A P53-Based Strategy to Reduce Hematological Toxicity of Chemotherapy: A Pilot Study

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Background

- P53 activation is the primary mechanism underlying pathological responses to DNA-damaging agents such as chemotherapy and radiotherapy.
- We recently showed in animal studies that low dose arsenic (LDA)-induced transient p53 inhibition selectively protected normal tissues from chemotherapy-induced toxicity.

Objectives

- Define the lowest safe dose of arsenic trioxide that blocks p53 activation in patients
- Assess the potential of LDA to decrease hematological toxicity from chemotherapy

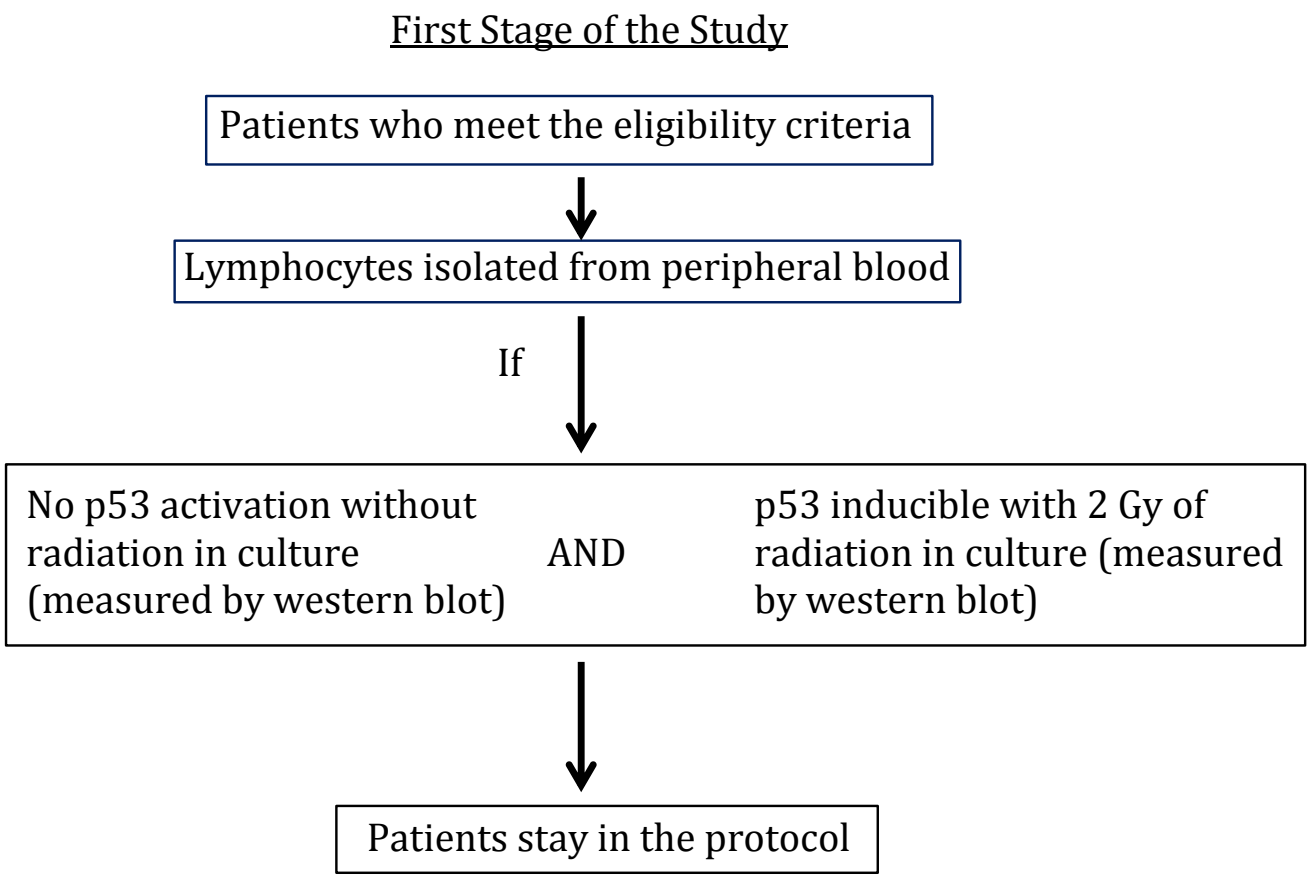
Methods

- Patients scheduled to receive a minimum of 4 cycles of myelosuppressive chemotherapy were eligible
- For objective 1, dose escalation started at 0.005 mg/kg/day for 3 days. This dose satisfied objective 1
- Subjects received this dose of LDA prior to cycles 2, 4 and 6 and no LDA prior to 1, 3, 5.

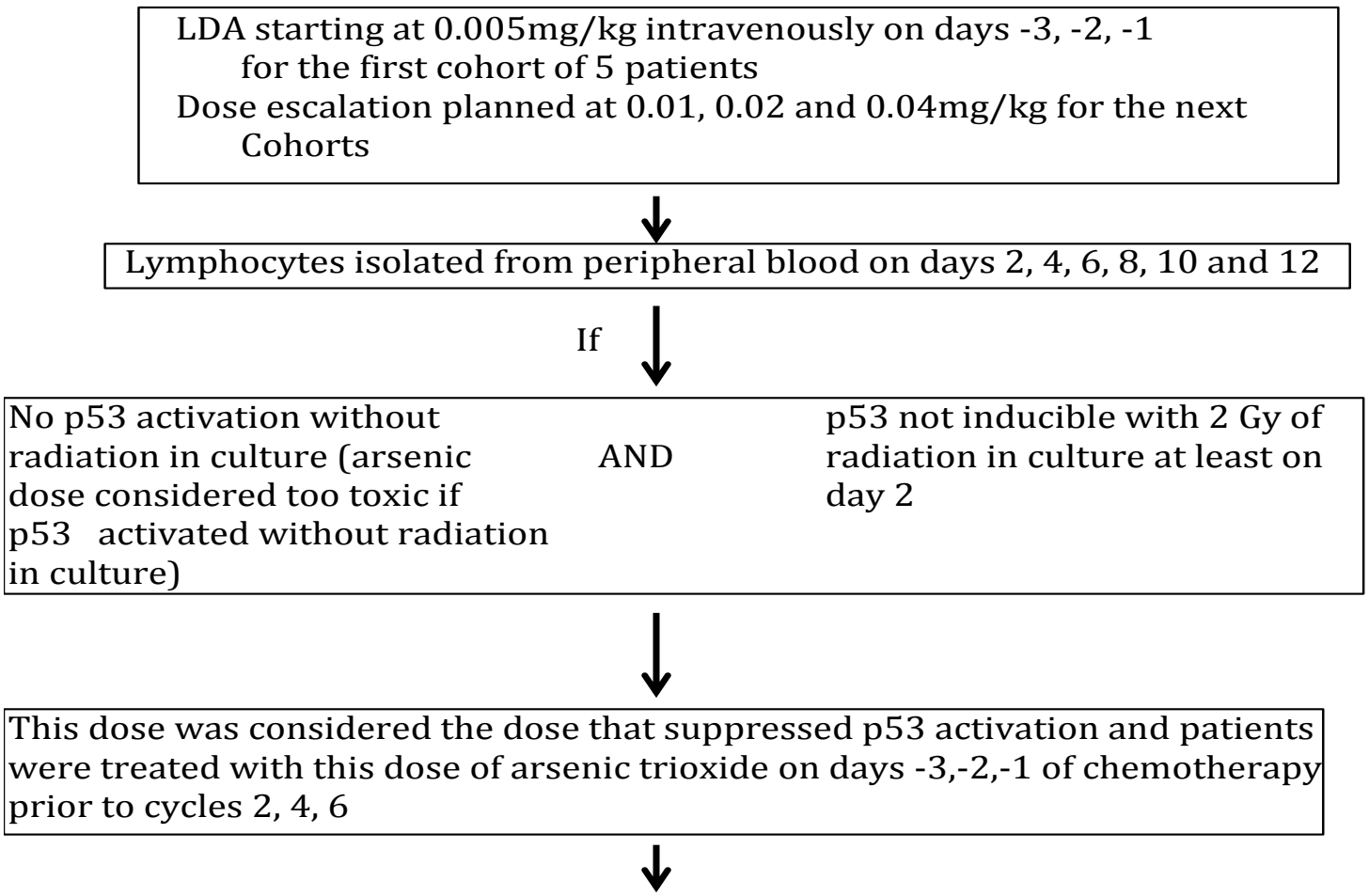
Methods

- P53 level in peripheral lymphocytes was measured on day 1 of each cycle by ELISA.
- Cycles 1, 3, 5 served as baseline for 2, 4, 6
- If p53 activity for the subsequent cycle was lower than baseline then p53 was labelled ‘suppressed’ for the pair of cycles.
- If higher, then ‘activated’.
- p53 activity groups: suppressed, activated

Study Diagram 1



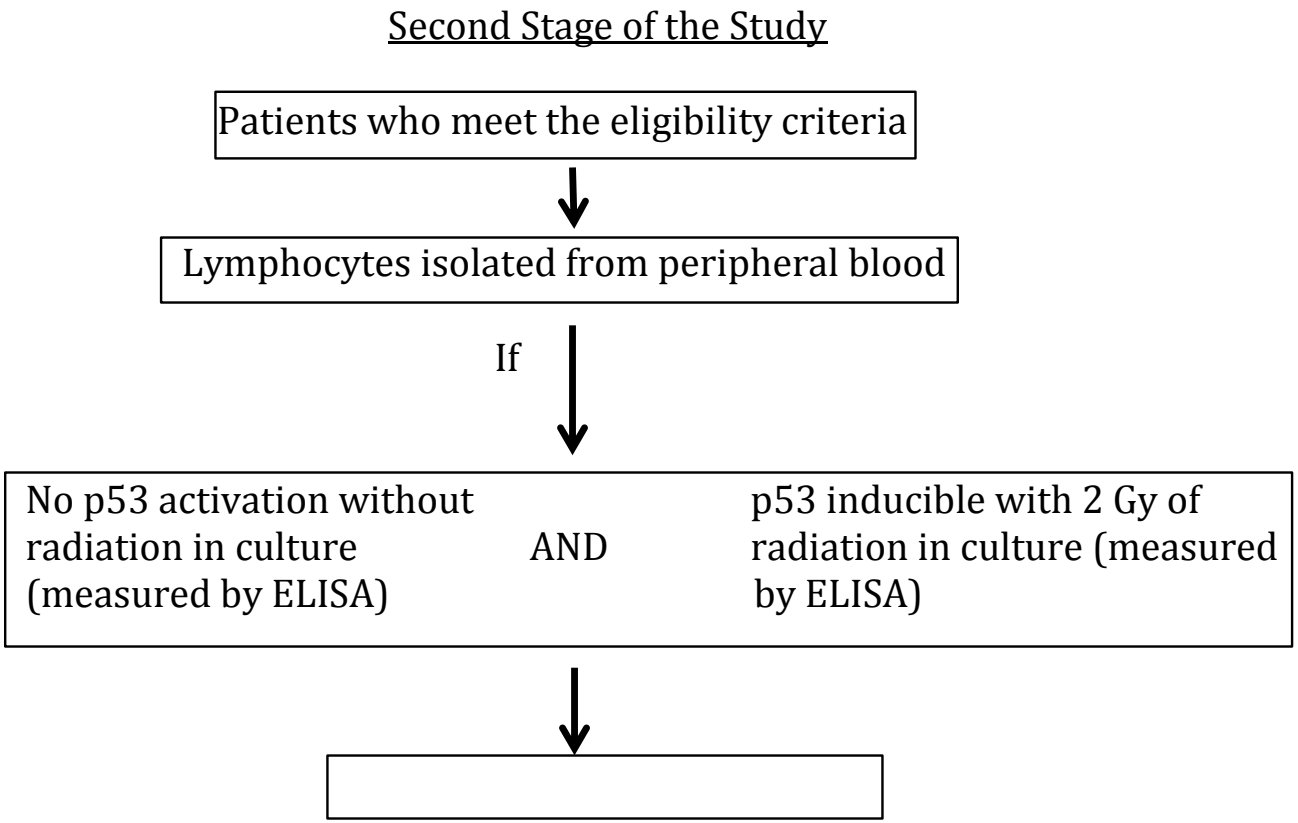
Study Diagram 2



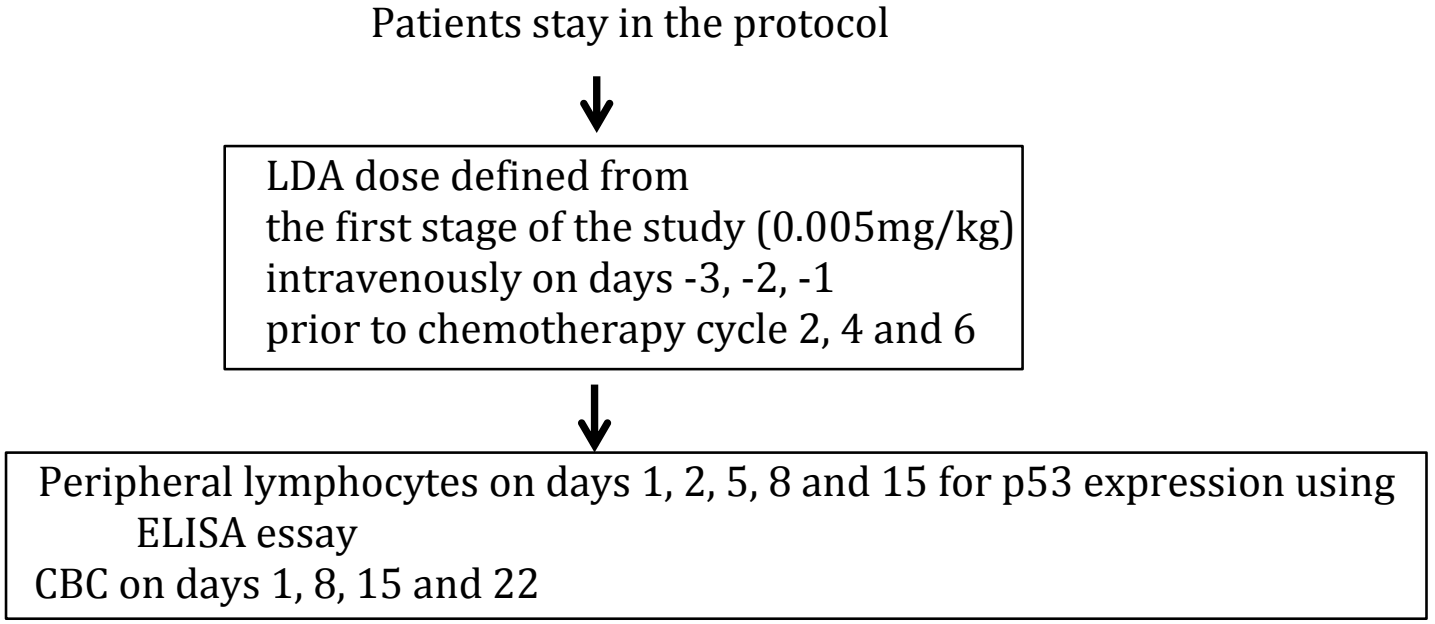
Study Diagram 3

Peripheral lymphocytes on days -2, 1, 3, 5, 7 and 9 for p53 expression using western blot

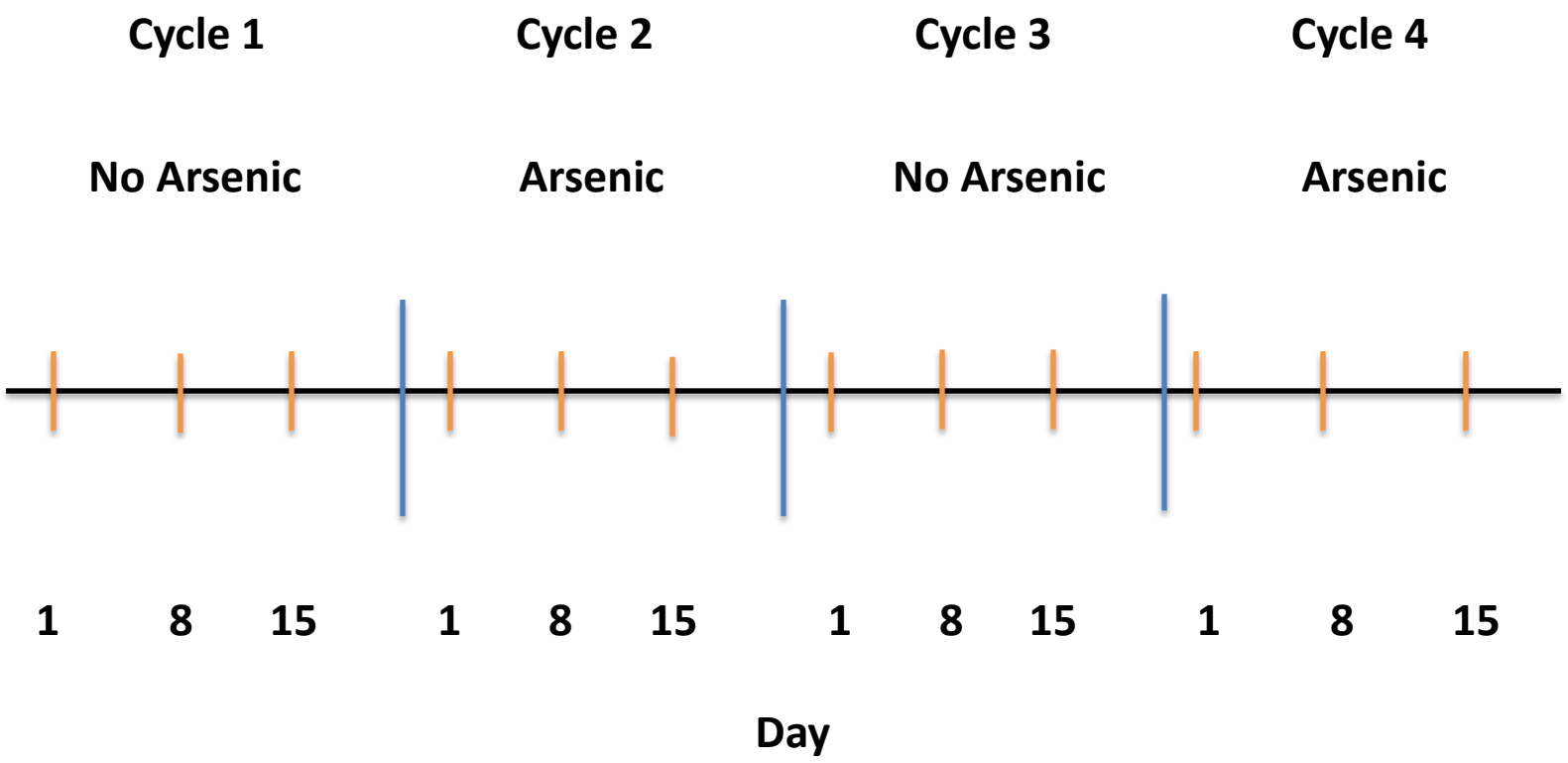
CBC on days 9 and 16



Study Diagram 4



Design


Cycle 1
Cycle 2
Cycle 3
Cycle 4
No Arsenic
Arsenic
No Arsenic
Arsenic
1
8
15
1
8
15
1
8
15
1
8
15
Day

Methods

- P53 activity groups were compared with regard to the Complete blood count (CBC)
  - ANC
  - Platelets
  - WBC
  - Hgb
- Repeated measures linear models of CBC in terms of day, cycle, p53 activity, interactions were used.

Results

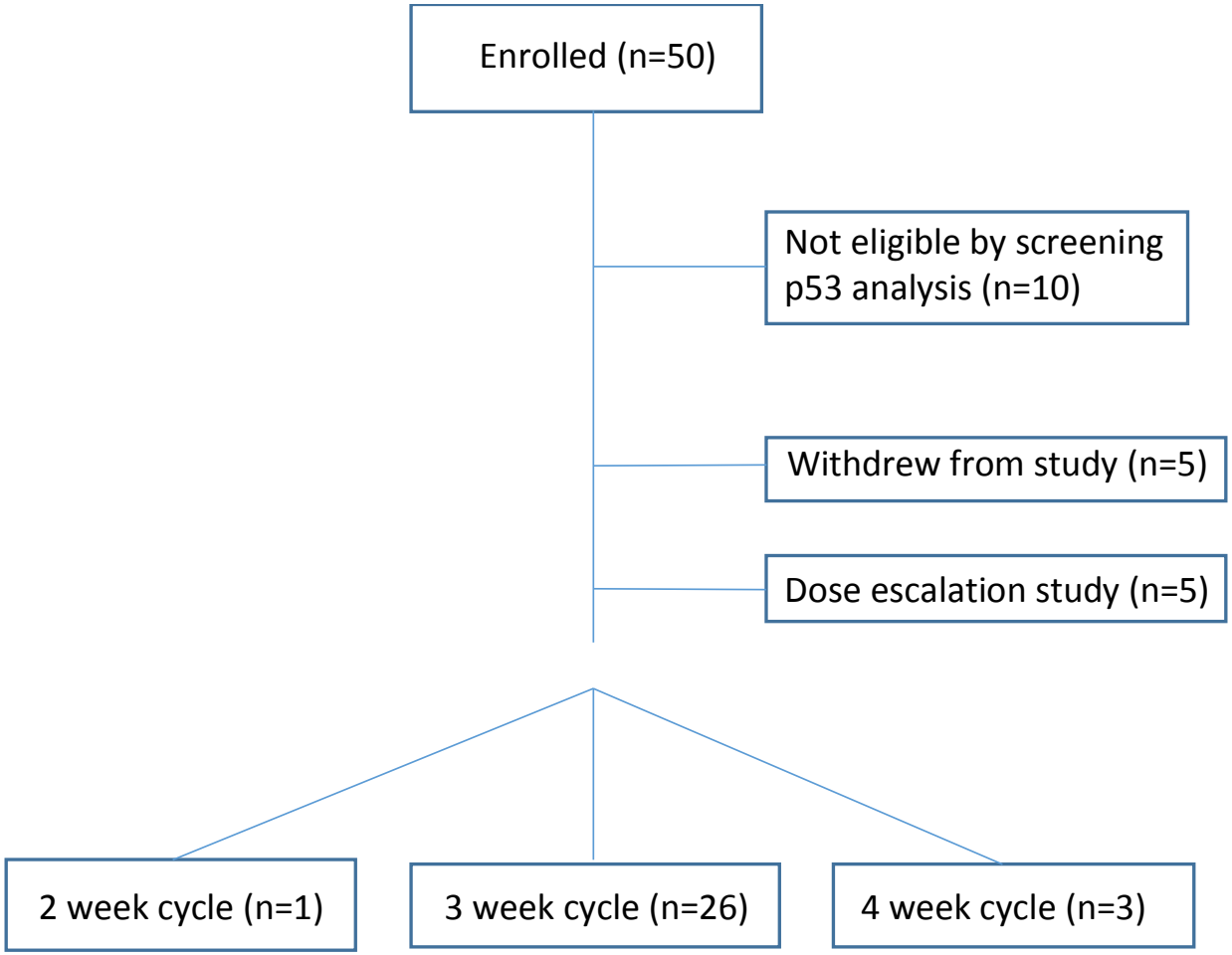
Dose Escalation

- The first 5 patients accrued had suppression of p53 activation on days 2 and 4 at the starting dose of 0.005 mg/kg for 3 consecutive days
- The suppression was temporary and reversed after day 4 for all 5 patients
- This dose was determined to be the lowest safe dose of LDA that suppressed p53 activity
- And was used to treat all subsequent patients

Excluded WBC and ANC

- Six patients were treated with a total of 19 doses of filgrastim or pegfilgrastim.
- We excluded the WBC counts and ANC during the cycles after the pegfilgrastim use.
- No patient received packed red blood cell transfusions during the first 2 cycles of chemotherapy.

Consort Diagram



Demographics

Characteristic	Total (N = 26)
Age (years)	
Mean±SD	52.7±11.3
Gender	
Female	17 (65.4%)
Male	9 (34.6%)
Total	26
Current Diagnoses	
Breast cancer	14 (53.9%)
Diffuse large B cell lymphoma	1 (3.9 %)
Lung cancer	5 (19.2%)
Multiple myeloma	1 (3.9%)
Prostate cancer	4 (15.4%)
Rhabdomyosarcoma	1 (3.9%)
Total	26
Previous Treatments	
Chemotherapy alone	2 (7.7%)
Chemotherapy and radiation therapy	6 (23.1%)
Radiation therapy alone	4 (15.4%)
None	14 (53.9%)
Total	26

Sample sizes

	P53 Expression				
Cycle	**Activated**	**Suppressed**	**NA**	**No Change**	**Total**
1	14	11	0	1	26
2	14	11	0	1	26
3	13	9	2	1	25
4	13	9	1	1	24
5	3	0	4	0	7
6	3	0	1	0	4

CBC by p53 activation

Count		Activated	Suppressed	Contrast
WBC	Mean±SE	1.13±0.055	1.41±0.068	-0.28±0.088
	95% CI			-0.454, -0.106
	p-value			0.002
HgB	Mean±SE	2.43±0.013	2.48±0.015	-0.051±0.02
	95% CI			-0.091, -0.012
	p-value			0.012
Platelets	Mean±SE	5.53±0.053	5.53±0.064	0.006±0.084
	95% CI			-0.161, 0.172
	p-value			0.945
ANC	Mean±SE	7.36±0.08	7.61±0.1	-0.26±0.13
	95% CI			-0.512, -0.004
	p-value			0.046

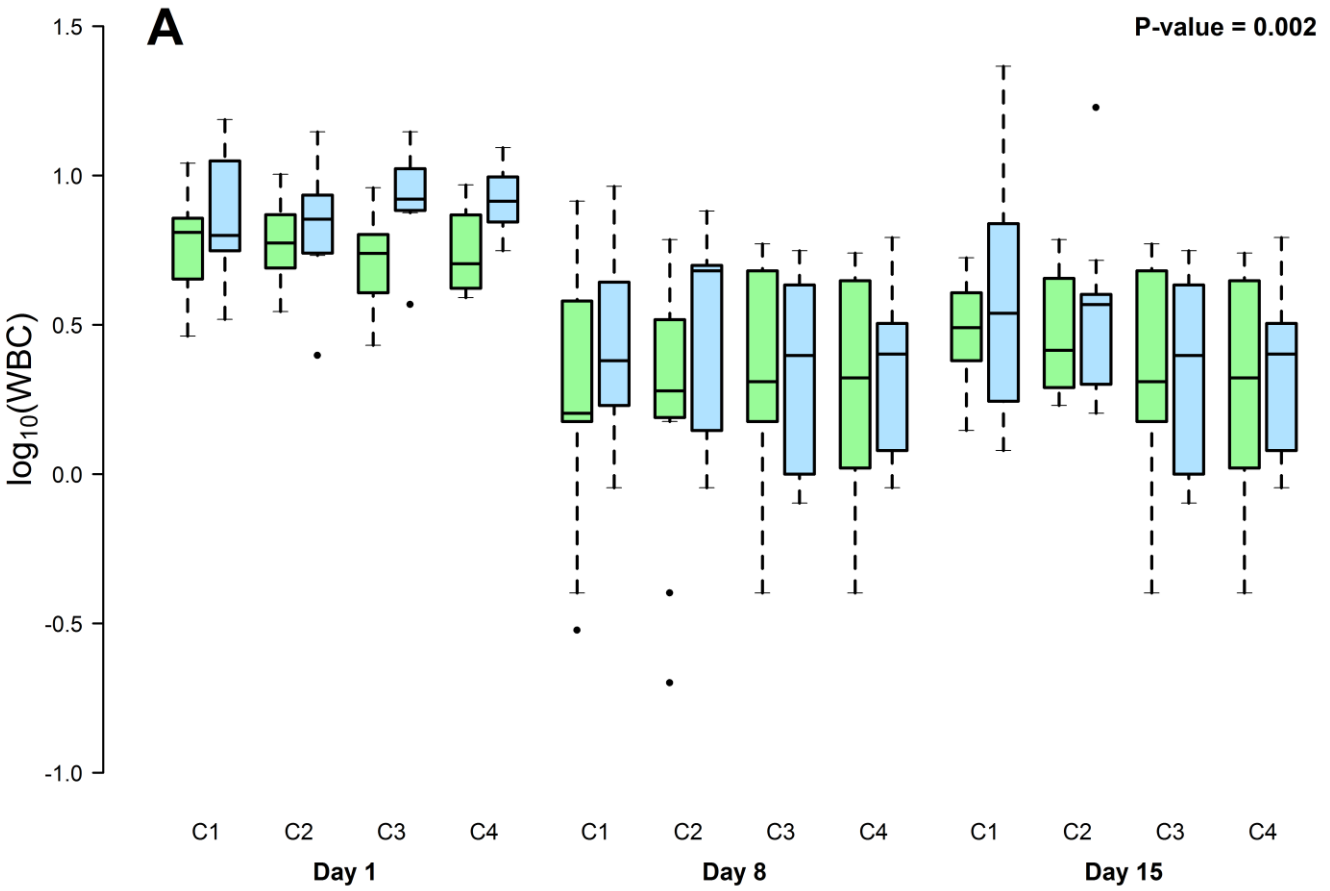
Chemotherapy Regimens

Regimen	N
Rituximab, doxorubicin, cyclophosphamide, vincristine, predisone	1
Docetaxel, cyclophosamide	7
Doxorubicin, cyclophosamide	5
Carboplatin, bevacizumab, premetrexed	2
Bortezombi, lenalidomide, dexamethasone	1
Docetaxel, prednisone	5
Doxorubicin, vincristine, etoposide, ifosfamide	1
Carboplatin, etoposide	1
Cisplatin, etoposide	1

Safety

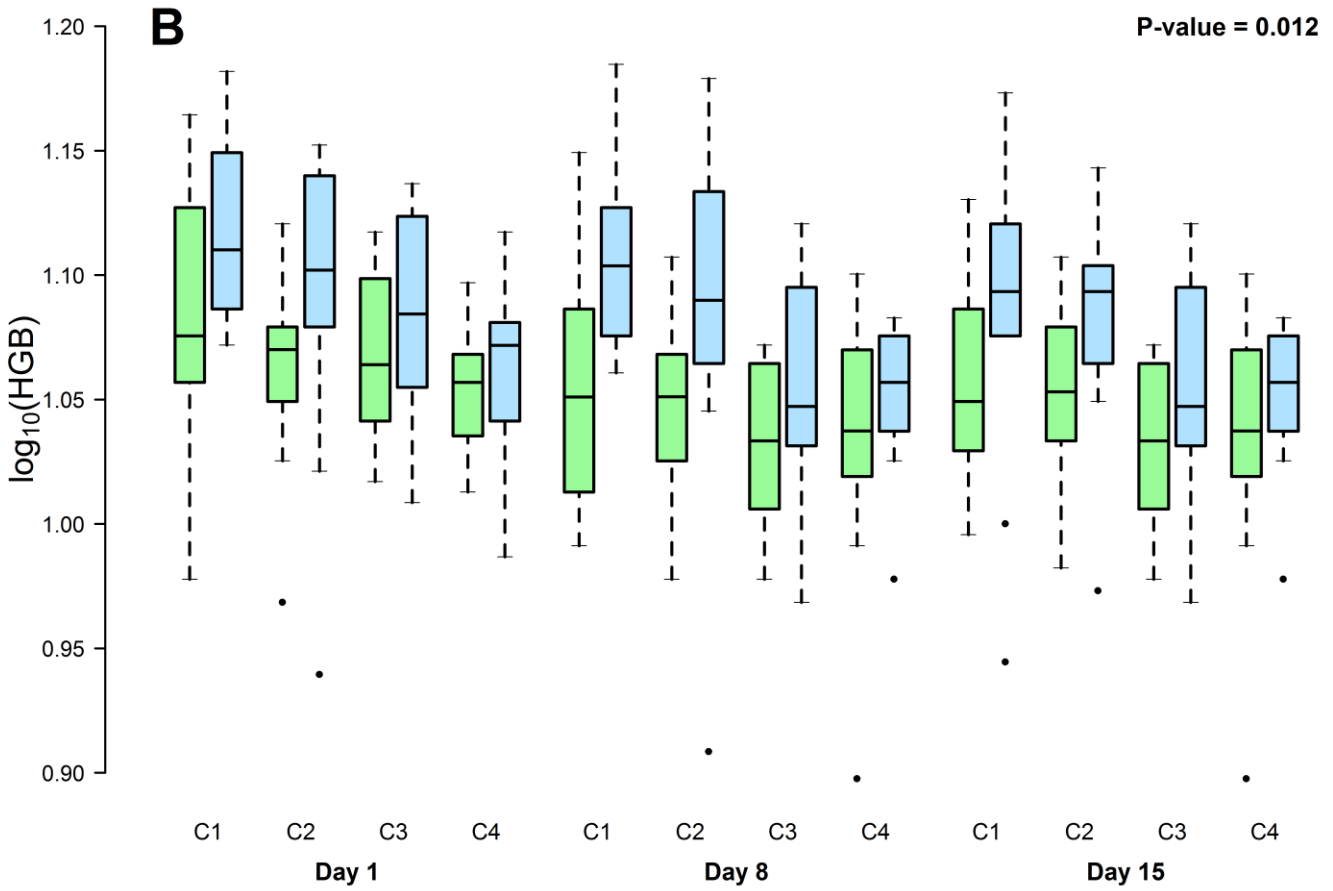
- No adverse events attributable to arsenic
- No patient was removed due to arsenic toxicity
- No clinically significant changes in electrocardiograms, including the QT interval in any subject

Figures



green: activated, blue: suppressed

Figures



green: activated, blue: suppressed

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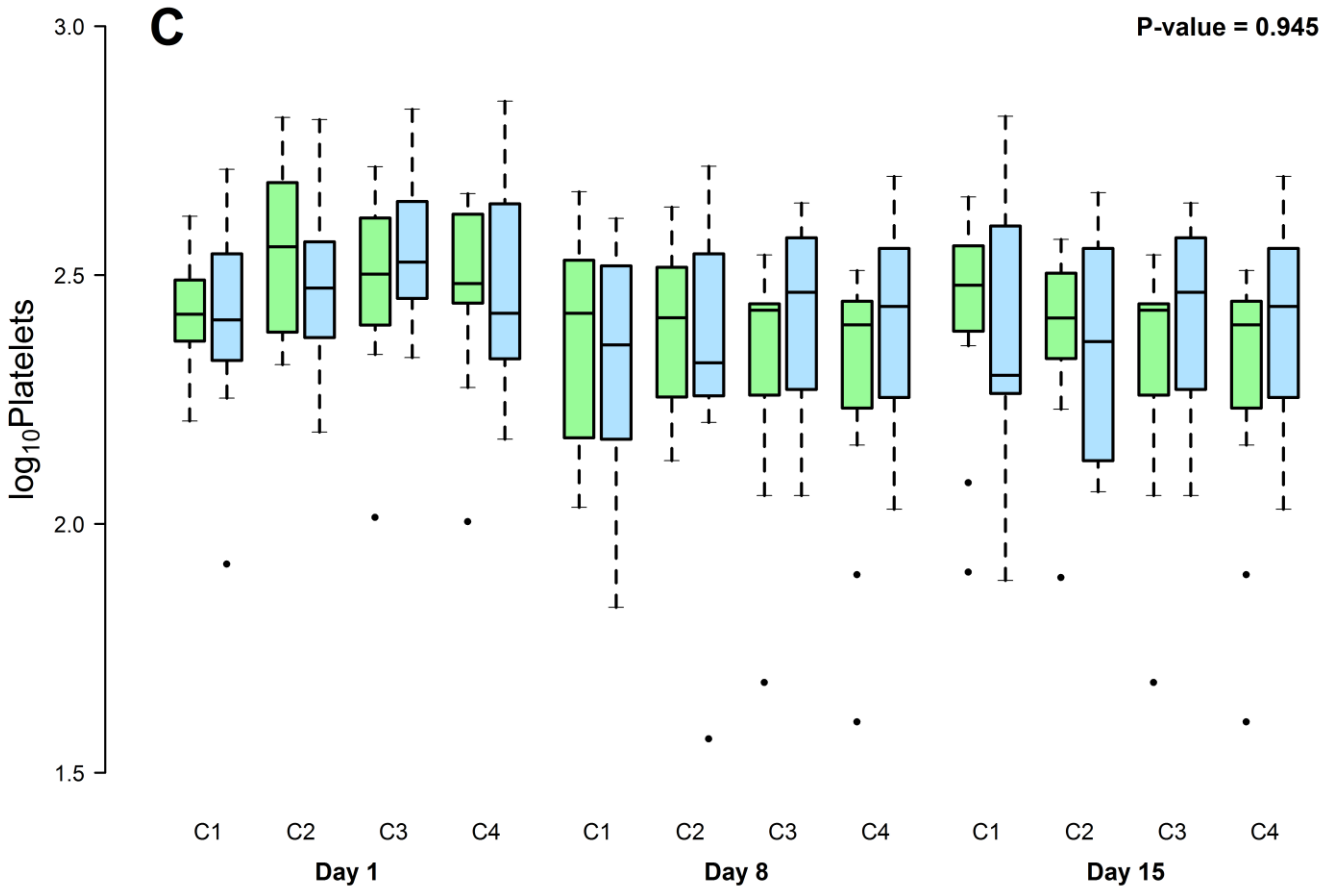

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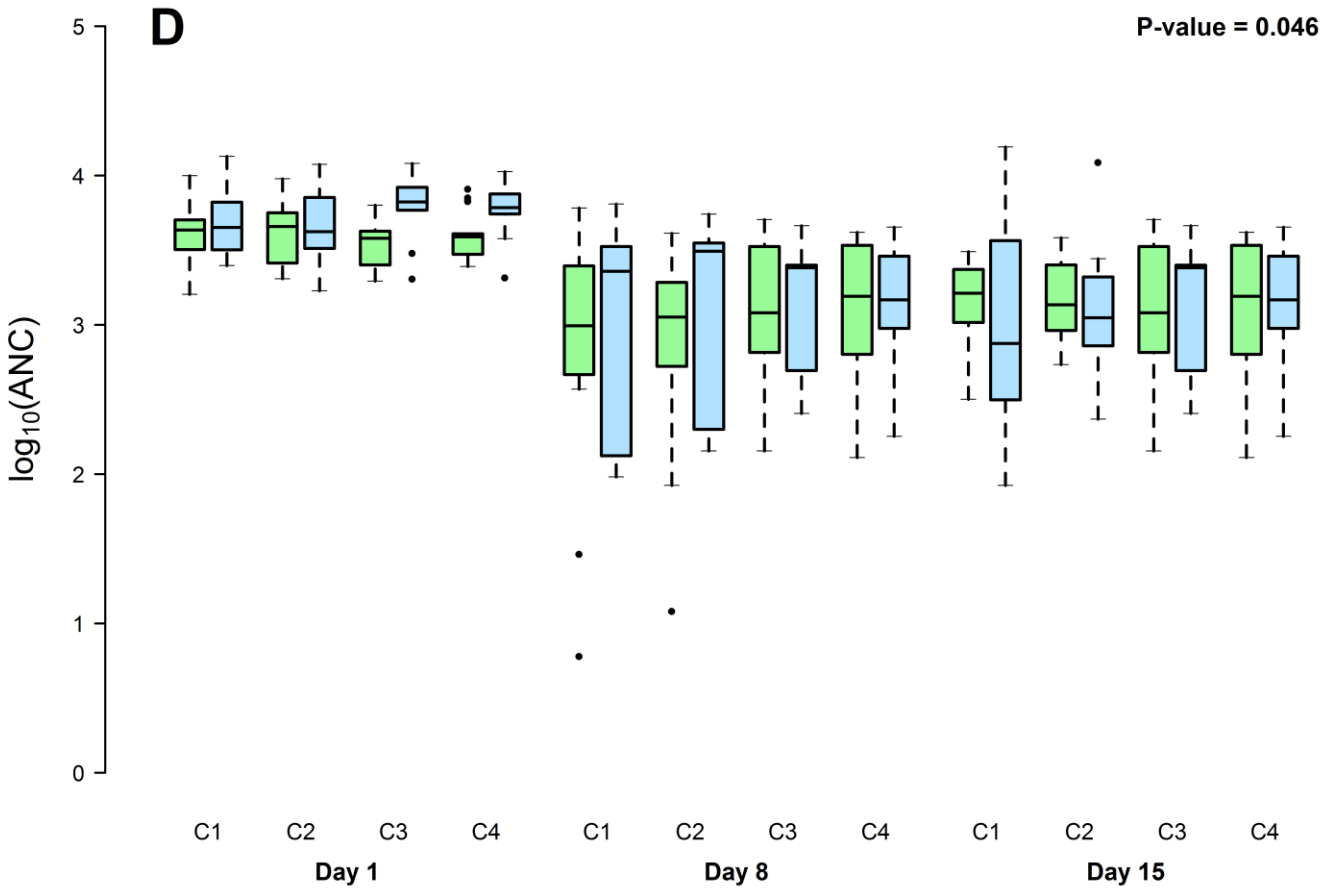

green: activated, blue: suppressed

Conclusion

- These data support the proof of principle that suppression of p53 could lead to protection of bone marrow in patients receiving chemotherapy

The End

- Questions?