ARISTOTLE UNIVERSITY OF THESSALONIKI

ΑΡΙΣΤΟΤΕΛΕΙΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΟΝΙΚΗΣ
Τμήμα Χημικών Μηχανικών

"The molecular biology of Lung Cancer."

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Lung cancer statistics

Lung cancer new cases 2.4 million people and resulted in 2.2 million deaths.(WHO data, 2017)

Is the 1st cause of cancer-related death in men.

2nd most common in women after breast cancer.

80-85% of cases of lung cancer are due to tobacco smoking.

15-20% of cases are due to genetic factor or environmental factors.

References: WHO, ACR

Gene Mutations in Lung Cancer

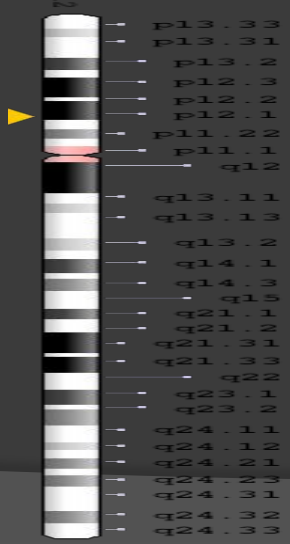
Kras gene: The protein relays signals from outside the cell to the cell's nucleus.

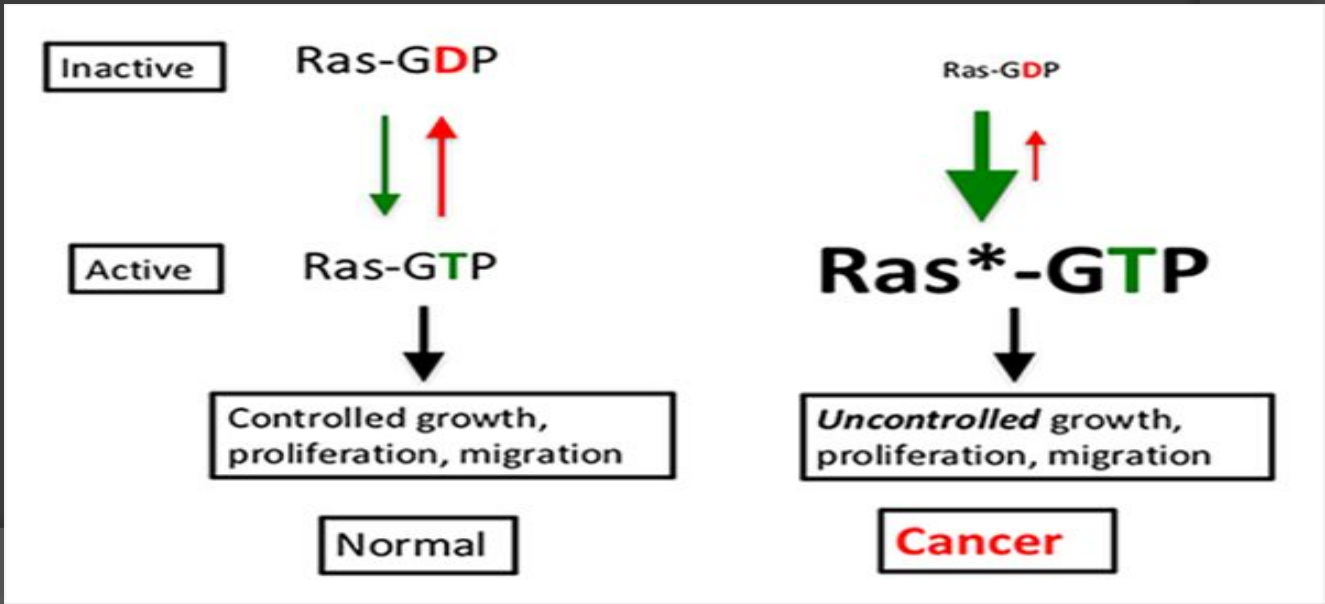
These signals instruct the cell to grow and divide (proliferate) or to mature and take on specialized functions (differentiate).

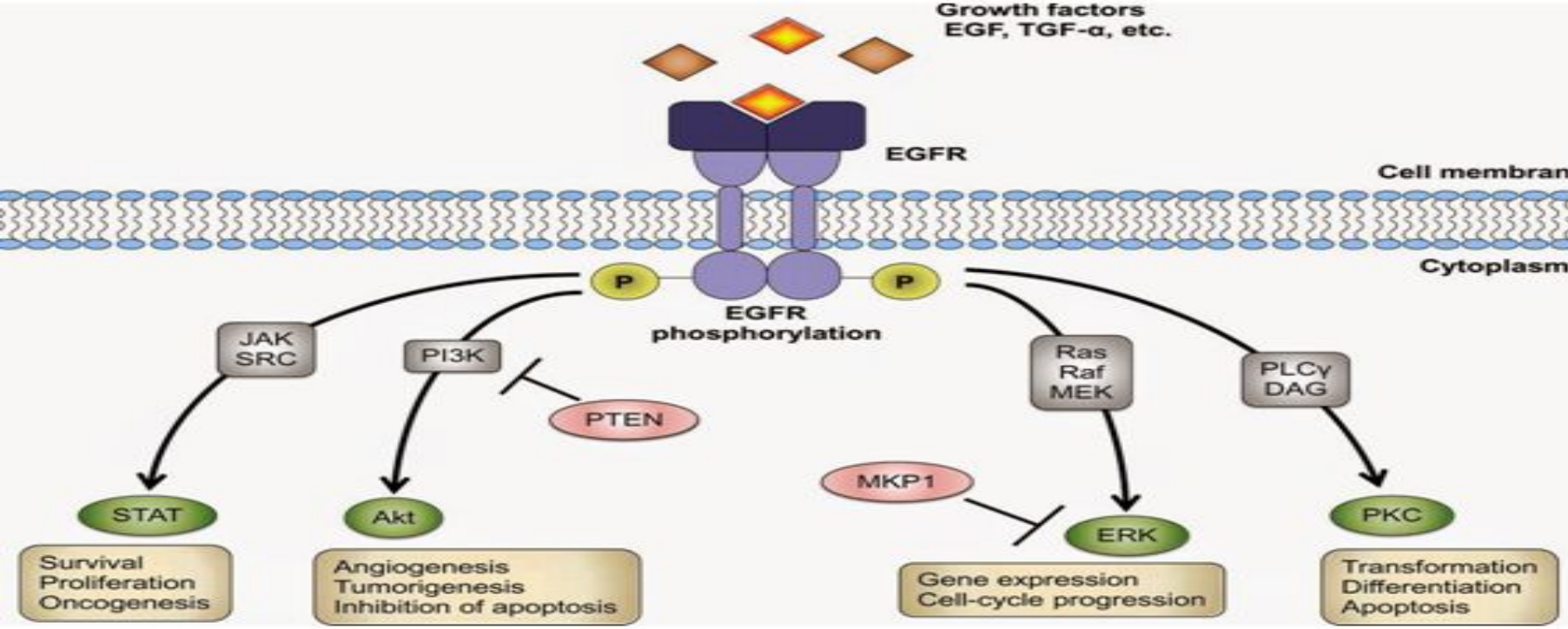
The K-Ras protein is a GTPase, which means it converts a molecule called GTP into another molecule called GDP.

In this way the K-Ras protein acts like a switch that is turned on and off by the GTP and GDP molecules

Cytogenetic Location: 12p12.1, which is the short (p) arm of chromosome 12 at position 12.1







The **epidermal growth factor receptor** (**EGFR**; **ErbB-1**; **HER1** in humans) is a transmembrane protein. It is activated by various ligands in extracellular space and transmits the cellular response to mediate various cellular activities, including cell proliferation, cell survival, growth and development.

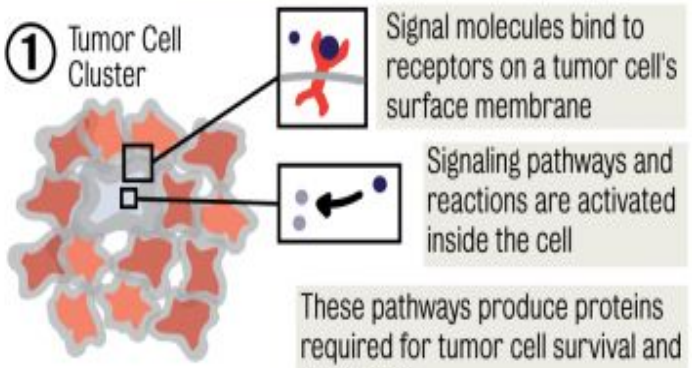
The epidermal growth factor receptor is a member of the ErbB family of receptors, a subfamily of four closely related receptor tyrosine kinases:
EGFR (ErbB-1), HER2/neu (ErbB-2), Her 3 (ErbB-3) and Her 4 (ErbB-4). In many cancer types, mutations affecting EGFR expression or activity result in cancer.

Epidermal growth factor and its receptor was discovered by Stanley Cohen of Vanderbilt University. (1986 Nobel Prize in Medicine)

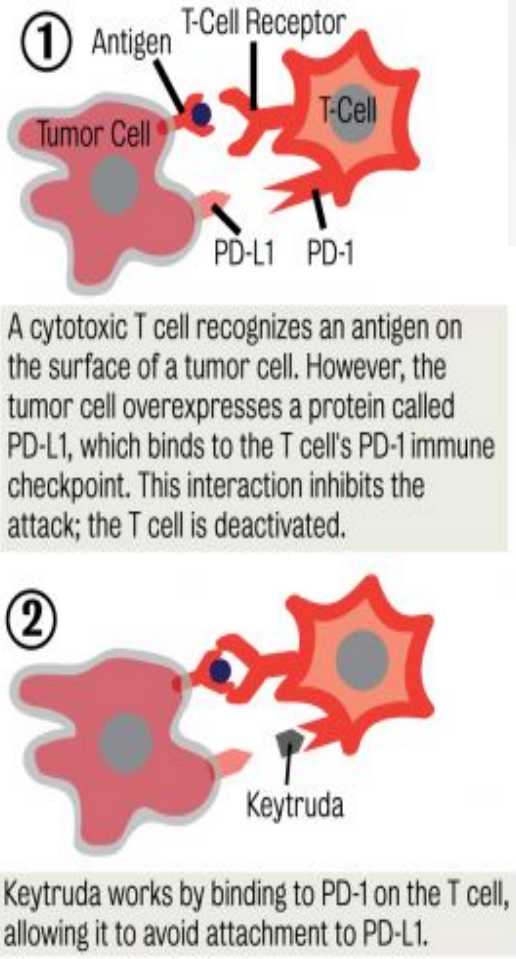
FDA APPROVES IMMUNOTHERAPY-BASED DRUG FOR LUNG CANCER TREATMENT

The drug pembrolizumab, marketed as Keytruda, underwent 4 years of testing before receiving first-line approval for the treatment of non-small cell lung cancer (NSCLC). Keytruda is an immunotherapy-based drug, in contrast to older classes of drugs called signal-transduction inhibitors.

Mutation-based therapy



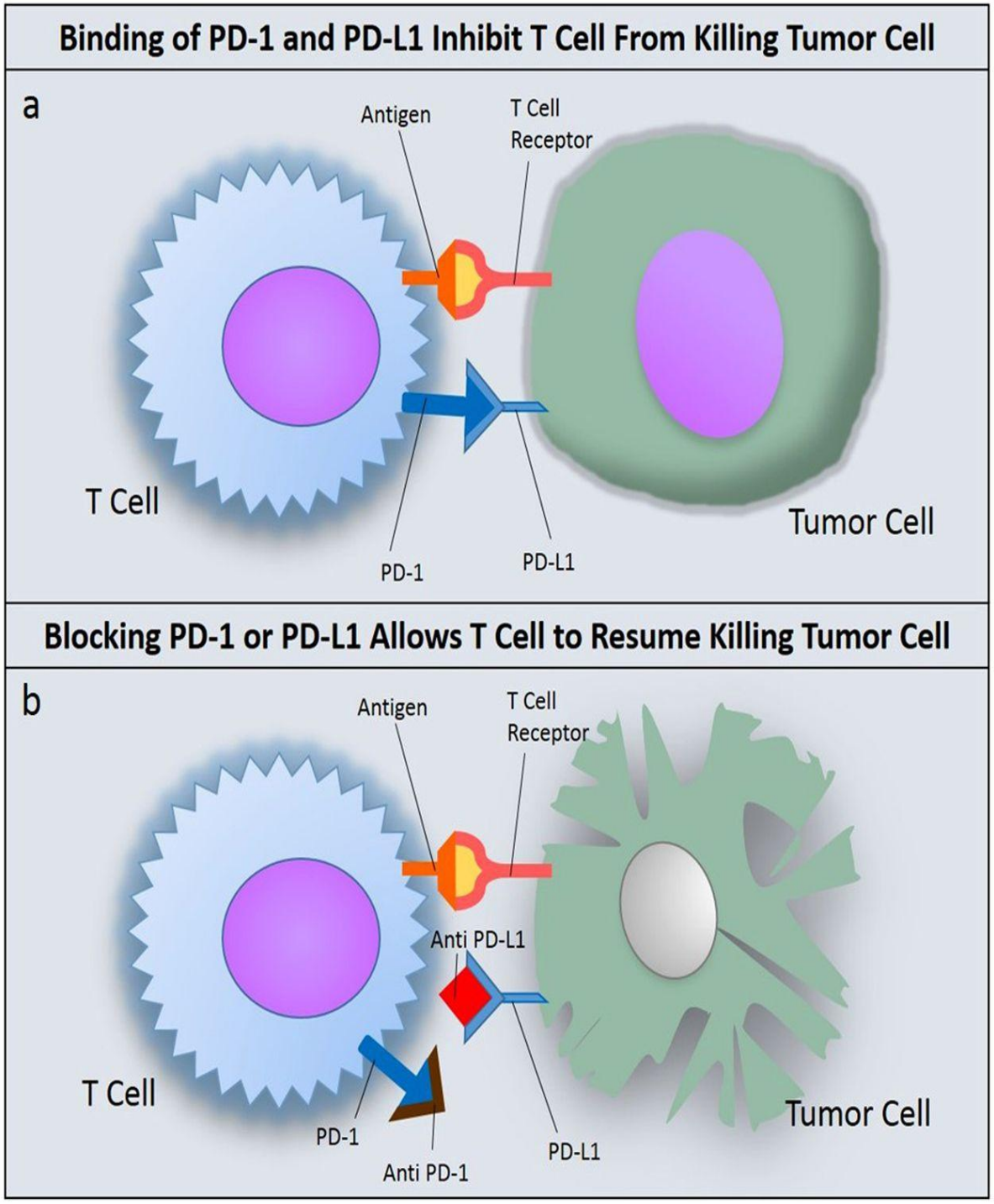
Immunotherapy



Price: € 1,892.00/ 50mg

The standard dosage is:
NSCLC: 200 mg every 3 weeks.

Administer as an intravenous infusion over 30 minutes.



Programmed death-ligand 1 (PD-L1) is a 40kDa type 1 transmembrane protein that plays a major role in suppressing the immune system

PD-1 on T cells

PD-L1 on cancer cells,

Professors James P. Allison and Tasuku Honjo (Nobel Prize in Medicine, 2018)

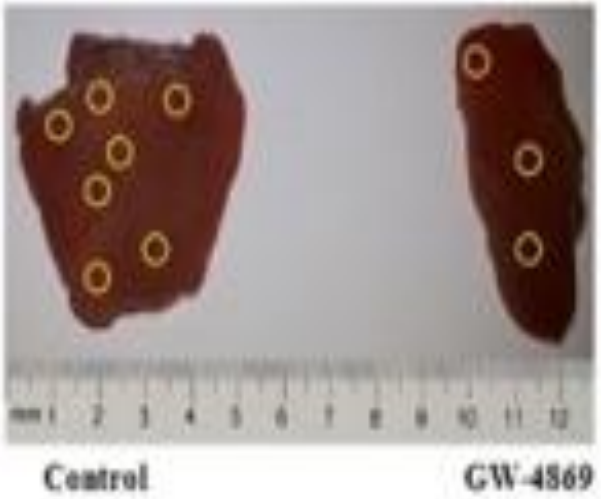
Immunomodulators

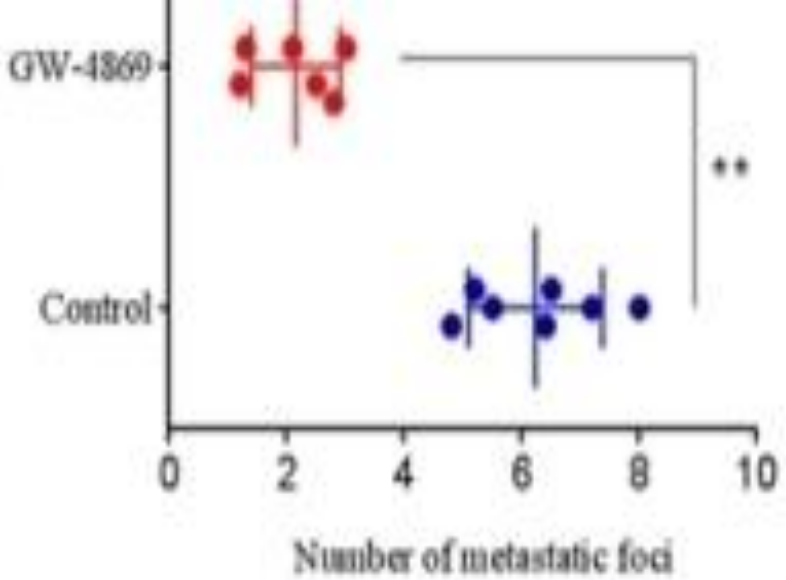
Atezolizumab (Tecentriq®): a checkpoint inhibitor that targets the PD-1/PD-L1 pathway; approved for subsets of patients with advanced non-small cell lung cancer (NSCLC)

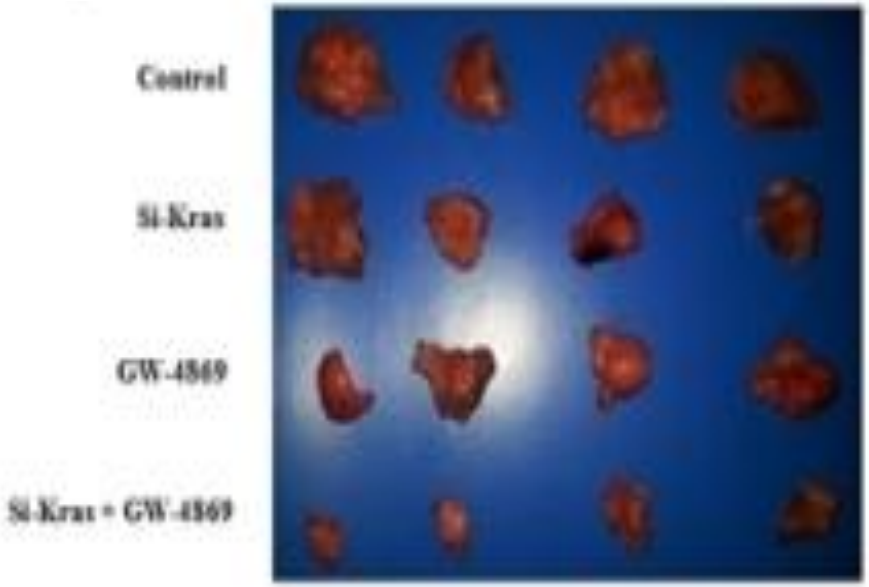
Durvalumab (Imfinzi™): a checkpoint inhibitor that targets the PD-1/PD-L1 pathway; approved for subsets of patients with advanced non-small cell lung cancer (NSCLC)

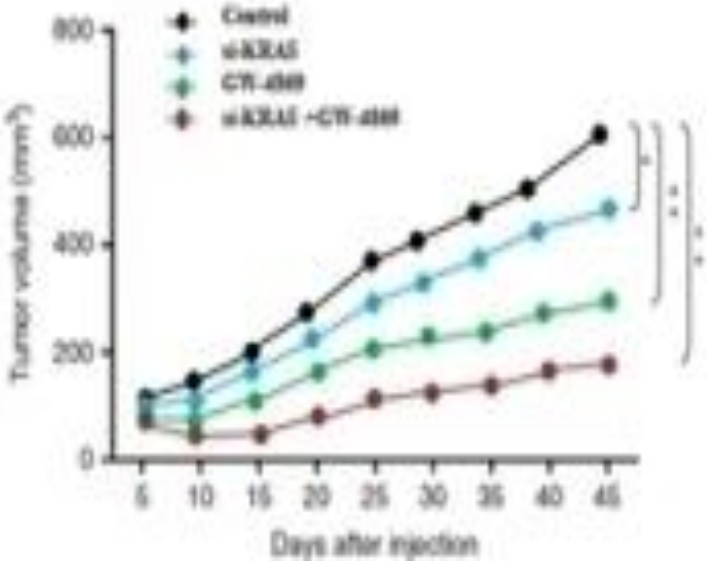
Nivolumab (Opdivo®): a checkpoint inhibitor that targets the PD-1/PD-L1 pathway; approved for subsets of patients with advanced non-small cell lung cancer (NSCLC) as well as those with metastatic small cell lung cancer (SCLC) that has advanced following treatment with platinum-based chemotherapy and at least one other line of treatment

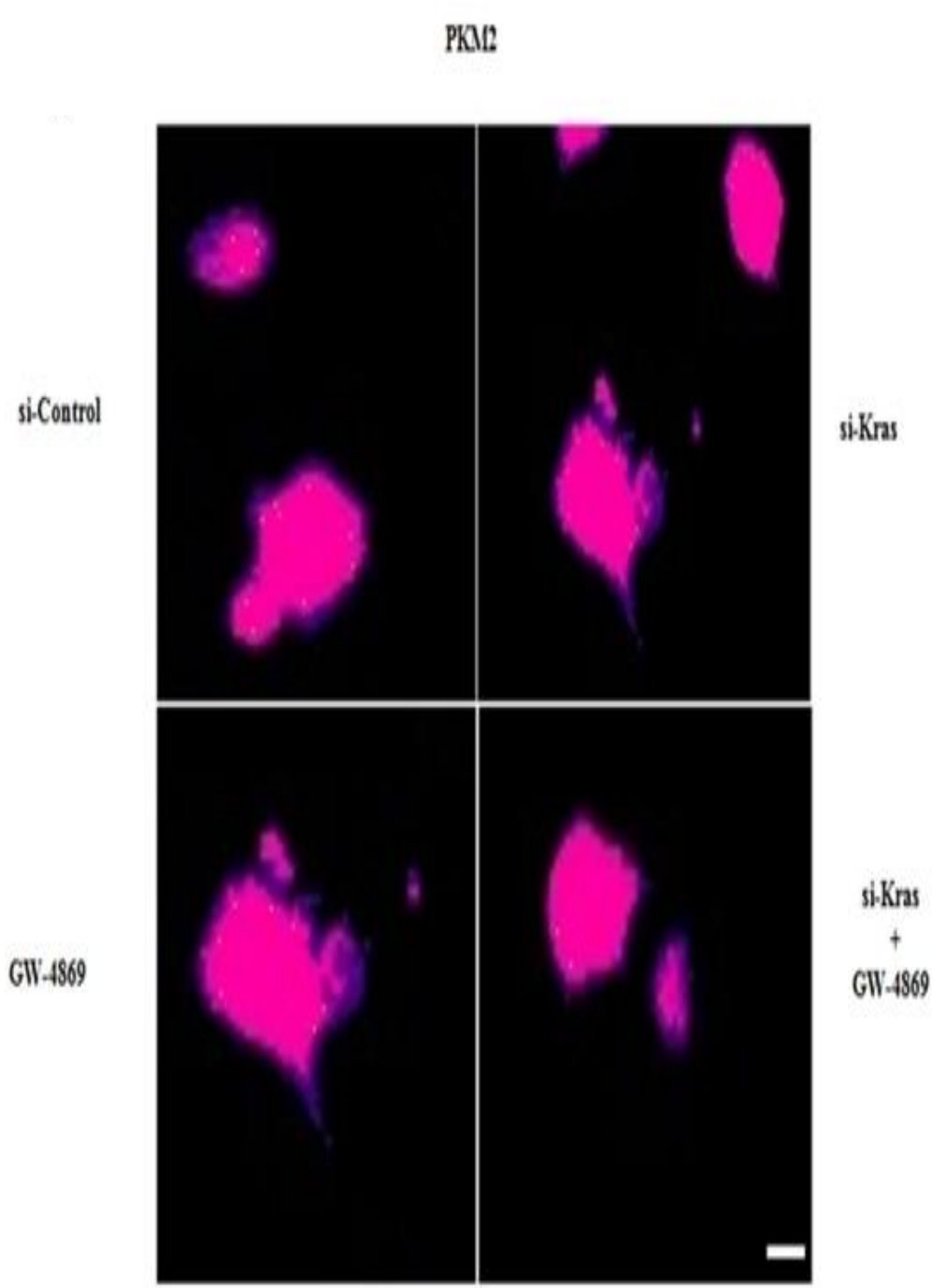
Lymph Nodes


Control
GW-4869

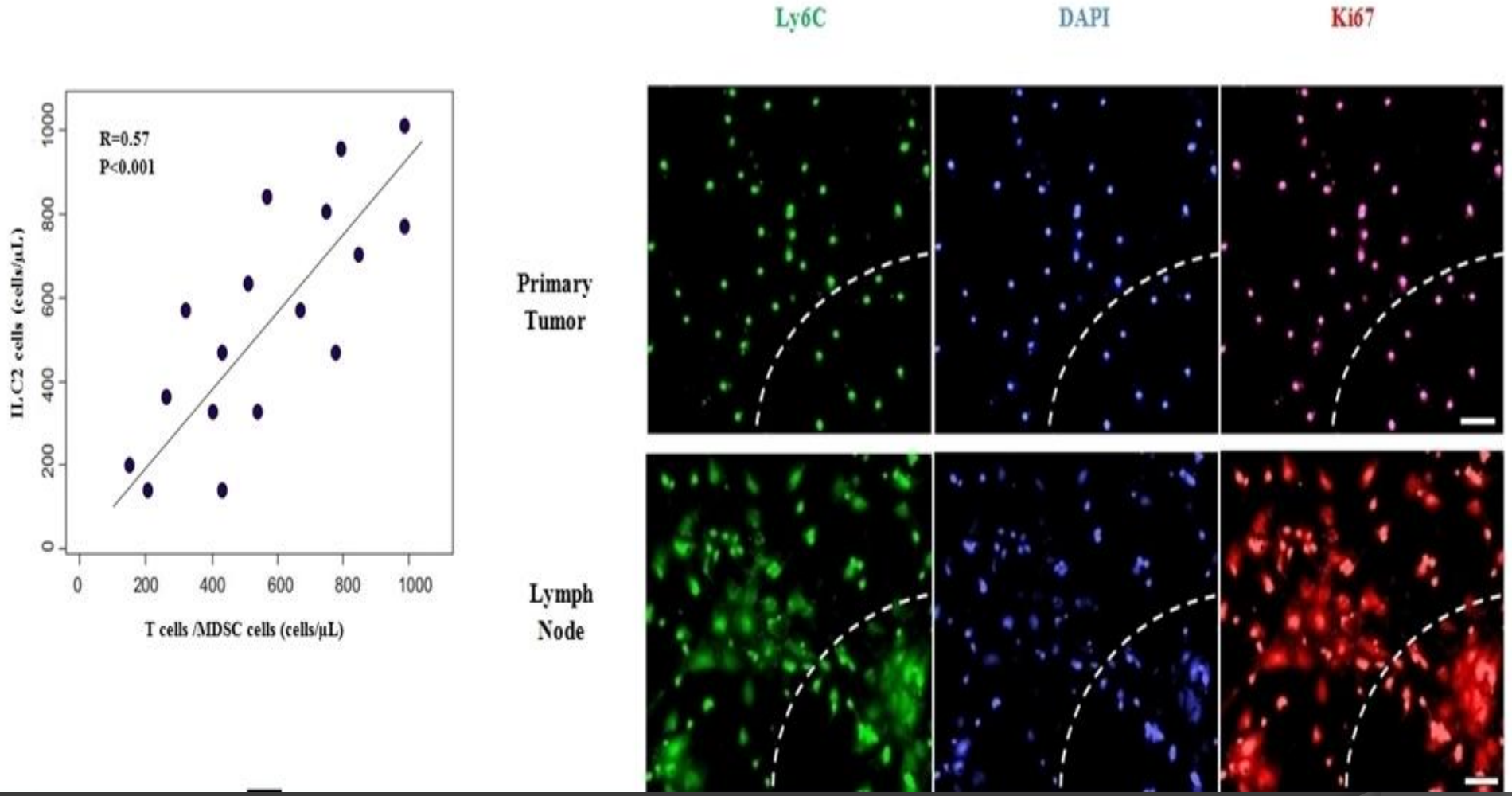

GW-4869
Control
**
0
2
4
6
8
10
Number of metastatic foci


Control
Si-Kras
GW-4869
Si-Kras + GW-4869


Control
si-KRAS
GW-4869
si-KRAS +GW-4869
Tumor volume (mm³)
800
600
400
200
0
5
10
15
20
25
30
35
40
45
Days after injection

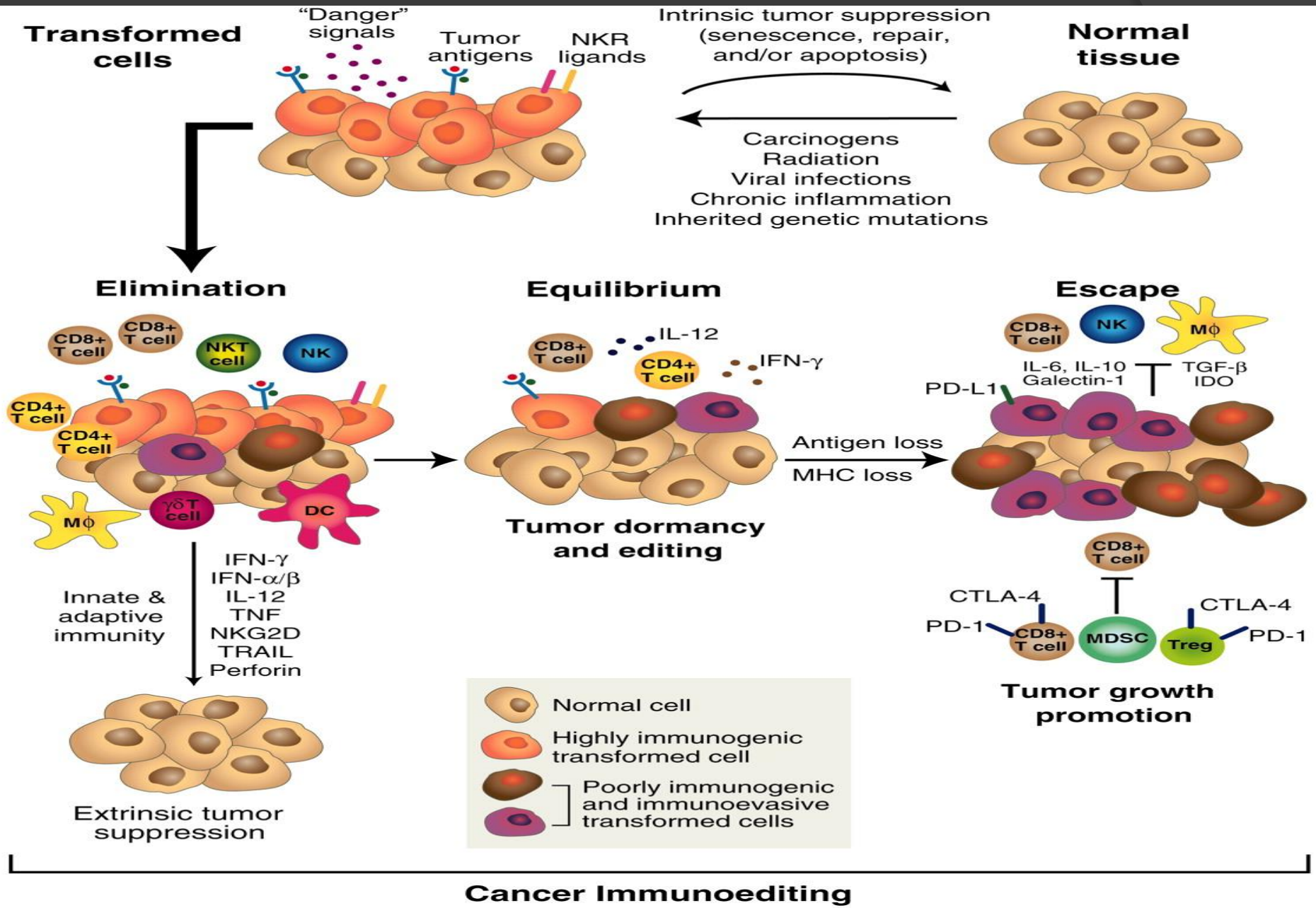


Immunofluorescence analysis of intracellular PKM2 localization in Kras (+) LC-DR cells (magnification × 400). Drug resistant cells were treated with siKras (4 μg, 48h) and GW-4869 (25 μM) for 24h. Data represent the mean ±SD of three independent experiments (*P < 0.05; **P < 0.01).



T cell/MDSC correlation in primary tumor and LN metastasis following chemotherapy treatment

The 3Es of Cancer Immunoediting



Nanoparticles targeting MDSC chemoresistant immunosuppression