<붙임 4>

기관고유연구사업 최종보고서

연구분야(코드)		과제번호	1110200	지원 프로그램	*(일반연구)과제*
과제성격(기초,응용,개발)	기초	실용화 대상여부	비실용화	공개가능여부 (공개,비공개)	*비공개*
연구과제명	(국문) 임상시험을 통한 폐암의 새로운 치료법 개발 IV				
	(영문) Development of new treatment for lung cancer by clinical trials IV				
과제책임자	소 속	폐암연구과	직 위	원장	
	성 명	이진수	전 공	내과학	

세부과제	구분	세부과제명	세부과제책임자		
			성명	소속(직위)	전 공
	1				
	2				
	3				

총 연구기간	2011년 1월~ 2013년 12월 (총 3년)	참여연구원수 (단위: 명, MY)	14

연구기간 및 연구비 (단위:천원)	구분	연 구 기 간	계	국 립 암센터	기 업 부 담 금		
					소계	현금	현물
	계	2011.1~2013.12	400,000	400,000			
	제1차	2011.1~2011.12	135,000	135,000			
	제2차	2012.1~2012.12	135,000	135,000			
	제3차	2013.1~2013.12	130,000	130,000			

참 여 기 업	명 칭		전화		FAX	

기관고유연구사업관리규칙에 따라 본 연구개발사업을 성실히 수행하였으며 아래와 같이 최종보고서를 제출합니다.

2013년 10월 일

과제책임자 이진수 (서명)

국 립 암 센 터 원 장 귀 하

(첨부서류)

목 차

< 요 약 문 >

(한글) 임상시험을 통한 폐암의 새로운 치료법 개발 IV

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

※ 여러개의 세부과제로 과제가 구성된 경우 위 목차와 동일하게 세부과제별로 작성함 (I. 총괄과제, II. 제1세부과제, III. 제2세부과제.....)

< 요 약 문 >

<table>
<tr><td>연구목표
(200자 이내)</td><td><최종목표>
임상시험을 통한 폐암의 새로운 치료법 개발
임상 시험의 효과적인 질 관리 체계 구축

<당해연도목표>
1. 개발된 protocol에 따른 임상 자료의 수집
2. 연구자 주도 임상시험의 기획
3. 신 치료법 적용을 위한 수탁 임상시험 과제 수행
4. 임상 시험 질 관리</td></tr>
<tr><td>연구내용 및 방법
(500자 이내)</td><td>1. 개발된 protocol에 따른 임상 자료의 수집
(1) 11개 진행 과제를 통해 지속적인 피험자 등록
NCC-164, 255, 333, 433, 371, 476, 489, 525, 527, 561, 581
(2) 임상 연구 등록 피험자들의 생존 자료 수집

2. 연구자 주도 임상시험의 기획
(1) 폐암 진단 병기 및 치료 단계별로 범주화 하여 임상 시험을 기획, 운영한다.
(2) 월 1회 임상 연구자 미팅을 통해 진행 준인 임상 시험의 등재 현황 공유 및 신규 과제 기획을 진행한다.
(3) 기존의 연구자료와 최신 연구 동향을 공유하며 폐암 치료를 선조해 나아갈 수 있는 임상 연구 디자인을 기획한다.

3. 신치료법 적용을 위한 수탁 임상과제 참여
(1) 새로운 치료법과 연구 디자인에 대한 지식과 경험을 쌓을 수 있는 과제를 중심으로 참여 여부를 결정한다.
(2) golbal phase I/II 과제에 적극 참여 한다.

4. 임상 시험 질 관리
(1) 연구자 주도 임상 시험 과제의 모티터링을 진행 한다.</td></tr>
<tr><td>연구개발에 따른
기대성과</td><td>
<table>
<tr><th>구분</th><th>달성치/목표치[1)]</th><th>달성도(%)</th></tr>
<tr><td>SCI 논문 편수</td><td>8/10</td><td>80%</td></tr>
<tr><td>IF 합</td><td>52.127/36.0</td><td>144.8%</td></tr>
<tr><td>Protocol 개발 건수</td><td>6/6건</td><td>100%</td></tr>
<tr><td>피험자 모집 현황</td><td>366/600명</td><td>61%</td></tr>
</table>
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색인어	국문	임상시험	폐암	항암요법
		항암-방사선 복합요법		
	영문	Clinical Trial	Lung	Chemotherapy
		Chemoradiotherapy		

※ 요약문의 총분량은 2page 이내로 제한함

Project Summary

Title of Project	Development of new treatment for lung cancer by clinical trials IV
Key Words	clinical trial, lung cancer, chemotherapy, chemoradiotherpy
Project Leader	Jin Soo Lee
Associated Company	National Cancer Center

Objectives:

1. Ultimate objective
   - Development of new treatment for lung cancer by clinical trials
   - Establish of Effective Quality Management system in clinical trials

2. Objective of this year
   - Continuance of existing clinical trials and collectionof clinical data according to the clinical trials.
   - Development of new Investigator-Initiated trials.
   - Participation of Investigator New Drug Study (Golbal clinical trials.)
   - Effeciteve Quality Mangament system in clinical trials

Details and Process of Study

1. Registration and Clnical data collection to the protocol.
   - Have been continued subject registration and clinical data collection from Studys. (NCC-164, 255, 333, 433, 371, 476, 489, 525, 527, 561, 581)

2. Development of new Investigator-Initiated trials.
   - we developed the 6 different studies to evaluate efficacy of new drugs and new treatment.

3. Development of new Multi-national clinical trials (Phase I/II trials)

4. Establish of Effective Quality Management system in clinical trials
   - Training: Acquisition ACRP certification (Association of Clinical Research Professional)
     Completion CRC professional Course
   - Establish monitoring process & system
   - Profress Monitoring (NCC-333,371, 581,525,433)
   - Audti (QA team): NCC-489, 525, 527, 561, 581

Result

구분	달성치/목표치[1)]	달성도(%)
SCI 논문 편수	8/10	80%
IF 합	52.127/36.0	144.8%
Protocol 개발 건수	6/6건	100%
피험자 모집 현황	366/600명	61%

※ 연구목표, 연구방법, 연구성과를 영문으로 요약하여 2쪽이내의 분량으로 작성

1. 연구의 최종목표

1. 연구 최종 목표

(1) 임상시험을 통한 효과적이 폐암의 새로운 치료법 개발

(2) 임상 시험의 효과적인 질 관리 체계 구축

2. 2013년도 목표

(1) 개발된 protocol에 따른 임상 자료의 수집

(2) 연구자 주도 임상시험의 기획

(3) 신치료법 적용을 위한 수탁 임상시험과제 수행

(4) 임상 시험 질 관리

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	2011년 ~ 2013년	계	2001년 ~ 2004년	2005년 ~ 2007년	2008년 ~ 2010년	2011년 ~ 2013년	계
신약의 제1상 임상시험	1	0	2	0	3	19	0	32	7	58
새로운 복합 항암화학요법의 제2/3상 임상시험	12	7	1	5	25	593	404	303	304	1,604
수술 및 방사선치료와 항암요법을 이용한 복합요법의 제2상 임상시험	4	4	0	0	8	159	191	116	23	489
국내 다기관 공동연구	0	1	2	1	4	0	203	0	32	442
계	17	12	5	6	40	771	798	456	366	2,391

2. 개발된 임상 시험 진행 현황 및 연구 실적

과제 번호	IRB승인 연구종료	제 목	학회/논문 발표
논문/학회 발표 과제			
124	2005년 2009년	진행성 비소세포폐암 환자에서 1차 항암요법으로 Irinotecan(캠푸토®) + Capecitabine(젤로다®) ± ISOSORBIDE-5-MONONITRATE (이스모®) 대 Irinotecan(캠푸토®) + Cisplatin(시스플라틴) ± ISOSORBIDE-5- MONONITRATE (이스모®) 복합항암요법 무작위 제 2상 임상연구	12‘ ASCO 학회발표 12′ Anals of Oncology 논문발표 12‘ The Pharmacogenomics Journal 논문발표
126	2005년 2010년	비흡연자에서 나타나는 진행성 또는 전이성 폐선암종의 1차 선택 치료로서의 게피티니브(IRESSA^{TM})와 표준화학요법 (Gemcitabine 1250mg/m^{2}와 Cisplatin 80mg/m^2 병용요법)의 비교, 무작위 배정 , 3상 연구	13‘ WCLC 학회발표 13‘ AACR 학회발표 12‘ Journal of Clinical Oncology 논문 발표 13‘ Neuro Oncology 논문 발표
156	2005년 2009년	1차 항암화학요법 혹은 항암화학/방사선 병용요법에 실패한 전이성 혹은 재발성 식도암 환자에서 파크리탁셀-카페시타빈(젤로다) 복합화학요법의 제 2상 임상연구	11‘ BMC Cancer 논문발표
176	2006년 2009년	확장기 소세포 폐암 환자의 1차 요법으로서 Irinotecan (캠푸토®) / Cisplatin(시스플라틴) 과 Simvastatin(심바스타틴)의 병용 투여대한 2상 임상연구	11‘ Cancer 논문발표
177	2006년 2010년	이전 항암치료에 실패한 진행성 비소세포 폐암 환자에서 Gefitinib(이레사)과 Simvastatin(심바스타틴) 병용요법 대 Gefitinib(이레사) 단독요법의 무작위 배정, 2상 임상연구	11‘ CCR 논문발표
255	2008년 등재중	수술이 불가능한 제3기 비소세포 폐암환자에서 상피세포성장인자수용체 (EGFR) 변이 여부에 따른 유도요법 및 방사선-항암제 동시치료에 대한 제2상 임상연구	13‘ WCLC 학회발표
285	2007년 2010년	항암화학요법에 실패한 소세포폐암 환자에서 2차 요법으로 수텐® (Sunitinib) 단독요법을 이용한 제 2상 임상 연구	11‘ ASCO 학회발표 12‘ Lung Cancer 논문발표

과제 번호	IRB승인 연구종료	제 목	학회/논문 발표
지속 수행 과제			
155	2005년 2009년	1차 항암화학요법 혹은 항암화학/방사선 병용요법에 실패한 전이성 혹은 재발성 소세포폐암 환자에서 파크리탁셀-젬시타빈 복합화학요법의 제 2상 임상 연구	논문 준비 중
157	2005년 2010년	진행성 (IIIB 혹은 IV기) 비소세포폐암 환자에서 젬자-엘록사틴 복합화학요법의 제 2상 임상연구	논문 준비 중
158	2005년 진행중	근치적 수술이 된 IB, II 혹은 IIIA 기 비소세포폐암 환자에서 수술 후 젬시타빈(젬시트) - 옥살리플라틴(옥살리틴) 보조화학요법과 젬시타빈(젬시트) - 시스플라틴 보조화학요법의 제 2 상 비교 임상시험	등재완료 자료 수집 진행중
164	2006년 2013년	조직학적으로 확진된 IIIA기 (N2) 비소세포폐암 환자에서 수술 전 선행화학 요법과 선행화학요법-방사선 요법 동시치료의 비교 제 2상 임상시험	등재 중
255	2008년 등재중	수술이 불가능한 제3기 비소세포 폐암환자에서 상피세포성장인자수용체 (EGFR) 변이 여부에 따른 유도요법 및 방사선-항암제 동시치료에 대한 제2상 임상연구	등재 중
333	2008년 등재중	진행성 또는 전이성 비소세포폐암 환자에서 이리노테칸 (Irinotecan®), 시스플라틴(Cisplatin®)과 에스-원 (S-1®) 복합항암요법을 이용한 제 1/2상 임상연구	등재 중
371	2009년 2013년	진행성 비소세포폐암 환자들에 대한 1차 요법제로서 젬시타빈/시스플라틴 혹은 이리노테칸/시스플라틴 병용 요법 후 2차/3차 요법으로 페메트렉시드와 도세탁셀의 순차적 치료에 관한 무작위 배정 2상 임상시험: 진행성 비소세포폐암환자에서 효과적인 맞춤 항암치료법 제안을 위한 약물유전체 연구	등재 완료 자료수집 진행중
433	2009년 2013년	재발한 또는 불응성의 진행성 비소세포 폐암 환자에서 보리노스탯 (vorinostat)과 게피티니브(gefitinib) 복합 요법의 1상, 2상 임상시험	등재 완료 자료수집 진행중
476	2010년 2013년	A randomized phase II study of Sorafenib maintenance in patients with extensive disease small cell lung cancer (ED-SCLS) after response to induction chemotherapy (**다기관 공동 연구 승인, PI: 국립암센터**)	등재 완료 조기종료
489	2010년 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 (**다기관 공동 연구 승인, PI: 국립암센터**)	등재 중
525	2011년 등재중	소세포 폐암 환자의 2차 치료제로서 BIBF1120 2상 연구	등재 중
527	2011년 등재중	확장기 소세포 폐암 환자의 1차 요법으로서 Irinotecan (캄푸토®) / Cisplatin(시스플라틴) 과 Simvastatin(심바스타틴)의 병용 투여에 대한 2상 임상연구	등재 중
561	2011년 등재 중	상피세포성장인자 수용체의 활성 변이를 동반하고 수술적 절제가 가능한 제2B기 및 3A기 비소세포폐암환자에세 수술 전 엘로티닙 치료요법에 관한 2상 임상 시험	등재 중
581	2011년 등재 중	비흡연자의 진행성 또는 전이성 폐선암종의 일차 치료 요법으로서 페메트렉시드/시스플라틴과 게피티니브 (IRESSA™)혹은 위약의 비동시적 병용 투여에 관한 단일 기관, 무작위 배정, 위약 대조, 이중 맹검, 2상 연구	등재 중

3. 연구결과 고찰 및 결론

1. Phase II study of weekly paclitaxel and capecitabine in patients with metastatic or recurrent esophageal squamous cell carcinoma, [BMC Cancer, 2011;11:3685]

Background: This phase II study assessed the response rate and toxicity profile of weekly paclitaxel and capecitabine in patients with metastatic or recurrent squamous cell carcinoma of the esophagus (SCCE)
Methods: Patients with histologically confirmed SCCE were treated with paclitaxel 80 mg/m2 intravenously ondays 1 and 8 plus capecitabine 900 mg/m2 orally twice a day on days 1-14. Treatment cycles were repeated every 3 weeks until disease progression or unacceptable toxicity.
Results: Between 2006 and 2009, 32 patients were enrolled. Twelve patients were chemotherapy-naïve. Twenty patients had received prior chemotherapy including platinum-based regimens. Patients received a median of 5 cycles of treatment (range, 1-12). The response rate was 75% (95%CI; 50.5~99.5%) in the first-line and 45% (95%CI; 26.9~73.1%) in the second-line. With a median follow-up of 20.7 months, median progression-free survival was 5.2 months (95% CI, 4.0 to 6.4) for all patients and median overall survival (OS) was 11.7 months (95% CI, 5.5 to 18.0) for all patients. The median OS was 14.3 months (95% CI, 10.6 to 18.0) for patients receiving therapy as 1st line and 8.4 months (95% CI, 6.6 to 10.1) for those receiving as 2nd-line therapy. Grade 3/4 neutropenia was observed in 53.3% of the patients, which was the most common cause of dose reduction. G3 non-hematologic toxicity included stomatitis (9.4%), asthenia (6.3%), and hand-foot skin reaction (3.1%).
Conclusions: Weekly paclitaxel and capecitabine is a highly active and well-tolerated regimen in patients withmetastatic or recurrent SCCE in the first-line as well as second-line setting.

2. A phse 2 study of irinotecan, cisplatin and simvastatin for untreated extensive-disease small cell lung cancer [Cancer, 2011:117(10): 2178-85]

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.

3. A randomized phse II study of gefitinib plus simvastatin versus gefitinib alone in previously treated patients with advanced non-small cell lung cancer [Clinical Cancer Research, 2011:17:1553-60]

Purpose: To evaluate the efficacy and safety of gefitinib plus simvastatin (GS) versus gefitinib alone (G)in previously treated patients with advanced non--small cell lung cancer (NSCLC).
Experimental Design: Between May 2006 and September 2008, 106 patients (51% men, 75% adenocarcinoma, 50% never smoker) were randomly assigned to G alone (250 mg/d, n ¼ 54) or GS (250 and 40 mg/d, respectively, n ¼ 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% 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 [M] (95% CI, 1.4--5.2M) for GS and 1.9M (95% CI, 1.0--2.8M) for G. The median OS was 13.6M (95% CI, 7.1--20.1M) for GS and 12.0M (95% CI, 7.8--16.2M) for G. In exploratory subgroup analysis, GS showed higher RR (40% vs. 0%, P ¼ 0.043) and longer PFS (3.6M vs. 1.7M, P ¼ 0.027) compared with G alone in patients with wild-type epidermal growth factor receptor (EGFR) nonadenocarcinomas. Adverse events in both arms were generally mild and mainly consisted of skin rashes.
Conclusions: Although no superiority of GS to G was demonstrated in this unselected NSCLC
population, GS showed higher RR and longer PFS compared with G alone in patients with wild-type EGFR nonadenocarcinomas. Simvastatin may improve the efficacy of gefitinib in that subgroup of gefitinib-resistant NSCLC patients.

4. A genome-wide association study for irinotecan-related severe toxicities in patients with advanced non-small cell lung cancer [The Pharmacogenoics Journal, 2013;13(5):

417-22]

The identification of patients who are at high risk for irinotecan-related severe diarrhea and neutropenia is clinically important.
We conducted the first genome-wide association study (GWAS) to search for novel susceptibility genes for irinotecan-related severe toxicities, such as diarrhea and neutropenia, in non-small-cell lung cancer (NSCLC) patients treated with irinotecan chemotherapy. The GWAS putatively identified 49 single-nucleotide polymorphisms (SNPs) associated with grade 3 diarrhea (G3D) and 32 SNPs associated with grade 4 neutropenia (G4N). In the replication series, the SNPs rs1517114 (C8orf34), rs1661167 (FLJ41856) and rs2745761 (PLCB1) were confirmed as being associated with G3D, whereas rs11128347 (PDZRN3) and rs11979430 and rs7779029 (SEMAC3) were confirmed as being associated with G4N. The final imputation analysis of our GWAS and replication study showed significant overlaps of association signals within these novel variants. This GWAS screen, along with subsequent validation and imputation analysis, identified novel SNPs associated with irinotecan-related severe toxicities.

5. First-SIGNAL: First-line Single-agent Iressa versus Gemcitabine and cisplatin trial in Never-smoker with Adenocarcinoma of the Lung. [Journal of Clinical Oncology, 2012; 30(10):1122-8]

Purpose: Gefitinib has shown high response rate and improved progression-free survival (PFS) in neversmokers with lung adenocarcinoma (NSLAs). We compared efficacy of gefitinib with gemcitabine and cisplatin (GP) chemotherapy in this group of patients as first-line therapy.
Patients and Methods: In this randomized phase III trial, a total of 313 Korean never-smokers with stage IIIB or IV lung adenocarcinoma, Eastern Cooperative Oncology Group performance status 0 to 2, and adequate organ function were randomly assigned to receive either gefitinib (250 mg daily) or GP chemotherapy (gemcitabine 1,250 mg/m2 on days 1 and 8; cisplatin 80 mg/m2 on day 1 every 3 weeks, for up to nine courses). The primary objective was to demonstrate better overall survival (OS) for gefitinib compared with GP in chemotherapy-naive NSLAs.
Results: Three hundred nine patients were analyzed per protocol (gefitinib arm, n 159; GP arm, n 150). Gefitinib did not show better OS compared with GP (hazard ratio [HR], 0.932; 95% CI, 0.716 to 1.213; *P* .604; median OS, 22.3 *v* 22.9 months, respectively). The 1-year PFS rates were 16.7% with gefitinib and 2.8% with GP (HR, 1.198; 95% CI, 0.944 to 1.520). Response rates were 55% with gefitinib and 46% with GP (*P* .101). Myelosuppression, renal insufficiency, and fatigue were more common in the GP arm, but skin toxicities and liver dysfunction were more common in the gefitinib arm. Two patients (1.3%) in the gefitinib arm developed interstitial lung disease and died.
Conclusion: Gefitinib failed to demonstrate superior OS compared with GP as first-line

therapy for NSLAs.

6. A randomized phase II study of irinotecan plus cisplatin versus irinotecan plus cacpecitabine with or without isosorbide-5-mononitrate in advanced non-small cell lung cancer [Annals of Oncology, 2012; 23(1): 2925-30]

Background: We investigated the efficacy of irinotecan/cisplatin (IP) versus irinotecan/capecitabine (IX) with or without isosorbide-5-mononitrate (ISMN) in chemo-naïve advanced non-small-cell lung cancer.
Patients and methods: Initially, 74 patients were randomly assigned to either IP or IX. Given the potential benefits of ISMN on chemotherapy, the protocol was amended during the study. Subsequently, 72 patients were randomly assigned to either IP + ISMN or IX + ISMN. Patients were treated with predefined second-line therapies (docetaxel/capecitabine for IP or IP + ISMN, docetaxel/cisplatin for IX or IX + ISMN) when disease progressed.
Results: A total of 146 received treatment. Response rate (RR), median progression-free survival (PFS) and overall survival (OS) were 49%, 5.5 months, 14.5 months in IP; 33%, 3.3 months, 13.0 months in IP + ISMN; 30%, 4.3 months, 16.1 months in IX; and 25%, 3.4 months, 13.6 months in IX + ISMN, respectively. While IP arm showed a trend toward higher RR and longer PFS than IX arm, IX arm showed a trend toward longer OS than IP arm. No significant differences were observed between IP + ISMN and IX + ISMN.
Conclusion: IP showed better RR and PFS but no OS benefit when compared with IX. The addition of ISMN to IP or IX chemotherapy did not seem to improve the treatment outcome.

7. A phase II study of sunitinib in patients with relapsed or refractory small cell lung cancer [Lung Cancer, 2012; 79(2): 137-42]

Purpose: This study was conducted to evaluate the efficacy and safety of sunitinib in patients with relapsed or refractory small cell lung cancer (SCLC).
Patients and methods: Eligibility included histologic or cytologic diagnosis of SCLC, ECOG PS of 0 - .2, cancer progression following one or two prior chemotherapy or chemo-radiotherapy (CRT) and adequate organ functions. Treatment regimen consisted of a 6-week cycle of sunitinib given as 50 mg p.o. daily for 4 weeks followed by 2 weeks off. The primary end point was objective response rate (ORR).
Results: From March 2008 to October 2010, 25 patients were enrolled and 24 received treatment. The median age was 64.5 years; 22 patients (92%) were male. Eight patients (33%) displayed sensitive relapse. Seven patients (29%) received CRT and fifteen patients (63%) had received one prior chemotherapy. A median of 1 cycle (range 1 - .4) of sunitinib was administered, and 23 patients were evaluable for response. Two patients displayed partial response, and seven patients presented stable disease with a ORR of 9% (95% CI, 1 - .28%). The median progression-free (PFS) and overall survivals were 1.4 months (95% CI, 1.1 - .1.7)

and 5.6 months (95% CI, 3.5 - .7.7), respectively. The common grade 3 or 4 toxicities included thrombocytopenia (63%), asthenia (29%) and neutropenia (25%).
Conclusions: Although tumor response was noted in 2 patients, the median PFS was short and most patients were unable to tolerate the treatment. At the current dose schedule, sunitinib does not appear to warrant further evaluation.

8. Impact of EGFR tyrosine kinase inhibitors versus chemotherpay on the development of leptomeningeal metastasis in nerves smokers with advanced adenocarcinoma of lung. [Journal of Neuro-Oncology, 2013; 115(1): 95-101]

This study investigated whether epidermal growth factor receptor tyrosine kinase inhibitors (EGFRTKI) increase the development of leptomeningeal metastasis (LM) compared with standard chemotherapy in EGFR mutation-enriched non- small cell lung cancer. The incidence of LM was longitudinally assessed in never smokers with advanced adenocarcinoma of the lung enrolled in a phase III randomized controlled study that compared gefitinib with gemcitabine plus cisplatin (GP) as first-line therapy (The First-SIGNAL study). Among 203 patients who were enrolled at the National Cancer Center Hospital (Goyang, Republic of Korea), LM occurred in 32 (15.8 %) with a minimum follow-up time of 55.1 months. The 1-, 2-,and 3-year actuarial incidence rates of LM were 5.3, 10.6,and 24.6 %, respectively. During first-line treatment, LM occurred in 2 patients (2.0 %) treated with gefitinib and in 3 patients (3.2 %) treated with GP. There was no difference in the incidence of LM during first-line treatment between the two groups (P = 0.934). The incidence of LM was significantly increased during second-line EGFR-TKI treatment compared with first-line EGFR-TKI treatment (P = 0.041). During the disease course, the cumulative incidence of LM was not significantly different between the two treatment groups (P = 0.514). The median time to LM was 21.4 and 24.0 months in the gefitinib and GP groups, respectively (P = 0.895). Similar trends were observed in the subset analysis with 23 EGFR-mutant patients. In conclusion, LM predominantly occurred in the late phase of disease in this population. EGFR-TKIs did not affect the incidence or timing of LM development.

4. 연구성과 및 목표달성도

1. 연구성과

가. 국내 및 국제 전문학술지 논문 게재 및 신청

논문명	저자 (저자구분[1])	저널명(I.F.)	Year; Vol(No):Page	구분	지원과제번호
Phase II study of weekly paclitaxel and capecitabine in patients with metastatic or recurrent esophageal squamous cell carcinoma (NCC-156)	윤탁(제1), 김홍태 (교신) 한지연, 이진수, 최현리, 김혜영, 남병호(공동)	BMC Cancer (IF: 3.153)	2011; 11:3685 (online published)	국외 SCI	없음
A phse 2 study of irinotecan, cisplatin and simvastatin for untreated extensive-disease small cell lung cancer (NCC-176)	한지연 (제1) 이진수(교신) 임근영, 유선영, 윤탁, 김홍태(공동)	Cancer (IF: 5.131)	2011; 117(10): 2178-85	국외 SCI	없음
A randomized phse II study of gefitinib plus simvastatin versus gefitinib alone in previously treated patients with advanced non-small cell lung cancer (NCC-177)	한지연(제1), 이진수 (교신), 이수현 유남진, 이축향, 문윤주 윤탁, 김홍태 (공동)	CCR (IF:7.338)	2011; 17:1553-60	국외 SCI	없음
A genome-wide association study for irinotecan-related severe toxicities in patients with advanced non-small cell lung cancer (NCC-124)	한지연(제1) 이진수(교신) 이연수, 신은순, 황정아, 남승연, 홍승현, 간호영, 김진영, 윤성진(공동)	The Pharmacogenomics Journal (IF: 4.536)	2013 13(5): 417-22	국외 SCI	없음
First-SIGNAL: First-line Single-agent Iressa versus Gemcitabine and cisplatin trial in Never-smoker with Adenocarcinoma of the Lung (NC-126)	한지연(제1) 이진수(교신) 박근칠, 김상위 이대호, 김혜영, 안명주, 윤탁 안진석, 서철원 윤성진, 한종희 이재원, 조숙정(공동)	Journal of clinical Oncology (IF: 18.970)	2012; 30(10): 1122-8	국외 SCI	없음
A randomized phase II study of irinotecan plus cisplatin versus irinotecan plus cacpecitabine with or without isosorbide-5-mononitrate in advanced non-small cell lung cancer (NCC-124)	한지연(제1) 이진수 (교신) 남병호, 김혜영, 윤성진, 김홍태 (공동)	Annals of Oncology (IF: 6.45)	2012; 23(11): 2925-30	국외 SCI	1110200
A phase II study of sunitinib in patients with relapsed or refractory small cell lung cancer (NCC-285)	한지연(제1) 이진수(교신) 김혜영, 임근영 한종희, 이유진 곽미향, 김학진 윤탁, 김홍태(공동)	Lung Cancer (IF: 3.434]	2012; 79(2): 137-42	국외 SCI	1110200
Impact of EGFR tyrosine kinase inhibitors versus chemotherpay on the development of leptomeningeal metastasis in nerves smokers with advanced adenocarcinoma of lung (NCC-126)	이영주(제1) 이진수(교신) 한지연, 김홍태, 윤탁, 이건국, 김혜영 (공동)	Journal of neurooncology (IF: 3.115)	2013; 115(1): 95-101	국외 SCI	1110200

나. 국내 및 국제 학술대회 논문 발표

논문명	저자	학술대회명	지역[1)]	지원과제번호
Phase II study of sunitiib as second-line therapy for relapsed or refractory SCLC (NCC-285)	한지연, 이진수,김혜영, 이건국, 김홍태	2011 American Society of Clinival Oncolgoy	국외	11110200
Genome-wide association study of survival in small cell lung cancer patients treated with irinotecan plus cisplatin chemotherapy (NCC-124)	한지연, 이연수, 김숙영, 김진영, 이진수	2012 American Society of Clinival Oncolgoy	국외	1110200
An association between genetic variant in *pidermal Growth Factor EGF*) gene and urvival benefit from epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) in never smokers with advanced adenocarcinoma of the lung (NCC-126	이영주 윤경아 이진수	2013 American Association for Cancer Research	국외	1110200
Incorporation erlotinib into induction chemotherapy followed by concurrent chemoradiation of unresectable stage III non-small cell lung cancer according to EGFR mutation status: preliminary result of a randomized phase II study (NCC-255)	이영주, 이진수, 문성호, 남병호, 임근영, 이건국, 김홍태, 윤탁, 조관호, 한지연, 오세희	2013 15th World Conference on Lung Cancer	국외	1110200
The predictive role of common BIM deletion polymorphism and BIM expression on the EGFR-TKI therapy in never-smoking lung adenocarcinoma (NCC-126)	한지연(제1),이진수(교신)이건국, 구새롬, 윤성진	2013 15th World Conference on Lung Cancer	국외	1110200

다. 기타연구성과

1. Global Phase III 책임연구자로 연구 진행하였으며, 제1 저자로 2012년 논물 발표.

Vandetanib versus placebo in patients with advanced Non-small cell lung cancer after prior therapy with an epidermal growth factor receptor tyrosine kinase inhibitor: A randomized, double-blind phase III trial (ZEPHYR). **[Journal of Clinical Oncology, IF: 18.97]**

2. Global Phase III 과제 공동 저자로 2013년도 논문 발표

Intercalated combination of chemotherapy and erlotinib for patients with advanced stage non-small-cell lung cancer (FASTACT-2): a randomixed, double-blind trial.
[Lancet Oncology, IF:21.856]

2. 목표달성도

가. 연구목표의 달성도

최종목표	연차별목표		달성내용	달성도(%)	
				연차	최종
임상시험	1차년도	- 기존 임상시험의 지속 시행	총 170명의 피험자가 등록됨	90%	28%

을 통한 폐암의 새로운 치료법 개발		- 연구자주도 임상시험의 기획	총 4개 과제 개발, 1개 과제 등재 시작		
		- 신치료법의 적용을 위한 수탁 임상시험과제 수행	WTKD 1건, 3상 3건 과제 참여 확정		
		- 임상시험 질관리를 위한 SOPs 개발	Association of Clinical Research Professional에서 발행하는 CRC certification 획득 (2명), CRC 전문가 과정 이수 (1명)		
	2차년도	- 개발된 protocol에 따른 임상자료의 수집	총 157명이 피험자 등록 됨	80%	53%
		- 연구자주도 임상시험의 기획	국내 신약을 활용한 신규 임상연구 1건 기획, 주관 기관으로 진행		
		- 신치료법의 적용을 위한 수탁 임상시험과제 수행	2상 2개, 3상 2개의 과제에 참여 진행 함		
		- 임상시험 질관리 전문 인력 양성 및 교육	교육 과정 이수, 5개 과제 database verification 시행 (NCC-333., 371, 581, 525, 433)		
	3차년도	- 개발된 protocol에 따른 임상자료의 수집	총 124명의 피험자 등록	75%	83%
		- 연구자주도 임상시험의 기획	1개 임상 연구 과제 개발, IRB 승인		
		- 신치료법의 적용을 위한 수탁 임상시험과제 수행	4개의 2상 임상연구과제 등록 및 3개 과제 피험자 등록 시작		
		- 정규 임상 시험 질 관리	NCC-489, 525, 527, 561, 581 과제 QA 진행 - 시정 사항 없이 진행 완료 됨		

나. 평가의 착안점에 따른 목표달성도에 대한 자체평가

평가의 착안점	자 체 평 가
기존 임상 시험이 지속적으로 잘 수행되고 있는가? (연간 피험자 등록률)	연간 200명의 임상시험참여자 모집을 목표하였으나, 총 124명의 참여자가 등록 됨.
새로운 치료법 개발을 위한 연구자 주도 임상 시험의 기획이 기획되었는가? (1 과제 등록 목표)	효율적인 폐암 치료를 위한 연구 디자인을 개발하여 IRB 승인 받음.
신 치료법 적용을 위한 수탁 임상시험과제의 참여가 활발하였는가?	기존 임상 시험과의 차별성, 신약 연구, 시험단계 등을 고려하여 총 4건의 2상 연구과제 참여 함
임상 시험의 질관리가 적절하게 이루어 지고 있는가?	2010년도 이후 피험자 등록이 시작 된 신규 과제를 중심으로 자체 QA를 실시함. 이후 식약서 기관 실사를 대비한 QA team의 audit에서 주의/ 시정 사항 없이 5-6개 미

	만의 권고 사항만을 지적 받음. - 연구자 주도 임상 과제의 관리가 우수하게 진행 되고 있음

다. 진행된 연구사업에 관한 자체 평가

(1) 임상 시험에 관한 인프라 구축

- 3년간 총 6개의 연구자 주도 임상 시험 계획, 시행 하였고, 8편의 논문을 발표함.

- 연구자 주도 임상과제와 다국적 신약 임상 시험에 적극 참여하여 참여 연구자들의 역량 강화와 연구 인프라 구축으로 다국가, 다기관 연구에서 그 역량을 인정 받아 다국가 연구의 책임연구자, 제1저자, 공동저자 등으로 활동 함.

(2) 폐암 치료를 위한 database 축적

- 연구 성과를 바탕으로 폐암의 진단과 치료를 위한 진단/ 치료 체계를 구축함.

- 임상 데이터베이스의 구축으로 인해 암유전체 연구, 생체 표지자 연구 결과를 임상과 접목함으로써 환자 맞춤 치료를 위한 지표 개발이 용이해 졌음.

- 이를 바탕으로 비소세포폐암의 진단을 위한 전통적으로 사용되어온 면역병리검사 항목의 변경을 진행하고 있으며, 이로 인해 효율적으로 진단하고 치료할 수 있기를 기대하고 있음.

5. 연구결과의 활용계획

(1) 연구종료 2년후 예상 연구성과

구 분	건 수	비 고
학술지 논문 게재	3	NCC-255, 371, 433

논문명	지원과제번호
수술이 불가능한 제3기 비소세포 폐암환자에서 상피세포성장인자수용체 (EGFR) 변이 여부에 따른 유도요법 및 방사선-항암제 동시치료에 대한 제2상 임상연구 (NCC-255)	0810090 1110200
진행성 비소세포폐암 환자들에 대한 1차 요법제로서 젬시타빈/시스플라틴 혹은 이리노테칸/시스플라틴 병용 요법 후 2차/3차 요법으로 페메트렉시드와 도세탁셀의 순차적 치료에 관한 무작위 배정 2상 임상시험: 진행성 비소세포폐암환자에서 효과적인 맞춤 항암치료법 제안을 위한	1110200

약물유전체 연구	
재발한 진행성 비소세포 폐암환자에 vorinostat(보리노스텟)과 gefetinib (이레사) 병합투여의 1,2상 임상연구 (NCC-433)	1110200

* 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.

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