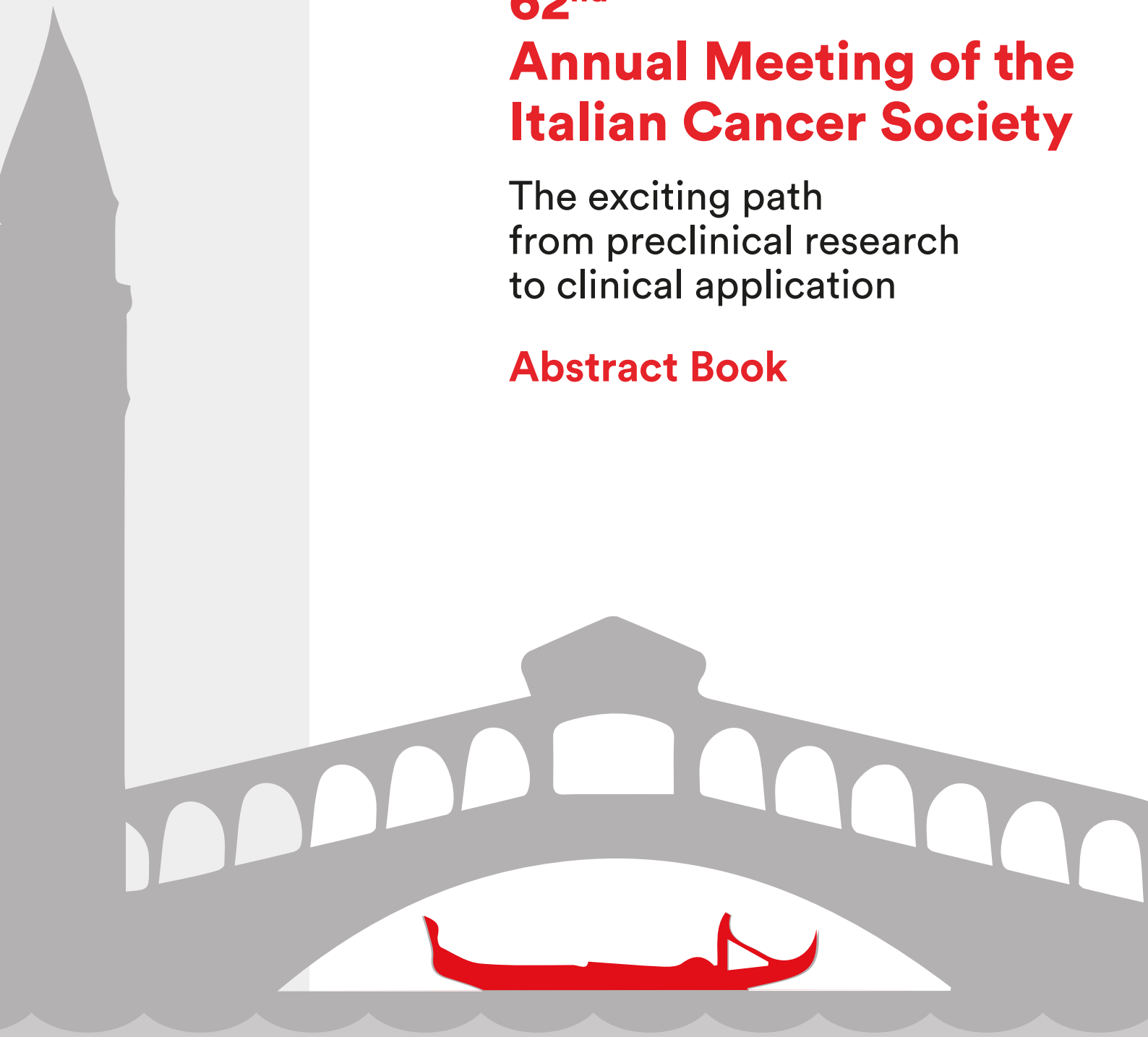
SIC

62nd Annual Meeting of the Italian Cancer Society

The exciting path
from preclinical research
to clinical application

Abstract Book



Venice, November 16-18, 2022

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Contents

K7

All-trans retinoic acid exhibits antineoplastic activity in Merkel cell carcinoma cells

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Merkel cell carcinoma (MCC) is a rare but aggressive skin cancer whose 5-yr survival rate is 50%. About 80% of MCCs, are linked to oncogenic Merkel cell polyomavirus (MCPyV), the remaining cases to UV exposure. Since the currently available MCC therapeutic options are remarkably limited, novel therapeutic approaches are required. The biological activity of retinoic acid or all-trans retinoic acid (ATRA) is mediated by RAR/RXR receptors, which are ligand-dependent transcription factors that activate genes crucial for cell differentiation. Dysregulations of RAR/RXR receptors lead to carcinogenesis. Although a strong in vitro/in vivo antitumor activity of ATRA has been proved in carcinoma of different histotypes, the effect of this drug in MCC is still unknown.
Herein, we investigated the antineoplastic effect of ATRA in vitro in MCPyV-positive, i.e., PeTa and WaGa, and -negative, i.e., MCC13 and MCC26, MCC cell lines and in human fetal lung fibroblasts (MRC5), as control.
The antineoplastic effect of ATRA was evaluated after 3 days of treatment by testing MCC cell proliferation, migration and colony formation abilities. Apoptosis/cell death were evaluated via Annexin-V and propidium iodide (P.I.) assays. Moreover, apoptosis was molecularly evaluated by RT^2 Profiler PCR mRNA array, that allows the analysis of 84 pro/anti-apoptotic genes, and by western blot (WB) analysis.
Results indicate that ATRA treatment led to a significant reduction in MCC cell proliferation, migration and colony formation abilities, while increasing apoptosis/cell death in MCC cell lines compared to untreated MCC cells. MCPyV-positive MCC cells were slightly more ATRA-sensitive compared to MCPyV-negative cells. No significant effects have been found in the ATRA-treated control cell line. Gene expression array indicated a significant overexpression of several pro-apoptotic genes in ATRA-treated MCC cells compared to untreated cells. High levels of pro-apoptotic proteins have been found following ATRA treatments in MCC cells, while these proteins were almost undetectable in untreated MCC cells. Upon ATRA treatment on the control cell line, pro-apoptotic mRNA/protein markers were almost undetectable. Overall, our in vitro data indicate that ATRA is effective in reducing MCC cell growth, while presenting strong pro-apoptotic effects and favoring cell death. These results, obtained for the first time, point to ATRA as a potential novel effective antineoplastic drug for the MCC therapy.

K8

STARD3: a new potential therapeutic target in colorectal cancer

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Colorectal cancer (CRC) is the third leading cause of cancer death in Europe, with a prevalence of more than a million cases every year. Primary or acquired resistances to therapies are the major limits to be addressed. The recent advances in in vitro 3D culture technologies, such as organoids, have opened new avenues for the development of novel and more physiological human cancer models. Organoids recapitulate the histological and genetic features of original tumors becoming essential for a more efficient precision medicine approach. In this scenario, considering the druggability (cholesterol-binding pocket on the START domain) and the number of publications related to cancer, we identified STARD3 as a potential theranostic target in mCRC (Alpy et al., 2013). STARD3 is a member of START protein family, it is involved in the shuttling of cholesterol, and it is overexpressed in several types of cancer such as breast, prostate and colon (Asif et al., 2021; Vassilev et al., 2015).
A COSMIC database analysis reveals STARD3 amplification in colon cancer. Our analysis showed that in 13,7% of tumour samples, STARD3 RNA is over-expressed with Z-score level higher than 2. STARD3 silencing in colon cancer cells dramatically suppresses proliferation, colony formation capacity and activates the apoptotic pathway. The overexpression of STARD3 in normal colon organoids was able to induce tumorigenesis in vitro and in vivo. On these bases, in order to identify drugs able to inhibit the activity of STARD3 protein, it was developed the first reported virtual screening platform for this target and the novel VS1 inhibitor (Lapillo et al., 2019). Finally, we investigate VS1 efficacy on 25 patient-derived human colon cancer organoids. In a group of patients, defined as VS1 sensitive, the IC50 of the STARD3 inhibitor was comparable if not lower than the first-line drugs. In summary, we reported a novel colon cancer gene, which the chemical inhibition could be a therapeutic choice after the first line treatment.