RECENT ADVANCES IN VACCINES AND OTHER IMMUNO MODULATOR IN LUNG CANCER

Dr Saurabh Maji

22nd August 2014

Introduction

- Globally lung cancer remains the number one cause of cancer-related death
- 1,378,400 deaths annually
- NSCLC accounts for approximately 85% of them
- Even in patient with completely resected NSCLC prognosis is poor
- 5-year mortality 40% in stage I, 66% in stage II and 75% in stage IIIA disease
- Patients with advanced or metastatic disease had a median survival of less than a year

- Jemal A et al. Cancer J Clin;2011:61(2)

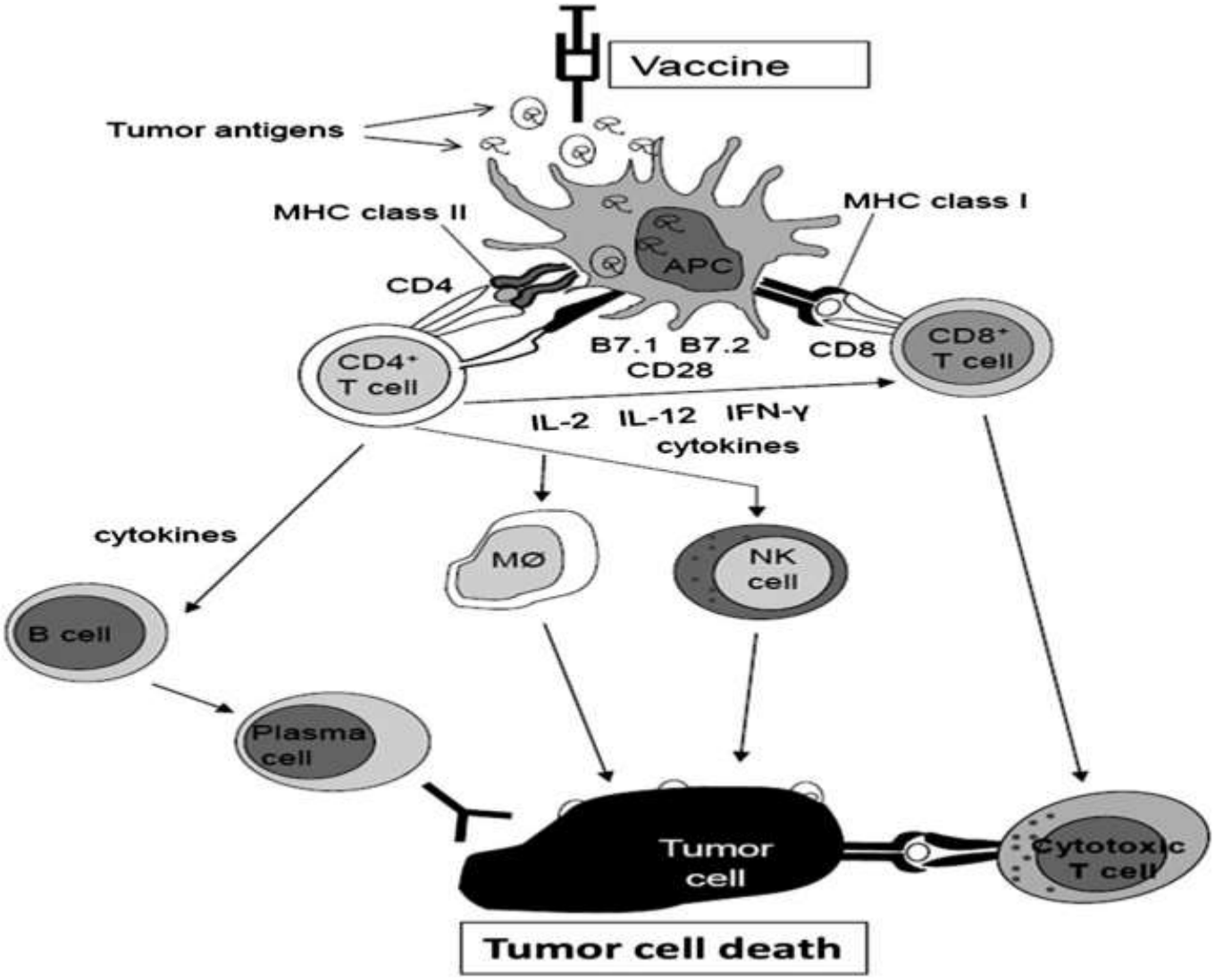
Introduction

India

- 47010 new cases in 2008
- Leading cause of cancer related death
- Non small cell lung cancer constitutes 75-80% of lung cancers
- More than 70 % diagnosed in Stages III and IV
- The 5 year survival is only 14%

Behera et al. Medicine Update 2012,vol22

Vaccine generated immune response



Julie R. et al, J Clin Oncol; 31:1021-1028

Vaccine generated immune response

- To augment adaptive immune response
- Uptake of antigen by antigen presenting cell(APC : dendritic cells and macrophage)

- Complex protein degraded to simple peptide
- Presented on cell surface and are bound to MHC class 1and class 2

Vaccine generated immune response

Mature APCS are interact with T cell receptor of CD4 lymphocyte via peptide bond and co- stimulatory b7.1 and b 7.2 protein on APCs cell surface

Activation of CD4 cell

secretion of IL2,IL12and interferon gamma

activation of cytotoxic T cell

Vaccine generated immune response

Activated cytotoxic T CELL recognise tumor cell that display target peptide or MHC complex

Cell death

Activated CD4 T cell

enhance Nkcells activity

increase phagocytic activity of macrophage

Trigger humoral immunity to produce antibody

Characteristic of tumor cell

Evade the immune response by following mechanism:

- Down-regulation of target antigen- failure of recognition by T cell
- TGFβ release decrease secretion of cytolytic product e.g. granzyme β, FAS ligand and Interferon γ
- Resistant to apoptosis

Annals of Oncology ;23: 1387–1393, 2012

Cancer immunotherapy

Three different approaches :

1. ‘supportive’ immunotherapy- non-specific enhancement of the innate immune system

   e.g.- Bacillus Calmette-Guerin

   Levamisole, interferons, and interleukins

   Talactoferrin ά- DC recruitment and activate gut-associated lymphoid tissue

   Ipilimumab— mAb acting on the CTLA- 4

Annals of Oncology ;23: 1387–1393, 2013

Cancer immunotherapy

3. Active immunotherapy: recognise the tumour as foreign

augment antitumour CD4+ helper and CD8+ cytotoxic lymphocytes thus turning the immunosuppressive envioronment to immunostimulatory envioronment

2. Passive immunotherapy: passive supply of immune response agents to the body e.g. cytotoxic T cells or antibodies such as cetuximab

Type of vaccines

I. Autologous cell vaccines-

- Elicit an immune response to a large variety of antigens expressed by the patient's tumour
- Production and standardization is complex and a major problem for largescale development

II. DC vaccines-

- APCs loaded with tumour antigen
- Technically challenging

Annals of Oncology ;23: 1387–1393, 2013

Type of vaccines

III. Peptide vaccines-

- Easy to manufacture
- Targeting only one or a few epitopes
- Poor immunogenicity

IV. Recombinant protein-based-

- Immune response against multiple epitopes
- Immunoadjuvants is required
- E.g. Melanoma AntiGEn A3 (MAGE-A3), epidermal growth factor (EGF)-directed vaccines

Annals of Oncology ;23: 1387–1393, 2013

Type of vaccines

V. Viral vaccines-

- suspension of attenuated Ankara virus
- A vaccinia virus- genetically modified to express antigens and co-stimulatory cytokines
- Effect limited by neutralizing immune responses

Annals of Oncology ;23: 1387–1393, 2013

Vaccines in Pipeline

In late-stages of development

- For early-stage NSCLC: the MAGE-A3 vaccine
- For locally advance stage: L-BLP25 vaccine
- For advanced stages: belagenpumatucel-L, the EGF vaccine, and the TG4010 vaccine
- Conventionally- Cancer immunotherapy is most likely to be successful in patients with low tumour burden
- However, recent phase III trials with Ipilimumab in metastatic melanoma and Sipuleucel-T in metastatic prostate cancer have challenged this view

Annals of Oncology ;23: 1387–1393, 2013

Rationale- Early stage lung cancer

- Stages I to (potentially resectable) IIIA NSCLC
- Rx mainly surgical resection
- High risk of relapse
- 5-year survival of resected stage IA is 73% and drops to only 24% in stage IIIA NSCLC
- Cisplatin-based neoadjuvant or adjuvant chemotherapy reduced the risk of relapse
- Compliance only 50% to 74%
- Postoperative vaccination to eliminate remaining cancer cells

Annals of Oncology ;23: 1387–1393, 2013

Melanoma AntiGEn A3 (MAGE-A3)

- Normal function of MAGE-A3 is unknown
- Presence on tumour cells worse prognosis
- MAGE-A3 antigen expressed in a variety of tumour cells but not in normal tissues
- Exception- the testis, which does not compromise true tumour specificity, as the antigen is not presented there in the absence of MHC molecules

Annals of Oncology ;23: 1387–1393, 2013

MAGE-A3

- In NSCLC expression in 35% of early-stage tumors
- MAGE-A3 vaccine is a recombinant protein antigen based vaccine
- The current vaccine is composed of a recombinant fusion protein (MAGE-A3 and protein D of Haemophilus influenzae) in combination with an immune response-enhancing adjuvant

Annals of Oncology ;23: 1387–1393, 2013

MAGE-A3

- Single phase II study, 182 patients
- Sage IB and II tumour
- MAGE A3 Detected by RT PCR from resected specimen
- Randomly (2:1) assigned to either the MAGE-A3 vaccine (300µg) or placebo
- Follow up-28 months
- Trend in favor of the MAGE-A3-
  - HR for Disease free interval (DFI)- 0.73 [95% CI 0.44–1.20,P= 0.107]
  - HR for Disease free survival (DFS)- 0.73 (95% CI 0.45–1.16, P = 0.093)
  -HR for OS- 0.66 (95% CI 0.36–1.20, P = 0.088)

Annals of Oncology ;23: 1387–1393, 2013

MAGE-A3

- Relative risk reduction of cancer recurrence
  - 25% in unselected NSCLC population
  - 43% in positive gene signature
- The treatment was well tolerated
- Only 3 had treatment-related adverse events
- One leading to treatment withdrawal

Annals of Oncology ;23: 1387–1393, 2013

MAGE-A3

Ongoing study

- Double-blind phase III trial (MAGRIT, NCT00480025)
- Stage IB/II/IIIA MAGE-A3-positive NSCLC
- randomise 2270 patients, either after surgery or after surgery plus adjuvant chemotherapy
- The primary end point for this trial is DFS
- Result will be published in 2015

Annals of Oncology ;23: 1387–1393, 2013

Mucinous glycoprotein 1 (MUC 1)

- Highly glycosylated transmembrane protein
- Present in normal tissue only at the apical surface of the epithelial cell
- MUC1 might be involved in promoting cell growth and survival

- Annals of Oncology;23: 1387–1393, 2013
- Lancet Oncol 2012; 13: e301–10

MUC1

- In cancer cells
  - Loses its polarity of expression
  - Often overexpressed
  - Aberrantly glycosylated
  - Unmasking of its peptide epitopes
  - Potential target for immunotherapy

- Annals of Oncology ;23: 1387–1393, 2013
- Lancet Oncol 2012; 13: e301–10

L-BLP25 Vaccine

- Peptide antigen based vaccine
- Targets exposed core peptide of the MUC1-associated antigen
- Contains the BLP25 lipopeptide and a liposomal delivery system- facilitates uptake by APCs
- Monophosphoryl lipid A- enhances immunogenecity
- Safety profile- Good, mostly grade I flu-like symptoms and injection site reactions

- Annals of Oncology ;23: 1387–1393, 2013
- Lancet Oncol 2012; 13: e301–10

L-BLP25 Vaccine

Small phase II randomised trial

- 171 patients, stage IIIB/IV NSCLC
- Disease control (response or stable disease) after first-line therapy
- Randomised to L-BLP25 with BSC or BSC alone
- Patients in the L-BLP25-arm received i.v. cyclophosphamide (300 mg/m2) 3 days before immunotherapy
- Weekly, 8 Injections f/b q6week (1000µg)
- The median OS 17.4 versus 13 months in the L-BLP25 group (adjusted HR 0.739; 95% CI 0.509–1.073; P = 0.112)- not significant

Stéphane C et al;J Thorac Oncol. 2014;9: 144–153

L-BLP25 Vaccine

Ongoing studies-

- Large phase III trial started in December 2006
- Recruitment was completed early June 2011
- This START-trial (NCT00409188) randomized 1464 patients with Unresectable stage III NSCLC
- Patients (2 : 1) received L-BLP25 plus BSC or placebo plus BSC
- The primary end point was OS Simultaneously
- Second phase III trial with similar study design and end points is ongoing in Asia (INSPIRE, NCT01015443)

- Annals of Oncology ;23: 1387–1393, 2013
- Lancet Oncol 2012; 13: e301–10

Advanced stage NSCLC: metastatic context

- Belagenpumatucel-L (Lucanix)
- Allogeneic cell vaccine
- Four different NSCLC lines (two adenocarcinoma, one squamous cell carcinoma, and one large cell carcinoma)
- Downregulation of TGF-ß2 by transfecting the cells with a TGF-ß2 antisense gene

- Annals of Oncology ;23: 1387–1393, 2013
- Lancet Oncol 2012; 13: e301–10

Belagenpumatucel-L (Lucanix)

- Phase ll study, dose-range study 12.5, 25, or 50 × 10^6 cells per injection monthly
- 75 NSCLC patients
- 14 with stage ll/IIIA and 61 with stage IIIB/IV
- In the subgroup of 61 patients with advanced (stages IIIB and IV) disease, a partial response rate of 15% was achieved

- Annals of Oncology ;23: 1387–1393, 2013
- Lancet Oncol 2012; 13: e301–10

Belagenpumatucel-L (Lucanix)

- Advanced stage- high-dose better OS
- Estimated 2-year survival of 47% versus 18%
- Subgroup analysis
  - patients with both cellular and humoral immune response to the vaccine could be demonstrated had improved OS compared with patients classified as immune response negative
  - Median OS 32.5 versus 11.6 months, P= 0.011

- Annals of Oncology ;23: 1387–1393, 2013
- Lancet Oncol 2012; 13: e301–10

Belagenpumatucel-L (Lucanix)

- This vaccine is currently further being evaluated for efficacy and safety in the STOP trial (NCT00676507)

- Randomised phase III trial comparing intradermal belagenpumatucel-L (25 × 106 cells in 0.4 ml) versus placebo following platinum-based chemotherapy

- Once monthly for 18 months and then once at 21 and 24 months if no disease progression or unacceptable toxicity in 700 patients with stage IIIA (T3N2 only), IIIB, or IV NSCLC

- Annals of Oncology ;23: 1387–1393, 2013
- Lancet Oncol 2012; 13: e301–10

EGF vaccine

- EGF is involved in cell proliferation, apoptosis, angiogenesis, and metastasis

- Different inhibitors of the EGFR signalling pathway, including mAb and small-molecule tyrosine kinase inhibitors, are already being used in clinical practice

- The EGF vaccine developed in Cuba with recombinant human EGF coupled to a carrier protein (P64K Niesseria meningitides protein) and with an immunoadjuvant (aluminium hydroxide or Contained ISA51)

- Annals of Oncology ;23: 1387–1393, 2013
- Lancet Oncol 2012; 13: e301–10

EGF vaccine

- Phase II study, 80 patients, stage IIIB or IV
- Randomised after completion of first-line chemotherapy to receive BSC alone or with the EGF vaccine
- Primed with cyclophosphamide (200 mg/m2)
- 50 µg equivalents of EGF was administered on days 1, 7, 14, and 28 and monthly thereafter
- A trend towards increased survival, median survival of 6.5 versus 5.3 months (P = 0.098)

- Annals of Oncology ;23: 1387–1393, 2013
- Lancet Oncol 2012; 13: e301–10

EGF vaccine

- In subgroup analysis of patients younger than 60 years, this was 11.6 versus 5.3 months (P = 0.0124)

- Patients with a good antibody response (defined by anti-EGF antibody titres 1 : 4000 and at least four times their pre-immunisation values had a median OS of 11.7 versus 3.6 months for the others (P = 0.002)

- Annals of Oncology ;23: 1387–1393, 2013
- Lancet Oncol 2012; 13: e301–10

TG4010 vaccine

- Targets the MUC1 antigen
- Suspension of attenuated Ankara virus, a vaccinia virus, genetically modified to express not only MUC1 but also IL-2
- It has been demonstrated that addition of exogenous IL-2 is a strong Immunoadjuvants as it is able to reverse the suppression of T-cell response caused by the cancer-associated MUC1

- Lancet Oncol 2012; 13: e301–10

TG4010 vaccine

- Phase II randomised study, 148 untreated patients with MUC1+ stage IIIB/IV NSCLC
- Randomised to receive up to six cycles of cisplatin–gemcitabine with or without TG4010
- The vaccine was given s.c. weekly for 6 weeks and then q3 weeks until disease progression

- Lancet Oncol 2012; 13: e301–10

TG4010 vaccine

- Primary endpoint- PFS at 6 months 44% versus 35%, P=0.13)
- Objective response rate (ORR) was seen in the vaccinated group (43% versus 27%, P = 0.03)
- Subgroup analysis in patients with a normal level of activated natural killer cells
  - PFS at 6 months was 58% versus 38%, P = 0.04
  - OS 18 vs 11.3 months, P = 0.020

- Lancet Oncol 2012; 13: e301–10

TG4010 vaccine

Ongoing trials

- Phase IIB/III, double blind RCT (NCT01383148)
- Aiming to enroll 1000 MUC1-expressing stage IV patients with normal levels of activated natural killer cells is started at end of 2011

Checkpoint inhibiter

- Immune checkpoint pathways play a key role in regulating T-cell responses
- The two inhibitory pathways involve signaling through CTLA-4 or PD-1
- CTLA-4 pathway in early T-cell activation

CTLA-4

- Ipilimumab blocks the interaction between CTLA-4 and its ligands, CD80 and CD86
- Blocking this interaction promotes T-cell activation
- Ipilimumab in combination with chemotherapy has shown some promise in patients with NSCLC

Phase II Trial of IPI and Chemotherapy in NSCLC

Result	IPI+Chemo Concurrent	IPI+Chemo phased	Chemo only
no. of patients	70	68	66
Median PFS, (months)	5.52	5.68	4.63
Overall HR for PFS	.81	.72	
95% CI	0.55 to1.17	0.5-to 1.06	
P	.13	.05	
Overall HR for OS 95% CI P	.99 0.67 to 1.46 .48	.87 0.59 to1.28 .23	
OS HR Squamous 95% CI Nonsquamous 95% CI Median OS, months	 1.02 0.5 to2.08 0.96 0.6 to1.53 9.96	 .48 0.22 to 1.03 1.17 0.74 to1.86 12.22	 8.28

PD-1

- PD-1 receptor binds with its ligand(PD-L1/B7-H1),
- T-cell inhibition
- Downregulation of T-cell responses
- Tumor express of PD-L1 on the cell surface
- This allows tumors to directly suppress antitumor cytolytic T-cell activity, known as adaptive resistance
- Blocking this binding by blocking PD-1orPD-L1 via monoclonal antibodies augment T1 cell response

Clinical Activity of the Anti–PD-1 (BMS-936558) and Anti–PD-L1 (BMS-936559) Antibodies

antibody	No. of Patients Evaluable for Efficacy (all dose levels)	ORR (%)	95%CI (%)	6 month PFS	95%CI (%)
Anti PD1 NSCLC(all type) Squamous Non squamous unknown	 76 18 56 2	 18 33 12 1	 10-29 13-59 5-24 -	 26 33 12 -	 16-36 12-55 10-34
AntiPDL1 NSCLC(all type) Squamous Non squamous	 49 13 36	 10 8 11	 3-22 6-36 3-26	 31 43 26	 17-45 15-71 10-42

MYCOBACTERIAL ADJUVENT BASED AGENTS

- Cell wall components of Mycobacterium spp induce non-specific immune stimulation

- In a randomised phase 2 study of 28 previously untreated patients with NSCLC and mesothelioma, administration of SRL172—a suspension of heat-killed Mycobacterium vaccae—combined with chemotherapy did not significantly affect response rates (54% vs 33%, p=0·3) and median survival (9·7 months vs 7·5 mnth, P=0·235) compared with chemotherapy alone

www.the lancet.com/oncology, vol13,july 2012

MYCOBACTERIAL ADJUVENT BASED AGENTS

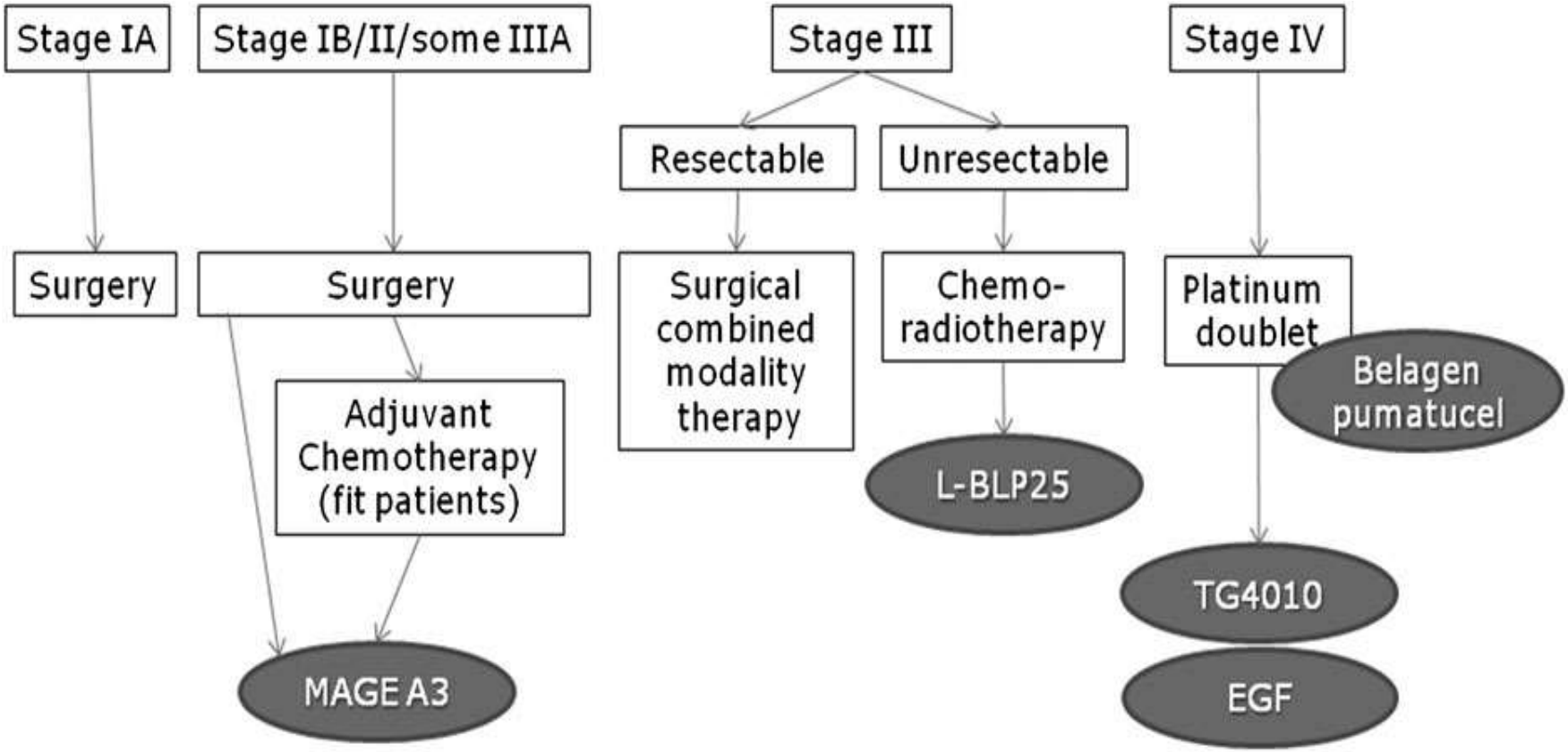
- Results of an open-label, randomised phase 3 study of 419 NSCLC patients showed no difference between the treatment groups for overall survival, progression-free survival, or objective response rate

www.the lancet.com/oncology, vol13,july 2012

Mycobacterium indicus pranii

- synergistic effects with chemo therapeutic agents in preclinical studies
- In a randomised phase 2 study of 221 chemotherapy-naive NSCLC patients, addition of cadi-05 to paclitaxel and cisplatin improved overall survival (9·8 vs 7·8 months, HR 0·55, 95% CI 0·37–0·82; p=0·0034) and progression- free survival (8·4 vs 5·2 months, 0·43, 0·25–0·73; p=0·0446). However, these results were not significant in the intention-to-treat population

Treatment Algorithm for NSCLC



Annals of Oncology ;23: 1387–1393, 2013