First-in-Human Results of STX-478, A Mutant-Selective PI3Kα Inhibitor, in HR+ Breast Cancer and Advanced Solid Tumor Patients

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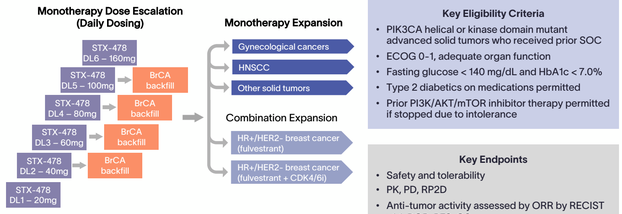
Background

- PI3Kα is mutated in over 30% of patients with breast cancer[1,2]
- Clinical benefit has been established with the approval of two PI3Kα inhibitors (alpelisib and inavolisib) in HR+/HER2- breast cancer
- However, non-mutant selective PI3Kα inhibitors cause significant wildtype toxicities, including hyperglycemia, rash, and diarrhea
- STX-478 is an allosteric, oral, CNS-penetrant, mutant-selective inhibitor that targets mutant PI3Kα and minimizes wildtype toxicities[3]

Methods

Figure 1. STX-478 Phase 1/2 study design



Data as of June 21st, 2024; monotherapy dose escalation/expansion are reported

Key Eligibility Criteria

- PIK3CA helical or kinase domain mutant advanced solid tumors who received prior SOC
- ECOG 0-1, adequate organ function
- Fasting glucose < 140 mg/dL and HbA1c < 7.0%
- Type 2 diabetics 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

Results

Table 1. Patient demographics

	All Tumors (n=61)	HR+/HER2-BC (n=29)
Age, median (range), yr	64 (32 – 82)	64 (37 – 81)
Female, n (%)	50 (82)	29 (100)
Male, n (%)	11 (18)	0 (0)
ECOG 0, n (%) ECOG 1	25 (41) 36 (59)	13 (45) 16 (55)
Pre-diabetic[1], n (%) Type 2 Diabetic[1]	23 (38) 10 (16)	11 (38) 4 (14)
PI3Kα-mutation, n (%) Kinase domain Helical domain Double mutant / Not available	 33 (54) 22 (36) 5 (8) / 1 (2)	 17 (59) 8 (28) 3 (10) / 1 (3)
Visceral disease (%)	46 (75)	25 (86)
Median prior metastatic therapies (range)	3 (1 – 7)	3 (1 – 7)
Prior CDK inhibitor, n (%)	28 (46)	28 (97)
Prior fulvestrant or oral SERD	21 (34)	21 (72)
Prior chemotherapy/ADC	56 (92)	26 (90)
Prior PI3Kα- or mTOR or AKT-inhibitor, n (%)	13 (21)	12 (41)

[1]Definition based on HbA1c/fasting glucose levels, medical history and diabetic medication use.
BC: breast cancer

A heavily pre-treated, high-risk population is enrolled:

- >50% are pre-diabetic or have Type 2 diabetes
- >40% of breast cancer patients receiving prior PI3K pathway inhibitors previously discontinued due to toxicity

Table 2. Treatment-related AEs (TRAEs) by grade

N=61 patients (all tumors)

Adverse Event[1]	Grade 1	Grade 2	Grade 3	Grade 4	Any
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 (12)	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

[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 & neutrophil count decreased, [6]includes thrombocytopenia & platelet count decreased, [7]due to TEAEs

Dose Modifications[7]

Interruptions	26%
Reductions	13%
Discontinuations due to AE	0%

- STX-478 was well-tolerated with 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
- Minimal dose modifications seen, with no discontinuations due to AEs

Figure 2. STX-478 induces minimal changes to fasting glucose at any dose level

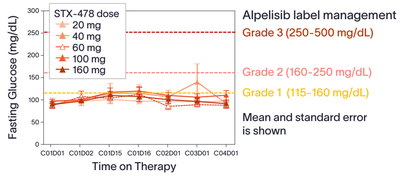
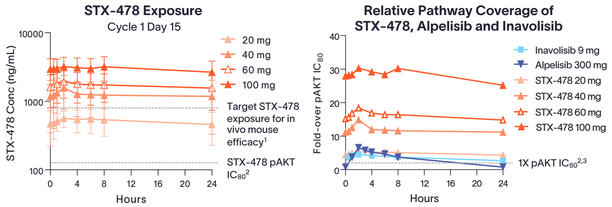


Figure 3. PK data and relative PI3K pathway coverage



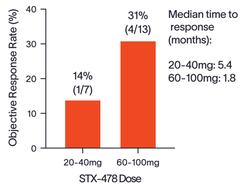
[1]Based on mouse efficacious exposure 100mg/kg in 3 CDX models, [2]Based on in vitro T47D (H1047R) cell pAKT assay, [3]Matched unbound pAKT suppression in head-to-head benchmarked T47D in vitro assays

- Exposure is dose proportional and linear, with a $T_{1/2}$ of ~60 hours
- At doses ≥ 40mg QD, STX-478 achieved target coverage significantly higher than other PI3K inhibitors at their RP2D

Figure 4. STX-478 efficacy and dose-response relationship

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

HR+/HER2- breast cancer

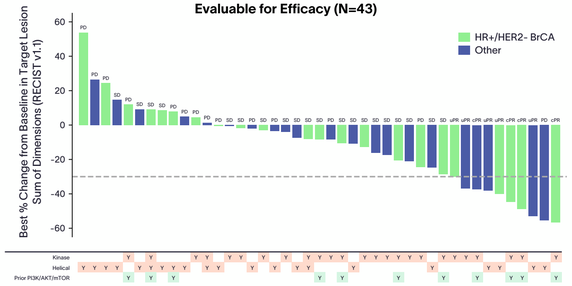


Median time to response (months):
20-40mg: 5.4
60-100mg: 1.8

[1]Includes unconfirmed (uPR) and confirmed (cPR) partial responses, [2]Efficacy evaluable and measurable disease patients shown. *All 5 patients with uPRs have converted to cPRs after the data cut

- A monotherapy ORR of 23% compares favorably to other PI3K pathway inhibitors (ORR 4-6%)[4,5]
- A dose-response relationship is observed with faster median time to response at higher doses

Figure 5. Waterfall plot in all tumors, including HR+ breast cancer



- Responses seen in both PIK3CA kinase and helical domain mutations and in patients receiving prior PI3K pathway inhibitors
- Multiple responding patients deepened their responses over time on therapy, with patient longest in PR on treatment > 12 months

Figure 6. Durable response in a patient with PI3Kα^{H1047R} kinase domain mutant HR+/HER2- breast cancer intolerant to alpelisib

- 81 year-old female with metastatic PI3Kα^{H1047R} mutant HR+/HER2- BC
- Pre-diabetic (HbA1c 6.7%)
- 3 prior lines of therapy
  - Neoadjuvant letrozole
  - Palbociclib + fulvestrant
  - Alpelisib (*discontinued due to hyperglycemia and diarrhea*)

Best response: PD, SD

- Started STX-478 at 20mg, increased to 40mg with PR at C7, on therapy > 12 mo

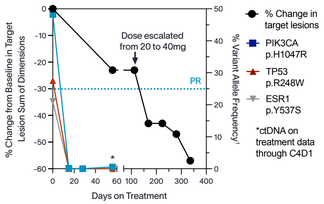
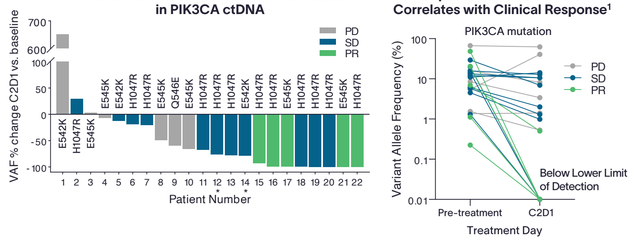


Figure 7. PIK3CA mutant variant allele frequency and correlation with clinical response



Patients of all tumor types 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

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 PI3Kα inhibitors
- STX-478 dosing achieves target coverage several fold higher than other PI3Kα inhibitors
- STX-478 is active in breast cancer, with a monotherapy ORR exceeding that of approved PI3K pathway inhibitors
- Efficacy is observed in patients with either PIK3CA kinase or 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

References

1. Mayer and Arteaga. Annu Rev Med 2016; 2. Fruman et al. Cell 2017; 3. Buckbinder et al. Cancer Discov 2023; 4. Banerji et al. JCO 2018; 5. Juric et al. JCO 2018

Acknowledgements

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