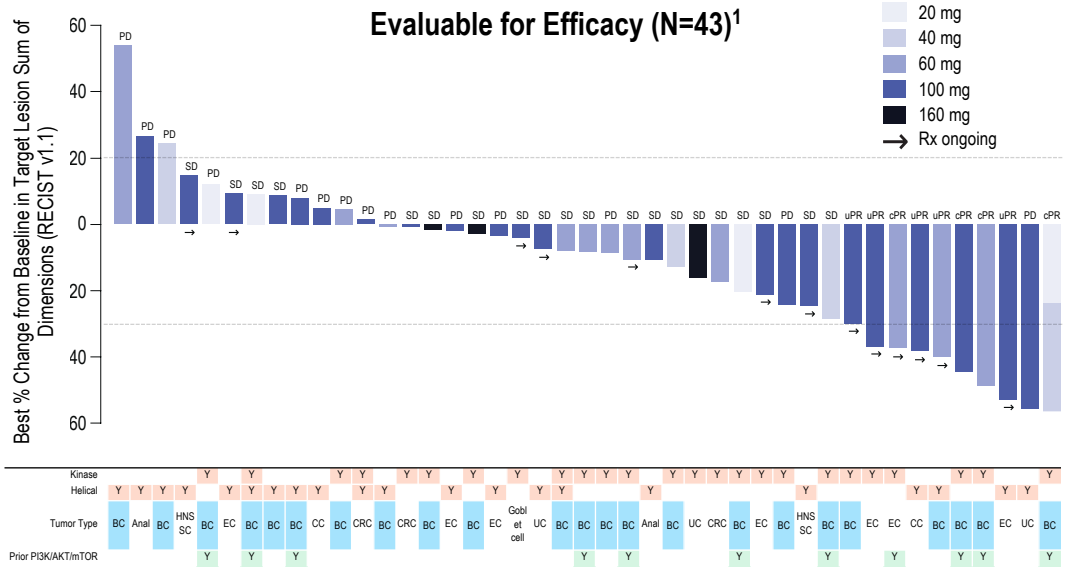
# STX-478 Anti-Tumor Activity

| Best overall response N (%) | All Tumors (n=43) | HR+/HER2- breast (n=22) | Gynecologic tumors (n=9) |
|---|---|---|---|
| **ORR[2] (cPR + uPR)** | **9 (21)** | **5 (23)** | **4 (44)** |
| DCR (CR+PR+SD) | 29 (67) | 15 (68) | 6 (67) |
| cPR | 4 (9) | 3 (14) | 1 (11) |
| uPR* | 5 (12) | 2 (9) | 3 (33) |
| SD | 20 (47) | 10 (46) | 2 (22) |
| PD | 14 (33) | 7 (32) | 3 (33) |

*All 5 patients with uPRs have converted to cPRs after the data cut




- STX-478 monotherapy ORR of 21 – 23% in all-comers and breast cancer, respectively, compares favorably to approved PI3K pathway inhibitors (monotherapy ORR 4 – 6%)[3,4]
- Multiple responses are seen in both PIK3CA kinase and helical domain mutations, in multiple solid tumors, at multiple STX-478 dose levels, and in patients receiving prior PI3K/AKT/mTOR inhibitors

[1] Efficacy evaluable and measurable disease patients shown, [2]includes unconfirmed and confirmed PRs, [3]Banerji et al., 2018, [4]Juric et al., 2018. BC: breast cancer, CC: cervical cancer, cPR: confirmed partial response, CRC: colorectal cancer, DCR: disease control rate, EC: endometrial cancer, HNSCC: head and neck cancer, UC: urothelial cancer, uPR: unconfirmed partial response



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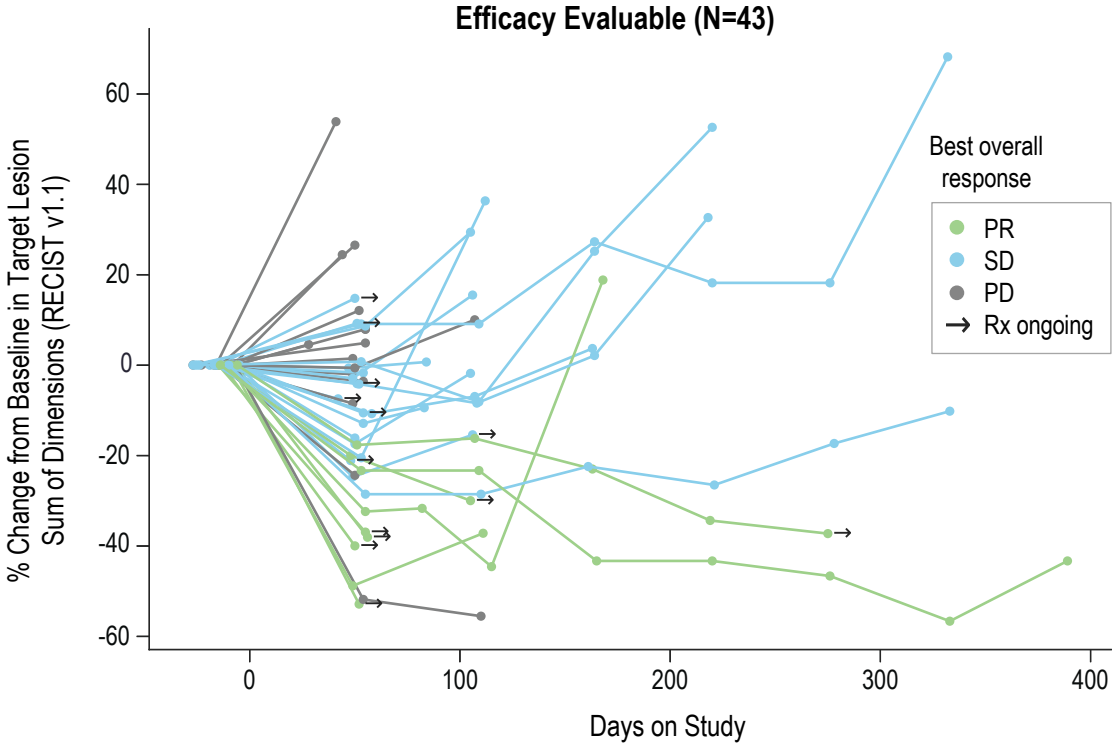
# STX-478 Duration of Treatment and Response




- Median duration of treatment for all enrolled patients is 1.9 months (range 0.03 – 13 months)
- Median time to response is 1.8 months (range 1.6 – 7.2)
- Multiple responding patients have deepened their responses over time on therapy
- Patient longest in PR has been on treatment >12 months

Median follow-up is 1.8 months (range 0.1 – 12.8 months)



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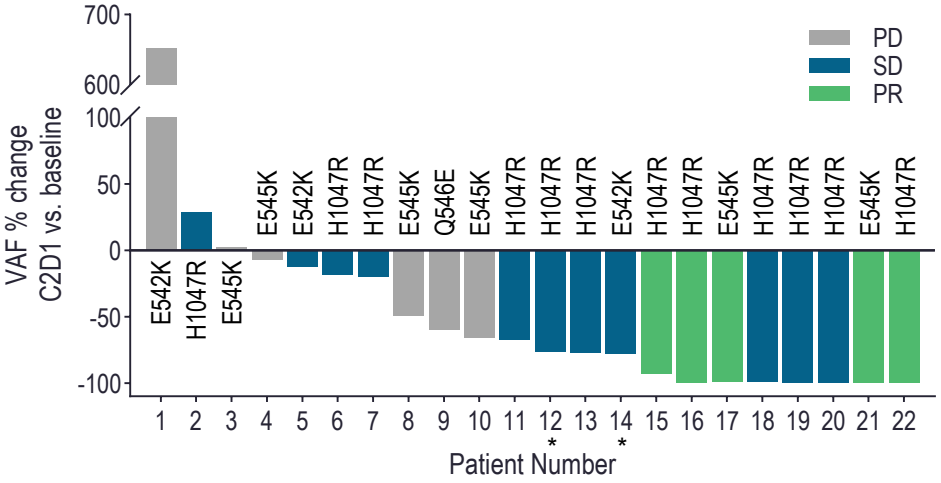
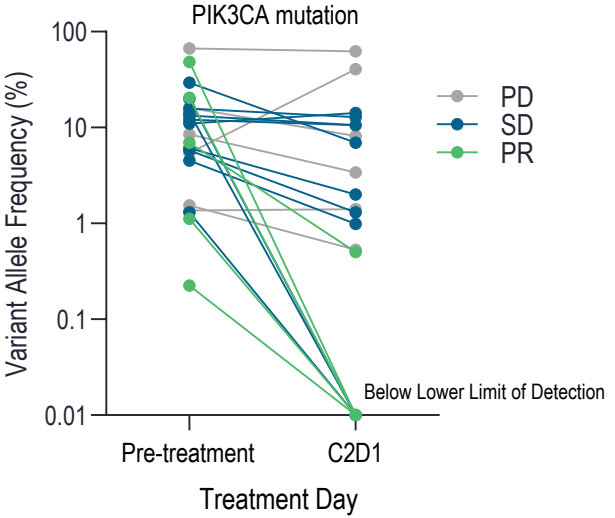
# PIK3CA Mutant Variant Allele Frequency and Correlation with Response

## 86% of Patients Assessed Have Decreases in PIK3CA ctDNA




## Depth of ctDNA Decrease Correlates with Clinical Response[1]




Patients with available longitudinal ctDNA are included. *Left: patients 12 and 14 have two PIK3CA mutations, only one represented

[1] Neogenomics Invision 37 gene liquid biopsy test (including PIK3CA) utilized

VAF: variant allele frequency



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# Case Report 1: Patient with PIK3CA Mutant Endometrial Cancer (Partial Response)

## Patient History

- 71 year-old woman
- Metastatic endometrial cancer (uterine papillary serous carcinoma) with PI3Kα$^{H1047R}$ kinase domain mutation

## Prior Metastatic Treatment

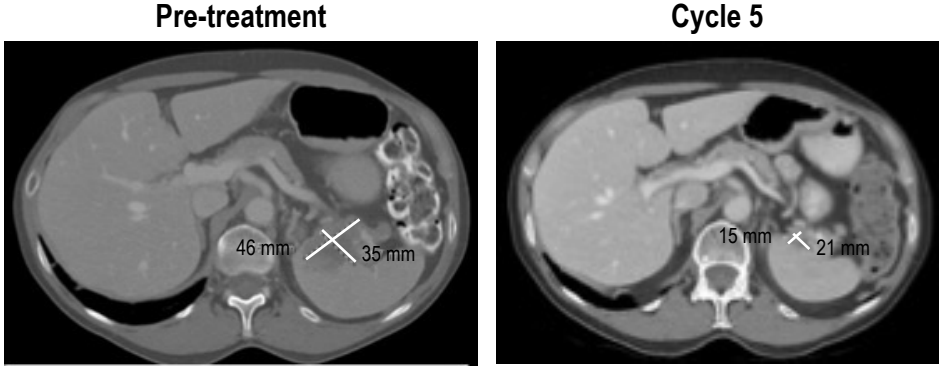
6 prior lines of therapy, refractory to last 3 prior lines

1. Carboplatin + paclitaxel
2. Liposomal doxorubicin
3. Gemcitabine + cisplatin
4. Docetaxel
5. Gemcitabine + cisplatin
6. CLN-418 (B7H4 x 4-1BB bi-specific)

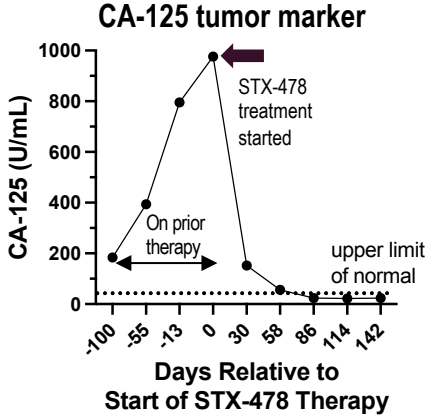
Best response: PD

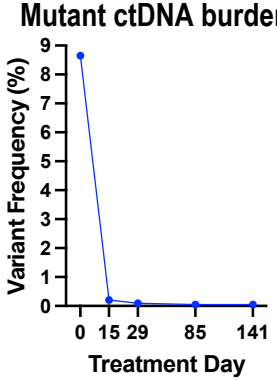
## STX-478 Treatment and Response

- Treated with STX-478 at 100mg PO QD
- 97% decline in CA-125 tumor marker
- 99.4% decline in mutant allele burden
- uPR (37% reduction) at Cycle 3
- cPR (54% reduction) at Cycle 5, occurring after the data-cutoff




Target lesion



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# Case Report 2: Significant Reduction in Tumor Lesions in a Patient with Head and Neck Squamous Cell Cancer

## Patient History

- 76 year-old male
- HPV+ metastatic HNSCC with PI3Kα$^{E545K}$ helical domain mutation
- Type 2 diabetes mellitus on metformin

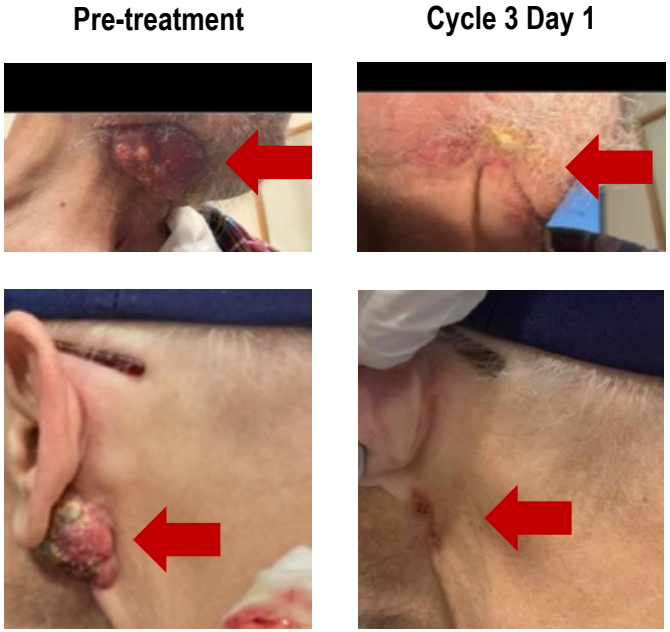
## Prior Treatment

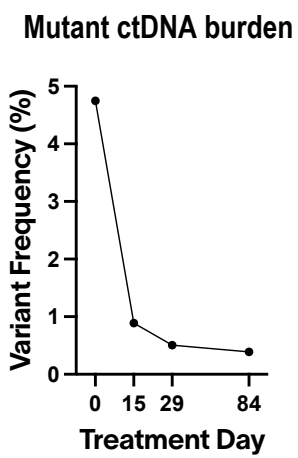
5 prior lines of therapy

1. Pembrolizumab (adjuvant)
2. Cetuximab (adjuvant)
3. Carboplatin + paclitaxel
4. SGN-B6A (integrin beta-6 ADC)
5. Carboplatin + gemcitabine

## STX-478 Treatment and Response

- Treated with STX-478 at 100mg PO QD
- Significant/rapid reduction of external lesions
- 92% decline in mutant allele burden
- 25% reduction (SD) in target lesions on Cycle 3 Day 1



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# Conclusions

- STX-478 is a potential best-in-class oral, allosteric mutant-selective PI3Kα inhibitor
- STX-478 is well-tolerated with limited PI3K wildtype toxicities in a high-risk patient population, including those with diabetes and/or intolerant to other PI3K inhibitors
- STX-478 dosing achieves target coverage several fold higher than other PI3Kα inhibitors
- STX-478 is active in breast cancer and other solid tumors, with a monotherapy ORR exceeding that of approved PI3K pathway inhibitors
- Efficacy is observed in patients with both PIK3CA kinase and helical domain mutations, with multiple responses deepening over time
- Enrollment is ongoing, including STX-478 combinations with fulvestrant +/- CDK4/6 inhibitors in patients with HR+/HER2- breast cancer



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