Correlative studies from NPCF Phase II trial of Gemcitabine and nab-paclitaxel for recurrent Osteosarcoma.

Masanori Hayashi, MD
Associate Professor

University of Colorado Denver, Children's Hospital Colorado

BACKGROUND

- The combination of gemcitabine and docetaxel is often used to treat patients with recurrent osteosarcoma. Nab-paclitaxel has preclinical activity against osteosarcoma and is potentially less myelosuppressive than docetaxel.
- Osteosarcoma tumors tend to calcify even when responding to therapy, with no change in measurable size. This can make the assessment of tumor response challenging when using conventional radiological response criteria such as RECIST.
- Unmet need for predictive biomarkers in bone sarcomas to guide patient selection and assess response to therapy.
- The use of "**liquid biopsies",** such as circulating tumor cells (CTC) or circulating tumor DNA (ctDNA) in peripheral blood, have been increasingly used as an alternative to tumor biopsies to identify and track disease characteristics.

Dhir A et al. Clin Cancer Research. 2024

NPCF Study MCC18613
Phase II Trial of Gemcitabine and nab-paclitaxel for Recurrent Osteosarcoma

Patient eligibility

Patients Aged 12–30 years with relapsed or refractory OS and measurable disease

Drug administration

Both nab-paclitaxel and gemcitabine were administered on days 1, 8, and 15 of a 4-week cycle.

Correlative studies

Serial assessment of circulating tumor cells (CTC) and circulating tumor DNA (ctDNA) using ultralow passage whole-genome sequencing

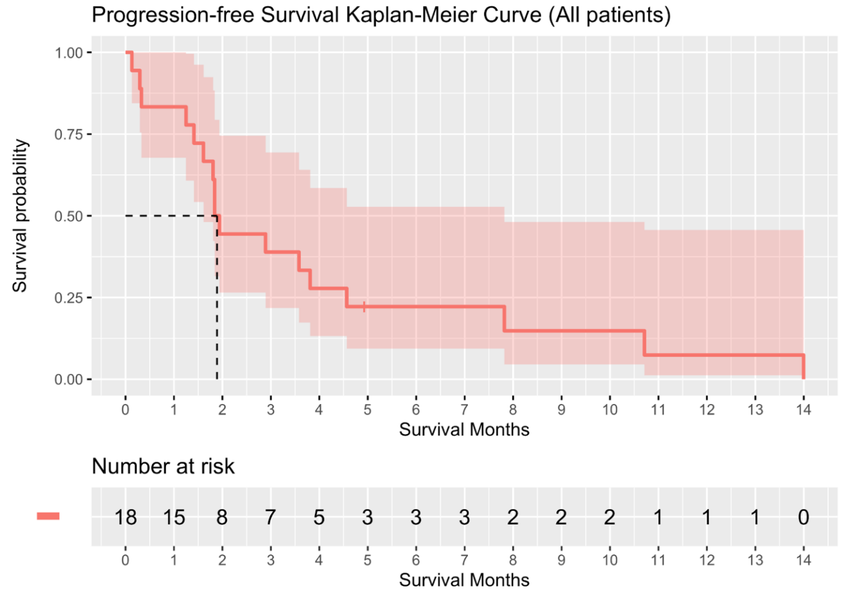
Statistical design

Simon's two-staged design in which the null hypothesis that the PFS-4 was ≤ 10% was tested against a one-sided alternative PFS-4 of ≥ 35% with 80% power. This target response rate was chosen because this level of activity has been achieved by other available salvage regimens

Dhir A et al. Clin Cancer Research. 2024

RESULTS

- Eighteen patients with a median age of 16 years (range 12- 26) received 56 total cycles (median 2, range 1 – 12).
- The median number of prior chemotherapy regimens was 2 (range 1-7).
- Two patients (11%) experienced confirmed partial response, and 6 (33%) received up to 4 cycles.
- Six patients (33%) required dose reduction and three patients were removed due to toxicities.
- Median PFS was 1.9 months (95% CI 1.6-7.8).
- Five patients out of the 18 eligible patients were progression free at 4 months, and therefore the PFS-4 was 28% (95% CI 13-59%), with a p-value of 0.028 compared to the historical rate of 10%.



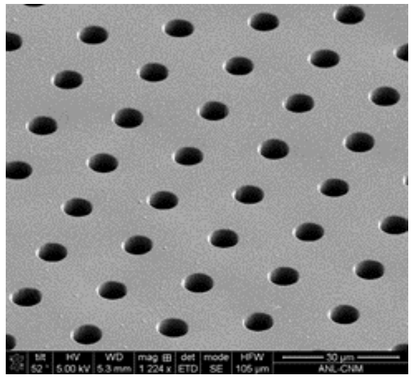
Dhir A et al. Clin Cancer Research. 2024

Circulating tumor cell (CTC) detection

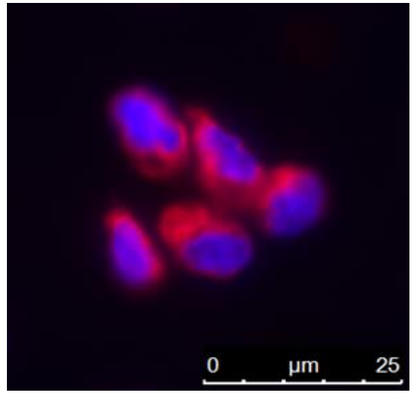
Size based CTC detection with CellSieve™ filter system

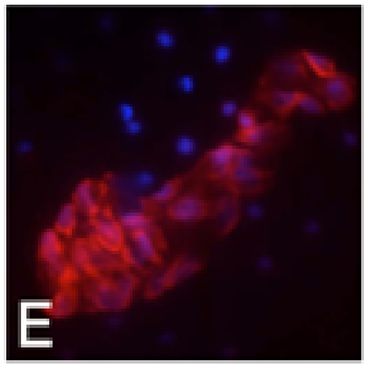
Isolation of CTC utilizing cell size differences using a 7µm pore filteration system.

CellSieve™ has been adapted for sarcomas using Vimentin positivity, CD45 negativity, and morphology.



CellSieve™ membrane





Adams D et al. PNAS. 2014
Adams D et al. Scientific Reports. 2016
Hayashi M et al. Oncotarget. 2017
Dhir A et al. Clin Cancer Research. 2024

Circulating tumor cell (CTC) detection

Patient ID	Baseline	C1	C2	C4	C6	C8	C10	C12	Response
1	16	27	200						PD
2	2	3	212						PD
3	5								PD
4	0	0	22						PD
5	2	4	2						PD
6	13	32	30						PD
7	0	0	11						PD
8	10	26	4	4	48				SD
9	5	5	9	3					PR
10	14								PD
11	4								PD
12	2	10	0	0	3	108	120	41	SD
13	10	9	8						PD
14	7	28							PD
15	16	0	4						PD
16	8	9	2	2					PR
17	5	0	52						PD
18	4	2	0						SD

Loose correlation with increase of CTC with PD

Time of Progression

Dhir A et al. Clin Cancer Research. 2024

ctDNA detection by ULP-WGS

Patient ID	Baseline	C1	C2	C4	C6	C8	C10	C12	Response
1	5.89%	0	0						PD
2	10.91%	7.71%	0						PD
3	15.45%								PD
4	0	0	0						PD
5	0	0	0						PD
6	0	0	0						PD
7	5.36	0	0						PD
8	0	0	0	0	21.1%				SD
9	0	0	0	0					PR
10	40.44%								PD
11	0								PD
12	0	0	0	0	0	0	0	0	SD
13	0	0	0						PD
14	9.76%	8.45%							PD
15	25.19%	3.51%	3.8%						PD
16	0	0	0	0					PR
17	17.41%	14.99%	8.83%						PD
18	0	0	0						SD

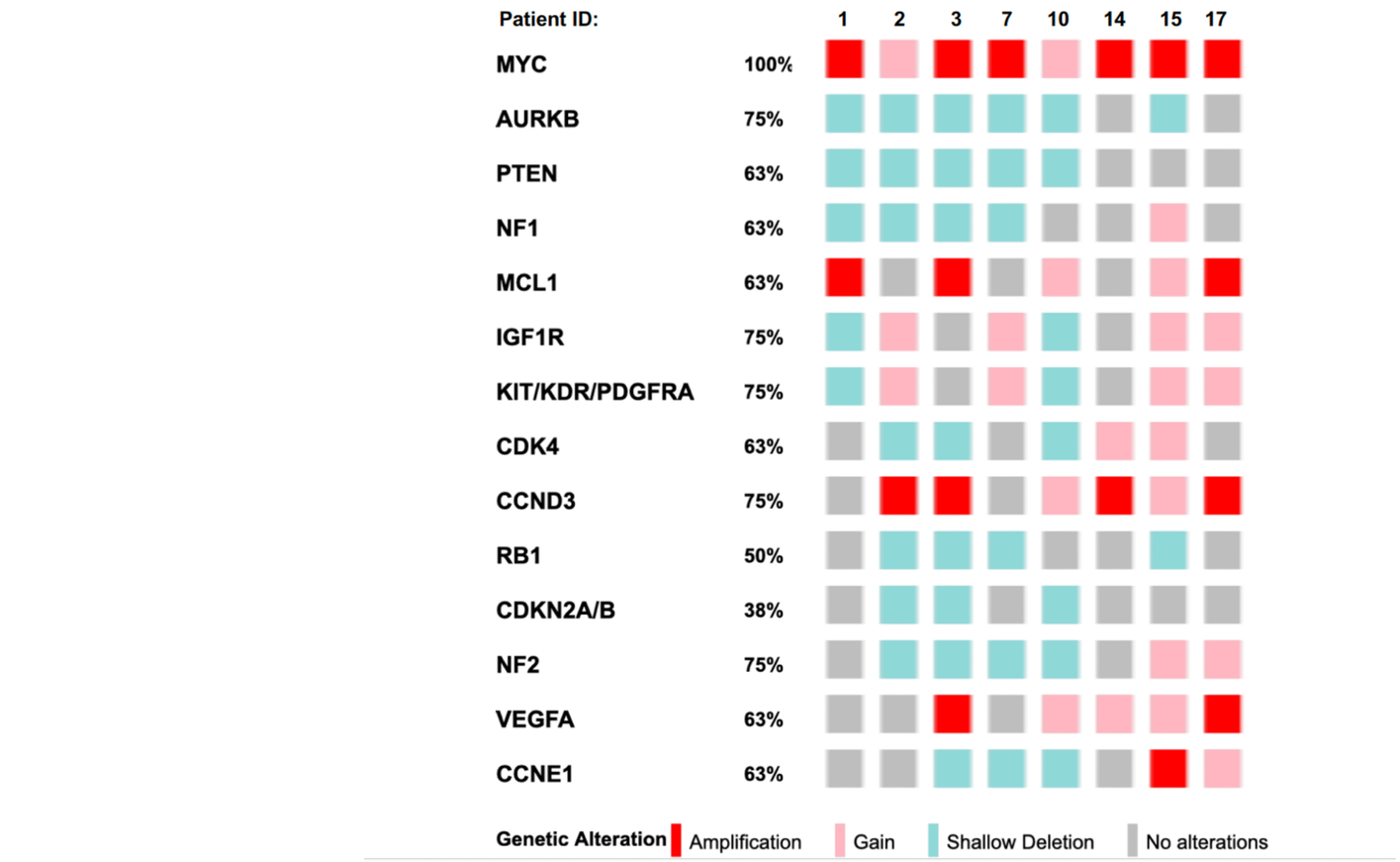
8 of 8 patients with detectable ctDNA at baseline progressed.

5 of 10 patients with negative ctDNA at baseline responded.

Time of Progression

Dhir A et al. Clin Cancer Research. 2024

MYC amplification is a common finding



Dhir A et al. Clin Cancer Research. 2024

Conclusion

Only a small subset of pretreated patients with relapsed OS and measurable disease had clinical benefit from the combination of gemcitabine and nab-paclitaxel in this study.

CTC appeared to be better suited to detect disease progression, while ctDNA detection was able to yield molecular disease characteristics that were not available in CTC enumeration.

The patients enrolled in our cohort were all patients with recurrent/refractory OS, and the high ratio of patients with *MYC* gain/amplification in our ctDNA results are certainly consistent with these previous reports, with all of them experiencing disease progression.

Prospective biomarker study MCC20320 has completed enrollment of 60 newly diagnosed osteosarcoma patients. CTC and ctDNA detection as a biomarker to predict progression and relapse is primary endpoint.

Dhir A et al. Clin Cancer Research. 2024

Acknowledgements

1. Hayashi Lab
   - Avery Bodlak
   - Josh Broadman
   - Sydney Hakim
   - Naoki Oike
   - Tim Porfilio
   - Ryota Shirai
2. University of Colorado Cancer Center Biostatistics and Bioinformatics Shared Resources
   - Andrew Goodspeed
3. National Pediatric Cancer Foundation
   - Lars Wagner
   - Javier Oesterheld
   - Aditi Dhir
   - All the site PIs
   - All the patients who participated
4. Collaborators and Mentors
5. Current and previous funding sources

THE Morgan Adams FOUNDATION
Funding Kids' Cancer Research

CDMRP

NATIONAL PEDIATRIC CANCER FOUNDATION
RISE UP FOR A FASTER CURE

1 MILLION 4 ANNA foundation

Hyundai Hope On Wheels®
Helping Kids Fight Cancer

St. Baldrick's FOUNDATION
Conquer Childhood Cancers

NIH
Eunice Kennedy Shriver National Institute of Child Health and Human Development

the pablove foundation
pablove.org
fighting childhood cancer with love

American Cancer Society®

Sarcoma SFA Foundation of America
finding the cure in our time

SARC
collaborating to cure sarcoma