Targeting CDK4 in Melanoma: Mechanisms of Resistance and Novel Combinational Therapies

Shatha AbuHammad
The Cyclin Dependent Kinase 4 (CDK4) Pathway

- CDK4/Cyclin D complex drives the cell cycle progression by phosphorylating and inhibiting the Retinoblastoma (RB) protein.

- The tumour suppressor p16, which is encoded by the CDKN2A\textsuperscript{p16} gene, is a direct inhibitor of CDK4/Cyclin D complex.

- Dysregulation of the CDK4 pathway occurs in \~90\% of melanomas.

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Acquired resistance to palbociclib develops upon chronic exposure

**BRAF\textsuperscript{V600E}**

- A375

**NRAS\textsuperscript{Q61K/L}**

- C002

**BRAF\textsuperscript{WT}/NRAS\textsuperscript{WT}**

- CHL1

Confluency (%) vs. Time (Days)

Legend:
- ●●● Parental – No drug
- ▪ Parental – 2μM Palbociclib
- • Resistant – No drug
- ◊ Resistant – 2μM Palbociclib
CDK2 activation drives resistance to CDK4 inhibition and combining palbociclib with CDK2 inhibitors overcomes resistance.
Multiple mechanisms of resistance and activation of CDK2 pathway

- **Loss of p21 induction**
- **Increased Cyclin E**
- **Reduced RB expression**

**2μM Palbociclib**

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<tr>
<th></th>
<th>Parental</th>
<th>Resistant</th>
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<tbody>
<tr>
<td>p21</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tubulin</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>A375 (BRAF^{V600E})</td>
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**Cyclin E**

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<td>HT144 (BRAF^{V600E})</td>
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<tr>
<td>CHL1 (WT/WT)</td>
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<tr>
<td>C002 (NRAS^{Q61K})</td>
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<tr>
<td>D04 (NRAS^{Q61K})</td>
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Depletion of p21 and p53 confers resistance to CDK4 inhibitors
Summary

- The resistance to CDK4 inhibitors develops due to multiple mechanisms including:
  - CDK2 activation:
    • Loss of p21 induction in a p53-dependent pathway.
    • Overexpression of Cyclin E.
  - Down-regulation of RB.
- Inhibition of CDK2 restores sensitivity to CDK4 inhibitors.
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