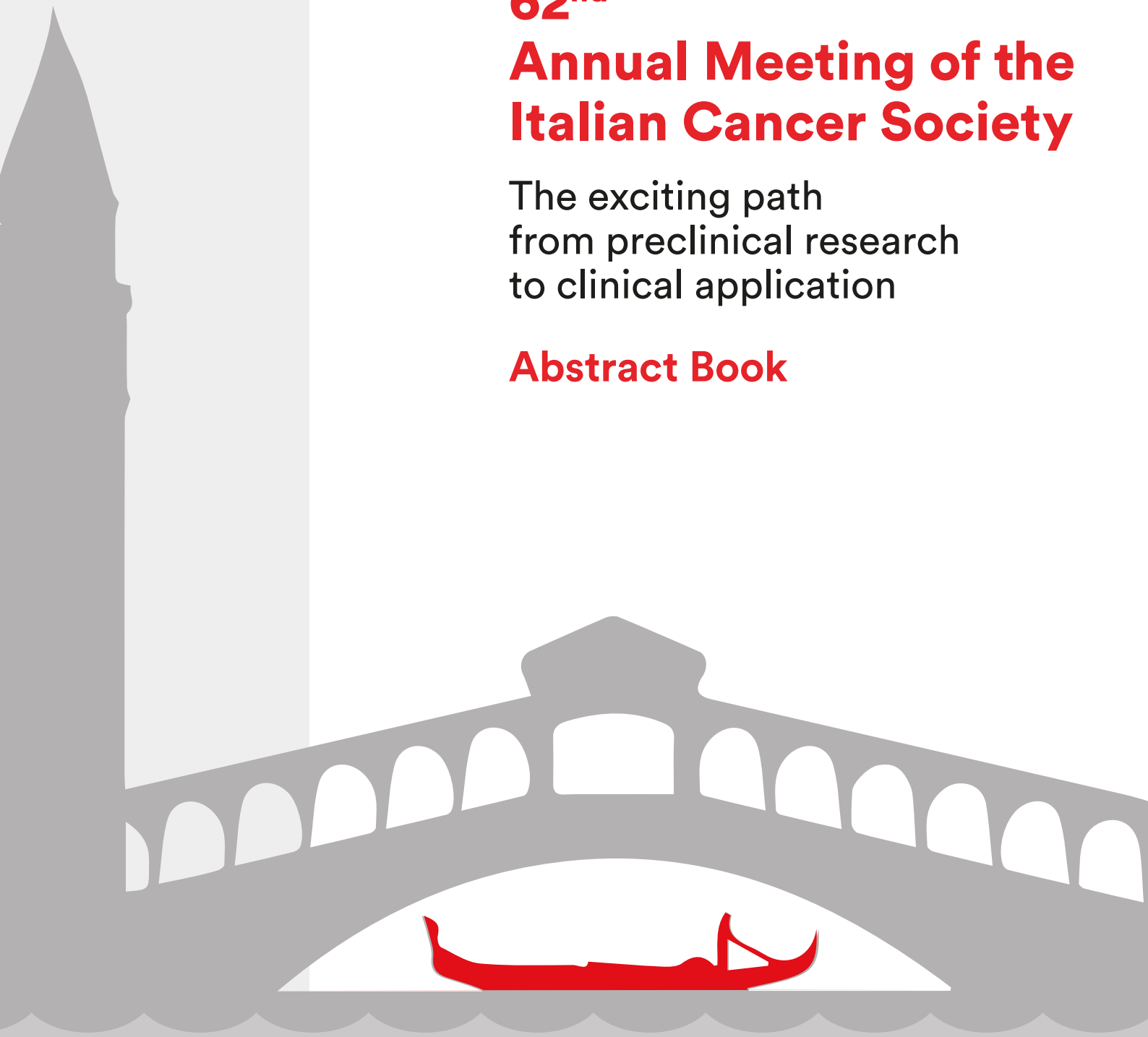
SIC

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

H1

Impaired IgG antibody response to Merkel cell polyomavirus in patients affected by malignant pleural mesothelioma and workers exposed to asbestos

Rotondo J.C. [1], Mazziotta C. [1], Tramarin M.L. [1], Cervellera C.F. [1], Badiale G. [1], Bononi I. [1], Libener R. [2], Grosso F. [3], Tognon M. [1], Martini F. [1]
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Malignant pleural mesothelioma (MPM) is a rare but aggressive tumor of the serosal cavities. Previous data suggest that alongside the inhalation of carcinogenic asbestos, other factors are involved in the MPM onset, including oncogenic viruses. Merkel cell polyomavirus (MCPyV) is a near-ubiquitous small DNA tumor virus linked to Merkel cell carcinoma, a skin tumor that primarily arises in conditions of immune suppression. The MCPyV seroprevalence in MPM patients and in workers ex-exposed to asbestos (WEAs) is unknown.
Herein, an indirect enzyme-linked immunosorbent assay (ELISA) method with two peptides mimicking MCPyV antigens was used to investigate immunoglobulins G (IgGs) to MCPyV in sera from MPM patients (n=108), WEA individuals (n=62) and healthy subjects (HS) (n=110). MCPyV seroprevalence and serological profiles were determined. To assess the humoral immune status of MPMs and WEAs, the total serum IgGs were evaluated, too.
A lower rate of serum anti-MCPyV IgGs was detected in MPM (26.9%) and WEA (29%) compared to HS (60.9%) ($p<0.001$). Serological profile indicated lower optical densities (ODs) in MPM and WEA compared to HS ($p<0.05$). The mean total IgG concentration resulted similar among MPM, WEA and HS groups ($p>0.05$). Receiver-operating characteristic (ROC) curves indicated that MCPyV serology proved high sensitivity (77.2-91.2%) and specificity (77.8-93.5%) in distinguishing both MPM and WEA from HS, with moderate J indexes (0.55-0.84); areas under the curves (AUCs) (0.85-0.98) were within the moderate/accurate reference range, and higher than that of a worthless test (0.5, $p<0.001$). WEAs with the highest asbestos exposure had the lower rate of serum anti-MCPyV IgGs (5.5%) compared to WEAs (45.5%) with the lower exposure. Serological profile confirmed these data.
We provided the first evidence of the MCPyV serology in MPM and WEA. Our data suggest that MPMs and WEAs are experiencing a specific impairment of their immune response to MCPyV, which might rely to the immunomodulatory effect of asbestos, a well-known immunosuppressive mineral. Both MPMs and WEAs may be predisposed to a reduced ability to present MCPyV antigens, thus resulting to a possible increase in viral activity. Verifying how and whether MCPyV plays a role in MPM is a future area of study. Evaluating MCPyV serology may complement current follow-up analyses, thus giving additional information on exposed subjects who are at risk of developing asbestos-related tumors, such as MPM.

H2

Targeting CDK as a new potential therapeutic approach for malignant pleural mesothelioma treatment

Zoppi S. [1], Terenziani R. [1], Galetti M. [2], La Monica S. [1], De Forni D. [3], Poddesu B. [3], Lori F. [3], Petronini P.G. [1], Bonelli M. [1]
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The loss of the CDKN2A/ARF gene is the most common genetic alteration in malignant pleural mesothelioma (MPM), with a percentage of incidence varying from 50% to 100% depending on the tumor histotype, thus representing a novel target approach for the therapy of this untreatable tumor.
Previously, we demonstrated the efficacy of the treatment with the CDK4/6 inhibitor palbociclib, alone or combined with PI3K inhibitors, in inhibiting cell proliferation and impairing tumor cellular metabolism in a panel of MPM cell lines (Bonelli M, Neoplasia 2017, Bonelli M, Int J Mol Sci 2020).
In the present work we evaluated the antitumor potential of combining the standard chemotherapy regimen indicated for unresectable MPM with CDK4/6 inhibitors, including the new promising drug abemaciclib. Abemaciclib differs from other CDK inhibitors because it exerts some inhibitory effects on CDK9, in addition to its specific CDK4/6 target. Our findings demonstrated that the simultaneous treatment of abemaciclib combined with cisplatin and pemetrexed has a greater antiproliferative effect than the combination of cisplatin with pemetrexed in commercially available MPM cell lines and in primary culture cells obtained by pleural effusion of MPM patient. This simultaneous treatment induced cellular senescence or autophagic cell death, depending on the cell type. Notably, the effect of such combination was irreversible and no resumption in tumor cell proliferation was observed after drug withdrawal.
Moreover, we investigated the efficacy in vitro and in vivo of VS2-370, a new compound with promising anti-tumor activity, developed by the Italian company ViroStatics. Differently from commercial CDK4/6 inhibitors, VS2-370 targets both CDK4/6 and CDK9 to a similar extent. VS2-370 exhibited greater anti-proliferative efficacy than commercially available CDK4/6 inhibitors (including abemaciclib and palbociclib), with ca. 50-fold reduction in IC50 and with induction of apoptosis. The efficacy of this molecule has been demonstrated also in vivo in an immune-competent orthotopic rat recurrence model of MPM: the treatment with VS2-370 strongly prevented tumor relapse compared to control or to palbociclib treated animals.
Overall, our results demonstrated the therapeutical potential of CDK inhibitors for the treatment of MPM, alone or combined with standard chemotherapy, consistent with the recent positive results of the MiST2 arm in abemaciclib-treated patients (Fennell DA, Lancet Oncol 2022).