The Year’s 10 Most Important Papers
SELECTION CRITERIA

• advance in treatment of a serious major disease
• advance in treatment or understanding of a serious new disease
• important demonstration of translational research
• demonstration of a new technical approach
• important “proof of concept”
#1
“For the public health community, Zika represents an unprecedented emergency. Never before, to our knowledge, has a mosquito-borne virus been associated with human birth defects or been capable of sexual transmission. The effects of brain damage due to microcephaly and consequences of other Zika-related birth defects are likely devastating, lifelong, and costly. However, most people infected with Zika have no symptoms, and concern among the general public has been muted even in some affected locales. Zika is a silent epidemic.”

Congenital Zika virus syndrome in Brazil: a case series of the first 1501 livebirths with complete investigation

Giovanny V A França, Lavinia Schuler-Faccini, Wanderson K Oliveira, Claudio M P Henriques, Eduardo H Carmo, Vaneide D Pedi, Marília L Nunes, Marcia C Castro, Suzanne Serruya, Mariângela F Silveira, Fernando C Barros, César G Victora

Summary

Background In November, 2015, an epidemic of microcephaly was reported in Brazil, which was later attributed to congenital Zika virus infection. 7830 suspected cases had been reported to the Brazilian Ministry of Health by June 4, 2016, but little is known about their characteristics. We aimed to describe these newborn babies in terms of clinical findings, anthropometry, and survival.

Methods We reviewed all 1501 liveborn infants for whom investigation by medical teams at State level had been completed as of Feb 27, 2016, and classified suspected cases into five categories based on neuroimaging and laboratory results for Zika virus and other relevant infections. Definite cases had laboratory evidence of Zika virus infection; highly probable cases presented specific neuroimaging findings, and negative laboratory results for other congenital infections; moderately probable cases had specific imaging findings but other infections could not be ruled out; somewhat probable cases had imaging findings, but these were not reported in detail by the local teams; all other newborn babies were classified as discarded cases. Head circumference by gestational age was assessed with InterGrowth standards. First week mortality and history of rash were provided by the State medical teams.

Findings Between Nov 19, 2015, and Feb 27, 2016, investigations were completed for 1501 suspected cases reported to the Brazilian Ministry of Health, of whom 899 were discarded. Of the remainder 602 cases, 76 were definite, 54 highly probable, 181 moderately probable, and 291 somewhat probable of congenital Zika virus syndrome. Clinical, anthropometric, and survival differences were small among the four groups. Compared with these four groups, the 899 discarded cases had larger head circumferences (mean Z scores −1.54 vs −3.13, difference 1.58 [95% CI 1.45–1.72]); lower first-week mortality (14 per 1000 vs 51 per 1000; rate ratio 0.28 [95% CI 0.14–0.56]); and were less likely to have a history of rash during pregnancy (20.7% vs 61.4%, ratio 0.34 [95% CI 0.27–0.42]). Rashes in the third trimester of pregnancy were associated with brain abnormalities despite normal sized heads. One in five definite or probable cases presented head circumferences in the normal range (above −2 SD below the median of the InterGrowth standard) and for one third of definite and probable cases there was no history of a rash during pregnancy. The peak of the epidemic occurred in late November, 2015.
Both *Aedes aegypti* and *A. albopictus* have low vector competence (intrinsic ability to biologically transmit disease), but *aegypti* has high vectoral capacity because it feeds mainly on humans, bites multiple humans in single blood meal, has almost imperceptible bite, and feeds during daytime.

Petersen LR. NEJM 2016
Figure 3. Approximate Ranges of *A. aegypti* and *A. albopictus* in the United States (as of March 2016).
These mosquitoes may not be present in all areas, and vector density may vary considerably within these ranges.

Petersen LR. NEJM 2016
TIMETABLE

- late 2014: reports of a new exanthematic disease in northeast Brazil
- early 2015: identification of Zika outbreak
- September 2015: accumulating reports of microcephaly in northeast Brazil
- Brazilian Ministry of Health (MOH) establishes surveillance program
- as of June 4, 2016: 7830 suspected cases of microcephaly reported
MOH Protocol instituted Nov. 19, 2015

1. Live newborns with microcephaly reported to system (head circum. < 33 cm., later reduced to 32 cm.)
2. Local investigation (including imaging and serology) with results submitted to MOH
The data in the MOH registry were reviewed by the authors (including medical geneticist, pediatrician, obstetrician) and each case assigned to one of five categories:
**Definite:** positive Zika serology or PCR during pregnancy

**Highly probable:** positive imaging studies available for review; negative serology for syphilis, toxoplasmosis, CMV

**Moderately probable:** imaging as above, but lacking one or more serologies

**Somewhat probable:** positive imaging report without actual study result available; negative or unavailable serology

**Discarded Cases:** not included in the above categories
RESULTS

The peak of the microcephaly epidemic in Brazil occurred the last week of November, 2015, compatible with the peak of the Zika infection epidemic late Feb/early March 2015.
Most of the definite/highly probable cases had a rash while most discarded cases did not. Timing of rash was important.

**Presence of Rash**

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite</td>
<td>71.4%</td>
</tr>
<tr>
<td>Highly Probable</td>
<td>75.0%</td>
</tr>
<tr>
<td>Discard</td>
<td>20.7%</td>
</tr>
</tbody>
</table>

In Definite/Probable Cases, rash most often occurred early:

- 1st trimester – 77%
- 2nd trimester – 18%
- 3rd trimester – 5%

Size of head (z-score) varied according to timing of rash:

- 1st trimester: -3.0
- 2nd trimester: -2.4
- 3rd trimester: -1.5
MORTALITY

Average early neonatal mortality in N.E. Brazil: 10/1000

Early neonatal mortality of discarded cases: 14/1000

Early neonatal mortality in definite/probable: 51/1000

Definite/probable with rash: 97/1000
Microcephaly and Normal Head Circumference

Due to errors in calculating gestational age and application of guidelines, many cases had normal (z-score > -2.0) head circumference:

<table>
<thead>
<tr>
<th>Case Category:</th>
<th>Definite</th>
<th>High</th>
<th>Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal z-score:</td>
<td>13.2</td>
<td>14.3</td>
<td>21.7</td>
</tr>
</tbody>
</table>

A mature skull size with typical Zika-associated brain abnormalities suggests late infection (after skull is mature) can still cause brain damage. Can post-birth infections cause damage to developing brain?
#2
Chimeric Antigen Receptor T Cells against CD19 for Multiple Myeloma

Chimeric Antigen Receptor T Cells???

“World’s Quickest Explanation”
In order for a T cell to attack a tumor cell it must:

**Attach to the tumor cell via a tumor cell protein:**
The “target” (protein on tumor cell surface) must first be internalized by the tumor cell, processed, then re-presented on the surface of the tumor cell by the Major Histocompatibility Complex (MHC)

**Be stimulated by the interaction with the tumor cell:**
Various proteins (ligands) on the tumor cell surface adjacent to the MHC interact with receptors associated with the T cell’s receptor resulting in either T cell stimulation or suppression – a smart (resistant) tumor cell will present only the suppressive proteins and turn the T cell off
Normal T Cell Receptor vs. Chimeric Antigen Receptor

Fesnak AD. Nature Reviews: Cancer 2016
Creating Chimeric Antigen Receptor T Cells

1. Create a gene for the desired CAR
2. Collect T cells from the patient
3. Introduce the CAR gene into the T cell
4. Stimulate the CAR T cells to reproduce until you have plenty of them
5. Inject back into the patient the T cells with this special receptor directed at the tumor
Multiple Myeloma

- many different drugs available along with autologous BM transplant
- median survival has doubled (3 years to 6 years) during the past 20 years
- despite dramatic tumor-reduction by various drugs, no cure to date
- subset of MM cells (stem cells?) express CD19 (B-cell marker) but not CD38 (the most common MM marker)
- currently used cytotoxic therapy kills the CD38 MM cells but not the CD19 (stem?) cells

Rollig et al. Lancet 2015
New idea of Garfall et al: Can we eliminate the bulk of the myeloma cell burden with high dose standard cytotoxic chemotherapy (CD 38 cells) and target the usually resistant CD19 (stem?) cells with CAR T cells?
Test Patient: 43 yo woman with MM and vertebral compression fractures

- lenalidomide, bortezomib, dexamethasone
- cisplatin, doxycycline, cyclophosphamide, etoposide
- autologous stem-cell transplant
- maintenance lenalidomide, addition of bortezomib
- various combinations of carfilzomib, pomalidomide, vorinostat, clarithromycin, elotuzumab

Continued disease progression
Novel Intervention:

- 99.5% of patient marrow cells were CD38+/CD19-
- 0.5% were CD19+
- harvested marrow stem cells and T cells
- manufactured 5x 10^7 anti-CD19 CAR T cells
- High-dose chemo to wipe out CD38 cells
- infusion of anti-CD19 CAR T cells (CTL019) to wipe out the remaining CD19+ MM stem cells
10 patients treated with this protocol: 6/10 remain disease-free.
Persistent challenge in cancer immunotherapy

What are the mechanisms by which some patients have dramatic responses and others no response?
A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*
Hypertension affects ~1 billion persons worldwide.

What should be our BP treatment goal in hypertension?
STUDY HYPOTHESIS

Treatment of isolated systolic hypertension with a goal of 120 mm Hg results in fewer cardiovascular events than treating to a goal of 140 mmHg.
Inclusion Criteria

- age $\geq$ 50 years
- systolic BP 130 - 180 mm Hg
- increased cardiovascular risk

Diabetics and patients with previous stroke were excluded
INTERVENTION (ACCORD ALGORITHM)

• begin with 2 or 3 drug regimen (thiazide, ACE-I/ARB, CCB)
• encourage initial use of thiazide; loop-diuretic in advanced CKD, ß-blocker in CAD
• monthly visit x 3 then every 3 months follow-up
• at “MilePos”t visits (every 6 month visit) add another drug if not at BP goal
END POINTS

Primary Outcome: composite of MI, ACS, stroke, acute decompensated CHF, death from cardiovascular cause

Secondary Outcome: death from any cause
The graph illustrates the systolic blood pressure over five years for two treatment groups: Standard treatment and Intensive treatment. The y-axis represents systolic blood pressure in millimeters of mercury (mm Hg), while the x-axis represents the years from 0 to 5.

The table below provides the number of participants with data and the mean number of medications for each group:

<table>
<thead>
<tr>
<th></th>
<th>Years</th>
<th>Standard Treatment</th>
<th>Intensive Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. with Data</td>
<td></td>
<td>4683, 4345, 4222, 4092, 3997, 3904, 3115, 1974, 1000, 274</td>
<td>4678, 4375, 4231, 4091, 4029, 3920, 3204, 2035, 1048, 286</td>
</tr>
<tr>
<td>Mean No. of Medications</td>
<td></td>
<td>1.9, 1.8, 1.8, 1.8, 1.8, 1.8, 1.8, 1.8, 1.8, 1.9</td>
<td>2.3, 2.7, 2.8, 2.8, 2.8, 2.8, 2.8, 2.8, 2.8, 3.0</td>
</tr>
</tbody>
</table>
November 2010 – March 2013: 9361 subjects enrolled

August 2015: Study stopped early after significant divergence of outcomes measured on 2 sequential interim analyses
Primary Outcome – Composite Endpoint

A Primary Outcome

Hazard ratio with intensive treatment, 0.75 (95% CI, 0.64–0.89)

Cumulative Hazard

Standard treatment

Intensive treatment

No. at Risk

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Years 0</th>
<th>Years 1</th>
<th>Years 2</th>
<th>Years 3</th>
<th>Years 4</th>
<th>Years 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard treatment</td>
<td>4683</td>
<td>4437</td>
<td>4228</td>
<td>2829</td>
<td>721</td>
<td></td>
</tr>
<tr>
<td>Intensive treatment</td>
<td>4678</td>
<td>4436</td>
<td>4256</td>
<td>2900</td>
<td>779</td>
<td></td>
</tr>
</tbody>
</table>
Death from Any Cause

Hazard ratio with intensive treatment, 0.73 (95% CI, 0.60–0.90)

No. at Risk

<table>
<thead>
<tr>
<th>Treatment</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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</thead>
<tbody>
<tr>
<td>Standard treatment</td>
<td>4683</td>
<td>4528</td>
<td>4383</td>
<td>2998</td>
<td>789</td>
<td></td>
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<tr>
<td>Intensive treatment</td>
<td>4678</td>
<td>4516</td>
<td>4390</td>
<td>3016</td>
<td>807</td>
<td></td>
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</tbody>
</table>
QUESTION
Why did SPRINT show a positive result but not ACCORD?

Pathophysiologic differences between patients with and without diabetes?

Methodologic differences between the studies?
#4
When to perform CABG to improve survival?

Class I recommendation evidence level B

1. Left main coronary artery disease ≥ 50% stenosis
2. Three major coronary arteries with ≥ 70% stenosis or LAD plus one other major artery
3. ≥ 70% stenosis of major coronary artery in patient with sudden death (PCI is an accepted alternative)

2011 ACCF/AHA/SCAI Guidelines for Percutaneous Coronary Intervention
Coronary-Artery Bypass Surgery in Patients with Left Ventricular Dysfunction

Eric J. Velazquez, M.D., Kerry L. Lee, Ph.D., Marek A. Deja, M.D., Ph.D., Anil Jain, M.D., George Sopko, M.D., M.P.H., Andrey Marchenko, M.D., Ph.D., Imtiaz S. Ali, M.D., Gerald Pohost, M.D., Sinisa Gradinac, M.D., Ph.D., William T. Abraham, M.D., Michael Yii, M.S., F.R.C.S., F.R.A.C.S., Dorairaj Prabhakaran, M.D., D.M., Hanna Szwed, M.D., Paolo Ferrazzi, M.D., Mark C. Petrie, M.D., Christopher M. O’Connor, M.D., Pradit Panchavinnin, M.D., Lilin She, Ph.D., Robert O. Bonow, M.D., Gena Roush Rankin, M.P.H., R.D., Robert H. Jones, M.D., and Jean-Lucien Rouleau, M.D., for the STICH Investigators*

STICH Trial – Median f/u 56 mos.
Velazquez EJ. NEJM 2011
STICH INCLUSION CRITERIA

- LVEF ≤ 35%
- CAD suitable for revascularization
- absence of left main CAD ≥ 50%
- absence of class 3 angina or greater

Intervention:
CABG vs. medical therapy
PRIMARY OUTCOME
• Death from any cause

SECONDARY OUTCOME
• Death from cardiovascular cause
## Subject Characteristics at Baseline

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>MEDICAL (N = 602)</th>
<th>CABG (N = 610)</th>
</tr>
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<tbody>
<tr>
<td>Median Age</td>
<td>59</td>
<td>60</td>
</tr>
<tr>
<td>Female</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>White</td>
<td>67%</td>
<td>64%</td>
</tr>
<tr>
<td>Previous MI</td>
<td>78%</td>
<td>76%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>40%</td>
<td>39%</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>20%</td>
<td>21%</td>
</tr>
<tr>
<td>NYHA Class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td>II</td>
<td>51%</td>
<td>52%</td>
</tr>
<tr>
<td>III</td>
<td>34%</td>
<td>34%</td>
</tr>
<tr>
<td>IV</td>
<td>3%</td>
<td>3%</td>
</tr>
</tbody>
</table>
Coronary-Artery Bypass Surgery in Patients with Left Ventricular Dysfunction

A

Hazard ratio, 0.86 (95% CI, 0.72–1.04)
P=0.12

Hazard ratio, 0.81 (95% CI, 0.66–1.00)
P=0.05

No. at Risk
Medical therapy 602 532 487 435 312 154 80
CABG 610 532 486 459 340 174 91

No. at Risk
Medical therapy 602 532 487 435 312 154 80
CABG 610 532 486 459 340 174 91

Velazquez EJ. NEJM 2011.
Coronary-Artery Bypass Surgery in Patients with Ischemic Cardiomyopathy

Eric J. Velazquez, M.D., Kerry L. Lee, Ph.D., Robert H. Jones, M.D., Hussein R. Al-Khalidi, Ph.D., James A. Hill, M.D., Julio A. Panza, M.D., Robert E. Michler, M.D., Robert O. Bonow, M.D., Torsten Doenst, M.D., Mark C. Petrie, M.D., Jae K. Oh, M.D., Lilin She, Ph.D., Vanessa L. Moore, A.A.S., Patrice Desvigne-Nickens, M.D., George Sopko, M.D., M.P.H., and Jean L. Rouleau, M.D., for the STICHES Investigators*

ABSTRACT

STICH Trial  9.8 year f/u
Velazquez EJ. NEJM 2016
A  Death from Any Cause (Primary Outcome)

Hazard ratio, 0.84 (95% CI, 0.73–0.97)
P=0.02 by log-rank test

Years since Randomization

Event Rate (%)

No. at Risk
| Medical therapy | 602 | 532 | 487 | 435 | 404 | 357 | 315 | 274 | 248 | 164 | 82 | 37 |
| CABG            | 610 | 532 | 487 | 460 | 432 | 392 | 356 | 312 | 286 | 205 | 103| 42 |

Velazquez EJ. NEJM 2016
B Death from Cardiovascular Causes

Hazard ratio, 0.79 (95% CI, 0.66–0.93)
P=0.006 by log-rank test

No. at Risk
Medical therapy  602  532  487  435  404  357  315  274  248  164  82  37
CABG            610  532  487  460  432  392  356  312  286  205 103  42

Velazquez EJ. NEJM 2016
The initial lower survival in the CABG group due to peri-operative deaths is offset after 2 years by improved survival in the surgical group and the two survival curves continue to diverge for at least ten years follow-up, indicating a long term persistent benefit of CABG in subjects with significant ischemic cardiomyopathy.
#5 and #6
Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Marso SP. NEJM 2016

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Wanner C. NEJM 2016
Cardiovascular event-free survival

Becker A et al. Eur Heart J 2003
New Cases of Kidney Failure by Primary Diagnosis-2011, United States Renal Data System

- Diabetes: 44%
- High Blood Pressure: 28%
- Other: 23%
- Unknown: 5%

National Chronic Kidney Disease Fact Sheet, 2014
“Various approaches in the treatment of type 2 diabetes have been introduced recently, but whether these therapies alter cardiovascular and renal risk remains uncertain.” – Ingelfinger and Rosen, editorial NEJM 2016.
The “New” Diabetes Drugs

Glucagon-like peptide 1 (GLP-1) agonists
- liraglutide, exenatide, dulaglutide, albiglutide

Dipeptidyl peptidase 4 (DPP-4) inhibitors
- salogliptin, alogliptin, linagliptin

Na-glucose co-transporter (SGLT) inhibitors
- cangliflozin, dapagliflozin, empagliflozin
Trials of DPP-4 Inhibitors

1. EXAMINE trial (alogliptin) – no reduction in cardiovascular outcomes
2. SAVOR-TIMI 53 trial (saxagliptin) – no reduction in cardiovascular outcomes
3. TECOS trial (sitagliptin) – no reduction in cardiovascular outcomes
4. Linagliptin metanalysis – no reduction in cardiovascular outcomes
Trials of GLP-1 Agonists

1. ELIXA trial (lixisenatide) – no reduction in cardiovascular outcomes

Trials of SGLT Inhibitors

1. EMPA-REG OUTCOME – (empagliflozin) – Cardiac Outcome – reduction of cardiovascular outcomes and death from any cause
Pioglitazone (thiazolidinedione)

PROactive trial (pioglitazone) – reduced cardiovascular endpoints
BUT increased outcome of edema and heart failure
Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D.,
for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

ABSTRACT

Marso SP. NEJM 2016
LEADER Trial
Multicenter, randomized, double-blind, placebo control study

410 sites in 32 countries

Patients with type 2 diabetes at high risk for cardiovascular disease randomized to liraglutide (daily injection) or placebo while continuing usual therapy

Primary outcome: composite outcome of a) death from cardiovascular causes, b) non-fatal MI, and c) non-fatal stroke
Inclusion Criteria

Type 2 Diabetics

Age > 50 with known cardiovascular disease

Age > 60 with one or more cardiovascular risk factors
Treatment

Control Group: placebo with adjustment of anti-hyperglycemic drugs to achieve HgbA1c ≤ 7%

Intervention Group: liraglutide 0.6 mg SC daily with escalation to 1.2 mg then 1.8 mg maximal dose as tolerated. Other anti-hyperglycemic drugs adjusted as required
Table S2. Baseline characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Liraglutide (N=4,668)</th>
<th>Placebo (N=4,672)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>3011 (64.5)</td>
<td>2992 (64.0)</td>
</tr>
<tr>
<td>Age, years</td>
<td>64.2 ± 7.2</td>
<td>64.4 ± 7.2</td>
</tr>
<tr>
<td>Diabetes duration, years</td>
<td>12.8 ± 8.0</td>
<td>12.9 ± 8.1</td>
</tr>
<tr>
<td>Glycated hemoglobin, %</td>
<td>8.7 ± 1.6</td>
<td>8.7 ± 1.5</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>32.5 ± 6.3</td>
<td>32.5 ± 6.3</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>91.9 ± 21.2</td>
<td>91.6 ± 20.8</td>
</tr>
<tr>
<td>Heart failureᵃ</td>
<td>835 (17.9)</td>
<td>832 (17.8)</td>
</tr>
<tr>
<td>Established CVD (age ≥50)</td>
<td>3831 (82.1)</td>
<td>3767 (80.6)</td>
</tr>
<tr>
<td>CVD risk factors (age ≥60)</td>
<td>837 (17.9)</td>
<td>905 (19.4)</td>
</tr>
<tr>
<td>Microalbuminuria or proteinuria</td>
<td>501 (10.7)</td>
<td>558 (11.9)</td>
</tr>
<tr>
<td>Hypertension and left ventricular hypertrophy</td>
<td>248 (5.3)</td>
<td>251 (5.4)</td>
</tr>
<tr>
<td>Left ventricular systolic or diastolic dysfunction</td>
<td>203 (4.3)</td>
<td>191 (4.1)</td>
</tr>
<tr>
<td>Ankle-brachial index &lt;0.9</td>
<td>110 (2.4)</td>
<td>116 (2.5)</td>
</tr>
<tr>
<td>Renal function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (eGFR ≥90)</td>
<td>1620 (34.7)</td>
<td>1655 (35.4)</td>
</tr>
<tr>
<td>Mild impairment (eGFR 60–89)</td>
<td>1932 (41.4)</td>
<td>1975 (42.3)</td>
</tr>
<tr>
<td>Moderate impairment (eGFR 30–59)</td>
<td>999 (21.4)</td>
<td>935 (20.0)</td>
</tr>
<tr>
<td>Severe impairment (eGFR &lt;30)</td>
<td>117 (2.5)</td>
<td>107 (2.3)</td>
</tr>
</tbody>
</table>
A. HbA1c

- Placebo
- Liraglutide

Time since randomization (months)

Number of patients at each visit

Placebo: 4672 4423 4299 4053 3877 3640 3742 2303 756 87 3561
Liraglutide: 4468 4402 4355 4295 4125 4034 3877 3810 2349 809 101 3703

B. Body Weight

- Placebo
- Liraglutide

Time since randomization (months)

Number of patients at each visit

Placebo: 4672 4423 4299 4053 3877 3640 3742 2303 756 87 3561
Liraglutide: 4468 4402 4355 4295 4125 4034 3877 3810 2349 809 101 3703

C. Systolic and Diastolic Blood Pressure

- Placebo
- Liraglutide

Time since randomization (months)

Blood pressure (mmHg):
- SBP
- DBP

D. Heart Rate

- Placebo
- Liraglutide

Time since randomization (months)
Primary Outcome: composite of cardiovascular death, MI, stroke

Hazard ratio, 0.87 (95% CI, 0.78–0.97)
P<0.001 for noninferiority
P=0.01 for superiority

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Liraglutide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4668</td>
<td>4672</td>
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<tr>
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<tr>
<td></td>
<td>4072</td>
<td>4010</td>
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<tr>
<td></td>
<td>3982</td>
<td>3914</td>
</tr>
<tr>
<td></td>
<td>1562</td>
<td>1543</td>
</tr>
<tr>
<td></td>
<td>424</td>
<td>407</td>
</tr>
</tbody>
</table>
Secondary Outcome: cardiovascular death

Hazard ratio, 0.78 (95% CI, 0.66–0.93)
P = 0.007

Patients with an Event (%)

Months since Randomization

No. at Risk
Liraglutide  4668  4641  4599  4558  4505  4445  4382  4322  1723  484
Placebo    4672  4648  4601  4546  4479  4407  4338  4267  1709  465
Secondary Outcome: death from any cause

Hazard ratio, 0.85 (95% CI, 0.74–0.97)  
P=0.02

No. at Risk
Liraglutide  4668  4641  4599  4558  4505  4445  4382  4322  1723  1723  484
Placebo  4672  4648  4601  4546  4479  4407  4338  4268  1709  465
ADVERSE EVENTS

• more severe hypoglycemia in the placebo group: 2.4% vs. 3.3% (p = 0.02)

• more acute gallstone disease in the liraglutide group: 3.1% vs. 1.9% (p < 0.001)

• pancreatic cancer: 0.3% vs. 0.1% (p = 0.06)
Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Christoph Wanner, M.D., Silvio E. Inzucchi, M.D., John M. Lachin, Sc.D.,
David Fitchett, M.D., Maximilian von Eynatten, M.D.,
Michaela Mattheus, Dipl. Biomath., Odd Erik Johansen, M.D., Ph.D.,
Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Bernard Zinman, M.D.,
for the EMPA-REG OUTCOME Investigators*

ABSTRACT

Wanner C. NEJM 2016
Empagliflozin

• selective inhibitor of the renal tubular sodium-glucose co-transporter
• reduces renal glucose reabsorption thus increasing urine glucose loss
• decreases total body sodium
• reduces renal ultrafiltration
EMP-REG OUTCOME trial

• empagliflozin 10 mg vs. 25 mg vs. placebo
• primary outcome: cardiovascular (previously reported)
• secondary outcome: composite of microvascular events
  ▪ various ophthalmologic events
  ▪ incident/worsening nephropathy
• microvascular results now released
Renal Endpoints

- progression to macroalbuminuria (> 300 mg albumin/gm creatinine)
- doubling of serum creatinine with EGFR dropping below 45ml/min
- initiation of renal replacement therapy
- death from renal disease
INCLUSION CRITERIA

- EGFR ≥ 30 ml/min
- established cardiovascular disease
- HgbA1c 7 – 9% if not on diabetes meds
- HgbA1c 7 – 10% if on diabetes meds
RESULTS

• 7020 subjects analyzed from 590 sites in 42 countries
• previously reported results: decrease in cardiovascular endpoints
• no difference in ophthalmologic endpoints between groups
• empagliflozin did not decrease the incidence of new albuminuria
• empagliflozin did improve other renal outcomes
Composite renal outcome: new macroalbuminurina; or doubling of creatinine with EGFR < 45; or initiation of dialysis; or death from renal disease.
A. Change in eGFR over 192 Wk

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Empagliflozin, 10 mg</th>
<th>Empagliflozin, 25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. in Follow-up Analysis</td>
<td>Total</td>
<td>7020 7020 6996 6931</td>
<td>6864 6765 6696 6651 6068 5114 4443 3961 3488 2707 1703</td>
</tr>
</tbody>
</table>

Week

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>4</th>
<th>12</th>
<th>28</th>
<th>52</th>
<th>66</th>
<th>80</th>
<th>94</th>
<th>108</th>
<th>122</th>
<th>136</th>
<th>150</th>
<th>164</th>
<th>178</th>
<th>192</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>2323</td>
<td>2295</td>
<td>2267</td>
<td>2205</td>
<td>2121</td>
<td>2064</td>
<td>1927</td>
<td>1981</td>
<td>1763</td>
<td>1479</td>
<td>1262</td>
<td>1123</td>
<td>977</td>
<td>731</td>
<td>448</td>
</tr>
<tr>
<td>Empagliflozin, 10 mg</td>
<td>2322</td>
<td>2290</td>
<td>2264</td>
<td>2235</td>
<td>2162</td>
<td>2114</td>
<td>2012</td>
<td>2064</td>
<td>1839</td>
<td>1540</td>
<td>1314</td>
<td>1180</td>
<td>1024</td>
<td>785</td>
<td>513</td>
</tr>
<tr>
<td>Empagliflozin, 25 mg</td>
<td>2322</td>
<td>2288</td>
<td>2269</td>
<td>2216</td>
<td>2156</td>
<td>2111</td>
<td>2006</td>
<td>2067</td>
<td>1871</td>
<td>1563</td>
<td>1340</td>
<td>1207</td>
<td>1063</td>
<td>838</td>
<td>524</td>
</tr>
</tbody>
</table>

Adjusted Mean eGFR (ml/min/1.73 m²)
QUESTIONS

Why was the empagliflozin 25 mg dose no more effective than the 10 mg dose (lack of dose-response)?

Why did these two trials have positive outcomes while others with similar agents did not?
CONCLUSION

We now have high quality evidence that addition of a “new” anti-hypoglycemic drug can reduce the adverse cardiovascular and renal outcomes in type 2 diabetics. This is an initial very small step in controlling the morbidity and mortality of this disease.
Original Investigation

Repetitive Transcranial Magnetic Stimulation Treatment for Chronic Tinnitus
A Randomized Clinical Trial

Robert L. Folmer, PhD; Sarah M. Theodoroff, PhD; Linda Casiana, MS, CCRP; Yongbing Shi, MD, PhD; Susan Griest, MPH; Jay Vachhani, AuD

**IMPORATANCE** Chronic tinnitus negatively affects the quality of life for millions of people. This clinical trial assesses a potential treatment for tinnitus.

**OBJECTIVES** To determine if repetitive transcranial magnetic stimulation (rTMS) can reduce the perception or severity of tinnitus and to test the hypothesis that rTMS will result in a statistically significantly greater percentage of responders to treatment in an active rTMS group compared with a placebo rTMS group.
IS THIS FOR REAL??????
<table>
<thead>
<tr>
<th>Site of Stimulation</th>
<th>Observed Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left Motor Cortex</td>
<td>Decreased motor-evoked potentials in ipsilateral and contralateral motor cortex</td>
</tr>
<tr>
<td></td>
<td>Increased blood flow in motor cortex</td>
</tr>
<tr>
<td></td>
<td>Decreased slope and duration of pre-motor action potentials</td>
</tr>
<tr>
<td>Right Motor Cortex</td>
<td>Decreased glucose uptake in bilateral motor cortex</td>
</tr>
<tr>
<td></td>
<td>Decreased motor-evoked potentials and increased motor threshold</td>
</tr>
<tr>
<td>Visual Cortex</td>
<td>Increased phosphene response (illusory flashes of light) threshold</td>
</tr>
<tr>
<td>Pre-motor Cortex</td>
<td>Decreased motor evoked potentials</td>
</tr>
</tbody>
</table>

Hoffman RE. Am J Psychiatry 2002
TINNITUS

- Affects an estimated 60 million Americans
- Most common disability among discharged military personnel
- Subset of tinnitus patients suffer decreased functional status and quality of life
- Multitude of different therapies is consistent with none being especially effective
- Lack of standardized outcome measures for clinical research
- Previous studies small and plagued by methodological issues
Rational for Treatment

- tinnitus characterized by increased auditory cortex activity in absence of external auditory stimulation
- state of activation of auditory cortex in tinnitus affects both negatively and positively the state of activation of associated brain regions
- rTMS reduces neural activity in directly stimulated regions
- rTMS reduces neural activity in structurally connected remote brain regions

Burton H. BMC Neuroscience 2012
Folmer et al. JAMA Otolaryngol

- Portland VAMC
- prospective, randomized, double-blinded, parallel group trial of repetitive transcranial magnetic stimulation treatment for tinnitus
- utilized a validated, widely-accepted outcome measure (Functional Tinnitus Index or FTI)
- follow-up for 6 months after treatment
Placebo version supplies all the same clicks, noises, and enough output to make the scalp tingle.
Lengthy Inclusion - Exclusion Criteria

• other neurologic disease/TBI
• taking: tricyclic; anti-psychotic; anti-viral; amphetamines; cocaine, MDMA; phencyclidine; ketamine, etc.
• participation in 2 or more tinnitus trials in the past
• history of tinnitus for ≤ 1 year
• anxiety, neurosis, psychosis, PTSD are NOT necessarily exclusionary, but subject must be able to cope and respond appropriately to treatment/questionnaires
This is clearly a select population of patients who have tinnitus.
PROTOCOL/RESULTS

- randomized to receive 2000 1-Hz pulses daily for 10 days or placebo
- FTI and other tests administered at baseline, immediately after session #10
- follow-up at weeks 1, 2, 4, 13, 26 after treatment with repeat FTI/other tests

At 26 weeks the difference between the groups was significant at the p = 0.007 level.
Responders had a higher baseline FTI score than non-responders: more severe tinnitus is more likely to respond.
Editorial by Jay F. Piccirillo, who had previously published 2 negative studies of TMS for tinnitus:

“In conclusion, the results from the clinical trial by Folmer et al suggests that rTMS might be an effective treatment for tinnitus and should reignite enthusiasm for research into the role of rTMS for tinnitus.”

Piccirillo JF. JAMA 2016
Human neural stem cells in patients with chronic ischaemic stroke (PISCES): a phase 1, first-in-man study

Dheeraj Kalladka, John Sinden, Kenneth Pollock, Caroline Haig, John McLean, Wilma Smith, Alex McConnachie, Celestine Santosh, Philip M Bath, Laurence Dunn, Keith W Muir

Summary
Background CTX0E03 is an immortalised human neural stem-cell line from which a drug product (CTX-DP) was developed for allogeneic therapy. Dose-dependent improvement in sensorimotor function in rats implanted with CTX-DP 4 weeks after middle cerebral artery occlusion stroke prompted investigation of the safety and tolerability of this treatment in stroke patients.

Methods We did an open-label, single-site, dose-escalation study. Men aged 60 years or older with stable disability (National Institutes of Health Stroke Scale [NIHSS] score ≥6 and modified Rankin Scale score 2–4) 6–60 months after ischaemic stroke were implanted with single doses of 2 million, 5 million, 10 million, or 20 million cells by stereotactic ipsilateral putamen injection. Clinical and brain imaging data were collected over 2 years. The primary endpoint was safety (adverse events and neurological change). This trial is registered with ClinicalTrials.gov, number NCT01151124.
CTX0E03: clonal human cortical multipotential neuronal stem cell line

- single integrated copy of the fusion gene cmycER\textsuperscript{TAM}
- cmycER\textsuperscript{TAM} protein is tamoxifen-dependent
- adding tamoxifen induces clonal expansion
- depriving of tamoxifen halts cell replication

CTX-DP is proprietary “drug” – stable solution of viable CTX0E03 cells for injection
Pre-Human Studies

- rat model with middle cerebral artery occlusion strokes
- injection of CTX-DP into ipsilateral putamen resulted in improved motor and behavior function
- a positive dose-response was observed
- histologic examination indicates CTX0E03 cells differentiate into oligodendroglial and endothelial phenotypes
- no adverse effects of CTX-DP noted clinically or histologically
Current study is the first to use **human neuronal stem cells**, bypassing the need to obtain human fetal tissue for transplant.

Previous similar studies used human embryonic carcinoma-derived cell line or porcine cell line: 11% incidence of post-procedure seizures no apparent clinical benefit

Kondziolka D. J Neurosurg 2005  *and* Stavitz SI. Cerebrovasc Dis 2005
PISCES I Trial

Subject inclusion criteria:

- men age $\geq 60$ years
- 6 – 60 months s/p first ischemic stroke
- moderate to severe disability
- stable neurologic status
- examined 3 times during the two months prior to intervention to assure clinical stability
13 patients screened

2 patients excluded
1 positive HLA result before surgery
1 seizure before surgery

3 patients assigned to cohort 1 (2 million CTX0E03 hNSCs)

3 patients assigned to cohort 2 (5 million CTX0E03 hNSCs)

3 patients assigned to cohort 3 (10 million CTX0E03 hNSCs)

2 patients assigned to cohort 4 (20 million CCTX0E03 hNSCs)
CTX-DP was injected into the ipsilaterial putamen stereotactically with CT and MRI guidance via 1-4 separate tracts depending upon dose.
Stroke Severity Score – lower score is lower severity
Spasticity Score – lower is less spastic
ADL score – higher is more independent
Overall health self-assessment – higher is better
Increased white matter hyperintensity around infarct site; axial slices along these tracts showed increased fractional anisotropy.
PISCES-I was a Phase I study: intended only to determine safety of various doses

PISCES-II, a Phase II study designed to determine the efficacy of the treatment, is already underway
Clinical Significance of Symptoms in Smokers with Preserved Pulmonary Function

Prescott G. Woodruff, M.D., R. Graham Barr, M.D., Dr.P.H., Eugene Bleecker, M.D., Stephanie A. Christenson, M.D., David Couper, Ph.D., Jeffrey L. Curtis, M.D., Natalia A. Gouskova, Ph.D., Nadia N. Hansel, M.D., Eric A. Hoffman, Ph.D., Richard E. Kanner, M.D., Eric Kleerup, M.D., Stephen C. Lazarus, M.D., Fernando J. Martinez, M.D., Robert Paine, III, M.D., Stephen Rennard, M.D., Donald P. Tashkin, M.D., and MeiLan K. Han, M.D., for the SPIROMICS Research Group*

ABSTRACT

Woodruff PG. NEJM 2016
Definition

Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease 2013

Spirometry is required to make the diagnosis in the clinical context; the presence of a post-bronchodilator FEV1/FVC less than 0.70 confirms the presence of persistent airflow limitation and thus of COPD.
The nonlinear relationship between age and forced expiratory volume in 1 s (FEV1) in a) males and b) females.
Which reference set standard should be used for PFTs?
<table>
<thead>
<tr>
<th></th>
<th>White</th>
<th>Black</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (years)</td>
<td>34.7</td>
</tr>
<tr>
<td></td>
<td>Height (inches)</td>
<td>69.9</td>
</tr>
<tr>
<td>FEV₁₀ (litres)</td>
<td>4.16</td>
<td>0.76</td>
</tr>
<tr>
<td>FVC (litres)</td>
<td>5.2</td>
<td>0.89</td>
</tr>
<tr>
<td>TLC (litres)</td>
<td>7.10</td>
<td>1.21</td>
</tr>
<tr>
<td>RV (litres)</td>
<td>1.90</td>
<td>1.05</td>
</tr>
</tbody>
</table>
THE PROBLEM

The wide variation of FEV1 and FVC in the normal population results in significant overlap between what represents healthy and diseased lungs.
Hypothesis: many current and former smokers with respiratory symptoms but not meeting COPD spirometry criteria have a clinical picture similar to COPD.

- multi-center prospective observational study
- enrolled 2736 subjects age 40 - 80, healthy (normal spirometry) never smokers and current/former smokers (> 20 pack years) regardless of COPD diagnosis
- measured symptoms, exacerbations, lung CT metrics
- average follow-up of 2.3 years
COPD Assessment Test

Self-rating 0 (good) – 5 (bad)

- cough
- phlegm
- chest tightness
- exertional dyspnea
- ADL limitation
- confidence leaving home
- sleep
- energy level

Score > 10/40 correlates with need for inhaler therapy in COPD
Exacerbations

• prospectively surveyed subjects every 3 months.
• defined exacerbation as
  ▪ antibiotic use
  ▪ systemic steroid use
  ▪ healthcare utilization
• severe exacerbation: hospitalization or ED visit
High Resolution CT Scanning

% lung volume with emphysematous features

wall thickness of airways with 10 mm luminal perimeter
Preserved Pulmonary Function = normal PFTs

Mild-to-Moderate COPD = GOLD stages 1 and 2
* indicates a significant difference (p < 0.05) when compared with current/former smokers with normal PFTs and CAT score < 10.
# 6-Minute Walk Test

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never-smoking Controls</td>
<td>Ever-Smokers with preserved spirometry and CAT&lt;10 (less symptoms)</td>
<td>Ever-Smokers with preserved spirometry and CAT ≥10 (more symptoms)</td>
</tr>
<tr>
<td>N</td>
<td>199</td>
<td>424</td>
</tr>
<tr>
<td>Six minute walk distance (meters)</td>
<td>479.5±101.9</td>
<td>461.7±91.4</td>
</tr>
<tr>
<td>* vs. C,D,E</td>
<td>* vs. C,E</td>
<td>* vs. A,B,D</td>
</tr>
</tbody>
</table>

* Indicates p < 0.05
Conclusion:

1. Smokers with normal PFTs have pulmonary symptoms similar to, but less severe, than those with COPD.

2. Symptomatic smokers (CAT score > 10) with normal PFTs have a frequency of pulmonary exacerbations approaching those with symptomatic COPD.

3. Symptomatic smokers with normal PFTs have reduced exercise capacity (6 minute walk) compared to healthy controls.

4. Symptomatic smokers with normal PFTs have small airway disease (increased wall thickness) compared to healthy controls.
Small-Airway Obstruction and Emphysema in Chronic Obstructive Pulmonary Disease

CONCLUSIONS
These results show that narrowing and disappearance of small conducting airways before the onset of emphysematous destruction can explain the increased peripheral airway resistance reported in COPD. (Funded by the National Heart, Lung, and Blood Institute and others.)
Can Spirometry Reveal Early Small Airway Disease?

- FEV3/FVC
- FEV1/FEV6
- FEV3/FEV6
Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01)

Katsuhiko Uesaka, Narikazu Boku, Akira Fukutomi, Yukiyasu Okamura, Masaru Konishi, Ippei Matsumoto, Yuji Kaneoka, Yasuhiro Shimizu, Shoji Nakamori, Hirohiko Sakamoto, Soichiro Morinaga, Osamu Kainuma, Koji Imai, Naohiro Sata, Shoichi Hishinuma, Hitoshi Ojima, Ryuzo Yamaguchi, Satoshi Hirano, Takeshi Sudo, Yasuo Ohashi, for the JASPAC 01 Study Group

Summary

Background Although adjuvant chemotherapy with gemcitabine is standard care for resected pancreatic cancer, S-1 has shown non-inferiority to gemcitabine for advanced disease. We aimed to investigate the non-inferiority of S-1 to gemcitabine as adjuvant chemotherapy for pancreatic cancer in terms of overall survival.
Pancreatic Adenocarcinoma

- 4th leading cause of cancer death in the United States
- no effective screening test
- lowest survival of all cancer types:
  8% at 5 years
- surgery is the only means of cure:
  15 – 20% undergo “curative” resection
  ~20 – 25% 5 year survival after surgery
Adjuvant (post-operative) chemotherapy improves survival

- gemcitabine has become standard of care
- 6 months of gemcitabine alone or with capecitabine or leucovorin-modulated fluorouracil
- no major improvements in therapy since 2007
Targeted Therapy for Pancreatic Cancer
disappointing results to date

Recently reviewed by Mosquera (Cancer Genetics 2016)

• 14 completed and 17 ongoing phase II/III trials in North America

• all trials involve metastatic/unresectable disease, NOT adjuvant therapy

• only erlotinib (EGFR tyrosine kinase inhibitor) has shown an improvement in overall survival:
  gemcitabine + erlotinib vs. gemcitabine alone:
  23% vs. 17% one-year survival
Can we use established cytotoxic therapy more effectively?
S-1 (TS-1; Taiho Pharmaceutical, Tokyo, Japan)

- **oral** 3-drug combination (tegafur; gimeracil; oteracil)
- tegafur – pro-drug of fluorouracil
- gimeracil – inhibits dihydropyrimidinase which metabolizes fluorouracil; results in persistently higher blood and tumor concentrations of fluorouracil
- oteracil – blocks phosphorylation of fluorouracil in GI tract, thus limiting GI toxicity
• randomized, adjuvant trial of S1 vs. gemcitabine
• s/p resection of stage I, II, or III pancreatic cancer with no gross residual disease (R0) or with only microscopic (R1) residual disease
• ECOG functional status 0-1 (0 = asymptomatic; 1 = able to carry out all but strenuous activities)
• stratified by residual disease status (R0 vs. R1) and regional lymph node status (negative vs. positive regional lymph node metastases)
• total of 24 weeks of treatment or until recurrence
<table>
<thead>
<tr>
<th></th>
<th>Gemcitabine (n=190)</th>
<th>S-1 (n=187)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66 (59-73)</td>
<td>66 (60-73)</td>
</tr>
<tr>
<td>≥65</td>
<td>116 (61%)</td>
<td>111 (59%)</td>
</tr>
<tr>
<td>&lt;65</td>
<td>74 (39%)</td>
<td>76 (41%)</td>
</tr>
<tr>
<td>Performance status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>128 (67%)</td>
<td>131 (70%)</td>
</tr>
<tr>
<td>1</td>
<td>62 (33%)</td>
<td>56 (30%)</td>
</tr>
<tr>
<td>Residual tumour status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R0</td>
<td>164 (86%)</td>
<td>164 (88%)</td>
</tr>
<tr>
<td>R1</td>
<td>26 (14%)</td>
<td>23 (12%)</td>
</tr>
<tr>
<td>Primary tumour status†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>10 (5%)</td>
<td>11 (6%)</td>
</tr>
<tr>
<td>T2</td>
<td>12 (6%)</td>
<td>10 (5%)</td>
</tr>
<tr>
<td>T3</td>
<td>168 (88%)</td>
<td>164 (88%)</td>
</tr>
<tr>
<td>T4</td>
<td>0</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Regional lymph node status†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>73 (38%)</td>
<td>67 (36%)</td>
</tr>
<tr>
<td>N1</td>
<td>117 (62%)</td>
<td>120 (64%)</td>
</tr>
</tbody>
</table>

**Table 1:** Baseline characteristics of the patients in the per-protocol population
Pancreas Cancer Staging*

**T1** Tumor limited to the pancreas, 2 cm or less in greatest dimension

**T2** Tumor limited to the pancreas, more than 2 cm in greatest dimension

**T3** Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery

**T4** Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)
Overall survival

HR 0.57 (95% CI 0.44–0.72); p_{non-inferiority} < 0.0001, p_{superiority} < 0.0001

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Gemcitabine</th>
<th>S-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>190</td>
<td>187</td>
</tr>
<tr>
<td>1</td>
<td>151</td>
<td>172</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>130</td>
</tr>
<tr>
<td>3</td>
<td>73</td>
<td>111</td>
</tr>
<tr>
<td>4</td>
<td>58</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>80</td>
</tr>
</tbody>
</table>
B  Relapse-free survival

HR 0.60 (95% CI 0.47–0.76); $p_{\text{non-inferiority}} < 0.0001$, $p_{\text{superiority}} < 0.0001$

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>Time since randomisation (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine</td>
<td>0  1  2  3  4  5</td>
</tr>
<tr>
<td>190</td>
<td>90 55 43 37 32</td>
</tr>
<tr>
<td>S-1</td>
<td>125 90 73 66 61</td>
</tr>
</tbody>
</table>
Figure 4: EQ-5D utility index over time for patient health-related quality of life

The mean values (SD) of the utility index are shown. The analysis of covariance, including the individual’s baseline EuroQol 5-dimensional questionnaire (EQ-5D)