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Paxalisib in newly diagnosed glioblastoma patients with unmethylated MGMT promoter status: Final phase 2 study results

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BACKGROUND

- Glioblastoma multiforme (GBM) is the most common and aggressive form of primary brain cancer, survival rates are poor: 3-4 months (untreated) and 12-15 months (with treatment).
- Approximately two-thirds of patients have unmethylated MGMT promotor status; temozolomide has little to no benefit in these patients.[1]
- Paxalisib, a potent, oral, selective small molecule inhibitor of PI3K and mTOR kinase crosses the blood-brain barrier,[2,3] showed promising Phase 1 (NCT01547546) results,[4] and is being developed as an anti-cancer therapeutic agent specifically aimed at treating GBM.

OBJECTIVES

- Phase 2 progressive design 2-year trial in patients with newly diagnosed glioblastoma and unmethylated MGMT promotor status designed to:
  - Establish maximum tolerated dose (MTD) for once-daily (QD) dosing.
  - Evaluate safety, tolerability, pharmacokinetics, and clinical activity.

METHOD

- Open-label, multicentre (6-8 sites in the US), conducted in two stages.
- Eligibility:
  - Male/female patients ≥ 18 years, prior surgical resection of tumor(s).
  - Patients had a life expectancy ≥ 12 weeks and were progression free before starting adjuvant paxalisib.
- Design:

Stage 1 Dose escalation
Standard 3+3 design:
- Determine MTD in newly-diagnosed patients
- Further define safety, tolerability and PK

Stage 2 Expansion cohort
Two-arm, open-label design:
- Assess single agent activity of paxalisib
- Explore effect of fed vs. fasting state on PK

- Treatment:

CONCOMITANT XRT/TMZ
Temozolomide 75 mg/m² po QD
XRT 2Gy/d (5 d/week) **Total: 60Gy**

ADJUVANT PAXALISIB*
Paxalisib dosing:
- Stage 1: Cohort 1; 60 mg
- Stage 1: Cohort 2; 75 mg
- Stage 2: 1:1 fed/fasted; 60 mg

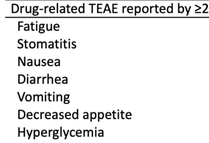
*PO QD in 28-day cycles

0 Weeks 6 (until disease progression or unacceptable toxicity)

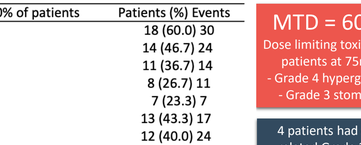
PATIENT POPULATION

- N=30, 21 (70%) males, mean age 58.5 years.
- Mean time since diagnosis 3.75 (3.0-5.7) months.
- All (100%) patients had Grade 4 histological diagnosis.

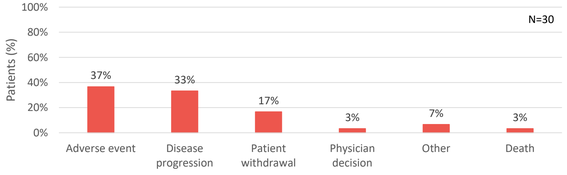
Baseline KPS:



Surgical history:



- Exposure to paxalisib:
  - Mean duration of exposure: 99 (9-833‡) days.
  - Adverse events or progressive disease were the main reasons for treatment discontinuation:

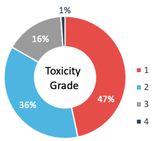


‡ The majority of patients had 1-6 cycles of paxalisib; 1 patient had 29 cycles (cycles 1-2: 75 mg, cycles 3-4: 40 mg, cycles 5-29: 45 mg)

MTD, SAFETY & TOLERABILITY

	Patients (%) Events
Treatment-emergent adverse events (TEAE)	30 (100.0) 549
Serious adverse events	18 (60.0) 41
Fatal TEAE	1 (3.3) 1
TEAE leading to study discontinuation	1 (3.3) 3
TEAE leading to study drug discontinuation	14 (46.7) 26
TEAE leading to study drug reduction/interruption	24 (80.0) 80
TEAE related to study drug	28 (93.3) 316

Drug-related TEAE reported by ≥20% of patients	Patients (%) Events
Fatigue	18 (60.0) 30
Stomatitis	14 (46.7) 24
Nausea	11 (36.7) 14
Diarrhea	8 (26.7) 11
Vomiting	7 (23.3) 7
Decreased appetite	13 (43.3) 17
Hyperglycemia	12 (40.0) 24
Rash maculo-papular	9 (30.0) 15
Rash	7 (23.3) 14
Platelet count decreased	7 (23.3) 9
Neutrophil count decreased	7 (23.3) 13
Weight decreased	7 (23.3) 7

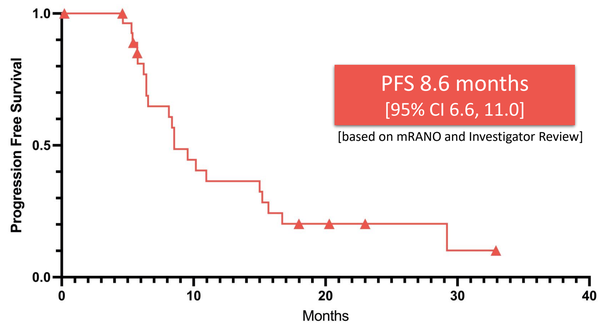


MTD = 60mg
Dose limiting toxicity in 2 patients at 75mg =
- Grade 4 hyperglycemia
- Grade 3 stomatitis

4 patients had drug-related Grade 3 or 4 hyperglycemia, which resolved following treatment with insulin or metformin.

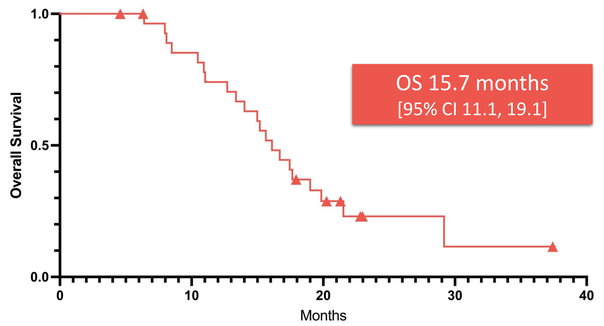
EFFICACY

- Progression free survival from date of diagnosis (ITT population):



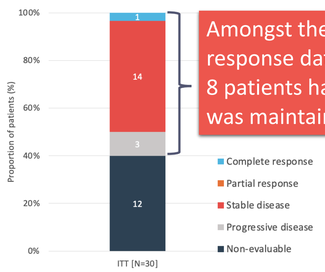
PFS 8.6 months
[95% CI 6.6, 11.0]
[based on mRANO and Investigator Review]

- Overall survival from date of diagnosis (ITT population):



OS 15.7 months
[95% CI 11.1, 19.1]

- Best overall response (ITT population):



Amongst the 18 patients in whom response data were available, 8 patients had stable disease that was maintained for at least 6 weeks.

[based on mRANO and Investigator Review]

PHARMACOKINETICS

- Paxalisib is characterized by:
  - Rapid absorption (median Tmax 2.5 to 4 h).
  - Steady elimination (mean half-life 20.2 to 29.0 h).

Effect of food:
- C_{max} 52% increase
- $AUC_{0\text{-last}}$ 33% increase
- T_{max} No difference

Parameter	Fed	Fasted	Ratio of GSLM (90% CI)	Within-patient CV%
$AUC_{0\text{-last}}$ (h*ng/mL)	2190 (34.5)	1640 (67.1)	133.780 (91.770, 195.019)	53.158
$AUC_{0\text{-inf}}$ (h*ng/mL)	4030 (83.0)[b]	3800 (115)[c]	106.061 (43.175, 260.545)	102.405
C_{max} (ng/mL)	173 (24.2)	114 (44.2)	152.235 (117.092, 197.926)	35.815
T_{max} (h)[a]	4.00 (2.80, 8.00)	3.93 (3.00, 8.00)	0.133 (-0.200, 1.033)	

$AUC_{0\text{-inf}}$ = area under the curve from time 0 to infinity; $AUC_{0\text{-last}}$ = area under the curve from time 0 to the last measurable time; CI = confidence interval; C_{max} = maximum concentration; CV = coefficient of variation; GLSM = geometric least squares mean; $t_{1/2}$ = plasma half-life; T_{max} = time to reach the maximum concentration; Note: Geometric mean (geometric CV%) data are presented. [a] The n, median, and Hodges-Lehmann estimate of median difference (90% CI) from the Wilcoxon rank-sum test presented, [b] N=5, [c] N=7

CONCLUSIONS

- The primary study endpoints were met:
  - An MTD of 60 mg was established for QD dosing.
  - PK and safety were consistent with prior clinical experience.
- PFS and OS provide an encouraging efficacy signal in this difficult to treat patient cohort.
- Further efficacy confirmation of paxalisib 60 mg QD in newly diagnosed and recurrent GBM in a pivotal trial is ongoing (GBM AGILE, NCT03970447).

Acknowledgements:
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SCAN ME

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