NSCLC
New Advances in Treatment
2002-2005

STAGE-1 NSCLC

$T_1\ N_0M_0$

$T_2\ N_0M_0$

- Sx is TOC
- Lobectomy > Segmentectomy/Wedge Resection
- Ass with ↓ Locoregional recurrence
  However, no overall survival difference .
- Inoperable disease but sufficient Pul. Reserve

  ↓

  RT with curative intent
- Adjuvant Therapy
  - Sx → RT in St. I & II ass. ↓ survival
  - Sx → CT

INT. ADJUVANT LUNG CANCER TRIAL [IALT]

- 1867 Patients
- St. I: 36.5% St. II: 24.2% St III: 39.3%
- Cisplatin + Etoposide 56.5%
  Vinorelbine 26.8%
  Vinblastine 11%
  Vindesine 5.8%
- Sx: Pneumonectomy- 34% Lobectomy: 64%

IALT

1867 Patients

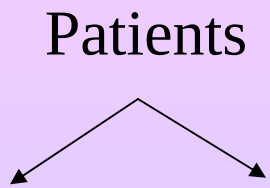
	932 Patient (Adj. CT)	935 (Control)	
Survival 5 years	44.5%	40%	($p < 0.03$)
Disease free survival 5 years	39.4%	34.3%	($p < 0.003$)

Conclusion: Cisplatin based adjuvant CT improves survival amongst completely resected NSCLC

NEJM 2004; 350: 351-60

JAPAN LUNG CANCER RESEARCH GROUP

- 979 Patients.
- St I; 75% (adeno carcinoma)



	Adj. UFT 2 yrs	No Post-op T/T	
5 yrs survival	88%	85%	
St. 1a: 716 pts.			
5yrs survival	89%	90%	(No Benefit)
St. 1b: 263 pts.			
5yrs Survival	85%	74%	

Conclusion : Adjuvant UFT improved survival among patients with St. I adeno carcinoma

UFT :
- uracil-tegafur
- anti-angiogenic effect
- orally

NEJM 2004; 350: 1713-21

ADJUVANT LUNG PROJECT, ITALY

1209 Patients

	Mito/Vnd/Cis (3 cycles) n = 606	Control n = 603
I-	39%	38%
II-	31%	34%
IIIA-	29%	28%
Sq. cell	51%	49%
Adeno	36%	38%
Pneumonectomy	24%	26%
RT (Post CT)	43%	43%

50-54 6y/5-6 wks.

Median OS	55.2 mths	48 mths
Median	36.5 mths	28.9 mths
Progression		
Free survival		

Differences not Statistically Significant

Conclusion: Failed to confirm statistically significant role of adj. CT in completely resected NSCLC.

J Natl. Cancer Inst. 2003; 95: 1453-61

Results from RCT: Adj. CT should be considered strongly in Ib or II NSCLC

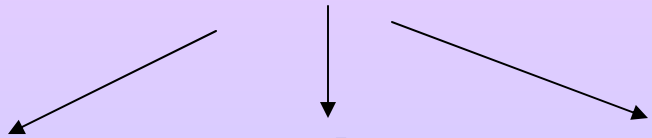
RADIO THERAPY

Conventional RT: - 10 weeks

- may result in tumor repopulation if extended beyond six weeks

- 1.6% loss of survival/day of treatment ↑ beyond six weeks

Limiting overall t/t time



Hypofractionation	Acceleration	Hyperfractionated Acceleration
Large daily fraction		short course
Over shorter course		multiple fractions/day

ACCELERATION

Netherland Cancer Institute

Dose/# : 2.25 Gy

Time : 6 weeks (5 days/wk)

: 30

3D CRT : higher dose delivered to tumor, sparing (N) tissue

55 Patients (26 St. I & II, Rest locally advanced)

rMLD = MLD/prescribed tumor dose

[Measure for RR to develop Radiation Pneumonitis]

Gr. I	: St. I & II (13 patients) 87.8 Gy
Gr. II/III	: (29 patients) $\rightarrow$ 81 Gy
IV	: (11 pts) $\rightarrow$ 74 Gy
Dose limiting toxicity	: 3 pts (Gr III/IV Pneumonitis)
Results	: 6 $\rightarrow$CR
	38 $\rightarrow$ PR
	6 $\rightarrow$ stable/progressive disease
Acceleration	: No additional toxicity

(Radiother Oncol 2003; 66: 119-26)

HYPOFRACTIONATION

Few, Large # over limited time period

Radiological effects:

1. ↓ Risk of Accelerated Repopulation by Shortening overall t/t time
2. Late toxicity: High (Lung/Spinal cord) because of high #
3. Useful in small tumors

   2 years OS: 46 – 81%

   Local control rates equivalent to conventional RT

25 Patients

Medically Inoperable : St.I/I – 9 Patients

: St. III – 16 Patients

11 Patients → Induction CT

Hypofractionated Accelerated RT

72 Gy/24 Daily # (i.e. 3 Gy/#)

22 Patients evaluable for Long term toxicity

CR : 7 Patients

PR : 8 Patients

Stable Disease : 5 Patients

Progression : 2 patients

AC Toxicity:	Gr. III Esophagitis	- 2 Patients
	Gr. III Pnenuonitis	- 1 Patient
	Gr. III Haemat toxicity	- 1 Patient
Long term toxicity:	Gr. I Pneumonitis	- 4 Patients
	Gr. I Esophagitis	- 1 Patients

Conclusion: Feasibility of this schedule in NSCLC

Racliother Oncol 2004; 71:163-166

STEREOTACTIC RT

- Most extreme from of hypofractionation

↓

Single # stereotatic radio Sx (SRS)

- Originally: Intra cranial lesions
- Fractionated Stereotactic RT:
  - Tumor localization & Immobilized as in SRS
  - Radiation-Multiple few #

- Accurate Tumor localization & Immobilization: Crucial

Reasons: 1. T/T delivered in smaller #

$\therefore$ Missing a part of tumor in one # $\rightarrow$ Greater effect.

2. Disproportionate $\uparrow$ in late (N) tissue toxicity

Accurate Localization

Frame-Based SRT (Custom built frame for immobilization)

Image guided SRT (CT Scanner, Fluroscopic simulator, Linear Accelerator)

Resp. motion: Reduced by

- Shallow breathing
- Mech. means: Diaphragm control system, Abd. belts
- Breath holding
- Resp. gating

Hara R et al

- Stereotactic single high dose irradiation ↓ Resp gating.
- 23 pts. Malignant peripheral tumors
  Tumors < 4 cm.
  F/u : 3-24 mths.
- 7 pts: Primary lung tumors (NSCLC)
  Rest: Mets with Primary in Breast/Liver/Bladder.
- Dose: 20-30 Gy to 22-35 Gy
- Local Regrowth: 3/10 pts : < 30 Gy
  1 pt : 30 Gy
- No significant toxicity
- Conclusion: 30 Gy controls tumor with diameter < 4 cm.

(Radiother Oncol 2002; 63:159-163)

Whyte R et al

- 23 pts → 15 : Primary Lung tumors
  8 : Metastatic
- CT guided percutaneous placement of 2-4 small metal fiducials
- 15 Gy single #
- 9 pts : Breath Holding technique
  16 pts : Resp gating
- Tumor size : 1-5 cm
- Complication with fiducial placement: Pneumothorax 3 pts.

- F/u: 1-26 mths
- No radiation related complications: Gr 3-5 severity

CR	: 2 pts.
PR	: 15 Pts
stable	: 4 pts
progression	: 2 pts

Conclusion: single # SRS safe & feasible

Ann Thorac Surg 2003; 75: 1097-101

Timmerman R et al

- 37 pts
- T_1/T_2 N_0 M_0 NSCLC
- Inoperable
- SRT: - 3 # over 2 weeks
  - 0.8 Gy – 20 Gy per # (Toal 2.4 Gy – 60 Gy)
- OR: 87% (CR – 27%)
- Median Fu

  15.2 mths: 6 pts $\rightarrow$ Local failure
  (Dose < 18 Gy/#)
- Complication: 1 pt – Gr. 3 Pneumonitis
- Conclusion: Very high dose t/t tolerated

Chest 2003; 124: 1946-1955

RADIOFREQUENCY ABLATION (RFA)

- Radiowaves emitted from probe placed directly into tumor percutaneously (Image guided)/Surgically
- Mo A: Radiowaves $\rightarrow$ Heat $\rightarrow$ Coagulative necrosis
- Complication: Pneumothorax $\rightarrow$ 30% - 50%

  (10-15% $\rightarrow$ ICT)

  PE, Pneumonitis, Fever
- Combined with Brachytherapy in NSCLC not amenable to Sx/EBRT
- Successful Radioablation: Tumor size 3-4 cm.

Hematol Onclol Clin N Am 2005; 19 (2): 237-61

STAGE-II NSCLC

$T_1N_1\ M_0$ $T_2N_1\ M_0$ $T_3N_0\ M_0$

- Sx $\rightarrow$ TOC
- Inoperable St. II: RT with curative intent

  3year. Survival: 20%
- Adj. CT useful

STAGE-III A

$T_1N_2\ M_0$ $T_2N_2\ M_0$ $T_3N_{1\text{-}2}\ M_0$

- RT,CT, Sx and combination of these modalities.
- CT combined with RT improves survival (cisplatin based)
- Neoadj. CT effective (↑ survival)
- Neoadj. CT + Sx → chest RT considered in pts with good performance status.
- Resected St. III a → Benefit from Adj. CT (Cisplatin based)
- Post-op RT in Node +ve → Improve local control

  ? Improve Survival

STAGE-III b NSCLC

Any T N_3 M_0 T_4 Any N M_0

- CT + RT [cisplatin based chemo RT $\rightarrow$ $\downarrow$ Risk of death by 10% C/W RT alone]
- Concurrent Chemo RT $\rightarrow$ Resection
- Performance status good: Combined modality
- Poor Performance Status: palliative RT
- CT alone

IIIrd Generation CT with RT [concurrently]

•Combination: New Rx for locally advanced St. III inoperable NSCLC.

•Local failure rates : 55-85%

5years SR : 5 –15%

• **Paclitaxel Chemoradiation**

Chen Y et al.

- Pulsed low dose paclitaxel & RT
- 41enrolled → 33 completed t/t
- St. III A – 15 pts III B – 22 pts St. I + II – 3 pts
- Paclitaxel: Thrice/week

	Dose	RT
Gr. I	15 mg/m^2	60-65 Gy
Gr. II	20 mg/ m^2	(1.8 Gy/#)
Gr. III	25 mg/ m^2	6 wks

Response Rate CR = 14%

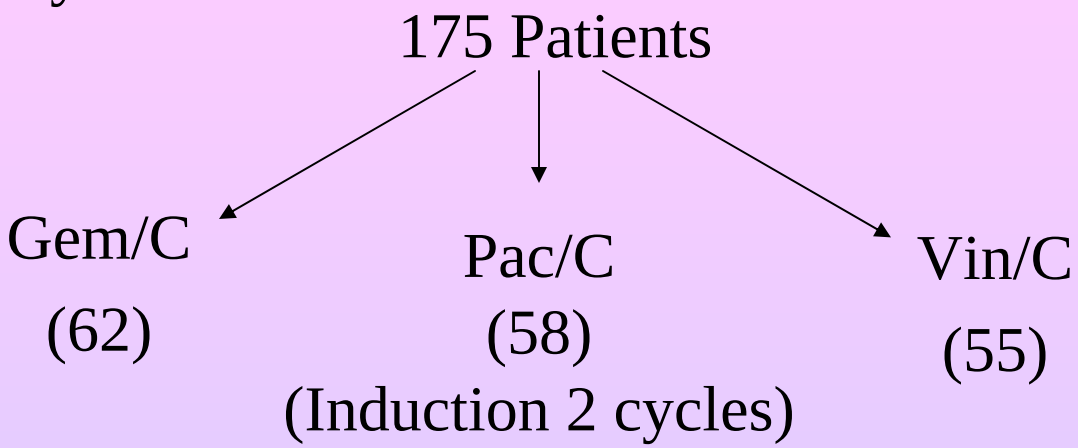
PR = 86%

Tumor Shrinkage: 83 ± 7%

Conclusion: Pulsed low dose Paclitaxel radiosensitization has a good control rate. M/b useful in poor performance/old age

Clin Cancer Res 2003; 9 : 969-975

CALGB study 9431



XRT : 66 Gy (2 Gy/day)

+ 2 cycles concurrent CT

CR	8%	19%	16%
PR	60%	47%	53%
Stable	16%	17%	20%
Progression	6%	9%	5%

Survival			
2year	28%	29%	40%

Conclusion: Induction CT added to chemo RT improves survival

J Clin Oncol 2002; 4191-98

Trodella L

36 pts (Stage III- 72% IV- 11%)

Gem. Weekly x 5 weeks

RT : 50 Gy (1.8 Gy/day)

CR	– 4 pts
PR	– 18 pts
Progression	– 2 pts
No Change	– 9 pts

J Clin Oncol 2002; 20: 804-810

Yameda M

31 Patients

Irinotecan & carboplatin wkly x 4 wks

RT $\rightarrow$ 60 Gy/30 #

Irinotecan Dose (30 –60 mg/m^2)

CR – 3 pts

PR – 15 pts

Median survival : 14.9 mths

Survival Rate 1 year : 51.6%

2 years : 34.2%

Rec. dose for irinotecan - 50 mg/m^2

Conclusion: Therapy active against inresctable NSCLC

Br. J Cancer 2002; 87: 258-63

$\therefore$ IIIrd gen CT $\rightarrow$ Independently active against NSCLC

$\rightarrow$ Potentiate RT effects

$\rightarrow$ $\uparrow$ Pneumonitis/Esophagitis with concurrent Chemoradiation

$\rightarrow$ Multi agent Chemoradiation $\uparrow$ toxicity.

Tumor response rates similar to single agent use.

$\rightarrow$ Induction CT $\rightarrow$ Chemoradiation improved survival & disease control.

STAGE IV

Any T Any N M_1

- Cisplatin based CT provide modest survival benefit in short term survival C/W BSC.
- Taxane + Platinum Compound $\rightarrow$ High response rate
  Better 1year survival
  Palliation of Symp
- No specific regimen can be regarded as Std. therapy
- CT recommended: - Good performance status who desire t/t

RT: Palliating local Symp, progressive disease while on CT,
Not fit/decline CT

- Untreated Metastatic NSCLC
  - Median Survival : 4-5 mths
  - 1 year Survival: 10%
- Metanalysis: - Older Chemotherapy regimens for adv. NSCLC → better survival C/W BSC.

	BSC	Older CT	2nd Gen	3rd Gen Taxaxes/ Topoisomerase (-)
Median Survival	4-5 mths	5-6 mths	6mths	8-9 mths
1year survival	5-10%	10-15%	20-25%	35-40%

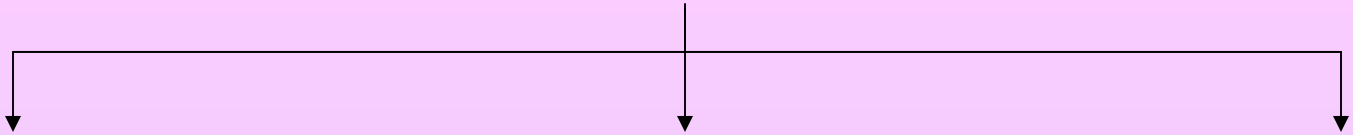
- 1st line therapy: Platinum based regimen → Std. Of care
- Triplets not more effective than Doublets

  - More toxic & expensive
- 4 cycles → Sufficient
- Poor PS : ↑ toxicity/Few Benefit
- 2nd line therapy : Docetaxel extensively studied & approved.

NCI, Canada

503 Patients

NSCLC St. III/IV



Cis/Vin	Cis/Gem	Gem/Vin
n = 252	n = 126	n = 251

n = 252

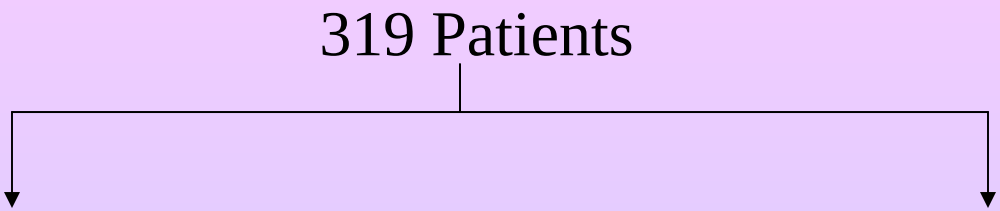
	Cis/Gem	Gem/Vin
Median Survival	38 wks.	32 wks
Response Rate	30%	25%
QOL Improved	63%	62%
Worse	37%	38%
SE: Gr. III/IV Myelosuppression	30%	15%
Vomiting	65%	36%

Conclusion:
- Global QOL not improved with Gem/vin
- Gem/vin less toxic than Cisplatin based therapy.

J Clin Oncol 2003; 21: 3025-34

Georgoulias V

Multicentre Ph. III trial



	Cis/Doc n = 167	Doc (n = 152)
OR	37%	22%
OS median	10.5 mths	8 mths
Survival 1year	44%	43%
2 years	19%	15%

Gr. 2/3 Anemia	33%	16%
Febrile Neutropenia	9%	8%

Conclusion:

- Doc/Cis higher RR
- OS similar in both gr.
- Doc suitable front line CT for pts. who cannot tolerate Cis.

J Clin Oncol 2004; 22: 2602-9

EORTC 08975

Ph. III trial

480 pts. NSCLC

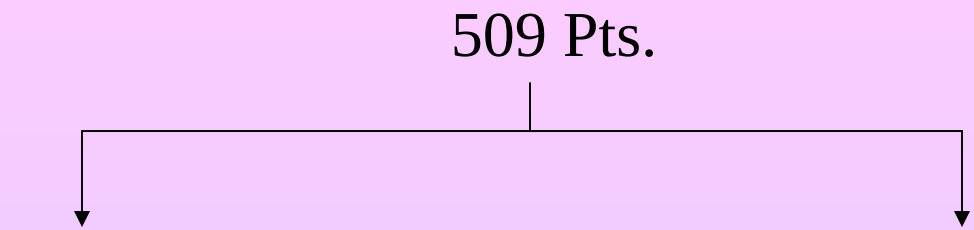
	Pac/Cis (n = 159)	Gem/Cis (n = 160)	Pac/Gem (n = 161)
Median Survival	8.1 mths	8.9 mths	6.7 mths
RR	31.8%	36.6%	27.7%
Gr. III Neutropenia	34%	43%	30.4%%

Conclusion: -Gem/Cis, Pac/Gem donot ↑ survival c/w Cis/Pac

-T/T well tolerated, most QOL parameters similar.

J Clin Oncol 2003; 3909-3917

Kosmidis P et al

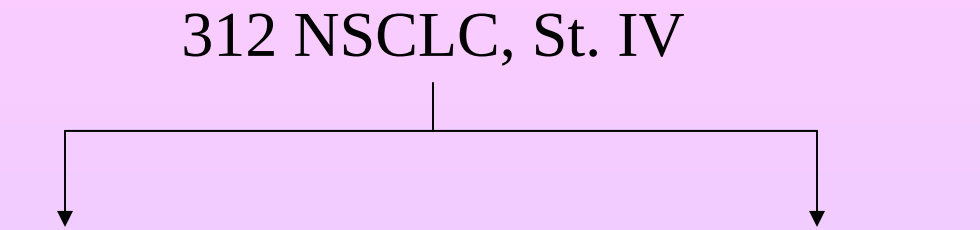


Median Survival time	10.1 mths	9.8 mths
1yr survival	41.7%	41.4%
RR	28%	35%
Gr. III/IV Heamat toxicity	22%	18.%

Conclusion: -Pac/Gem equally effective as Pac/Carb

J Clin Oncol 2002; 20: 3578-85

JAPANESE TAXOTERE LUNG CANCER STUDY GR.



OR	37%	21%
Median Survival	11.3 mths	9.6mths
2 years survival	24%	12%
Gr.3 Neutropenia	35.1%	50.3%

Conclusion: Doc/Cis greater clinical benefit Vind/Cis

J Clin Oncol 2004; 22: 254-61

RECURRENT NSCLC

- Solitary cerberal mets after resection of primary NSCLC

  Sx Excision + Post op whole Brain RT

- Metastatic Disease → CT

  - Good performance status: Platinum based CT

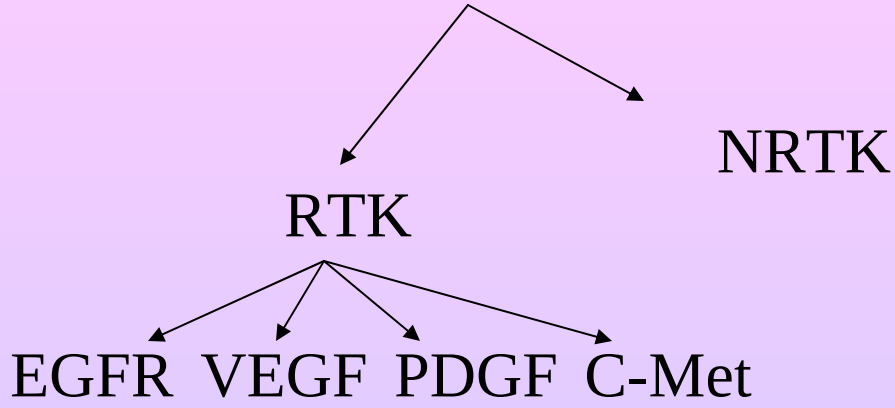
  - Platinum based CT → Relapsed

    IInd line CT → Docetaxel

    Erlotinib
    Gefitinib
    } after failure of both platinum based & Docetaxel CT

NOVEL THERAPIES IN LUNG CANCER

Protein tyrosine kinase- Largest family of oncogenes



EGFR (HER 1; erb B-1)

- Over expressed in 40-80% NSCLC
- Ass. With poor prognosis
- EGFR (-) → ↓ Cell proliferation
  ↑ Apoptosis
  ↓ Angiogenesis

- RTK inhibitors: compete with ATP for intracellular catalytic site
- Administered Orally
- Toxicity:- -Acneiform rash
  - Diarrhea
  - ILD – less commonly

Gefitinib [Iressa]

- First targeted therapy approved by FDA
- Used alone & in combination with cytotoxic drugs

Ideal-1 (Iressa Dose Evaluation in Advanced Lung Cancer)

RCT, Double blind multicenter Ph-II 43 centres [Europe/Australia/SA/Japan]

IDEAL – 1

209 Patients

(advanced NSCLC previously Rx with one/two CT regimens)

↓

Gefitinib

	250mg OD (n = 103)	500mg OD (n = 106)
CR	0	1%
PR	17.5%	18.1%
Stable disease	35.9%	32.4%
Progressive disease	40.8%	41.9%
Median Overall Survival time	7.6 mths	8.0 mths

AE: Mild- skin reaction /Diarrhea

More frequent in 500mg gr.

Withdrawal due to drug related AE 1.9% & 9.4%

Conclusion: Meaningful anti-tumor activity

250 mg/d $\rightarrow$ favourable AE profile

(J Clin Oncol 21:2003;2237-46)

IDEAL – 2

IDEAL-2: Response Rate of Gefitinib as IIIrd line therapy

216 Patients; 30 Medical Centres in US

	250 mg	500mg
Response Rate	12%	9%
1year OS	25% in both groups	

JAMA 2003; 290: 2149-58

FDA approved Gefitinib for NSCLS Patients who failed therapy with Platinum + Docetaxel.

INTACT – 1

Gefitinib Combined with Std CT regimens

INTACT-1. (Iressa NSCLC Trial Assessing Combination Treatment)

-Ph-III, double blind placebo controlled multi-centre trial.

-Unresectable stage III/IV NSCLC

-Cisplatin/Gemcitabine

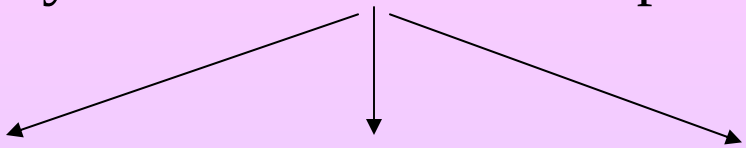
-Gefitinib	250	500	Placebo
n	362	365	363
Median survival time	9.9	9.9	10mths
Response rates (CR + PR)	51.2%	50.3%	47.2%

(J Clin Oncol 2004;22:777-84)

INTACT – 2

Ph-III, randomized placebo controlled double blind trial

6 cycles- Paclitaxel/Carboplatin



	250mg/d	500mg/d	Placebo
n =	(345)	(347)	(345)
OS	8.7	9.8	9.9 mths

(J Clin Oncol 2004;22:785-94)

These 2 trials: No clinical benefit in survival on adding Gefitinib to combination CT

-↑ Response noted in Women

Adeno Ca histology

Non- smokers

Patients of Asian descent

ERLOTINIB (TARCEVA)

-EGFR tyrosine kinase (-)

-Approved by FDA in NSCLC

-Placebo controlled double blind RCT

-Stage III/IV NSCLC received 1/2 Previous CT

731 Patients

	Erlotinib	Placebo
n	488	243
CR	0.7%	1%
PR Median	8.2%	
Duration of Response	7.9mths	3.7 mths
OS	6.7 mths	4.7 mths

ERLOTINIB (TARCEVA)

Conclusion

- Erlotinib prolong survical in NSCLC after 1st/2nd line CT

NEJM 2005; 353: 123-32

- Two RCT – Ph III (TALENT and TRIBUTE)
- Erlotinib + (Cisplatin/Gemcitabine)
- Erlotinib + (Carboplatin/Paclitaxel) as 1st line therapy in advance NSCLC

↓

- No advantage in response rates/survival
- Other EGFR TK (–) in pipeline
- EKB-569, CI-1033, 6W-572016, PKI-166

MONOCLONAL AB AGAINST EGFR EXTRACELLULAR DOMAIN

- Cetuximab: Binds EGFR

↓

(-) EGF RTK activation

	Cetuximab + Cisplatin/Vinorelbine	C/V
RR	53%	26%
Disease Control Rate	93%	77%

- Panitumumab: Human monoclonal Ab

Similar action.

- Combination EGFR TKI + EGFR Monoclonal Ab

↓

Maximize EGFR (-)

↓

Higher Response Rates.

HUMAN EPIDERMAL GROWTH FACTOR-2/neu

- HER 2/neu- over expressed in 25-30% NSCLC, Breast tumors
- Transtuzumab [Herceptin]
- Humanized monoclonal Ab against Her 2/neu
- ECOG trial

  Ph-II study

52 Patients

↓

Transtuzumab + Paclitaxel/Carboplatin (Wkly)

OR : 24.5%

Median survival : 10.1mths

(J Clinical Oncol 2004; 22:1180-7)

Another trial Transtuzumab Gemcitabine/cisplatin

Gem/Cis

↓

No clinical benefit

- Subset of patients with somatic mutations in Her 2/neu

↓

May Benefit from Transtuzumab

C-Met

- Involved in cellular proliferation & motility.
- Expressed in 72% Adeno ca; 38% Sq. cell ca
- Ass. With poor prognosis.
- c-Met (-): Pre clinical stages

  SU 11274 → cell cycle arrest, apoptosis

  PHA 665752 → (-) tumor growth

ANGIOGENESIS INHIBITORS

Tumor growth & metastasis

VEGF &VEGFR → Endothelial Cell Proliferation
Formation of new blood vessels
Vascular permeability

- ↑ levels: Poor prognosis in Lung/Breast/Colon Ca.

Bevacizumab:	Humanized monoclonal Ab + CT [Carb /Pacl]	CT alone
RR	31.5%	18.8%
	2.8 mth ↑ in survival	
SE	Haemoptysis 6/67	
	4 → Fatal	
	[Sq. cell ca]	

VEGF RTK inhibitors: Vatalanib, SU 668, ZD 6474 } Ph I/II trials

Retenoid Signalling Pathways

Retinoic Acid Receptors [RAR]
Retenoid X-Receptors [RXR] + Retenoids

[Nucleus]

↓

Influence cell growth, Division, Reproduction, Differentiation

RETENOID PATHWAY

↓ expression RXR, RAR → NSCLC

RXR (-) Tumor growth

↓ expression: Poor prognosis

Bexarotene: Selective RXR retenoid

↓

(+) RXR

Ph-II trials: Combination of Baxarotene + CT

Ass. with ↑ survival & better RR.

PROTEASOME INHIBITOR

"cellular housekeepers"

Degrade cellular proteins (cyclins, cyclin dependent kinases, nuclear factor kB (NFkB)

•<u>Bortezomib:</u> - Inhibition of Proteasomes

- Cell Cyle arest in G2-M phase

- ↑ Apoptosis

- Combined with CT in NSCLC cell lines

↓

80% cells killed

- Sequential administr of Bortezomib after cytotoxic agents(Gemcitabine/Carboplatin) more useful

CYCLIN DEPENDENT KINASES (CDK)

- RB protein phosphorylation is important in cell cycle progression.
- RB phosphorylation: Regulated by CDK
- Aberrant Expression of CDK: Malignant tumor
- Flavopiridol: (-) ATP binding site of CDK

  ↓

  (-) CDK activity

  ↓

  Cell cycle arrest

  Pre-clinical date : synergistic cytotoxicity with taxanes.

TUMOR VACCINES

- Gene modified vaccines: Cytokine Secr (GMCSF) into tumor cells
  ↓
  (+) T-Cells
  ↓
  Immune reaction against tumor cells
- 38 Patients with metastatic NSCLC
  Tumor tissue from Lung/LN obtained
  ↓
  Tumor cells infected with Adenovirus that enclosed GM-CSF
  ↓
  Patients Vaccinated with these tumor cells
  Immune reaction seen in 18 patients
  S/E: - Local skin reactions, Flu like symptoms

(J Clin Oncol 2003; 21: 624-30)

- SRL172 Vaccine (Suspesion of killed M. Vaccae)

  several immune modulating functions
- 400 patients: Platinum based CT with/without

  monthly SRL172 vaccination

  ↑ QOL in vaccine arn

  No improvement in OS & RR.