PLK1 expression and KRAS mutations in colorectal cancer (CRC)

Priya Jayachandran[1], Andrew Elliott[2], Francesca Battaglin[1,3], Emil Lou[4], Wu Zhang[1], Shivani Soni[1], Hiroyuki Arai[1], Jingyuan Wang[1], Joshua Millstein[5], Albert Lockhart[6], W. Michael Korn[2] and Heinz-Josef Lenz[1]

1 Division of Medical Oncology, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA. 2 Caris Life Sciences, Phoenix, AZ, USA. 3 Medical Oncology Unit 1, Clinical and Experimental Oncology Department, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy. 4 Division of Hematology, Oncology and Transplantation, University of Minnesota, Minneapolis, MN, USA. 5 Preventive Medicine, Keck School of Medicine, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, USA. 6 University of Miami/Sylvester Comprehensive Cancer Center, Miami, FL, USA

Keck School of Medicine of USC

PRECISION ONCOLOGY ALLIANCE™ Powered by Caris Life Sciences

Abstract ID: 2046

Background

- Polo-like Kinase 1 (PLK1) is a serine/threonine protein kinase that has emerged as a next generation antimitotic target in cancer therapy, with several PLK inhibitors in development.
- PLK1 is highly expressed in many cancers and is associated with poor prognosis.
- Oncogenic mutations in the GTPase protein KRAS are prevalent (35-40%) in colorectal cancer (CRC) and are associated with resistance to targeted therapies.
- KRAS-mutant (MT) cells are particularly dependent on genes implicated in mitotic functions, such as PLK1.

Objectives

Primary Objectives:

- Evaluate gene expression levels of PLK1 in KRAS-MT versus KRAS-WT colorectal cancer
- Determine if PLK1 expression is associated with DNA mutations, activated pathways and clinical characteristics in CRC.

Hypothesis/Goal:

- Inhibition of PLK1 expression could reverse the drug resistance of cancer cells and increase sensitivity to radiotherapy and chemotherapy even in difficult to treat mutant KRAS cancers.
- A better understanding of whether PLK1 is overexpressed in KRAS-MT versus WT colorectal cancers, and whether this is associated with other molecular and genetic features or clinical outcomes will help in determining its role as a therapeutic target.
  - A phase II trial for mutant KRAS mCRC in second line in combination with FOLFIRI and bevacizumab (NCT03829410) is recruiting patients
  - Preclinical data suggest synergism with irinotecan and bevacizumab

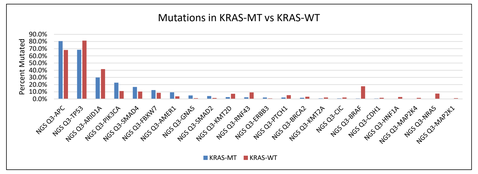
Methods

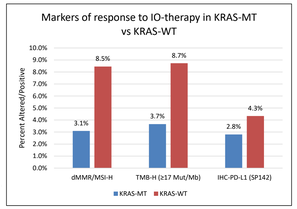
- We retrospectively reviewed 4551 CRC tumors profiled with Caris Life Sciences from 2019 to 2020.
- Profiling included whole transcriptome sequencing, targeted next-generation sequencing, tumor mutational burden (TMB), deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) status, and immunohistochemistry.
- The Microenvironment Cell Populations (MCP)-counter method was used to assess immune infiltration the tumor microenvironment.

Results

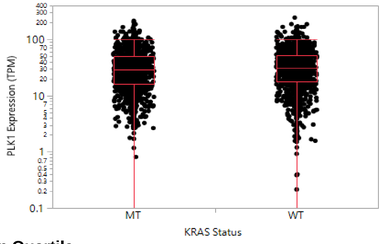
- Median PLK1 expression was similar in KRAS-MT vs KRAS-WT tumors (29.1 vs 31.2 transcripts per million [TPM]; p=0.043).
- Metastases had significantly lower PLK1 expression compared to primary tumors (26.6 vs 32.9 TPM; p<0.001).
- Tumors in the top quartile (Q4) PLK1 expression group were more frequently associated with a rectal primary site compared to the bottom quartile (Q1) group (27.3% vs 17.7%; p<0.001). Q4 tumors had increased mutation rates of TP53 (81.3% vs 68.1%), APC (78.7% vs 66.9%), and MSH6 (4.0% vs 1.3%) compared to Q1 (p<0.001). dMMR/MSI-H (8.6% vs 2.7%) and TMB (8.8% vs 2.9%) were significantly increased in Q4 compared to Q1 (p<0.001). Relative immune cell population and checkpoint gene expression increased gradually from Q1 to Q4 (p<0.001).

1. Mutations and Markers of response to IO therapy in KRAS-MT vs KRAS-WT





2. Median PLK1 expression is similar in KRAS-MT (29.1 TPM) vs KRAS-WT (31.2 TPM) tumors (p = 0.0429)



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
MT	0	9.031572	15.98465	29.0989	50.05265	75.455	213.41
WT	0	9.5603	17.94363	31.1665	51.47603	73.34179	243.514

Wilcoxon / Kruskal-Wallis Tests (Rank Sums)

Level	Count	Expected Score Sum	Score	Score Mean	(Mean-Mean0)/Std0
MT	2241	5010814	5100516	223597	-2.024
WT	2310	5347262	5257560	231483	2.024

1-Way Test, ChiSquare Approximation

ChiSquare	DF	Prob>ChiSq
4.0976	1	0.0429*

3. Clinical characteristics by PLK1 Expression Quartile

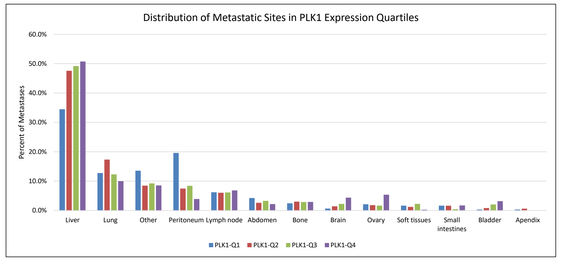
Median age (62 vs 61 years) and gender (44.9% vs 46.4% female) are not significantly different between top (Q4) and bottom (Q1) quartile PLK1 expression groups

Distribution of primary tumor locations (27.3% vs 17.7% rectal) and tumor specimen sites (36.1% vs 54.0% metastatic) are significantly different in Q4 compared to Q1

Characteristic	PLK1 TPM Q1	PLK1 TPM Q2	PLK1 TPM Q3	PLK1 TPM Q4	Q1 vs Q4 P-value
Total, N cases	1137	1139	1138	1137	N/A
Age					
- Median, years (SD)	61 (13.1)	62 (12.8)	63 (12.8)	62 (13.0)	0.2068
- Age Range, years	15-90	15-90	25-90	18-90	(Wilcoxon)
Gender					
- Male, N (%)	610 (53.6%)	655 (58.4%)	623 (54.7%)	626 (55.1%)	0.5006
- Female, N (%)	527 (46.4%)	474 (41.6%)	515 (45.3%)	511 (44.9%)	(Chi-square)
Primary Tumor Location					
- Left, N (%)	317 (27.0%)	365 (32.0%)	340 (29.9%)	305 (26.8%)	< 0.0001***
- Right, N (%)	226 (22.7%)	279 (24.5%)	278 (24.4%)	288 (25.3%)	(Chi-square)
- Transverse, N (%)	45 (3.8%)	61 (5.4%)	58 (5.1%)	51 (4.5%)	
- Rectal, N (%)	208 (17.7%)	225 (19.8%)	262 (23.0%)	310 (27.3%)	
- Unclear, N (%)	301 (25.7%)	209 (18.3%)	200 (17.6%)	183 (16.1%)	
Tumor Specimen Site					
- Metastatic, N (%)	612 (54.0%)	496 (43.6%)	488 (42.9%)	410 (36.1%)	< 0.0001***
- Primary, N (%)	522 (46.0%)	641 (56.4%)	649 (57.1%)	727 (63.9%)	(Chi-square)
- [Unclear, N]	[3]	[2]	[1]	[0]	

4. Metastatic sites in PLK1 Expression Quartiles

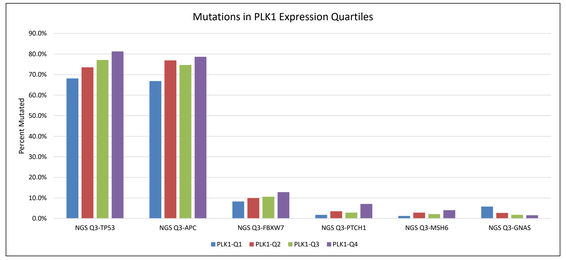
Sites with increased proportion in Q4 compared to Q1: Liver, Brain, Ovary, and Bladder



5. Mutations in PLK1 Expression Quartiles

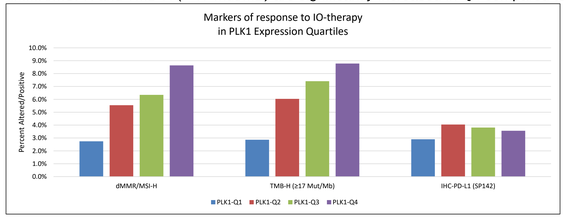
6 biomarkers with significantly different mutation rates in Q1 vs Q4 (p < 0.05)

5 biomarkers more frequently mutated in Q4: TP53, APC, FBXW7, PTCH1, and MSH6



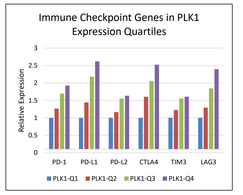
6. Markers of response to IO-therapy in PLK1 Expression Quartiles

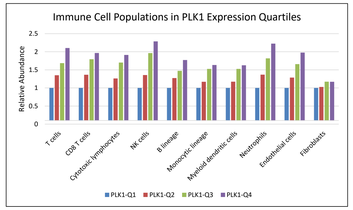
dMMR/MSI-H and TMB-H (≥ 17 mut/MB) are significantly increased in Q4 compared to Q1



7. Tumor Microenvironment in PLK1 Expression Quartiles

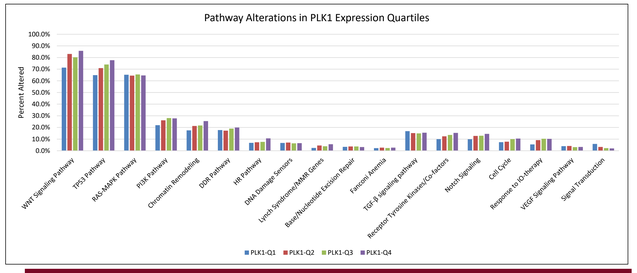
Cell population abundance shows graded increase from Q1 to Q4 for each cell population except fibroblasts. Immune checkpoint gene expression shows increase from Q1 to Q4





8. Biomarker results by Pathway in PLK1 Expression Quartiles

7 pathways more frequently altered in Q4: WNT Signaling, TP53, Chromatin Remodeling, Lynch Syndrome/MMR, Receptor Tyrosine Kinases/Co-factors, Notch, and Response to IO-therapy



Conclusions

- A lack of increased PLK1 expression suggests similar potential for PLK1 inhibitors in KRAS-MT tumors compared to KRAS-WT.
- Among PLK1 expression groups, proportionate increases in dMMR/MSI-H, TMB, and other immune-related markers suggest a potential response to immunotherapy in tumors with increased PLK1 expression.
- Combining immunotherapy with a PLK1 inhibitor might be a synergistic approach to increase sensitivity in PLK1-overexpressing CRC regardless of KRAS status.

References

1. Golsteyn R.M. The family of polo-like kinases. Prog Cell Cycle Res. 1996;2:107–114.
2. Liu Z, Sun Q, Wang X. PLK1, A Potential Target for Cancer Therapy. *Transl Oncol.* 2017;10(1):22–32.
3. Degenhardt Y, Lampkin T. Targeting Polo-like Kinase in Cancer Therapy. Clin Cancer Res January 15 2010 (16) (2) 384-389.
4. Mundt K.E. On the regulation and function of human polo-like kinase 1 (PLK1): effects of overexpression on cell cycle progression. Biochem Biophys Res Commun. 1997;239(2):377–385.
5. de Cárcer, G., Venkateswaran, S.V., Salgueiro, L. *et al.* Plk1 overexpression induces chromosomal instability and suppresses tumor development. *Nat Commun* 9, 3012 (2018)
6. Klauck, P.J., Bagby, S.M., Capasso, A. *et al.* Antitumor activity of the polo-like kinase inhibitor, TAK-960, against preclinical models of colorectal cancer. *BMC Cancer* 18, 136 (2018)

Priya.Jayachandran@med.usc.edu