기관고유연구사업 결과 보고

결 재	과제책임자	과 장	부 장

※ 협조 : 폐암센터장 한지연 (인)

본인이 수행한 2008 ~ 2010 년도 기관고유연구사업 과제 연구결과를 붙임과 같이 보고합니다.

과제명	임상시험을 통한 폐암의 새로운 치료법 개발 III
과제책임자 (소속, 성명)	폐암 연구과 이진수
총연구비	429,000천원 (2008년: 144,000, 2009년: 150,000, 2010년: 135,000)
총연구기간	2008년 1월 1일 ~ 2010년 12월 31일

붙임 : 기관고유연구사업 최종보고서 1부

2010 년 12월 30일

과제책임자 이 진 수

작 성 요 령

기관고유연구사업 최종보고서

(과제번호 : 0810090)

임상시험을 통한 폐암의 새로운 치료법 개발 III

Development III of New Treatment for Lung Cancer by Clinical Trials

과제책임자 : 이진수

국 립 암 센 터

1. 이 보고서는 국립암센터 기관고유연구사업 최종보고서입니다.

2. 이 보고서 내용을 인용할 때에는 반드시 국립암센터 연구사업 결과임을 밝혀야 합니다.

임상시험을 통한 폐암의 새로운 치료법 개발 III

국립암센터

제 출 문

국립암센터 원장 귀하

이 보고서를 기관고유연구사업 “임상시험을 통한 폐암의 새로운 치료법 개발 III” 과제의 최종보고서로 제출합니다.

2010. 12. 30

국 립 암 센 터

과 제 책 임 자 : 이진수

연 구 원 : 조재일

〃 : 김홍태

〃 : 한지연

〃 : 윤 탁

〃 : 이희석

목 차

< 요 약 문 >

(한글) 임상시험을 통한 폐암의 새로운 치료법 개발 III

(영문) Development III of new treatment for lung cancer by clinical trials

< 요 약 문 >

<table>
<tr><td colspan="2">연구분야(코드)</td><td colspan="2">C3</td><td>과제번호</td><td colspan="2">0810090</td></tr>
<tr><td colspan="2">과 제 명</td><td colspan="5">임상시험을 통한 폐암의 새로운 치료법 개발 III</td></tr>
<tr><td colspan="2" rowspan="4">연구기간/연구비
(천원)</td><td>합계</td><td colspan="3">2008년 1월 1일 ~ 2010년 12월 31일</td><td>429,000</td></tr>
<tr><td>1차년도</td><td colspan="3">2008년 1월 1일 ~ 2008년 12월 31일</td><td>144,000</td></tr>
<tr><td>2차년도</td><td colspan="3">2009년 1월 1일 ~ 2009년 12월 31일</td><td>150,000</td></tr>
<tr><td>3차년도</td><td colspan="3">2010년 1월 1일 ~ 2010년 12월 31일</td><td>135,000</td></tr>
<tr><td colspan="2" rowspan="2">과제책임자</td><td>성 명</td><td>이진수</td><td>주민등록번호</td><td colspan="2"></td></tr>
<tr><td>전화번호</td><td>031-920-1501</td><td>전 자 우 편</td><td colspan="2">jslee@ncc.re.kr</td></tr>
<tr><td rowspan="2">색인단어</td><td>국문</td><td colspan="5">임상시험, 폐암, 항암요법, 항암-방사선요법</td></tr>
<tr><td>영문</td><td colspan="5">clinical trial, lung cancer, Chemotherapy, Chemoradiotherapy</td></tr>
</table>

◆ 연구목표

<최종목표>
- 임상시험을 통한 효과적인 폐암의 새로운 치료법 개발

<당해년도 목표>
- 개발된 protocol에 따른 임상자료의 수집
- 연구자 주도 임상시험의 기획
- 신치료법의 적용을 위한 수탁임상시험과제 수행

◆ 연구내용 및 방법

(1) 개발된 protocol에 따른 임상 자료의 수집

- 2008년도 이전에 개발되어 지속 수행 되었던 23개의 과제가 피험자 등록 및 임상 자료 수집이 완료되었으며 (IIT: 11개, SIT: 8개, 국내 다기관: 4개), 3개 과제가 지속 수행 중임

(2) 신약 및 신 치료법의 효능 평가를 위한 연구자 주도 임상 시험의 개발

- 총 8개의 연구자 주도 임상 과제가 개발되었으며, 이중 5개의 과제는 IRB 및 KFDA의 승인 후 피험자 등록 및 임상 자료 수집을 진행 중에 있으며, 3개 과제는 IRB 심의 진행 중에 있음. (2008년: 1개 과제, 2009년 2개 과제, 2010년 5개 과제)

(3) 신치료법의 적용을 위한 수탁 임상 시험 과제 수행

- 총 15개의 신약 또는 신 치료법의 효능 평가를 위한 다국가 임상 시험에 참여하여, 피험자 등록 및 임상 치료를 수행하고 있음.
(2008년: 7개, 2009년: 3개, 2010년 5개 과제)

(4) 국내 다기관 임상 연구의 참여

- 총 3개의 다기관 임상 연구에 공동 연구 기관으로 참여하여 피험자 모집을 수행하고 있음.

◆ 연구성과

-정량적 성과
(1) 논문 발표

구분	달성치/목표치	달성도(%)
SCI 논문 편수	11/13	84.6%
IF 합	58.65/50.0	117.3%

-정성적 성과

(1) 임상 시험을 통한 폐암 환자의 database 구축

총 35개의 과제를 통해 164명의 피험자가 등록되었고, 46개의 과제를 통해 연구 자료의 수집이 지속되었다. 이로써 2,428명의 폐암환자의 치료, 생존에 관한 data base가 구축됨
연구자 주도 임상 과제에서 총 6편의 논문 (NCC-040, 055, 056, 079, 176, 177)이 발표되었으며, 국내 다기관 연구과제에 공동 저자로 2편, 다국가 임상 연구에 교신저자 (NCC-192), 공동 저자 (NCC-108)로 참여하는 성과를 얻었다.

(2) 신약 및 신 치료법의 효능 평가를 위한 연구자 주도 임상 시험의 개발

총 8개의 연구자 주도 임상 과제가 개발되었다.
(1/2상 임상 시험 2 과제, 2상 임상 시험 6과제)
진행성 비소세포 폐암 환자를 대상으로 하는 1차 요법 연구 3개 과제, 재발한 비소세포 폐암 환자를 대상으로 하는 연구 2과제, 확장기 소폐포 폐암의 유지 요법 1과제, 확장기 소세포 폐암의 1차 치료 요법 1과제, 재발한 소세포 폐암 환자 대상 연구 1과제 등 다양한 환자군을 대상으로 하는 연구 과제가 개발되었다.

(3) 신치료법의 적용을 위한 수탁 임상 시험 과제 수행

총 15개의 다국가 임상 과제 중 4개의 2상 임상 시험을 수행하고 있다.
audit (NCC-428), KFDA Inspection (NCC-464)를 통해 연구 진행 사항을 점검 받았다.

◆ 참여연구원 (최종연도 참여인원)	성 명	이진수, 조재일, 김홍태, 한지연, 윤 탁, 이희석, 윤성진, 유선영, 한종희, 황금희, 문혜미, 오세희, 이은숙, 김윤정
	주민등록번호	

※ 요약문의 총분량은 2page 이내로 제한함

Project Summary

Title of Project	Development IIII of new treatment for lung cancer by clinical trials
Key Words	Clinical Trial, lung cancer, chemotherapy, chemoradiotherapy
Project Leader	Jin Soo Lee
Associated Company	None

Objectives:

1. Ultimate objective
   - Development of new treatment for lung cancer by clinical trials
2. Object of this year
   - Continuance of existing clinical trials and collection of clinical data according to the protocol
   - Development of new Investigator-Initiated trials
   - Participation of Investigator New Drug Study (global clinical trials)

Detials and Process of Study:

1. Registration and Clinical data collection according to the protocol
   - On 23 of trials developed since 2008, we have been registered and completed data collection (IIT: 11 trials, SIT: 8 trials, national multi-center: 4 trials)
   - 3 of trials are ongoing. (patients registration & data collections)

2. Development of new Investigator-Initiated trials
   - we developed the 8 different studies to evaluate efficacy of new drugs and new treatment.
   - Patients registration and data collection began from 5 studies.
     (2008: 1, 2009: 2, 2010:5)

3. Development of new Multi-national clinical trial (SIT)
   Total 15 studies was opened. (2008: 7, 2009: 3, 2010:5)

4. Participation of National multi-center trials

Result of Study:

- quantitative outcome

구분	달성치/목표치	달성도(%)
Number of SCI papers	11/13	84.6%
Sum of IF	58.65/50.0	117.3%

- qualitative outcome

1. Construction of lung cancer patients database through clinical trials
   - Patients enrollment status: total 164 pts enrolled on 35 studies. (2008~2010)
   - collection of clinical data according to the 47 studies.
   - Cumulative number of registered patients: 2,428 patients
   - on 9 studies, 10 Papers published (NCC-040, 055, 056, 079, 176, 177/ NCC-078, 108, 192) and 4 papers prepared. (NCC-124, 126, 155, 156)
   - Oral presentation (09′ World Conference of Lung Cancer): First-SIGNAL (NCC-126)

2. Development of new Investigator-Initiated trials to evaluate efficacy of new drugs and new treatment
   - we were developed 8 cinical trials (phase I/II: 2 trials, phase II: 6 trials)
     (1) 1st line advanced NSCLC: 3 trials
         - with Irinotecan/Cisplatin plus TS-1 (phase I/II)
         - with GP vs. IP according ERCC1 expression level
         - with Pemetrexed/Cisplatin plus intercalated Gefitinib
     (2) recurrence or failure NSCLC; 2 trials
         - with Vorinostat (plus gefitinib) phase I/II
         - with BIBW 2992 plus simvastatin (randomized phase 2)
     (3) ED-SCLC: 1 trials with Irinotecan/Cisplatin plus simvastatin (randomized phase 2)
     (4) maintenance therapy (SCLC): 1 trials with Sorafenib
     (5) recurrence or failure SCLC: 1 trials with BIBF 1120

3. Participation of Investigator New Drug Study (global clinical trials)
   - Total 15 trials are ongoing (phase II: 4 trials. phase III: 11 trials)

   phase 2 studies;

   1. Phase IIb/III randomized, double-blind trial of BIBW 2992 plus best supportive vs. placebo plus BSC in NSCLC patients failling erlotinib or gefitinib (Boehringer-Ingelheim)
   2. A Randomized phase 2 study of exabepilone/carboplatin and paclitaxel/Carboplatin in subjects with advanced NSCLC (BMS)
   3. A double-blinde randomized, parallel 2-arm phase II trial of BMS-690514 versus erlotinib in chemotherapy refractory non-small cell lung cancer patients. (BMS)
   4. phase 2, open label single arm study of the efficacy and safety of crizotinib in patients with advanced NSCLC harboring a traslocation or inversion involing the ALK gene locus. (Pfizer)

1. 연구의 최종목표

임상 시험을 통한 효과적인 폐암의 새로운 치료법 개발

2. 연구의 내용 및 결과

1) 신규 과제 개발 및 환자 등재 현황

연구 수행 명	개발된 과제 수				등재된 환자 수			
	2001년 ~ 2004년	2005년 ~ 2007년	2008년 ~ 2010년	계	2001년 ~ 2004년	2005년 ~ 2007년	2008년 ~ 2010년	계
신약의 제1상 임상시험	1	0	2	3	52	0	31	83
새로운 복합항암화학요법의 제2/3상 임상시험	12	6	3	21	593	404	304	1,301
수술 및 방사선치료와 항암요법을 이용한 복합요법의 제2상 임상시험	4	3	1	8	159	191	116	466
다국적 임상 연구	6 (1상: 1과제)	11 (1상: 1과제)	16	33	44	106	161	311
국내 다기관 공동연구	0	4	4	8	0	248	19	267
계	23	24	26	73	848	949	631	2,428

2) 개발된 임상 시험 진행 현황 및 연구 실적

- 2008년도 이전에 개발되어 환자 등록 및 임상 자료 수집 지속 과제

연구 수행 명	번호 NCCCTS	IRB승인일 등재시작일 등재완료일	제 목	실제/목표 환자수(명)	비고
새로운 복학함암 화학요법의 제 2/3상 임상시험	055	2003.02.27 2003.03.05 2006.04.21	확장기 소세포폐암 환자에서 Irinotecan/ cisplatin 유도요법 후 유지요법으로 weekly Irinotecan vs. no further therapy의 무작위배정, 제3상 임상시험	120/120	08'ASCO발표 08'JTO저널발표
	078	2003.11.20 2004.07.14 2005.11.22	F-18 FDG PET-CT를 이용한 진행성 폐암의 항암치료후 반응 조기예측에 관한 연구	34/44	09'JTO저널발표
	079	2003.11.01 2003.12.11 2005.06.03	비소세포폐암 환자에서 Gemcitabine/Vinorelbine과 Irinotecan/Cisplatin 복합요법의 교차투여, 무작위배정 제2상 임상시험(previously untreated stage IIIB or IV)	146/146	08'Cancer저널발표
	124	2005.02.28 2005.06.10 2008.12.23	IB 혹은 II기 비소세포폐암 환자에서 수술 전 선행화학요법과 수술 후 보조화학요법의 제 2상 임상시험	153/156	등재완료, 임상자료수집완료 논문준비중
	155	2005.12.06 2005.12.21 2009.02.24	1차 항암화학요법 혹은 항암화학/방사선 병용요법에 실패한 전이성 혹은 재발성 소세포폐암 환자에서 파크리탁셀-젬시타빈 복합화학요법의 제 2상 임상 연구	35/37	등재완료, 임상자료수집완료 09'EMCTO발표 논문준비중
	156	2005.11.28 2006.02.16 2009.02.26	1차 항암화학요법 혹은 항암화학/방사선 병용요법에 실패한 전이성 혹은 재발성 식도암 환자에서 파크리탁셀-카페시타빈(젤로다®) 복합화학요법의 제 2상 임상연구	33/39	등재완료, 임상자료수집완료 10'BMCcancer submitted
	157	2005.11.28 2006.01.02 2009.05.07	진행성 (IIIB 혹은 IV기) 비소세포폐암 환자에서 젬자-엘록사틴 복합화학요법의 제 2상 임상연구	43/60	등재완료 임상자료수집완료 논문준비중
	176	2006.03.08 2006.04.27 2009.04.27	확장기 소세포 폐암 환자의 1차 요법으로서 Irinotecan (캠푸토)® / Cisplatin(시스플라틴) 과Simvastatin(심바스타틴)의 병용 투여대한 2상 임상연구	62/61	등재완료 임상자료수집완료 10'Cancer저널발표

연구 수행 명	번호 NCCCTS	IRB승인일 등재시작일 등재완료일	제 목	실제/목표 환자수(명)	비고
새로운 복학함암 화학요법의 제 2/3상 임상시험	177	2006.03.08 2006.05.15 **2008.09.24**	이전 항암치료에 실패한 진행성 비소세포 폐암 환자에서 Gefitinib(이레사)과 Simvastatin(심바스타틴) 병용요법 대 Gefitinib(이레사) 단독요법의 무작위 배정, 2상 임상연구	110/110	**등재완료, 임상자료수집완료 09'ASCO발표 10'CCR저널발표**
	285	2007.08.20 **2008.03.20 2010.10.18**	항암화학요법에 실패한 소세포폐암 환자에서 2차 요법으로 수텐® (Sunitinib) 단독요법을 이용한 제 2상 임상연구	25/42	**등재완료 조기종료 임상자료수집중 2011ASCO학회발표준비중**
수술 및방사선 치료와 항암 요법을 이용한 복합 요법의 제2상 임상시험	040	2002.07.31 2002.08.08 2005.11.04	뇌전이를 동반한 비소세포폐암환자에서 선항암치료-후방사선치료와 선방사선치료-후항암치료의 비교 제3상 임상시험	48/200	**08' Cancer 저널 발표**
	056	2003.03.25 2003.07.10 2006.06.22	비소세포폐암 환자에서 Irinotecan/cisplatin 항암요법과 방사선 치료의 복합요법 후 Amifostine vs. Epokine군간 비교의 무작위배정, 제2상 임상연구	77/80	**08'Cancer저널발표**
	158	2005.11.28 2006.06.01 **2009.02.17**	근치적 수술이 된 IB, II 혹은 IIIA 기 비소세포폐암 환자에서 수술 후 젬자-엘록사틴 보조화학요법과 젬자-시스플라틴 보조화학요법의 제 2 상 비교 임상시험	151/150	**등재완료, 임상자료수집중**
	164	2006.01.16 2006.04.27 **등재중**	조직검사로 확진된 IIIA 기(N2) 비소세포폐암 환자에서 수술 전 선행화학요법과 선행화학요법-방사선요법 동시치료의 비교 제 2 상 임상시험	34/102	**등재진행중 임상자료수집중**
	255	2007.04.05 200802.27 **등재중**	수술이 불가능한 제3기 비소세포폐암환자에서 상피세포성장인자수용체 (EGFR) 변이 여부에 따른 유도요법 및 방사선-항암제 동시치료에 대한 제2상 임상연구	39/212	**등재진행중 임상자료수집중 다기관 공동연구준비중**

연구 수행 명	번호 NCCCTS	IRB승인일 등재시작일 등재완료일	제 목	실제/목표 환자수(명)	비고
다국적 임상 연구 (연구비 미지원 과제)	072	2003.09.06 2004.05.13 2006.04.13	진행성(제3기말) 비소세포 폐암 환자에서 방사선-항암제(시스플라틴) 병합 치료 후 젬시타빈 단독요법, 젬시타빈+카보플라틴 복합항암요법 혹은 치료없는 관찰군의 무작위 제 2상 임상연구	16/30 (경쟁적 등재)	**임상자료 수집 완료**
	108	2004.08.13 2004.10.14 2005.06.21	국소진행성 또는 전이성 비소세포 폐암환자를 대상으로 한 ALIMTA와 시스플라틴 병용요법 대 젬자와 시스플라틴 병용요법의 무작위 배정 제3상 임상시험	27/27	**08' JCO 저널발표**
	128	2005.04.25 2005.09.02 2006.02.21	진행성 ⅢB/Ⅳ기의 비소세포폐암 환자에 대한 타쎄바TM (엘로티닙)요법의 EXPANDED ACCESS PROGRAM	14/120 (경쟁적 등재)	**09' JTO 저널발표**
	192	2006.05.15 2006.09.11 2007.03.29	Stage IIIB/IV 의 비소세포폐암 (NSCLC) 환자들에 대한 1 차 요법제로서 젬시타빈/플라티늄과 타쎄바®(엘로티닙) 혹은 위약의 연속 병용 투여에 관한 무작위 배정, 위약 대조, 이중 맹검, II 상 임상시험	15/30	**임상자료 수집완료** **08' ASCO 발표** **08, ASTRO 발표** **09' JCO 저널발표**
	213	2006.08.21 2006.11.29 **2008.10.28**	기존에 Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor (EGFR TKI) 치료를 받았던, 국소 진행성 또는 전이성 (Stage IIIB-IV) 비소세포폐암 (NSCLC) 환자에 대하여 'ZD6474(ZACTIMATM) + 최선의 지지 요법' 대 '위약 + 최선의 지지 요법'을 비교하여 그 유효성을 평가하기 위한 제 3상, 다국가, 무작위 배정, 이중 맹검, 평행군, 다기관 시험	41/930 (경쟁적 등재)	**등재 완료,** **임상자료 수집 완료,** **10' ASCO 발표**
	293	2007.11.19 **2008.05.13** **2008.06.29**	진행된 NSCLC 환자의 1차 치료에서 타세바■와 아바스틴■의 병용요법과아바스틴■과 화학요법의 병용치료를 비교하기 위한 제 2상 연구	1/4	**등재 완료** **임상자료 수집 완료**
	297	2007.11.19 **2008.04.21** **2009.10.20**	국소 진행성 또는 전이성 비소세포폐암(NSCLC)에 대한 백금을 기본 으로 하는 요법 1회 실패 후 도세탁셀 이차요법으로 치료받는 환자에서 Aflibercept와 위약을 비교하는 다국가, 무작위배정, 이중맹검 임상시험	10/15	**등재 완료** **임상자료 수집 중**

연구 수행 명	번호 NCCCTS	IRB승인일 등재시작일 등재완료일	제 목	실제/목표 환자수(명)	비고
다국적 임상 연구 (연구비 미지원 과제)	306	**2008.01.30** **2008.04.29** **2009.04.28**	시스플라틴(Cisplatin) 투여와 관련된 화학요법제 유도성 오심 및 구토(CINV) 예방을 위하여 MK-0517 단회용량 정맥주사시 안전성, 내약성 및 유효성을 조사하기 위한, 기관내 맹검 으로 진행되는, 3 상, 무작위배정, 이중맹검, 활성 대조, 평행군 임상시험	20/23	**등재 완료, 진행 중**
국내 다기관 임상 연구	121	2005.02.21 2005.06.23 **2009.07.16**	근치적 수술을 시행한 식도암 환자에서 수술을 시행한 군과 수술 후 Capecitabine과 Cisplatin 보조 항암화학요법을 시행한 군간의 제 3상 다기관 무작위 비교 임상연구	37/90 (경쟁적 등재)	**등재 완료** **임상자료 수집 중**
	126	2005.04.25 2005.10.18 2007.11.29	비흡연자에서 나타나는 진행성 또는 전이성 폐선암종의 1차 선택 치료로서의 게피티니브(IRESSA™)와 표준화학요법 (Gemcitabine 1250mg/m^2와 Cisplatin 80mg/m^2 병용요법)의 비교, 무작위 배정 , 3상 연구	203/314 (경쟁적 등재)	**임삼자료수집완료** **09'WCLC oralpresentation**
	145	2005.08.22 2005.09.02 2006.02.21	비소세포 폐암 환자에 대한 탈시바(얼로티니브)의 치료효과를 예측하기 위한 유전자 변화에 대한 연구	14/120 (경쟁적 등재)	**08' Cli Cancer Res 저널발표**
	203	2006.07.24 2006.08.17 2006.08.29	이전에 항암화학요법을 받았던 진행성 비소세포폐암 환자를 대상으로 한 ALIMTA 단독요법에 관한 임상연구	6/186 (경쟁적 등재)	**09' Lung Cancer 저널발표**

- 2008 ~ 2010년도 신규 개발 연구자 주도 임상 과제 및 다기관, 다국가 임상 연구

연구 수행 명	번호 (NCCCTS)	IRB승인일 등재시작일 등재완료일	제 목	실제/목표 환자수(명)	비고
신약의 제 1상 임상시험	333	2008.06.16 2008.10.07 등재 중	진행성 또는 전이성 비소세포폐암 환자에서 이리노테칸 (Irinotecan■), 시스플라틴(Cisplatin■)과 에스-원 (S-1■) 복합항암요법을 이용한 제 1/2상 임상연구	22/37	**등재진행중**
	433	2009.10.20 2010.07.09 등재 중	재발한 진행성 비소세포 폐암환자에 vorinostat(보리노스텟)과 gefetinib (이레사) 병합투여의 1,2상 임상연구	9/44	**등재진행중**

연구 수행 명	번호 (NCCCTS)	IRB승인일 등재시작일 등재완료일	제 목	실제/목표 환자수(명)	비고
새로운 복학함암 화학요법의 제 2/3상 임상시험	371	2009.02.05 2009.02.20 등재 중	andomized phase II study of irinotecan/cisplatin versus gemcitabine/ cisplatin as the first-line therapy followed by two different sequences of pemetrexed or docetaxel as the second	132/284	등재 진행 중
	476	2010.05.19 등재 전	A randomized phase II study of Sorafenib maintenance in patients with extensive disease small cell lung cancer (ED-SCLS) after response to induction chemotherapy	0/110	다기관 공동 연구 준비 중
	489	2010.06.21 2010.10.28 등재 중	이전에 치료를 받은 진행성 비선암종 비소세포 폐암(NSCLC) 환자를 대상으로 BIBW 2992 및 simvastatin을 BIBW 2992 및 최상의 지지요법과 비교하는 무작위 배정, 공개 라벨, 제II상 임상시험	6/84	등재 진행 중
	미정	심의 중	A ranomized placebo-controlled phase II study of intercalated administration of Pemetrexed/platinum with gefitinib or placebo as first-line treatment of stage IIIB/IV lung adenocarcinoma in never-smokers.	0/182	신규 개발 과제
	미정	심의 중	Randomized phase II trial comparing irinotecan/cisplatin chemotherapy induction followed by concurrent thoracic iriadiation with irinotecan/cisplatin chemotherapy with or without nitorgycerin in patients with limited disease small cell lung cancer	0/110	신규 개발 과제
	미정	심의 중	A phase II study of BIBF 1120 as second-line treatment for patients with small cell lung cancer	0/41	신규 개발 과제
다국적 임상 연구 (연구비 미지원 과제)	310	2008.02.18 2008.06.25 2009.08.19	Erlotinib 또는 gefitinib 치료에 실패한 비소세포폐암 환자들을 대상으로 최선의 지지요법 (BSC)을 병행한 BIBW 2992와 최선의 지지요법 (BSC)를 병행한 위약을 비교하는 제 IIb/III상, 무작위배정, 이중-눈가림 임상시험	12/12	등재 완료, 임상자료 수집 중

연구 수행 명	번호 (NCCCTS)	IRB승인일 등재시작일 등재완료일	제 목	실제/목표 환자수(명)	비고
다국적 임상 연구 (연구비 미지원 과제)	316	2008.06.11 2008.07.22 등재 중	절제가능한 MAGE-A3-양성 비소세포폐암 환자에서 보조요법으로서 recMAGE-A3 + AS15 항원-특이적 항암 면역요법제의 유효성을 평가하는 이중맹검, 무작위배정, 위약대조 제 3 상 임상시험	29/36	**등재 진행 중**
	330	2008.06.16 2010.03.08 등재 중	수술이 불가능한 3 기 비소세포성 폐암(non-small cell lung cancer, NSCLC) 환자를 대상으로 암백신 Stimuvax (L-BLP25 또는 BLP25 리포좀 백신)을 연구하기 위한 무작위배정, 이중맹검, 위약대조, 다기관, 제 3 상 임상시험 [EMR 63325-001]	1/5	**등재 진행 중**
	336	2008.10.22 2009.01.30 2009.05.28	비소세포폐암 환자에서 CP-751,871 의 파클리탁셀(PACLITAXEL)/카보플라틴(CARBOPLATIN)과의 병용요법과 파클리탁셀/카보플라틴 요법을 비교하는 무작위 배정, 공개, 제 3 상 임상시험 (A4021016)	5/10	**등재 완료.** **임상 자료 수집 중**
	337	2008.07.21 2009.02.24 2009.03.12	비선암종 조직형의 진행성비소세포폐암 환자에서 엘로티닙 단독 또는 CP-751,871 과 병용 투여하는 무작위배정, 공개, 제 3 상 임상시험 (A4021018)	2/6	**등재 완료,** **임상 자료 수집 중**
	348	2008.09.22 2009.01.30 2009.04.10	진행된 비소세포성폐암 (Advanced Non-Small Cell Lung Cancer) 피험자를 대상으로 익사베필론 (Ixabepilone)과 카보플라틴 (Carboplatin) 병용요법을 파클리탁셀 (Paclitaxel)과 카보플라틴 병용요법과 비교하는 무작위배정 제 2상 임상시험	2/9	**등재 완료,** **임상 자료 수집 중**
	376	2008.12.22 2009.08.25 등재 중	일차 화학요법에 실패한 병기 IIIB/IV이거나 재발성인 비소세포폐암 환자에서 경구 BIBF 1120과 표준 페메트렉시드 병용요법과 위약과 표준 페메트렉시드 병용 요법의 유효성과 안전성을 비교, 연구하는 다기관, 무작위 배정, 이중맹검, 제3상 임상시험	5/10	**등재 진행 중**
	388	2009.03.04 2009.05.04 2010.06.03	stage IIIB/IV 비소세포 폐암 (NSCLC) 환자에 대한 일차 요법으로서 젬시타빈/백금과 함께 타세바■ (엘로티닙) 또는 위약의 순차적 투여에 대한 무작위배정, 위약 대조, 이중 맹검 제 3상 시험	30/30	**등재 완료** **임상 자료 수집 중**
	399	2009.03.16 2009.07.24 2009.12.30	이전에 화학요법 치료를 받은 비소세포폐암 환자에서 BMS-690514 대 엘로티닙의 이중 눈가림, 무작위배정, 평행, 2 군 제 II 상 시험	3/7	**등재 완료** **임상 자료 수집 중**
	428	2009.09.21 2010.02.08 2010.02.25	이전에 두가지 이상 치료법에 실패한 비소세포폐암 환자에서 최적 지지요법에 추가한 경구 탈락토페린의 제 3 상, 무작위배정, 이중 눈가림, 위약 대조 시험	4/4	**등재 완료** **임상 자료 수집 중**

연구 수행 명	번호 (NCCCTS)	IRB승인일 등재시작일 등재완료일	제 목	실제/목표 환자수(명)	비고
다국적 임상 연구 (연구비 미지원 과제)	445	2009.12.31 2010.09.16 등재 중	역형성 림프종 인산화효소 (ALK) 유전자 위치에 전좌 또는 역위를 보이는 진행된 비소세포폐암(NSCLC) 환자에서 PF-02341066의 유효성과 안전성에 대한 공개, 단일군, 제2상 임상시험(A8081005)	4/10	**등재 진행 중**
	446	2010.01.05 2010.06.25 등재 중	역형성 림프종 인산화효소 (ALK) 유전자 위치에 전좌 또는 역위를 보이는 진행된 비소세포폐암(NSCLC) 환자에서 PF-02341066과 표준 치료 항암화학요법(페메트렉시드 또는 도세탁셀)을 비교하는 유효성과 안전성에 대한 무작위배정, 공개, 제 3상 임상시험(A8081007)	2/10	**등재 진행 중**
	462	2010.04.19 2010.05.24 등재 중	이전의 엘로티닙(erlotinib) 또는 게피티니브(gefitinib) 치료에 실패한 비소세포폐암 환자를 대상으로 BIBW 2992 단일요법 후, BIBW 2992와 1주 1회 파클리탁셀(paclitaxel)을 시험자가 선택한 화학요법과 비교하기 위한 제 3상 무작위배정 임상시험	9/12	**등재 진행 중**
	464	2010.02.22 2010.05.13 2010.06.01	진행성, 전이성 또는 재발성 비편평세포 비소세포성(NSCLC) 환자에서 베바시주맙-시스플라틴-페메트렉시드에 의한 일차 화학요법 후 페메트렉시드 병용 또는 비병용하였을 때의 베바시주맙(아바스틴®) 유지 요법에 대한 공개 임상시험	7/7	**등재 완료** **임상 자료 수집 중**
	491	2010.06.21 2010.11.25 등재 중	재발성 소세포폐암 환자를 대상으로 벨로테칸(캄토벨주®) 또는 토포테칸의 유효성 및 안전성을 비교평가하기 위한 후기2상, 무작위배정, 공개, 평행군, 다기관 임상시험	1/8	**등재 진행 중**
국내 다기관 임상 연구	381	2009.01.13 2009.09.08 등재 중	1차 또는 2차의 이전 항암요법에 실패한 비소세포폐암 환자에서 sorafenib와 erlotinib의 병용 효과를 보기 위한 제 2상 임상시험	1/47 (경쟁적 등재)	**등재 진행 중**
	382	2009.02.26 2009.06.05 등재 중	절제불가능한 침윤성흉선종 또는 흉선암에서 일차요법으로 파크리탁셀과 시스플라틴을 병용하는 공개 제 2상 임상시험	5/4	**등재 진행 중**
	434	2009.10.19 2010.11.16 등재 중	절제 불가 선양낭포암 환자에서 RAD001 단일요법의 2상 임상시험	1/4	**등재 진행 중**

3. 연구결과 고찰 및 결론

(1) 연구 결과 고찰

Primary Chemotherapy for Newly Diagnosed Nonsmall Cell Lung Cancer Patients With Synchronous Brain Metastases Compared With Whole-Brain Radiotherapy Administered First Result of a Randomized Pilot Study (NCC-040, 08′ Cancer)

BACKGROUND. This randomized pilot trial investigated whether primary chemotherapy was feasible in terms of efficacy, survival, toxicity profile, and quality of life compared with whole-brain radiotherapy (WBRT) given first in chemotherapy-naive patients nonsmall cell lung cancer (NSCLC) with synchronous brain metastasis when neurologic symptoms or signs are absent or controlled by supportive care.

METHODS. After stratification by Eastern Cooperative Oncology Group performance status (ECOG PS) (0 - .1 vs 2), the number of intracranial metastases (<3 vs 3), and the presence of extrathoracic extracranial metastasis, eligible patients were randomized to the primary chemotherapy arm or the WBRT-first arm. World Health Organization (WHO) response criteria, National Cancer Institute Common Toxicity Criteria (NCI-CTC; version 2.0), and the European Organization for Research and Treatment of Cancer (EORTC) C-30/LC-13 questionnaire were used.

RESULTS. A total of 48 patients were enrolled between August 2002 and November 2005. The response rate of chemotherapy and survival outcomes in the primary chemotherapy arm were not statistically different from those in the WBRTfirst arm (overall response rate, 28.0% vs 39.1%; progression-free survival, 3.6 months vs 4.4 months; overall survival, 9.1 months vs 9.9 months). There was close correlation noted between intracranial and extracranial tumor responses (k 5 0.82). However, in the WBRT-first arm, grade 3 of 4 neutropenia was more frequent (79% vs 40%) during chemotherapy and 4 patients (17.4%) did not receive further chemotherapy because of early death or poor performance after WBRT. Cognitive function appeared to deteriorate during primary chemotherapy, but was also found to deteriorate after WBRT.

CONCLUSIONS. Primary chemotherapy is more feasible and can be an appropriate option for patients with synchronous brain metastasis when neurologic symptoms or signs are absent or controlled. The role and timing of WBRT should be defined in further studies in this clinical setting

Randomized Phase II Study of Maintenance Irinotecan Therapy Versus Observation Following Induction Chemotherapy with Irinotecan and Cisplatin in Extensive Disease Small Cell Lung Cancer (NCC-055, 08′ Journal of Thoracic Cncology)

Introduction: To determine whether irinotecan maintenance therapy in extensive disease-small cell lung cancer can improve survival of patients who responded to irinotecan plus cisplatin (IP) induction therapy.

Methods: A total of 120 chemo-naive patients with adequate organ functions and Eastern Cooperative Oncology Group performance status of 0 to 2 were enrolled from March 2003 through April 2006. After IP induction therapy, with either schedule A (I: 60 mg/m2 intravenously (IV) on days 1, 8, and 15; P: 30 mg/m2 IV on days 1 and 8, every 4 weeks for six cycles) or schedule B (I: 60 mg/m2 and P: 30 mg/m2 IV on days 1, and 8, every 3 weeks for eight cycles), responding patients were randomized to either maintenance with irinotecan 100 mg/m2 IV on days 1, 8, and 15, every 4 weeks up to six cycles, or observation.

Results: Overall, 100 (83%) of 120 patients achieved objective tumor responses (12 complete responses, 88 partial responses) after IP induction therapy. Of those patients who remained in remission upon completion of planned cycles of induction therapy, 45 were randomized to maintenance (*n*21) or observation (*n*24). Median progression-free survival (PFS) and overall survival (OS) for all patients were 7.2 and 14.0 months, respectively. For the maintenance arm, median PFS and OS were 12.0 and 17.6 months, respectively. For the observation arm, median PFS and OS were 9.9 and 20.5 months, respectively, which was not significantly different from the maintenance arm.

Conclusions: IP chemotherapy is very useful for the treatment of small cell lung cancer. However, maintenance irinotecan therapy did not seem to further affect the clinical outcome of patients who had responded to IP induction therapy.

Randomized Phase 2 Study of Subcutaneous Amifostine Versus Epoetin-a Given 3 Times Weekly During Concurrent Chemotherapy and Hyperfractionated Radiotherapy for Limited-disease Small Cell Lung Cancer (NCC-056, 08, Cancer)

BACKGROUND. The purpose of the current study was to investigate the role of amifostine and epoetin-a in reducing severe toxicities during concurrent chemohyperfractionated radiotherapy (CCRT) for limited disease small cell lung cancer (LD-SCLC).

METHODS. Seventy-six patients with LD-SCLC were enrolled. The treatment schedule was consisted of two 28-day cycles of cisplatin at a dose of 30 mg/m2 (Days 1 and 8) and Irinotecan at a dose of 60 mg/m2 (Days 1, 8, and 15) followed by two 21-day cycles of cisplatin at a dose of 60 mg/m2 (Day 1) and etoposide at a dose of 100 mg/m2 (Days 1-3) with concurrent twice-daily thoracic radiotherapy for a total of 45 grays. Patients were randomly assigned at registration to either amifostine at a dose of 500 mg or epoetin-a at a dose of 10,000 IU subcutaneously 3 times weekly (n 5 36 patients and 40 patients, respectively). Fifteen of 36 patients assigned to the amifostine arm did not receive amifostine because of a lack of supply.

RESULTS. Amifostine treatment was associated with higher febrile neutropenia (P 5 .003) and grade 2 or 3 nausea (according to the National Cancer Institute Common Toxicity Criteria [version 3.0]) (P 5.03). It also demonstrated a trend toward higher grade 4 leukopenia (P 5 .05). Grade 3 esophagitis was reported in 30% of patients treated with amifostine and 9% of patients treated with epoetina (P 5.059). Epoetin-a treatment was associated with less grade 2 or 3 anemia (P 5 .031) and lower decreases in hemoglobin level during CCRT (P 5 .016). The median survival times for both treatment arms were comparable (22.6 months in the amifostine arm vs 25.6 months in the epoetin-a arm; P 5.447).

CONCLUSIONS. Although amifostine administered 3 times weekly during CCRT did not significantly reduce severe toxicities, epoetin-a was effective in preventing severe anemia during CCRT in patients with LD-SCLC. Other radioprotective strategies to minimize severe toxicities should be investigated

Randomized Phase 2 Study of Irinotecan Plus Cisplatin Versus Gemcitabine Plus Vinorelbine as First-line Chemotherapy With Second-line Crossover in Patients With Advanced Nonsmall Cell Lung Cancer (NCC-079: 08′ Cancer)

BACKGROUND. The current study was performed to compare the nonplatinumbased combination of gemcitabine and vinorelbine (GV) with the combination of irinotecan and cisplatin (IP) as first-line chemotherapy with second-line crossover in patients with advanced nonsmall cell lung cancer (NSCLC).

METHODS. Patients were randomly assigned to received either irinotecan at a dose of 65 mg/m2 plus cisplatin at a dose of 30 mg/m2 (Arm A) or gemcitabine at a dose of 900 mg/m2 plus vinorelbine at a dose of 25 mg/m2 (Arm B), each of which was administered on Days 1 and 8 every 3 weeks as the first-line therapy followed by crossover at the time of disease progression.

RESULTS. A total of 146 patients were enrolled (75 patients in Arm A and 71 patients in Arm B); 138 patients were evaluable for tumor response and toxicity. During first-line therapy, IP was found to result in more grade 21 nausea and vomiting (toxicity was graded according to the National Cancer Institute Common Toxicity Criteria [version 2.0]) (41% vs 12%; P 5.0001) and alopecia (36% vs 10%; P 5.0003). Pneumonitis was noted only with GV therapy (7% vs 0%; P 5.058). During second-line therapy, IP was found to result in more grade 3 diarrhea (17% vs 2%; P 5.039) and GV featured more cases of grade 31 neutropenia (78% vs 40%; P 5.0003). IP tended to generate more tumor responses (38% vs 26% as first-line therapy, and 30% vs 13% as second-line therapy) compared with GV. IP also demonstrated a favorable trend in median progression-free survival (4.6 months vs 3.8 months as first-line therapy and 4.5 months vs 2.6 months as second-line therapy) and overall survival (15.9 months vs 13.1 months; P 5.3), but this difference was not statistically significant. The majority of patients who were refractory to IP also failed to respond to GV in

the second-line setting.

CONCLUSIONS. The platinum-based IP regimen appeared to be superior to the GV combination in terms of response rate. However, given the similar survival and better tolerability of the nonplatinum GV regimen, either treatment sequence would appear to be acceptable for the treatment of patients with advanced NSCLC. Cancer 2008;113:388 - .95. 2008 American Cancer Society.

A Phase 2 Study of Irinotecan, Cisplatin, and Simvastatin for Untreated Extensive-disease Small Cell Lung Cancer (NCC-176, 10′ cancer)

BACKGROUND: The objective of this study was to investigate the efficacy of simvastatin in combination with irinotecan and cisplatin in chemotherapy-naive patients with extensive-disease small-cell lung cancer (ED-SCLC).

METHODS: In this phase 2 study, 61 patients received treatment with irinotecan (65 mg/m2) and cisplatin (30 mg/m2) on Days 1 and 8 every 3 weeks until either death or disease progression occurred. Patients also received oral simvastatin (40 mg daily) during the course of chemotherapy. The primary endpoint was 1-year survival. Secondary endpoints included the response rate (RR), progression-free survival (PFS), and toxicity.

RESULTS: The 1-year survival rate was 39.3%. The median overall survival (OS) was 11 months, and the median PFS was 6.1 months. Overall, the RR was 75%. The most common grade 3/4 toxicity was neutropenia (67%). Efficacy of the treatment was associated significantly with smoking status. Compared with never-smokers, ever-smokers had a better RR (40% vs 78%; P ¼ .01), a longer PFS (2.5 months vs 6.4 months; P ¼ .018), and had a trend toward an improved OS (9.0 months vs 11.2 months; P ¼ .095). The effect of smoking on survival was apparent when ever-smokers were subdivided according to packyears (PY) of smoking. Ever-smokers who had smoked >65 PY had a significantly longer OS compared with eversmokers who had smoked 65 PY or never-smokers (20.6 months vs 10.6 months vs 9.0 months, respectively; logrank P ¼ 0.032). In multivariate analysis, PY >65 was predictive of longer survival (hazard ratio, 0.280; 95% confidence interval, 0.113-0.694). CONCLUSIONS: The current results indicated that simvastatin in combination with irinotecan and cisplatin did not improve the survival of patients with ED-SCLC. Although the subgroup analysis by smoking status was exploratory, the addition of simvastatin to irinotecan and cisplatin may improve the outcome of heavy smokers with ED-SCLC.

A randomized phase II study of gefitinib plus simvastatin versus gefitinib alone in previously treated patients with advanced non-small cell lung cancer (NCC-177, 10′ CCR)

BACKGROUND: To evaluate the efficacy and safety of gefitinib plus simvastatin (GS) versus gefitinib (G) alone in previously treated patients with advanced non-small cell lung cancer (NSCLC).

METHODS: Between May 2006 and September 2008, 106 patients (51% male, 75% adenocarcinoma, 50% never smoker, 54% more than two prior regimens) were randomly assigned to G alone (250 mg/d, n=54) or GS (250 mg/d and 40 mg/d, respectively, n=52). One cycle was 4 weeks of treatment. Therapy was continued until disease progression or intolerable toxicity was observed. The primary endpoint was response rate (RR). Secondary endpoints included toxicity, progression-free survival (PFS) and overall survival (OS).

RESULTS: The RR was 38.5% (95% confidence interval [CI], 25.3 - 51.7%) for GS and 31.5% (95% CI, 19.1% - 43.9%) for G. The median PFS was 3.3 months (95% CI, 1.4 - 5.2) for GS and 1.9 months (95% CI, 1.0 - 2.8) for G. The median OS was 13.6 months (95% CI, 7.1 - 20.1) for GS and 12.0 months (95% CI, 7.8 - 16.2) for G. In exploratory subgroup analysis, GS showed higher RR (40% vs. 0%, P=0.043) and longer PFS (3.6 months vs. 1.7 months, P=0.027) compared with G alone in patients with wild-type epidermal growth factor receptor (*EGFR*)non-adenocarcinoma tumors. Adverse events in both arms were generally mild and mainly consisted of skin rashes.

CONCLUSION: Although no superiority of GS to G was demonstrated in this unselected NSCLC population, GS showed higher RR and longer PFS compared to G alone in patients with wild-type *EGFR* non-adenocarcinoma tumors. Simvastatin may improve the efficacy of gefitinib in that subgroup of gefitinib-resistant NSCLC patients.

First-line gefitinib treatment for patients with advanced non-small cell lung cancer with poor performance status. (10′ JTO)

BACKGROUND: Best supportive care only is recommended for patients with advanced non-small cell lung cancer (NSCLC) with poor performance status (PS) of Eastern Cooperative Oncology Group 3 or 4. Recently, the possibility of using epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor therapy has been reported for poor PS patients harboring EGFR mutations.

METHODS: We retrospectively analyzed 74 patients with advanced NSCLC who were treated with first-line gefitinib during hospitalization for Eastern Cooperative Oncology Group PS 3 or 4. All patients were classified according to three clinical parameters: smoking history, gender, and histology type.

RESULTS: The median age was 64 years (range, 35-86 years). The proportions of females, never smokers, and adenocarcinoma were 51.4%, 54.1%, and 78.4%, respectively. An overall response rate, median progression-free survival (PFS), and median overall survival (OS) was 27.0%, 32 days (95% confidence interval [CI], 22-48 days), and 61 days (95% CI, 7-115 days), respectively. Female gender, never smoking, and adenocarcinoma histology were strong

predictors of tumor response. Never smoking and adenocarcinoma were independent predictors of better PFS but not of OS. Seven patients experienced treatment-related adverse effects of grade 3 to 4, which included anorexia (n = 2), pneumonitis (n = 4), and elevated liver enzymes (n = 1). Never-smoker females with adenocarcinoma exhibited a response rate of 50.0%, median PFS of 130 days (95% CI, 51-209 days), and median OS of 236 days (95% CI, 150-322 days).

CONCLUSIONS: Gefitinib may provide clinical benefits for patients with NSCLC with poor PS who were selected according to clinically favorable parameters.

Early Predictionof response to Frist-line therapy Using Integrated 18F-FDG PET/CT for patients with advanced/metastatic Non-small cell lung cancer (NCC-078, 09′ JTO)

INTRODUCTION: Early prediction of treatment response is of great value to avoid unnecessary toxicity of ineffective treatment and to get a chance to receive another effective treatment earlier. We conducted a prospective study to evaluate the role of integrated 18-fluorodeoxyglucose positron emission tomography/computed tomography as a tool for early response predictor.

METHODS: Between May 2004 and November 2005, 31 patients with pathologically proven stage IIIB/IV non-small cell lung cancer participated in this study. Metabolic response was assessed prospectively after one cycle of systemic therapy, which was compared with conventional radiographic response according to the World Health Organization criteria.

RESULTS: By the World Health Organization criteria, 10 of 31 patients (32.3%) achieved a partial response, 7 stable diseases, and 14 progressive diseases, whereas there were 7 partial metabolic responses, 13 stable metabolic diseases, and 11 progressive metabolic diseases. Out of 7 partial metabolic responses, 5 achieved partial response, 1 stable disease, and 1 progressive disease (positive predictive value of 71.4% [5 of 7]), whereas 9 of the 11 progressive metabolic diseases had progressive diseases and the other 2 showed stable diseases (negative predictive value of 100% [11 of 11]). There were moderate correlation between early metabolic response and best overall response (Spearman r = 0.62, p <0.01). However, an early metabolic response did not translate into better survival outcome.

CONCLUSIONS: Single 18-fluorodeoxyglucose positron emission tomography/computed tomography scan taken after one cycle of treatment could predict progressive disease earlier than standard radiographic evaluation and can be used as a measure to avoid ineffective systemic chemotherapy.

Phase III study comparing cisplatin plus Gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small cell lung cancer (NCC-108, 08′ JCO)

Abstract

PURPOSE: Cisplatin plus gemcitabine is a standard regimen for first-line treatment of advanced non-small-cell lung cancer (NSCLC). Phase II studies of pemetrexed plus platinum compounds have also shown activity in this setting.

PATIENTS AND METHODS: This noninferiority, phase III, randomized study compared the overall survival between treatment arms using a fixed margin method (hazard ratio [HR] <1.176) in 1,725 chemotherapy-naive patients with stage IIIB or IV NSCLC and an Eastern Cooperative Oncology Group performance status of 0 to 1. Patients received cisplatin 75 mg/m(2) on day 1 and gemcitabine 1,250 mg/m(2) on days 1 and 8 (n = 863) or cisplatin 75 mg/m(2) and pemetrexed 500 mg/m(2) on day 1 (n = 862) every 3 weeks for up to six cycles.

RESULTS: Overall survival for cisplatin/pemetrexed was noninferior to cisplatin/gemcitabine (median survival, 10.3 v 10.3 months, respectively; HR = 0.94; 95% CI, 0.84 to 1.05). Overall survival was statistically superior for cisplatin/pemetrexed versus cisplatin/gemcitabine in patients with adenocarcinoma (n = 847; 12.6 v 10.9 months, respectively) and large-cell carcinoma histology (n = 153; 10.4 v 6.7 months, respectively). In contrast, in patients with squamous cell histology, there was a significant improvement in survival with cisplatin/gemcitabine versus cisplatin/pemetrexed (n = 473; 10.8 v 9.4 months, respectively). For cisplatin/pemetrexed, rates of grade 3 or 4 neutropenia, anemia, and thrombocytopenia (P <or= .001); febrile neutropenia (P = .002); and alopecia (P <.001) were significantly lower, whereas grade 3 or 4 nausea (P = .004) was more common.

CONCLUSION: In advanced NSCLC, cisplatin/pemetrexed provides similar efficacy with better tolerability and more convenient administration than cisplatin/gemcitabine. This is the first prospective phase III study in NSCLC to show survival differences based on histologic type.

Randomized, placebo-controlled, phase II study of sequential Erlotinib and chemotherapy as first-line treatment for advanced Non-small cell lung cancer

Abstract

PURPOSE: This study investigated whether sequential administration of erlotinib and chemotherapy improves clinical outcomes versus chemotherapy alone in unselected, chemotherapy-naïve patients with advanced non-small-cell lung cancer (NSCLC).

PATIENTS AND METHODS: Previously untreated patients (n = 154) with stage IIIB or IV NSCLC and Eastern Cooperative Oncology Group performance status of 0 or 1 were randomly assigned to receive erlotinib (150 mg/d) or placebo on days 15 to 28 of a 4-week cycle that included gemcitabine (1,250 mg/m(2) days 1 and 8) and either cisplatin (75 mg/m(2) day 1) or carboplatin (5 x area under the serum concentration-time curve, day 1). The primary end

point was nonprogression rate (NPR) at 8 weeks. Secondary end points included tumor response rate, NPR at 16 weeks, duration of response, progression-free survival (PFS), overall survival (OS), and safety.

RESULTS: The NPR at 8 weeks was 80.3% in the gemcitabine plus cisplatin or carboplatin (GC)-erlotinib arm (n = 76) and 76.9% in the GC-placebo arm (n = 78). At 16 weeks, the NPR was 64.5% for GC-erlotinib versus 53.8% for GC-placebo. The response rate was 35.5% for GC-erlotinib versus 24.4% for GC-placebo. PFS was significantly longer with GC-erlotinib than with GC-placebo (adjusted hazard ratio, 0.47; log-rank P = .0002; median, 29.4 v 23.4 weeks); this benefit was consistent across all clinical subgroups. There was no significant difference in OS. The addition of erlotinib to chemotherapy was well tolerated, with no increase in hematologic toxicity, and no treatment-related interstitial lung disease.

CONCLUSION: Sequential administration of erlotinib following gemcitabine/platinum chemotherapy led to a significant improvement in PFS. This treatment approach warrants further investigation in a phase III study

Efficacy and safety of cisplatin/pemetrexed versus cisplatin/gemcitabine as first-line treatment in East Asian patients with advanced non-small cell lung cancer: results of an exploratory subgroup analysis of a phase III trial.

INTRODUCTION: We conducted an exploratory, post hoc, subgroup analysis of the East Asian (EA) patients in a multinational phase III trial to determine whether the efficacy results for this subgroup were consistent with those observed for the entire study population.

METHODS: Thousand seven hundred twenty-five patients with advanced non-small cell lung cancer (NSCLC), including 126 EA patients (7.3%) from Taiwan and Korea, were enrolled in the trial and randomly assigned first-line chemotherapy with cisplatin and pemetrexed (CP; n = 862) or cisplatin and gemcitabine (CG; n = 863). Adjusted Cox proportional hazards models were used to compare overall survival and progression-free survival between the treatment arms in the EA subgroup. Median time-to-event data were estimated with the Kaplan-Meier method.

RESULTS: Consistent with the results for the entire study population, survival in the EA subgroup trended in favor of CP over CG in patients with non-squamous histology, despite the more frequent use of post discontinuation targeted therapy in the CG arm. The opposite trend was noted for patients with squamous tumors. A higher proportion of patients in the EA subgroup were never smokers compared with the entire study population. A trend toward improved survival with CP compared with CG was seen regardless of smoking status, particularly in non-squamous patients.

CONCLUSIONS: The key finding of this subgroup analysis was that the NSCLC histology

effect on treatment outcomes for pemetrexed-treated patients seen in the entire study population was also apparent in the EA subgroup. The potential prognostic influence of race, histology subtype, and smoking status should be assessed in future NSCLC studies.

First-SIGNAL: A Randomized Phase III Study of Gefitinib IRESSA^{TM}) versus Standard Chemotherapy (Gemcitabine plus Cisplatin) as a First-line Treatment for Never-smokers with Advanced or Metastatic Adenocarcinoma of the Lung (NCC-126)

Background: Gefitinib has shown high response rate and extended survival in never smoker lung adenocarcinoma patients. A randomized phase III trial was conducted to compare the efficacy of gefitinib as a first-line treatment with standard chemotherapy in this patient population. (ClinicalTrials.gov, NCT00455936)

Methods: From Oct 2005 to Nov 2007, a total of 313 never-smokers with chemonaïve stage IIIB/IV lung adenocarcinoma, ECOG PS 0-2 and adequate organ functions were randomly assigned to receive either gefitinib (250 mg/p.o. daily) or GP chemotherapy (G: Gemcitabine 1,250 mg/m^{2}onday1&8; P: Cisplatin 80 mg/m^{2}onday1every3weeks, up to 9 courses). Primary endpoint was overall survival (OS); secondary endpoints were objective response rate (ORR), progression-free survival (PFS), and toxicity. After initial disease progression, further treatment was at the discretion of the treating physicians.

Results: Of 309 patients who received actual treatment, 88.7% were female, 90.0% had stage IV disease, and 9.1% had PS2, with no difference between the two arms. The median(range) was 57(19-74) years. The gefitinib arm had a numerically higher ORR than the GP arm (85/159 [53.5%] vs. 63/150 [42.0%], p=0.0811) and significantly better PFS (HR=0.737 [95% CI, 0.580-0.938], p=0.0063 by log-rank test) with the median of 5.9 vs. 5.8 months (mo) while the curve crosses over around the median time. This crossing-over of the PFS curve was in part due to the difference in PFS by the EGFR mutation status. In the gefitinib arm with known EGFR mutation status, the PFS was significantly shorter in the mutation-negative subgroup (N=26) than the mutation-positive subgroup (N=27) with median of 2.1 vs. 7.9 mo (HR=0.385 [95% CI, 0.208-0.711], p=0.0090) while there was no such difference in the GP arm (median 5.5 vs. 5.8 mo; HR=1.223 [95% CI, 0.650-2.305], p=0.2657)

OS was similar between the two arms (HR=1.029 [95% CI, 0.756-1.401], p=0.4278 by log-rank test). The median and 1-year survival rate were 20.3 mo and 73.7% for the gefitinib arm, and 23.1 mo and 76.2% for the GP arm, respectively. Of note, 121 (80.7%) of the 150 GP arm patients received EGFR-TKI during their disease course. Grade 3/4 toxicity was less common in the gefitinib arm (28.3% vs. 67.3%, p<0.0001) while no unusual toxicity was noted in both

arms.

Conclusion: While gefitinib did not improve OS over the standard GP chemotherapy, unprecedented survival outcome along with high ORR and better toxicity profile suggests that gefitinib might be a reasonable first-line therapy for this group of never–smoker lung adenocarcinoma patients.

(2) 결론

폐암은 전 세계적으로 암 사망률 1위의 가장 치명적인 질환의 하나이다. 이에 전 세계적으로 폐암 환자들의 생존율 증가를 위하여 임상 시험을 통한 새로운 치료방법이 끊임없이 개발되고 있다. 이에 본 연구 기관에서는 폐암 환자의 생존율 증가를 위하여 2002년도부터 꾸준히 임상시험을 실시하였고, 다양한 임상시험을 통한 한국인 폐암 환자의 생존율을 증가 시킬 수 있는 새로운 치료방법을 개발해 왔다. 현재까지 전 세계적으로 보고 되고 있는 제 2상 임상 시험 결과와 비교하여 반응률과 생존 기간을 상당히 개선시킨 결과를 관찰할 수 있었다. 이와 같이 새롭게 개발된 치료방법을 기반으로 우리나라 폐암 환자의 치료에 널리 이용될 수 있는 기반을 마련하여, 우리나라 폐암 환자의 예후를 개선하고, 나아가 전 세계적으로 우수한 암치료 기관으로서의 입지를 마련하고자 한다.

4. 연구성과 및 목표달성도

(1) 연구성과

가. 국내 및 국제 전문학술지 논문 게재 및 신청

[연구자 주도 임상 과제]

논문명	저자 (저자구분)	저널명 (I.F.)	Year; Vol(No):Page	구분	지원과제번호
Primary Chemotherapy for Newly Diagnosed Nonsmall Cell Lung Cancer Patients With Synchronous Brain Metastases Compared With Whole-Brain Radiotherapy Administered First (NCC-040)	**Jin Soo Lee (교신저자)** Ji-Youn Han, Heung Tae Kim, Sung Jin Yoon, Hong Ryul lPyo, Kwan Ho Cho, Sang-Hoon Shin, Heon Yoo, Seung-Hoon Lee, (공동저자)	Cancer (4.632)	**2008;** 113(1):143-9	국외 SCI	**0210140** **0510140**
Randomized Phase II Study of Maintenance Irinotecan Therapy Versus Observation Following Induction Chemotherapy with Irinotecan and Cisplatin in Extensive Disease Small Cell Lung Cancer (NCC-055)	**Jin Soo Lee (교신저자)** Ji-Youn Han, (제1저자), Heung Tae Kim, Kun Young Lim, Sung Jin Yoon, Dae Ho Lee,Lee (교신저자)	Journal of thoracic oncology (1.429)	**2008**; 3(9):1039-45	국외 SCI	**0510140** **0510080**
Randomized Phase 2 Study of Subcutaneous Amifostine Versus Epoetin-a Given 3 Times Weekly During Concurrent Chemotherapy and Hyperfractionated Radiotherapy for Limited-disease Small Cell Lung Cancer (NCC-056)	Ji-Youn Han, (교신저자) Sun Young Yu, Hong Ryull Pyo, Hyae Young Kim, Kwan Ho Cho, Dae Ho Lee, Heung Tae Kim, **Jin Soo Lee, (공동저자)**	Cancer (4.632)	**2008** 113.(7): 1623-31	국외 SCI	**510140**
Randomized Phase 2 Study of Irinotecan Plus Cisplatin Versus Gemcitabine Plus Vinorelbine as First-line Chemotherapy With Second-line Crossover in Patients With Advanced Nonsmall Cell Lung Cancer (NCC-079)	**Jin Soo Lee (교신저자)** Ji-Youn Han, (제1저자) Dae Ho Lee, Jung Eun Song Sung Young Lee, Hyae Young Kim, Heung Tae Kim (공동저자)	Cancer (4.582)	**2008**; 29(1): 69-75	국외 SCI	**021014**0 **0510140**
A phase 2 study of irinotecan, cisplatin, and simvastatin for untreated extensive-disease small cell lung cancer. (NCC-176)	Ji-Youn Han, (제1저자) ung Young Lim, Sung Yuong You, Tak Yun, Heung Tae Kim, **Jin Soo lee (교신저자)**	Cancer (5.418)	2010 e-pup	국외 SCI	0810130
A randomized phase II study of gefitinib plus simvastatin versus gefitinib alone in previously treated patients with advanced non-small cell lung cancer (NCC-177)	Ji-Youn Han, (제1저자) Soo-Hyun Lee, Nam Jin Yoo, Suk Hyung Lee, Yoon Joo Moon, Tak Yun, Heung Tae Kim, **Jin Soo Lee (교신저자)**	Clinical Cancer Research (6.741)	2010 e-pup	국외 SCI	0810130

논문명	저자 (저자구분)	저널명 (I.F.)	Year; Vol(No):Page	구분	지원과제번호
First-line gefitinib treatment in advanced non-small cell lung cancer patients with poor performance status	Young Joo Lee (제1저자) Heung Tae Kim, Ji-Youn Han, Tak Yun, Goun Kook Lee, Hye Young Kim, Sung Jee Hyun, **Jin Soo Lee (교신저자)**	JTO (4.547)	2010;5(3): 361-8	국외	0810090
Early Predictionof response to Frist-line therapy Using Integrated 18F-FDG PET/CT for patients with advanced/metastatic Non-small cell lung cancer	Lee Dae H0 (제1 저자) Seo-Ki Kim, Ho-Young Lee, Sung Young Lee, Sun Hwa Park, Hyae Young Kim, Keon Wook Kang, Ji-Youn Han, Heung Tae Kim, **Jis Soo Lee (교신저자)**	JTO (3.508)	2009:4(7): 816-21	국외	0510140

* 0210140: 임상시험을 통한 폐암이 새로운 치룔법 개발 I
* 0510140: 임상시험을 통한 폐암의 새로운 치료법 개발 II
* 0810090: 임상시험을 통한 폐암의 새로운 치료법 개발 III

〔다국적 임상 연구 과제〕

논문명	저자 (저자구분)	저널명 (I.F.)	Year; Vol(No):Page	구분	지원과제번호
Phase III Study Comparing Cisplatin Plus Gemcitabine With Cisplatin Plus Pemetrexed in Chemotherapy-Naïve Patients With Advanced-Stage non - Small-Cell Lung Cancer (NCC-108)	Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, Serwatowski P, Gatzemeier U, Digumarti R, Zukin M, **Lee JS (공동저자),** Mellemgaard A, Park K, Patil S, Rolski J, Goksel T, de Marinis F, Simms L, Sugarman KP, Gandara D.	JCO (15.484)	2008:26(21);35 43-51	국외	없음
Randomized, placebo-controlled, phase II study of sequential Erlotinib and chemotherpay as first-line treatment for advanced Non-small cell lung cancer (NCC-192)	Mok TS, Wu YL, Yu CJ, Zhou C, Chen YM, Zhang L, Ignacio J, Liao M, Srimuninnimit V, Boyer MJ, Chua-Tan M, Sriuranpong V, Sudoyo AW, Jin K, Johnston M, Chui W, **Lee JS.(교신저자)**	JCO (17.157)	2009 e-publish	국외	없음
Efficacy and safety of cisplatin/pemetrexed versus cisplatin/gemcitabine as first-line treatment in East Asian patients with advanced non-small cell lung cancer: results of an exploratory subgroup analysis of a phase III trial.(NCC-108)	Yang CH, Simms L, Park K, **Lee JS, (공동저자)** Scagliotti G, Orlando M.	JTO (4.547)	2010:5(5); 688-95	국외	없음

나. 국내 및 국제 학술대회 논문 발표

논문명	저자	학술대회명	지역[1)]	지원과제번호
Randomized phase II study of maintenance irinotecan therapy versus observation following induction chemotherapy with irinotecan plus cisplatinin extensive disease small cell lung cancer (ED-SCLC)	Ji-Youn Han, (제1저자) Heung Tae Kim, MD, Kun Young Lim, MD, Sung Jin Yoon, RN, Dae Ho Lee, MD, **Jin Soo Lee, (교신저자)**	2008, American Society of Clinical Oncology	국외 (Chicago US)	510080
A randomized phase III study of Gefitinib (Iressa^{TM}) versus standard chemotherapy(Gemcitabine plus Cisplatin)as a first-line treatment for never smokings with advanced or metastatic adenocarcinoma of the lung (NCC-126)	Jin S. Lee, Keunchil Par, Sang W Kim, Dae H. Lee, Eung T. Kim, Ji-Y Han, Tak Yun, Nyung J. Ahn, Chelwon Suh, Jung S Lee, Sun Y Yu, Jong H. Han, Jea W.Lee, Sook J. Jo	2009 Wold Conferenc of Lung Cancer	국외 (San francisco)	없음
Randomized phase II study of gefitinib alone or with simvastatin in previously treated advanced non-small cell lung cancer (NCC-177)	Ji-Youn Han, Soo-Hyun Lee, Tak Yun, Yoon joo Moon, Hyun Lee Chol, in Hae Park, Heung Tae Kin, Jin Soo Lee	2009 American Society of Clinical Oncology	국외 Orando, USA)	0810090
A phase II study of weekly paclitaxel plus gemcitabine as second-line therapy in patients with metastatic or recurrment small cell lung cancer (NCC-155)	Heung Tae Kin, Tak Yun, Ji-Youn Han, Hyun Lee Choi, Hyae Young Kim, Jin Soo Lee	2009 European Multidisciplinary conference in Thoracic Oncology (EMCTO)	국외 (Lugano Switzerland)	0810090

* 0510140: 임상시험을 통한 폐암의 새로운 치료법 개발 II

* 0810090: 임상시험을 통한 폐암의 새로운 치료법 개발 III

다. 산업재산권

없음

라. 저 서

저서명	저자	발행기관(발행국, 도시)	쪽수	Chapter 제목, 쪽수 (공저일 경우)
폐암 100문 100답	이진수 외 폐암센터 연구자	국립암센터	1-138	

마. 연구성과의 정부정책 기여

없음

바. 기타연구성과

없음

(2) 목표달성도

가. 연구목표의 달성도

최종목표	연차별목표		달성내용	달성도(%)	
				연차	최종
	1차년도	기존 임상시험 지속 시행	지속 수행 과제 12개 중 2개 과제 등재 완료, 10개 과제 등재 진행 중	90%	30%
		기존 임상시험의 연구 실적 발표	국외 저널 발표 4편, 국외 학술대회 발표 1편임.		
		연구자주도 임상시험의 기획	총 2개 과제 승인, 1개 과제 심의 예정		
		신치료법의 적용을 위한 수탁임상시험 과제 수행	총 6개 과제 참여 결정, IRB 승인		
	2차년도	개발된 protocol에 따른 임상자료의 수집	총 33개 과제가 진행되었으며, 9과제가 피험자 등록이 완료 됨. 총 166명의 피험자를 등록 함.	90%	60%
		연구자 주도 임상 시험의 기획	총 3개 과제 개발 승인 과제 1개, 시정승인 과제 1개 임상 약 공급 조율 과제 1개		
		신 치료법의 적용을 위한 수탁 임상 시험 과제 수행	총 5개 과제 참여 결정, 진행 과제 3개, 준비 과제 2개		
	3차년도	개발된 protocol에 따른 임상 자료의 수집	총 23개 진행 과제의 환자 등록 및 임상시험 자료 수집이 완료 됨. (연구자 주도: 11개 과제 다국가 임상: 8개 과제 국내 다기관 임상: 4개 과제) 총 19개의 과제를 통해 피험자 등록 및 자료 수집이 지속 되고 있음. (연구자 주도: 6개 과제 다국가 임상: 10개 과제 국내 다기관 임상: 3개)	85%	85%
		연구자 주도 임상 시험의 기획	총 5개의 폐암의 새로운 기전 약물에 대한 2상 임상 과제를 개발함 총 2개의 과제에서 환자 등록을 시작하였으며, 3개 과제는 IRB 심의 진행 중임.		

		신치료법의 적용을 위한 수탁 임상 시험 과제 수행	다국적 임상시험에 주도적인 역할로 참여할 수 있는 과제 적극 유치를 통해 총 5개의 (2상:2개, 3상:3개) 과제에 참여하여 환자 등재 및 자료 수집을 진행하고 있음.		

나. 평가의 착안점에 따른 목표달성도에 대한 자체평가

평가의 착안점	자 체 평 가
기존 임상시험이 지속적으로 잘 수행되고 있는가? (연간 피험자 등록률)	피험자 등록이 원활하게 진행되었으나, 목표하였던 피험자 등록율(목표: 200명/year, 등록율: 164명)에는 미치지 못하였음. 등재가 지연되고 있는 과제의 다기관 공동 연구로 확장 진행하기 위해 의뢰 중임 (NCC-255) 등록율을 증가시키기 위한 다각적인 노력이 필요함.
새로운 치료법 개발을 위한 연구자 주도 임상 시험의 기획이 기획되었는가? (3과제 등록 목표)	총 5개의 2상 연구자 주도 임상 과제를 개발 하였으며, 암종별, 진행 단계별 다양한 폐암 환자를 대상으로 하는 연구과제를 개발하였으며, 정기적인 집담회를 통하여 새로운 치료법에 대한 의견을 교환하고, 진행 상태를 점검하였음.
신 치료법 적용을 위한 수탁 임상 시험 과제의 참여가 활발하였는가? (3개 과제 참여 목표)	총 5개의 참여 과제 중 2상 단계의 임상 시험이 2개 과제로 조기 임상 시험에 대한 참여율을 높였음. 의뢰사의 audit (NCC-428) 과 KFDA의 inspection (NCC-462)를 받았음.

다. 진행된 연구사업에 관한 자체 평가

(1) 임상 시험에 관한 인프라 구축

- 3년간 총 8개의 연구자 주도 임상 시험 계획, 시행 하였고, 8편의 논문을 발표함.
- 국내 다기관 공동 연구 기획, 연구자원 확보 및 성공적 시행

  (NCC-126, First-SIGNAL)
- 신 치료법을 적용한 다국적 임상 시험 중 2상 과제 적극적으로 참여하여 총 15과제 중 4개 참여 과제가 글로벌 2상 임상 과제 임.

(2) LCRG 등 다국적 공동 연구 기반 구축

(NCC-072, NCC-192)

(3) 국제 경쟁력 확보

- 다국적 제약 회사 주도 임상 연구 책임 연구자 선정 (NCC-213, ZACTIMA)
- 새로운 항암제 1상 연구기관 선정 (NCC-290, BMS-663513)
- 새로운 표적 치료 항암제의 phase II 임상시험 시행기관으로 선정

  NCC-310 (BIBW 2992), NCC-445 (Crizotinib)
- 다국적 임상시험 제 1 저자로 선정 (NCC-192)
- 다국적 임상시험 공동 연구자로 결과 발표 (NCC-108)

5. 연구결과의 활용계획

(1) 연구종료 2년후 예상 연구성과

구 분	건 수	비 고
학술지 논문 게재	4	NCC-124, 126, 156, 285

* 논문 게재 준비 과제

논문명	지원과제번호
진행성 비소세포폐암 환자에서 1차 항암요법으로 Irinotecan(캄토®)/Capecitabine(젤로다®) 대 Irinotecan(캄토®)/시스플라틴 복합항암요법 무작위 제 2상 임상연구	0510140 0810090
비흡연자에서 나타나는 진행성 또는 전이성 폐선암종의 1차 선택 치료로서의 게피티니브(IRESSA™)와 표준화학요법 (Gemcitabine 1250mg/m^{2}와 Cisplatin 80mg/m^2 병용요법)의 비교, 무작위 배정 , 3상 연구	없음.
1차 항암화학요법 혹은 항암화학/방사선 병용요법에 실패한 전이성 혹은 재발성 식도암 환자에서 파크리탁셀-카페시타빈(젤로다®) 복합화학요법의 제 2상 임상연구	0510140 0810090
항암화학요법에 실패한 소세포폐암 환자에서 2차 요법으로 수텐® (Sunitinib) 단독요법을 이용한 제 2상 임상 연구	0810090

* 0510140: 임상시험을 통한 폐암의 새로운 치료법 개발 II

* 0810090: 임상시험을 통한 폐암의 새로운 치료법 개발 III

(2) 연구성과의 활용계획

본 연구를 통하여 연구자들은 기존에 알려진 항암치료 방법 외에 효과적인 새로운 치료방법을 다양하게 개발하였고, 특히 암환자 치료 수준의 향상과 더불어 예후가 불량한 진행성 폐암환자들이 예후를 개선하여 왔다. 이와 같은 연구 결과는 국내의 유수 학회 및 세계적인 해외 저널에 논문 발표를 통하여 그 결과를 인정받았다. 이러한 지속적인 노력과 성과에도 불구하고 여전히 폐암은 예후가 나쁜 암종으로 분류되고 있다. 여러 연구들을 통해 폐암이 다양한 유전적 특이성을 가지고 있으며, 이러한 성질에 따라 치료 효과가 차이가 남을 밝혔내었다. 이러한 연구 결과를 바탕으로 폐암이 특성에 따른 맞춤 함암 치료를 위한 좀더 세분화 된 다양한 임상 연구가 지속적으로 필요할 것으로 사료된다. 본 연구자들은 앞으로도 지속적인 임상시험을 통하여 새로운 치료 방법을 개속 개발하여 전 세계적으로 인정받는 임상시험 선도 기관으로서의 입지를 구축할 예정이다.

6. 참고문헌

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3. Randomized Phase 2 Study of Subcutaneous Amifostine Versus Epoetin-a Given 3 Times Weekly During Concurrent Chemotherapy and Hyperfractionated Radiotherapy for Limited-disease Small Cell Lung Cancer
4. Randomized Phase 2 Study of Irinotecan Plus Cisplatin Versus Gemcitabine Plus Vinorelbine as First-line Chemotherapy With Second-line Crossover in Patients With Advanced Nonsmall Cell Lung Cancer
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