

A Phase I Pharmacokinetic Study of PR-104, a Hypoxia-Activated Nitrogen Mustard Prodrug, in Patients with Solid Tumors

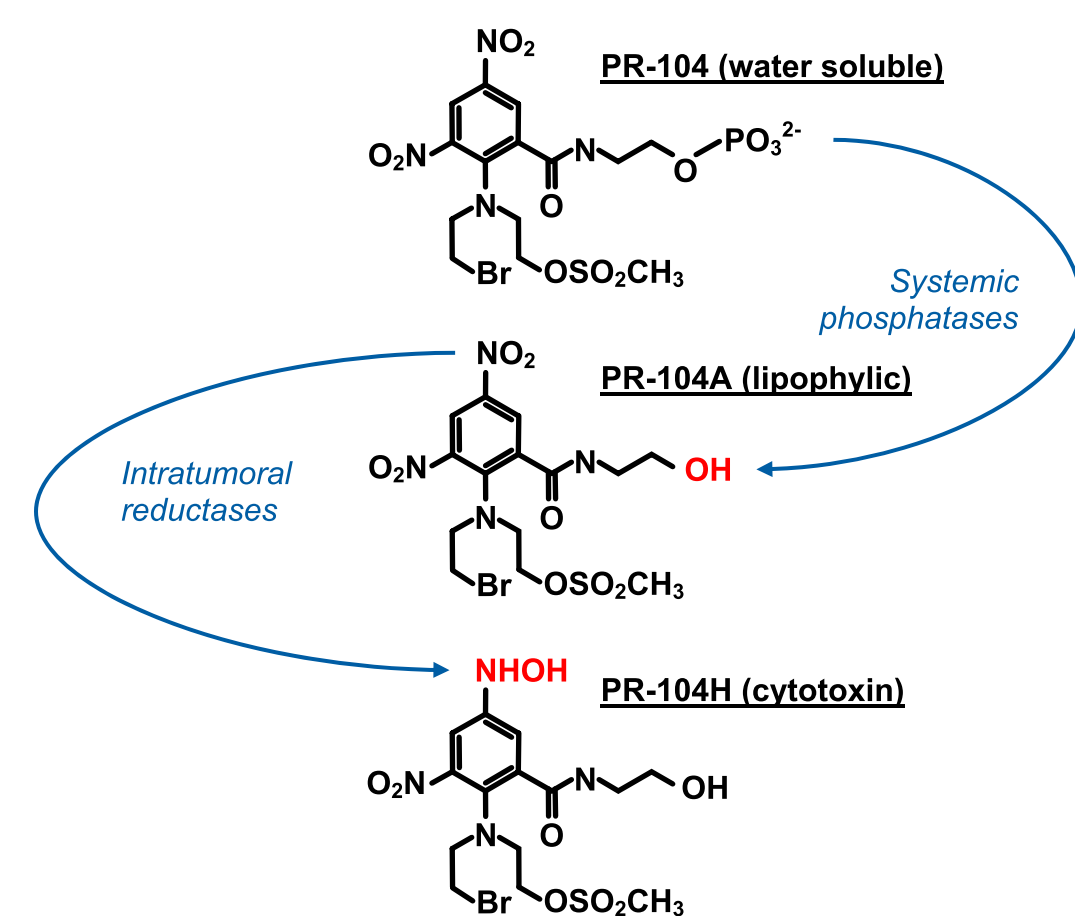
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Background

PR-104 is a novel pre-prodrug of the dinitrobenzamide mustard class, with selective toxicity to hypoxic tumor cells. PR-104 is a water-soluble phosphate ester that is hydrolyzed by phosphatases to the corresponding alcohol metabolite, a more lipophilic prodrug referred to as PR-104A. PR-104A is reduced selectively under hypoxic conditions to a hydroxylamine metabolite, PR-104H, which is a cytotoxic nitrogen mustard alkylating agent. PR-104H exerts its cytotoxic effect through the formation of DNA interstrand crosslinks. In xenograft models, PR-104 demonstrated anti-tumor activity as monotherapy against several human solid tumors (SiHa cervical, HT29 colon and H460 NSCLC).

Figure 1. Activation Pathway of PR-104



Trial Design

Study Objectives

Primary objectives:

- To evaluate the safety and tolerability of PR-104
- To determine the dose-limiting toxicities (DLT)
- To establish the maximum tolerated dose (MTD)

Secondary objectives:

- To characterize the pharmacokinetics (PK) of PR-104 and its alcohol metabolite
- To assess response

Key Eligibility Criteria

- ≥ 18 yrs of age
- Histologically confirmed solid tumor
- Karnofsky Performance Status ≥ 70%
- ≤ 3 prior myelosuppressive chemotherapy regimens
- Measurable or evaluable disease
- Adequate marrow function (ANC > 1.5 x 10⁹/L, PLT > 100 x 10⁹/L, HGB > 90 gm/L)
- Adequate liver function (ALT/AST < 2.5 x ULN)
- Adequate renal function (Creatinine clearance > 60 mL/min)

Treatment

PR-104 is administered by IV infusion over 1-hour on an every 3 week schedule.

Figure 2. Treatment Schema

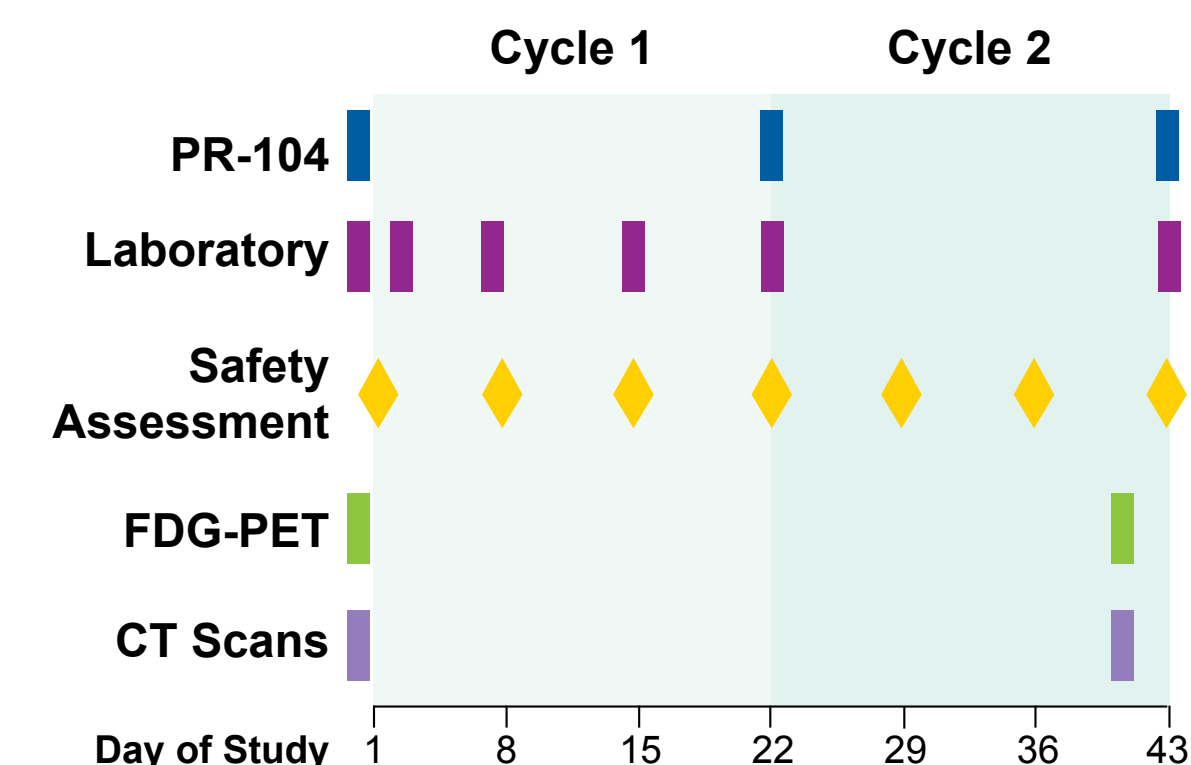


Table 1. Patient Characteristics

Characteristics	Patients (n = 27)
Median age, yrs (range)	56 (30-73)
Males, n (%)	15 (56)
Race, n (%)	
White	21 (78)
New Zealand Maori	3 (11)
Other Pacific Islander/ Asian	3 (11)
Karnofsky Performance Status, median (range)	90% (70 – 100%)
Diagnosis, n (%)	
Gastrointestinal	6 (22)
Breast	4 (15)
Head and Neck	4 (15)
NSCLC	3 (11)
Other	10 (37)
Prior Therapy, n (%)	
Chemotherapy	23 (85)
Immunotherapy alone	2 (7)
Radiotherapy alone	1 (4)
No prior therapy	1 (4)
Median no. of prior chemotherapy regimens, n (range)	2 (1-5)

Results

Safety

Table 2. Dose Escalations and Observed DLT During Cycle 1 of PR-104

Dose Level (mg/m ²)	No. Patients in Cohort	DLTs
1400	3	Grade 3 febrile neutropenia (n=1) Grade 3 infection w/ normal ANC (n=1)
1100	6	Grade 3 fatigue (n=1)
770	3	
550	3	
346	3	
216	3	
135	6	Grade 3 dehydration (n=1)

Figure 3. Proportion of Patients Experiencing Neutropenia During Cycle 1

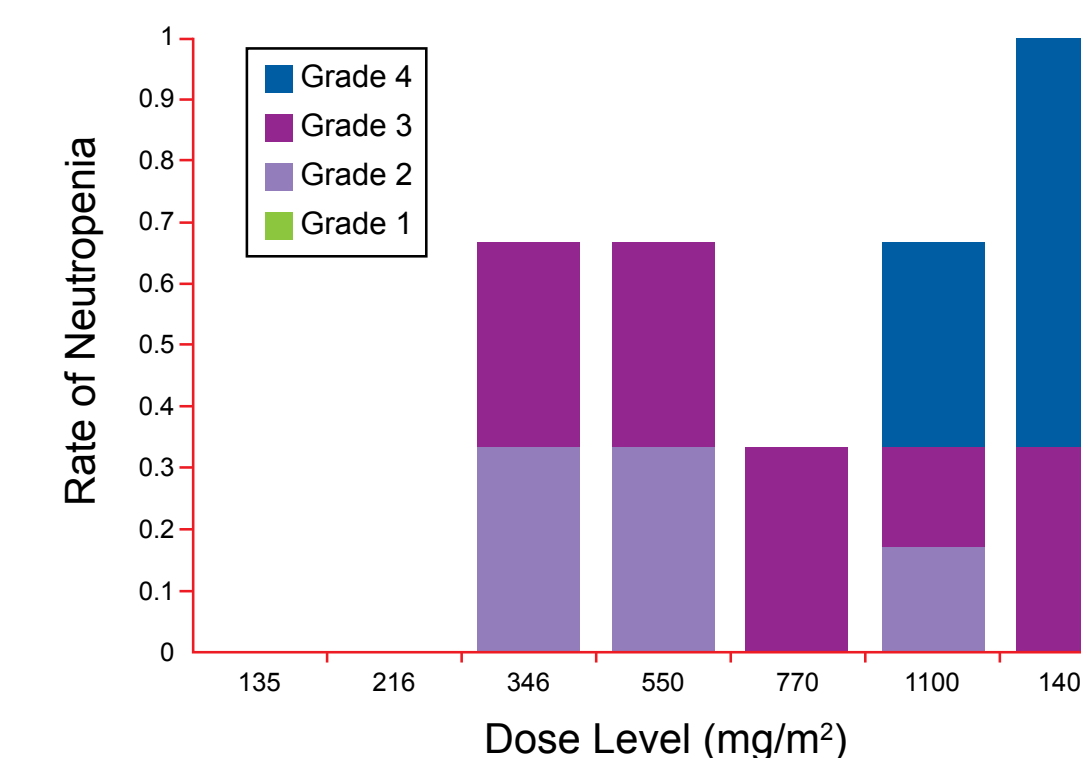


Table 3. Treatment-Related Adverse Events ≥ Grade 2 - Highest Grade per Patient

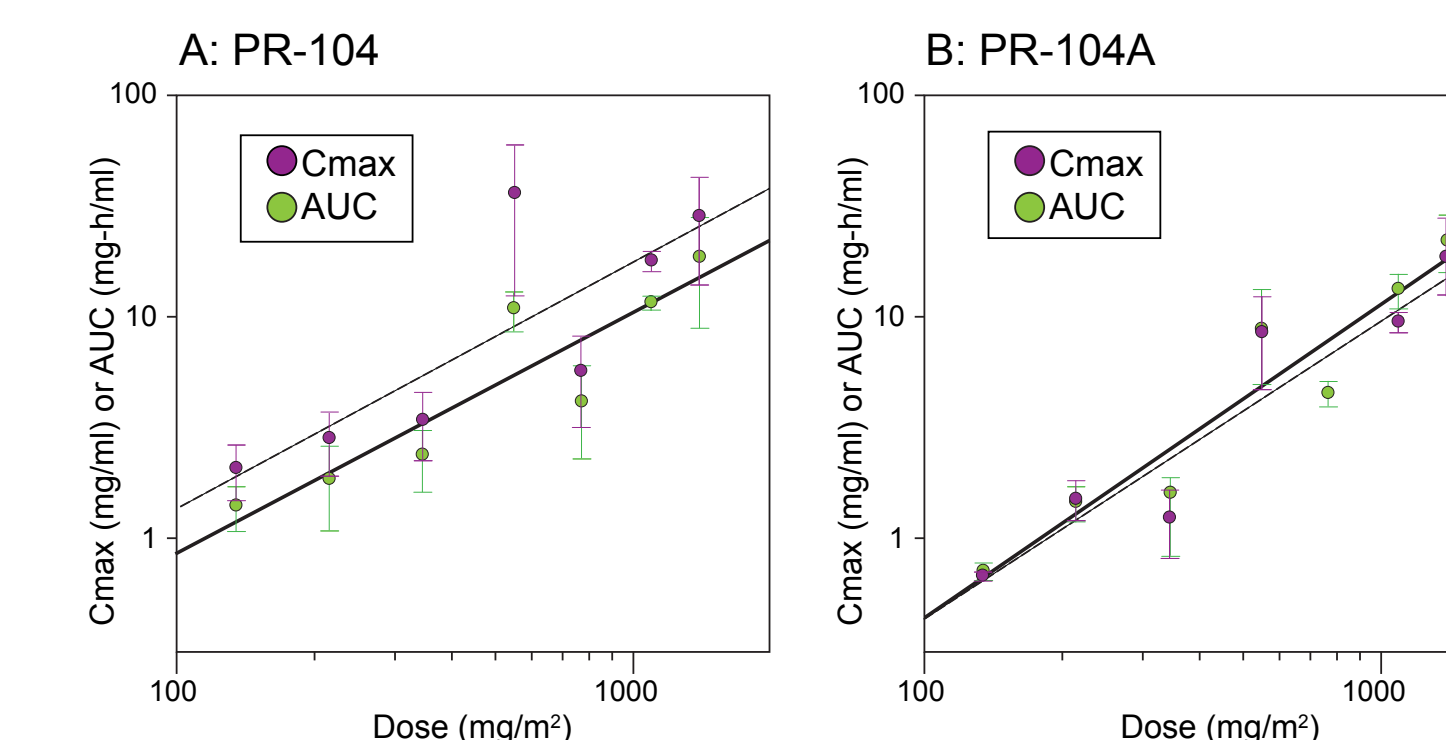
Adverse Event	Maximum Grade (CTCAE v3)			Total No.
	2	3	4	
Fatigue	12	2	-	14
Anemia	2	3	2	7
Neutropenia	1	3	3	7
Nausea	5	1	-	6
Thrombocytopenia	2	2	1	5
Vomiting	2	2	-	4
Leukopenia	1	2	-	3
Febrile neutropenia	-	2	-	2
Abdominal pain	1	-	-	1
Cholangitis	-	1	-	1
Dehydration	-	1	-	1
Dizziness postural	1	-	-	1
Dysgeusia	1	-	-	1
Dyspepsia	1	-	-	1
Dysphagia	-	1	-	1
Hemoptysis	-	1	-	1
Hiccups	1	-	-	1
Oral pain	1	-	-	1
Palmar-plantar syndrome	1	-	-	1
Pneumonia	-	1	-	1
Wound complication	1	-	-	1

Efficacy

Minor tumor regressions were observed in 2 patients (head and neck cancer, epithelioid sarcoma). At PR-104 doses ≥ 550 mg/m², symptomatic improvement was observed in 3 patients (head and neck cancer [n=2], breast cancer [n=1]).

Pharmacokinetics

Figure 4. Mean AUC and Cmax of PR-104 and PR-104A



Gradients: PR-104 - Cmax = 1.11; AUC = 1.08
PR-104A - Cmax = 1.07; AUC = 1.13

Conclusions

- This phase I trial represents the first clinical evaluation of PR-104, a first-in-class hypoxia-activated nitrogen mustard prodrug
- PR-104 can safely be administered as a 1-hour infusion every 3 weeks
- The MTD and recommended dose of PR-104 for phase II is 1100 mg/m²
- The major DLT of PR-104 is dose-dependent myelosuppression, predominately neutropenia
- No significant liver, renal or gastrointestinal toxicities were observed
- Minor tumor regressions and symptomatic improvement were observed
- At the MTD, the plasma pharmacokinetic parameters of PR-104A included a Cmax of 15400 ng/mL and AUC of 20100 ng.h/mL
- PR-104 was extensively converted to the hypoxia-activated prodrug PR-104A in patients, with essentially linear plasma pharmacokinetics for both species
- Plasma PK of PR-104A achieved levels associated with significant anti-tumor activity in pre-clinical tumor models