GENETIC TESTING IN LUNG CANCER

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CANCER: ORGAN SPECIFIC DISEASE TO GENETIC DISEASE

- PRIOR TO THE DEVELOPMENT OF FIELD OF GENETICS, CANCER CONSIDERED AN ORGAN SPECIFIC DISEASE
- WE CHARACTERIZE OF TUMOR BY SIZE, GRADE AND INVASIVENESS, LNS, REGIONAL SPREAD OR DISTANT METSTASIS- STAGING
- IN STAGING TRY TO GROUP CANCER CHARACTERISTICS INTO GROUPS WITH SIMILAR PROGNOSIS
- DOES NOT INFORM ABOUT THE INTRINSIC “AGGRESSIVENESS” CHARACTERISTICS OF THE TUMOR
- MOLECULAR STUDIES INFORM “PERSONALIZED” TREATMENTS

MAJOR GENE PROCESSES IN CANCER

- ONCOGENES
- PROMOTE TUMORIGENESIS
- PROLIFERATION
- INVASION
- INHIBIT APOPTOSIS
- ALLOW DNA INSTABILITY

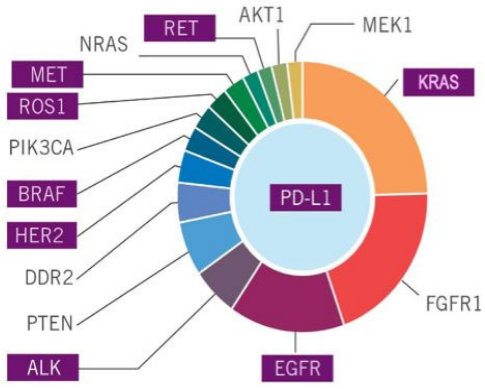
- TUMOR SUPPRESSORS
- INHIBIT TUMORIGENESIS
- INHIBIT PROLIFERATION
- INHIBIT INVASION
- PROMOTE APOPTOSIS
- PROMOTE DNA STABILITY

- GENETICS CODED IN SSDI'S
- HOWEVER, WHAT ARE WE CODING AND WHY IS IT IMPORTANT?
- COLLECT DATA FOR RESEARCHERS TO ID LINKS BETWEEN SPECIFIC GENE MUTATIONS
- IDENTIFY VIABLE GENETIC TARGETS – SPECIFIC MUTATIONS IN SPECIFIC CANCERS
- HOW NEW THERAPIES PERFORMING IN THE PRESENCE OF THESE MUTATIONS
- INFORM TREATMENT GUIDELINES
- LUNG CANCER WAS AMONG FIRST CANCERS WHERE TARGETED THERAPIES
- WERE TESTED

LUNG CASE SCENARIO

- **Pertinent Negative Results:**
- **AKT1, ALK, BRAF, CHEK1, DDR2, EGFR, ERBB2, FGFR1, MAP2K1M, MET, NRAS, NTRK1, PIK3CA, POLE, ROS1, STK11, TERT.**
- **KEYTRUDA PD-L1 Immunohistochemical Analysis (NSCLC):**
- **Tumor Proportion Score <1%/Negative**

LUNG BIOMARKER TESTING PER NCCN GUIDELINES

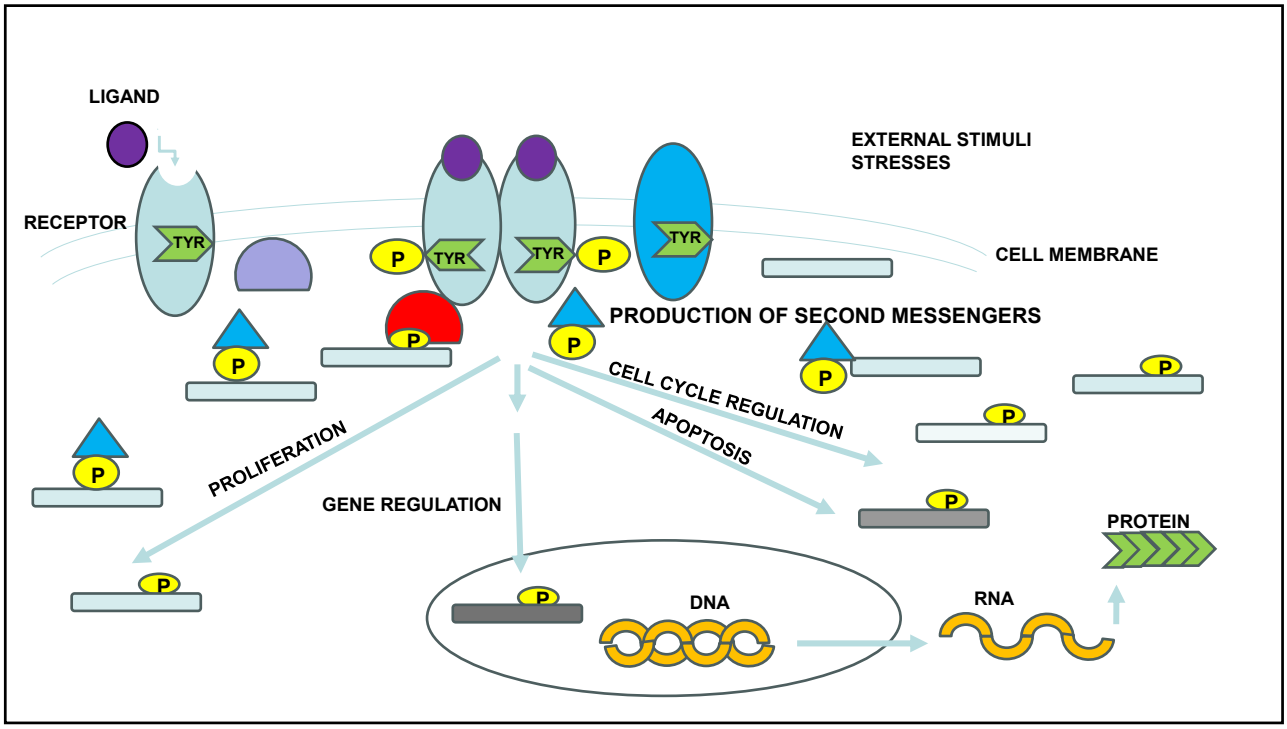


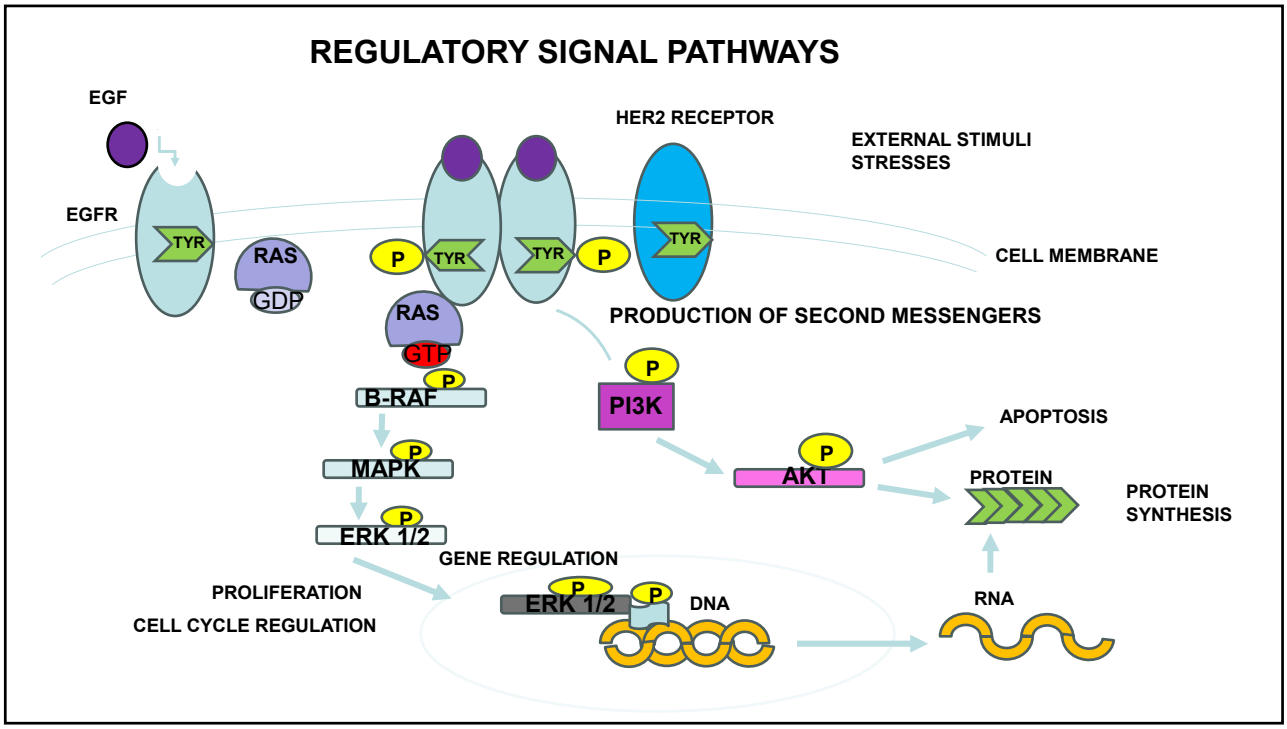
AKT1=AKR mouse thymoma kinase; ALK=anaplastic lymphoma kinase; BRAF=v-raf murine sarcoma viral oncogene homolog B1; DDR2=discoidin domain receptor 2; EGFR=epidermal growth factor receptor; FGFR1=fibroblast growth factor receptor 1; HER2=human epidermal growth factor receptor 2; KRAS=Kirsten rat sarcoma 2 viral oncogene homolog; MEK1=mitogen-activated protein kinase kinase 1; MET=met proto-oncogene; NRAS=neuroblastoma rat; PIK3CA=phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; PD-L1=programmed death-ligand 1; PTEN=phosphatase and tensin homolog; RET=rearranged during transfection; ROS1=ROS proto-oncogene 1.

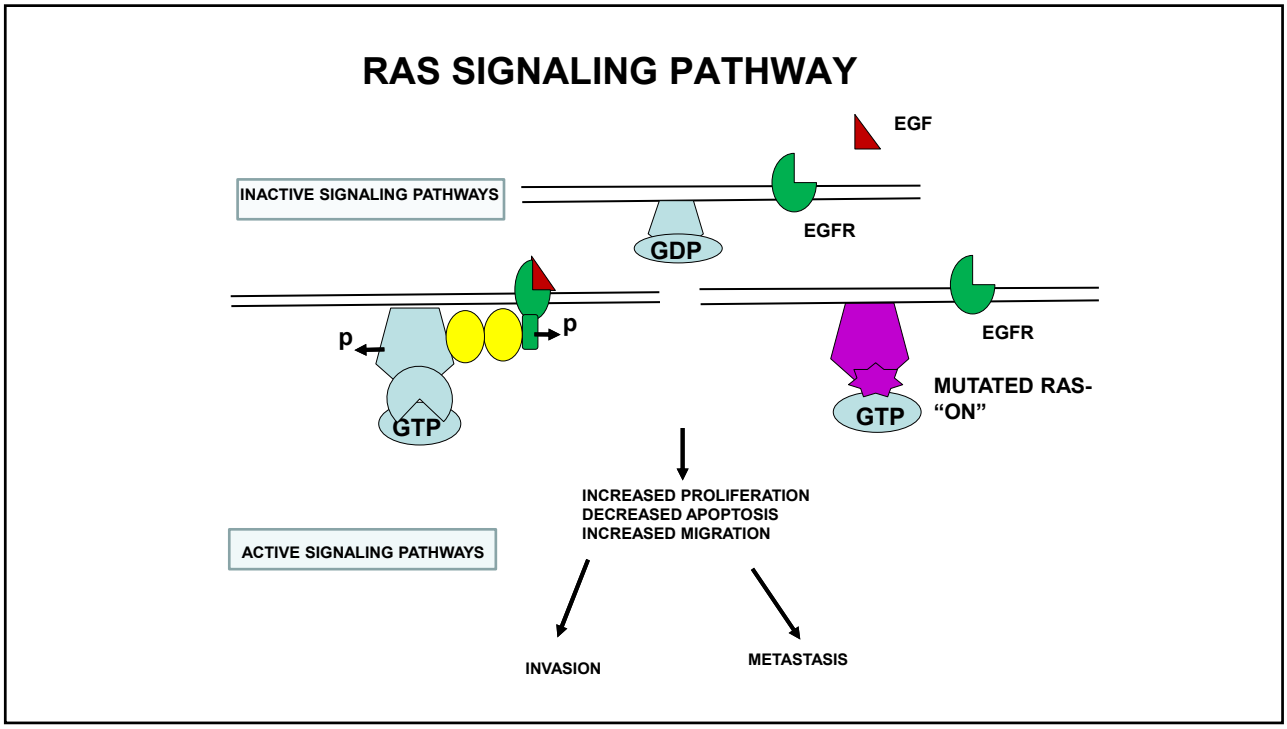
GENENTECH WEBSITE

SIGNAL TRANSDUCTION PATHWAYS

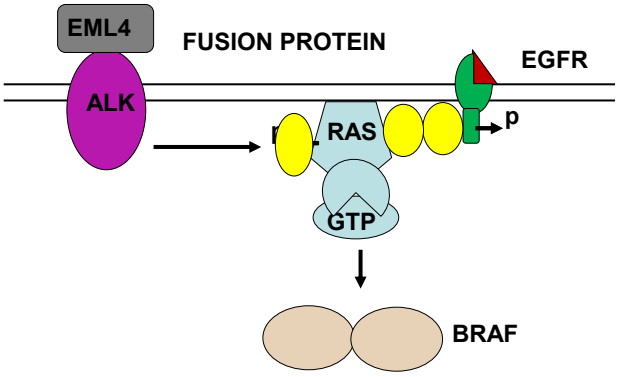
CHECKPOINT INHIBITOR PATHWAYS




REGULATORY SIGNAL PATHWAYS
EGF
EGFR
TYR
RAS
GDP
HER2 RECEPTOR
EXTERNAL STIMULI
STRESSES
CELL MEMBRANE
P
TYR
RAS
GTP
B-RAF
MAPK
ERK 1/2
PRODUCTION OF SECOND MESSENGERS
PI3K
AKT
APOPTOSIS
PROTEIN
PROTEIN
SYNTHESIS
GENE REGULATION
PROLIFERATION
CELL CYCLE REGULATION
DNA
RNA

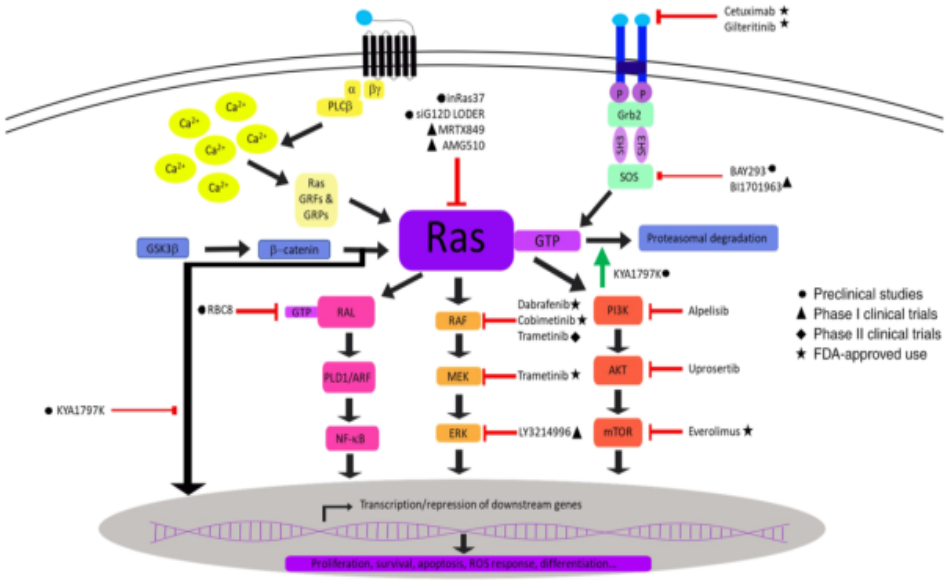

RAS SIGNALING PATHWAY
EGF
INACTIVE SIGNALING PATHWAYS
EGFR
GDP
p
p
GTP
EGFR
MUTATED RAS-
"ON"
GTP
INCREASED PROLIFERATION
DECREASED APOPTOSIS
INCREASED MIGRATION
ACTIVE SIGNALING PATHWAYS
INVASION
METASTASIS

ANAPLASTIC LYMPHOMA KINASE (ALK) GENE



- ALK POSITIVITY FOUND 4% LUNG CANCERS, MOSTLY ADENOCARCINOMA
- ASSOCIATED
  - YOUNGER AGE
  - NON SMOKING HX
- TREATMENT OPTIONS:
  - CRIZOTINIB
  - CERTINIB
  - ALECTINIB
  - BRIGATINIB
  - LORATINIB
- CHEMO- PEMETREXED

3 RAS-MEDIATED PATHWAYS AND ASSOCIATED INHIBITORS.



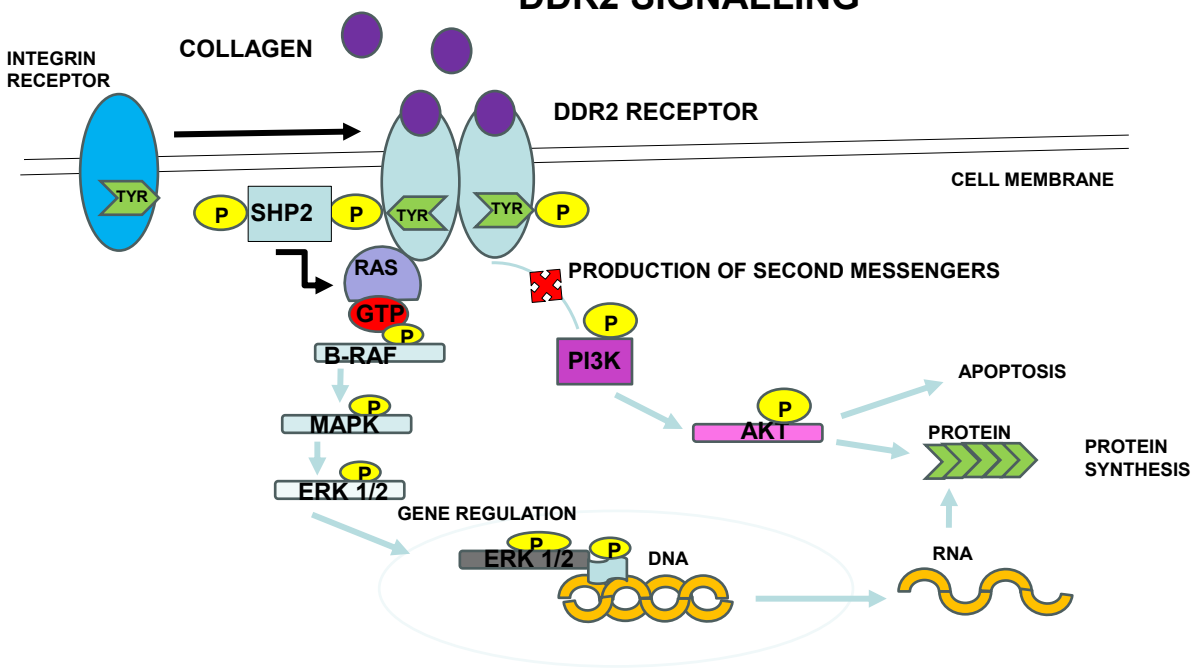
TARGETS OF SMALL MOLECULE INHIBITORS AND MONOCLONAL ANTIBODIES USED ACROSS A RANGE OF CANCERS TO INHIBIT PROLIFERATIVE SIGNALLING AND SURVIVAL OF CANCER CELLS.

FROM: Healy, Fiona M, Ian A Prior, and David J MacEwan. 2022. "The Importance of Ras in Drug Resistance in Cancer." *British Journal of Pharmacology* 179 (12): 2844–67. doi:10.1111/bph.15420

RAS PATHWAY

- RAS MUTATION OCCURS 19% OF ALL CANCERS
- CONTRIBUTES TO DRUG RESISTANCE
- DIFFICULT TO TARGET THE RAS PATHWAY
- LACK OF OF BINDING SITES FOR SMALL MOLECULE INHIBITORS AND ANTIBODIES DIFFICULTY CROSSING THE CELL MEMBRANE
- TARGET DOWNSTREAM MEK I TRAMETINIB- LUNG W/ BRAF V600E- BUT STLL ACTIVATION OF OTHER PATHWAYS eg AKT, PI3K
- <u>BUT</u> NEW PAN RAS ACTIVATION INHIBITORS IN CLINICAL DEVELOPMENT

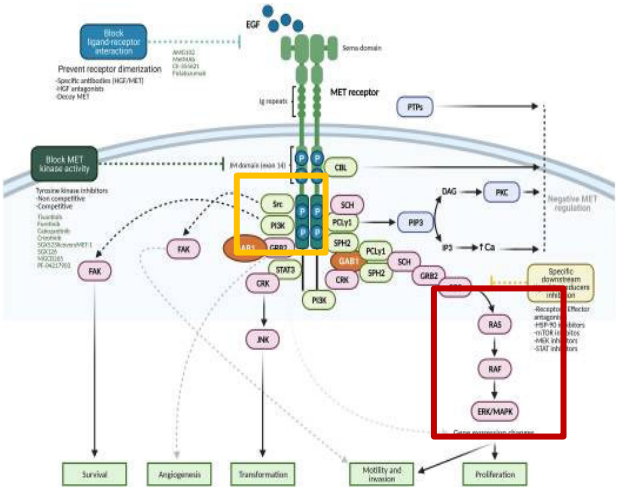
DDR2 SIGNALLING



DISCOIDIN DOMAIN RECEPTOR 2 (DDR2)

- DDR2 PRESENT IN 4% OF SCC LUNG CANCERS
- TUMOR SUPPRESSOR, DECREASED LUNG CANCER
- BUT MUTATED RECEPTOR ACTIVATES RAS/RAF PATHWAY
- TYROSINE RECEPTOR KINASE
- BINDS TO COLLAGEN
- CYTOSKELETAL REMODELLING AND SURVIVAL
- CONFERS SENSITIVITY TO DASATINIB
- MUTATION OVERCOMES EGFR TARGETING

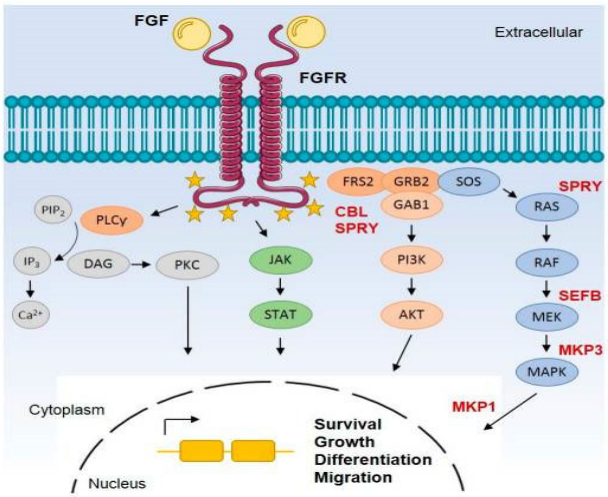
MET SIGNALING ADAPTORS AND MEDIATORS AND SIGNALING PATHWAYS AND ROS 1



MESENCHYMAL EPITHELIAL TRANSITION RECEPTOR (MET)
*LIGAND HGF
*MET IS A DRIVER ONCOGENE
*INTERARACTS EGFR RECEPTOR
*THERAPIES- CAPMATINIB
CABOZATINIB

c-ROS ONCOGENE 1 (ROS1)
*REARRANGEMENT IN LUNG ADENOCA
*MEMBER IGF FAMILY, RELATED TO ALK BUT NO KNOWN LIGAND)
*UNDERGOES FUSION/ REARRANGEMENT
*YOUNGER PTS, NEVER SMOKERS, WOMEN
*ALSO ACTIVATES SHP/PI3K
*TKIi:
CRIZOTINIB
ENTRECTINIB (CAN REACH BRAIN)
*AN EGFRi MECHANISM

FGFR SIGNALING PATHWAYS



FGFR1
- **GENE AMPLIFICATION**
- **7&% OCCURRENCE SCC**
- **RATHER THAN MUTATION**

THIS LEADS TO INCREASED RECEPTOR HOMODIMERIZATION = INCREASED RECEPTOR ACTIVATION
- **LEADS INCREASED FGFR1 INHIBITOR**
- **SENSITIVITY**
- **DOVITINB**

FROM: Pacini L, Jenks AD, Lima NC, Huang PH. Targeting the Fibroblast Growth Factor Receptor (FGFR) Family in Lung Cancer. Cells. 2021 May 10;10(5):1154. doi

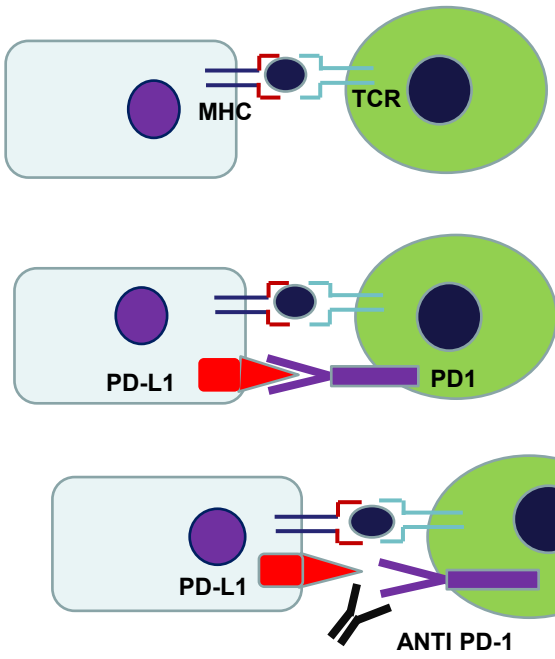
NEUROTROPHIC TROPOMYOSIN RECEPTOR KINASE (NTRK1)

- **NTRK1 PREDOMINANTLY IN NERVE TISSUE- BINDS NERVE GROWTH FACTOR**
- **MUTATION IN FORM OF FUSION PROTEINS HAVE NOW BEEN FOUND IN MANY SOLID TUMORS**
- **PRESENT LUNG CANER 0.1-0.3%**
- **TRK PATHWAY ACTIVATOR- MAY BE INVOLVED IN THE DEVELOPMENT OF EGFR INHIBITOR RESISTANCE**
- **IMPORTANCE- THERE ARE INHIBITORS**

- **ALSO SIGNALS THROUGH ANOTHER SIGNALING PATHWAY (JAK-STAT) TO INCREASE PDL-1 EXPRESSION IN TUMORS**

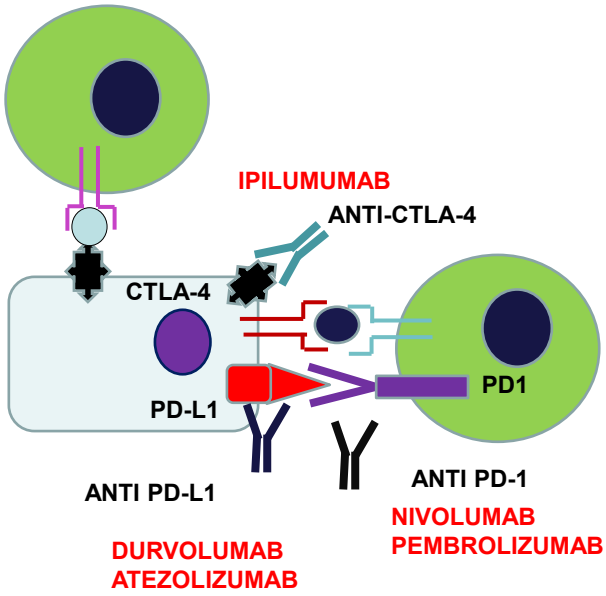
SIGNAL TRANSDUCTION PATHWAYS

CHECKPOINT INHIBITOR PATHWAYS



PD1 AND PDL-1 FUNCTION TO INHIBIT T-CELL ACTIVATION

IMMUNE CHECKPOINT INHIBITORS



TELOMERASE REVERSE TRANSCRIPTASE (TERT)

- CATALYTIC SUBUNIT OF TELOMERASE
- MAINTAINS TELOMERES ON THE END OF CHROMOSOMES
- TELOMERE LENGTH DETERMINES CELL AGE
- WHEN GETS SHORT ENOUGH- CELL STOPS DIVIDING AND ENTERS SCENESCENCE- AN ANTICANCER MECHANISM
- mutTERT- HIGHLY ACTIVE- CELLS DIVIDE BUT NOW LIABLE TO GET DNA REPLICATION ERRORS
- CONTRIBUTES HIGH TUMOR MUTATIONAL BURDEN
- TMB CELLS RESPONSIVE TO IPILUMUMAB- THE CTL4-A INHIBITOR

STK 11 GENE (LIVER KINASE B1 [LKB1] PROTEIN)

- TUMOR SUPPRESSOR
- INSERTION /DELETION MUTNS OR CHROMOSOME DELETION ASSOCD KRAS DELETION
- INVOLVED IN CELL METABOLISM
- SUBSRTATE INHIBITORS
- PREDICTOR OF PDL1 INHIBITOR RESPONSE
- LOSS OF THIS GENE ASSOCIATED WITH A LACK OF T-CELLS IN THE TUMOR MICROENVIROMENT

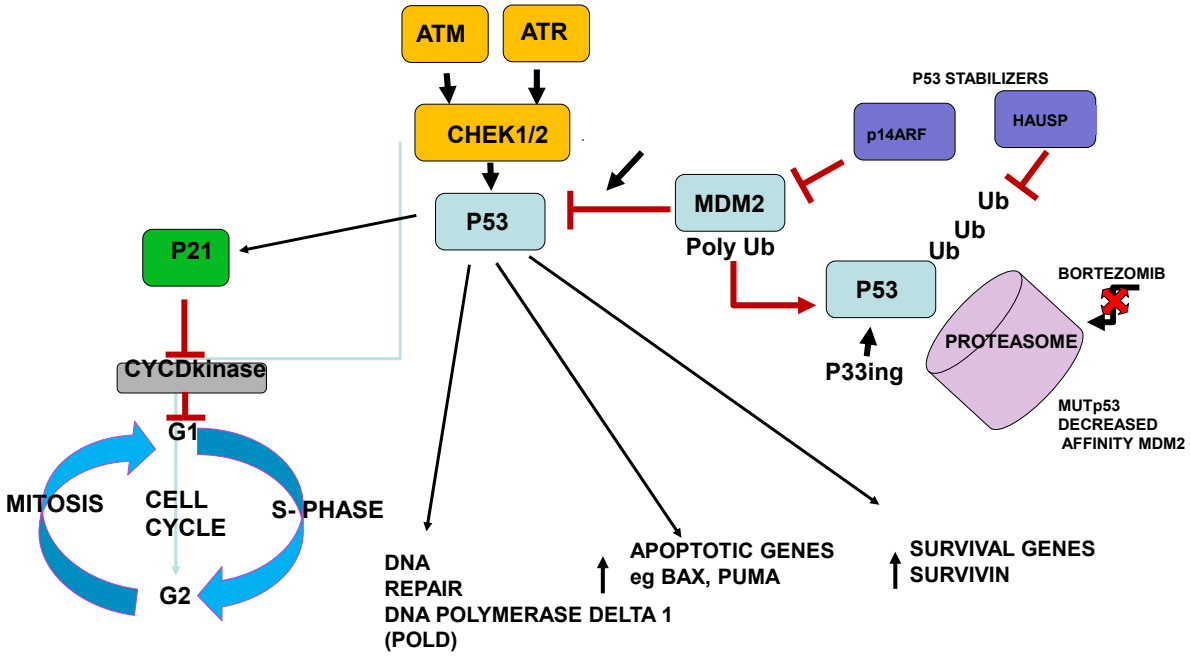
THE DNA POLYMERASE EPSILON (POLE) GENE

- ENCODES A SUBUNIT OF DNA POLYMERASE
- MUTATION OCCURS 3-4% NSCLC- ADENOCARCINOMA
- MUTATION IS ASSOCIATED WITH FAVORABLE PROGNOSIS
- ASSOCIATED:
  - HIGH TUMOR MUTATION BURDEN (TMB)
  - HIGH INFILTRATION OF T-CELLS INTO THE TUMOR MICROENVIROMENT

P53 TUMOR SUPPRESSOR GENE

- P53 MUTATED 33-90% LUNG CANCER (DEPENDING HISTOLOGICAL SUBTYPE.
- SCC>ADENOCARCINOMA
- SMOKING INCREASED INCIDENCE (DUE BENZOaPYRENE) THAN NON-SMOKERS
- NUCLEAR PROTIEN- TRANSCRIPTION FACTOR
- POINT MUTATIONS OCCUR PREDOMINANTLY IN THE CORE DNA BINDING DOMAIN EXONS 5-9
  - PROLONGS HALF LIFE
  - PROMOTES NUCLEAR ACUMULATION
- 85% LUNG CANCERS HAVE ABNORMALITIES IN GENES IN THE P53 PATHWAY
- LOSS OF P53- DEREGULATES CELL CYCLE AND APOPTOSIS
- ALSO "GSIN OF FUNCTION" PRO CANCER:
  - DISTANT METASTASES
  - INCREASED RESITANCE CANCER THERAPIES

P53 TUMOR SUPPRESSOR GENE PATHWAYS



P53 THERAPIES

- **TPmutp53- RESISTANCE TO XRT**
- **GENE THERAPY- ADENOVIRUSp53- BRONCHOSCOPIC INTRTUMORAL INJECTION**
- **TWO COMPOUNDS (NCI SCREENING CHEMICAL LIBRARY) THAT REACTIVATE p53 ACTIVATION AND FUNCTION (DNA BINDING)**
  - **RITA**
  - **PRIMA 1**

CONCLUSIONS

- **TARGETED THERAPIES HOLD PROMISE IN THE TREATMENT OF LUNG CANCER**
- **HOWEVER, THERE ARE CHALLENGES GIVEN THE ABILITY OF THE CANCER TO ACQUIRE NEW MUTATIONS AND SWITCH SIGNALING PATHWAYS**
- **GENETIC TESTING INFORMS BOTH INITIAL AND SUBSEQUENT TREATMENTS**

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