What dose and schedule of trastuzumab would you select for a patient with metastatic HER2-positive disease who has been in remission on maintenance intravenous trastuzumab for one year?

1. Continue three weekly intravenous trastuzumab
2. Change to three weekly subcutaneous trastuzumab at the next appointment
3. Change to three weekly subcutaneous trastuzumab when the disease progresses
4. Discontinue all trastuzumab until disease progresses

What dose and schedule of trastuzumab would you select for a patient with metastatic HER2-positive disease who has been in remission on maintenance intravenous trastuzumab for one year?

1. Continue three weekly intravenous trastuzumab

38.5%

2. Change to three weekly subcutaneous trastuzumab at the next appointment

42.3%

3. Change to three weekly subcutaneous trastuzumab when the disease progresses

9.6%

4. Discontinue all trastuzumab until disease progresses

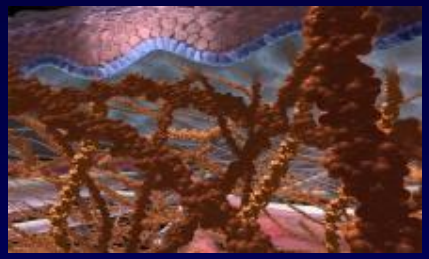
9.6%

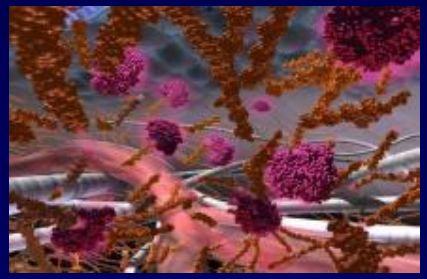
Consideration of Patient Preference in Selecting Anti-HER2 Therapy

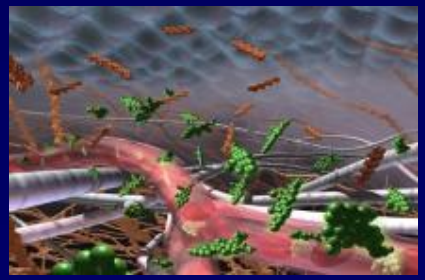
David Miles, MD, FRCP
Mount Vernon Cancer Centre
United Kingdom

Development of a SC Formulation of Trastuzumab

SC administration of trastuzumab has been made possible by the use of recombinant human hyaluronidase as an excipient







- **SC administration of large volumes is restricted by the structure and physiology of the SC layer**
  - **Contains a matrix of hyaluronan fibers and collagen fibers, which limits SC administration to <1 mL**
- **Hyaluronan is broken down by the naturally occurring enzyme, hyaluronidase, on a daily basis**
- **Recombinant human hyaluronidase (rHuPH20) causes temporary and local degradation of hyaluronan**
  - **Results in a temporary increase in the local SC dispersion area, enabling large volumes of fluids to be administered**

Recombinant Human Hyaluronidase (rHuPH20)

Mechanism of action enables injection of larger volumes

Bolus injection of 10 mL 10% IgG solution

Without rHuPH20

Before infusion

Immediately post-infusion

+ 2000 U/mL rHuPH20

Before infusion

Immediately post-infusion

IgG, immunoglobulin; U, units
Images show left and right arms of subject 106 in the HALO-104-103 study

Halozyme Therapeutics, data on file

HannaH: Noninferiority of SC vs IV Trastuzumab Demonstrated

	Trastuzumab IV N = 235	Trastuzumab SC N = 234
Primary endpoint: Observed C_{trough} pre-dose cycle 8		
Geometric mean (µg/mL)	**51.8**	**69.0**
Geometric mean ratio (90% CI)	**1.33 (1.24; 1.44)**	
	Non-inferiority of SC vs IV demonstrated as lower bound of 90% CI > pre-specified noninferiority margin of 0.8	

	Trastuzumab IV N = 263	Trastuzumab SC N = 260
Primary endpoint: pCR in the breast	**107 (40.7%)**	**118 (45.4%)**
Difference in pCR rates (95% CI)	**4.7% (-4.0%; 13.4%)**	
	Non-inferiority of SC vs IV demonstrated as lower bound of 95% CI > prespecified noninferiority margin -12.5%	

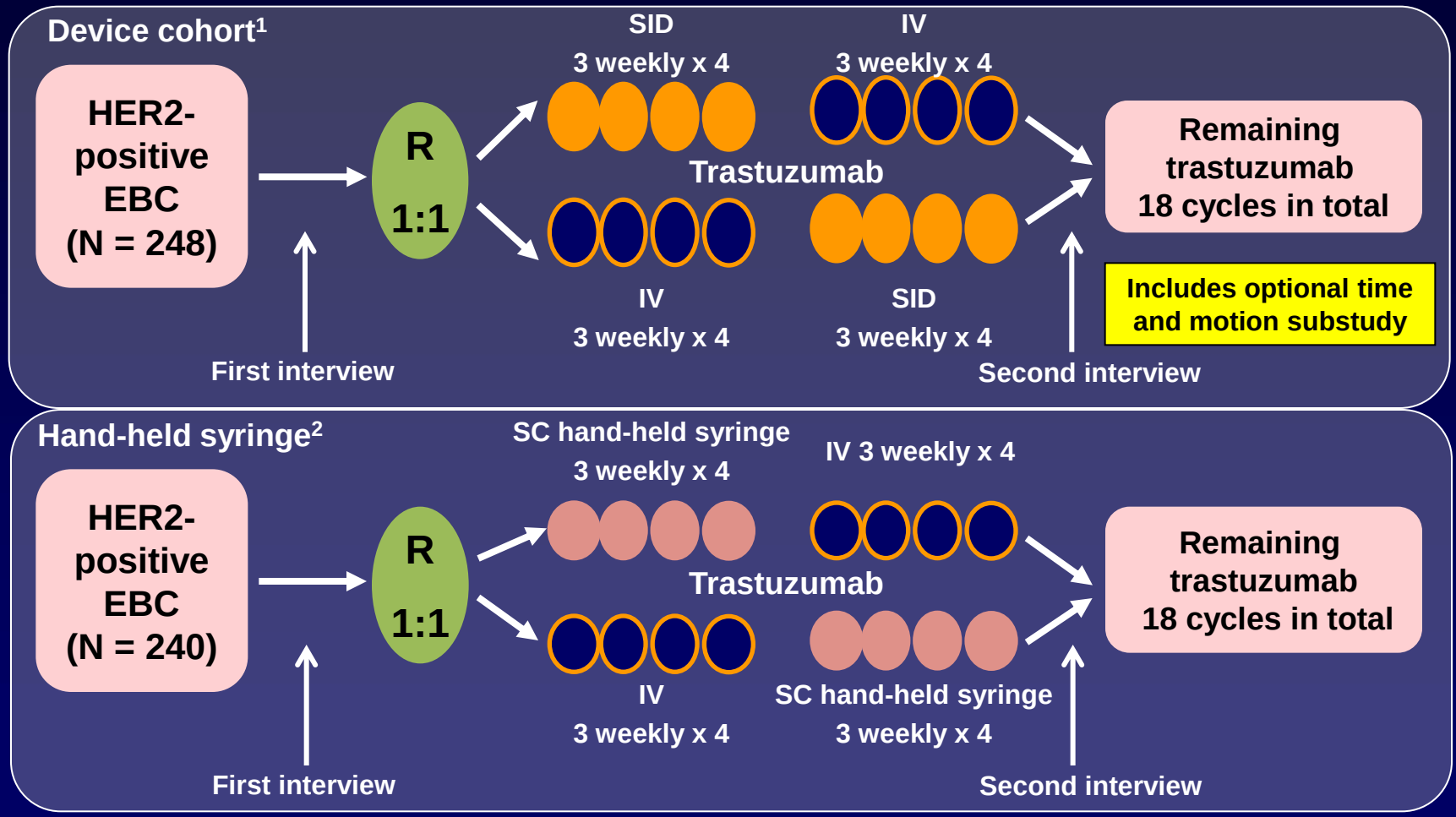
Ismael G, et al. *Lancet Oncol*. 2012;13(9);869-878.

SC Trastuzumab

- 600 mg/5 mL fixed dose
- Includes 10,000 U recombinant hyaluronidase as an excipient
- European Medicines Agency approval for early and metastatic breast cancer as an alternate to IV infusion based on results of the pivotal phase III HannaH study
- Trastuzumab SC could potentially improve patient convenience/compliance (injection time less than 5 minutes; important in long-term trastuzumab therapy) and reduce the use of hospital resources

Pivot X, et al. *Lancet Oncol.* 2013;14(10):962-970. Pivot X, et al. *Cancer Res*. 2013;73(24 Suppl): Abstract P4-12-11.

PrefHer Trial Design



SID, single-use injection device; EBC, early breast cancer

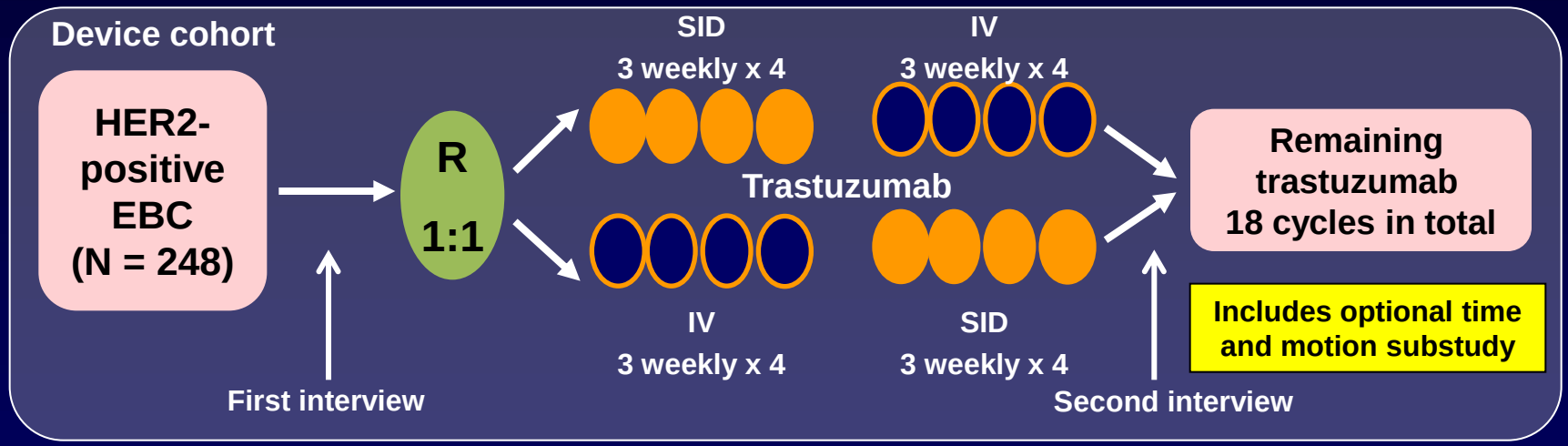
1. Pivot X, et al. *Lancet Oncol.* 2013;14(10):962-970. 2. Pivot X, et al. *Cancer Res*. 2013;73(24 Suppl): Abstract P4-12-11.

Study Endpoints

- Primary endpoint: Patient preference for the SC or IV route of trastuzumab administration
  - Assessed by study-specific patient interviews in the evaluable intention-to-treat (ITT) population
- Secondary endpoints: Included patient safety and tolerability and healthcare professional satisfaction
- Exploratory endpoints: Included factors that influenced patients' preferences
- A time and motion pharmacoeconomic substudy (Cohort 1) will assess medical care utilization, including collection of time of administration and resource data, at selected sites in both cohorts

Pivot X, et al. *Lancet Oncol.* 2013;14(10):962-970. Pivot X, et al. *Cancer Res*. 2013;73(24 Suppl): Abstract P4-12-11.

Cohort 1



Pivot X, et al. *Lancet Oncol.* 2013;14(10):962-970.

Patient Preferences for SC Trastuzumab

	Preference for SC trastuzumab
Patients receiving IV trastuzumab by cannula (n = 129)	94.6% (95% CI, 89.1-97.8)
Patients receiving IV trastuzumab by venous access device (n = 103)	87.4% (95% CI, 79.4-93.1)

Pivot X, et al. *Lancet Oncol.* 2013;14(10):962-970.

Primary Reasons for Patients' Preferences

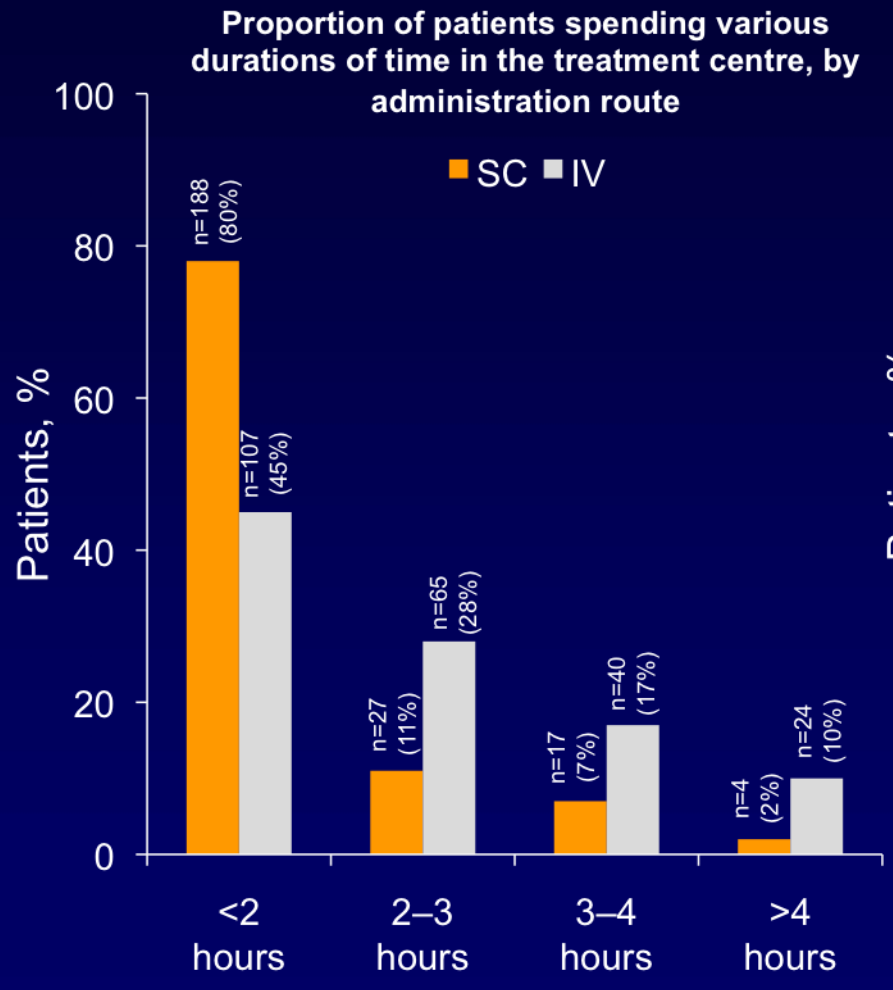
Reason category	Total, n*
SC preference, n = 216	
Time saving	195
Less pain/discomfort	88
Convenience to patient	35
Ease of administration	33
Problems with IV	25
Less stress/anxiety	15
Other	6
IV preference, n = 16	
Fewer perceived reactions (less pain, bruising, irritation, etc)	11
Other	5
Environment/staff	2
Perceived efficacy	1
Ecological considerations	1
No preference, n = 4	

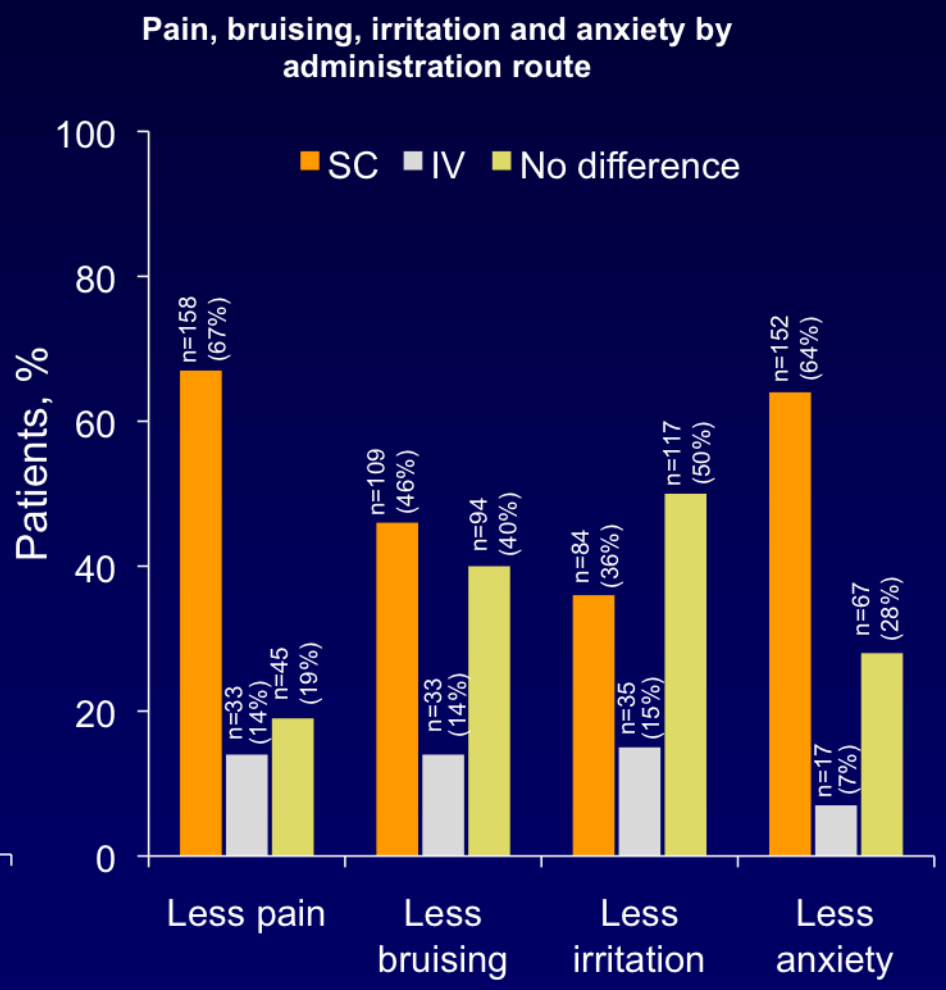
*Some patients gave >1 reason for preference

Pivot X, et al. *Lancet Oncol.* 2013;14(10):962-970.

Main Reasons for SC Preference

(Exploratory analysis, evaluable ITT population)





Percentages are based on total patients (n = 236)

Fallowfield L, *et al*. *Eur J Cancer.* 2013;49(Suppl 3): Abstract P719.

Strength of Patients' Preferences

Overall preference for trastuzumab SC

Strength of preference, n (%)	Trastuzumab SC	Trastuzumab IV
"Very Strong"	159 (67.4%)	8 (3.4%)
"Fairly Strong"	45 (19.1%)	3 (1.3%)
"Not Very Strong"	12 (5.1%)	5 (2.1%)

- None of the potentially influencing factors impacted the primary endpoint results

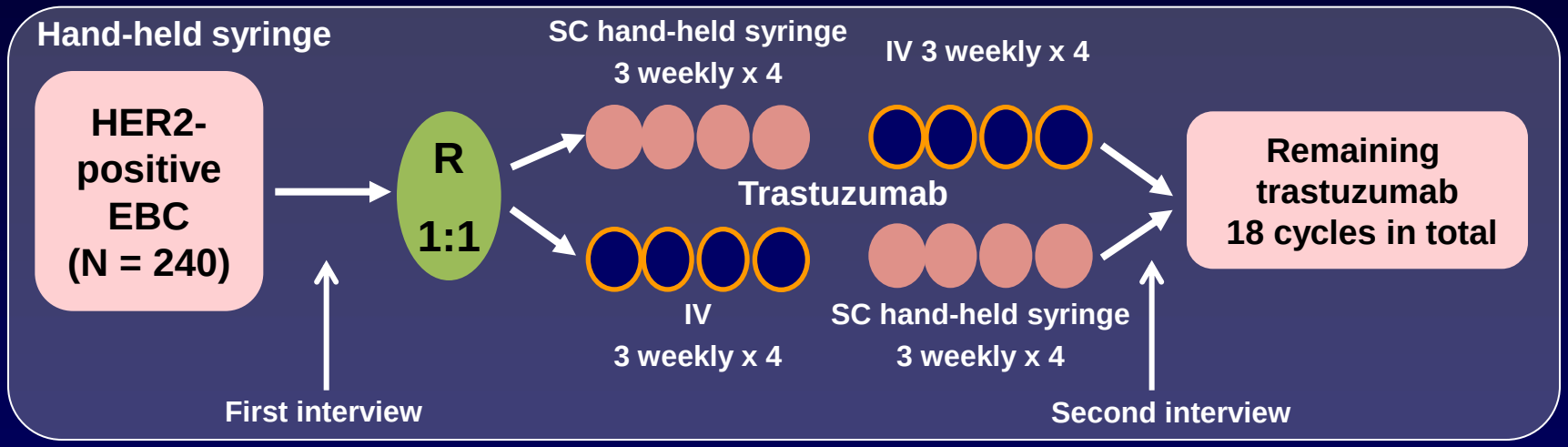
Pivot X, et al. *Lancet Oncol.* 2013;14(10):962-970.

Healthcare Professionals Satisfaction

- **Healthcare professionals (n = 103) were more satisfied with trastuzumab SC (73.8%, 95% CI 64.2% to 82.0%) compared with IV (1.9%). The remaining 24.3% did not indicate a preference.**

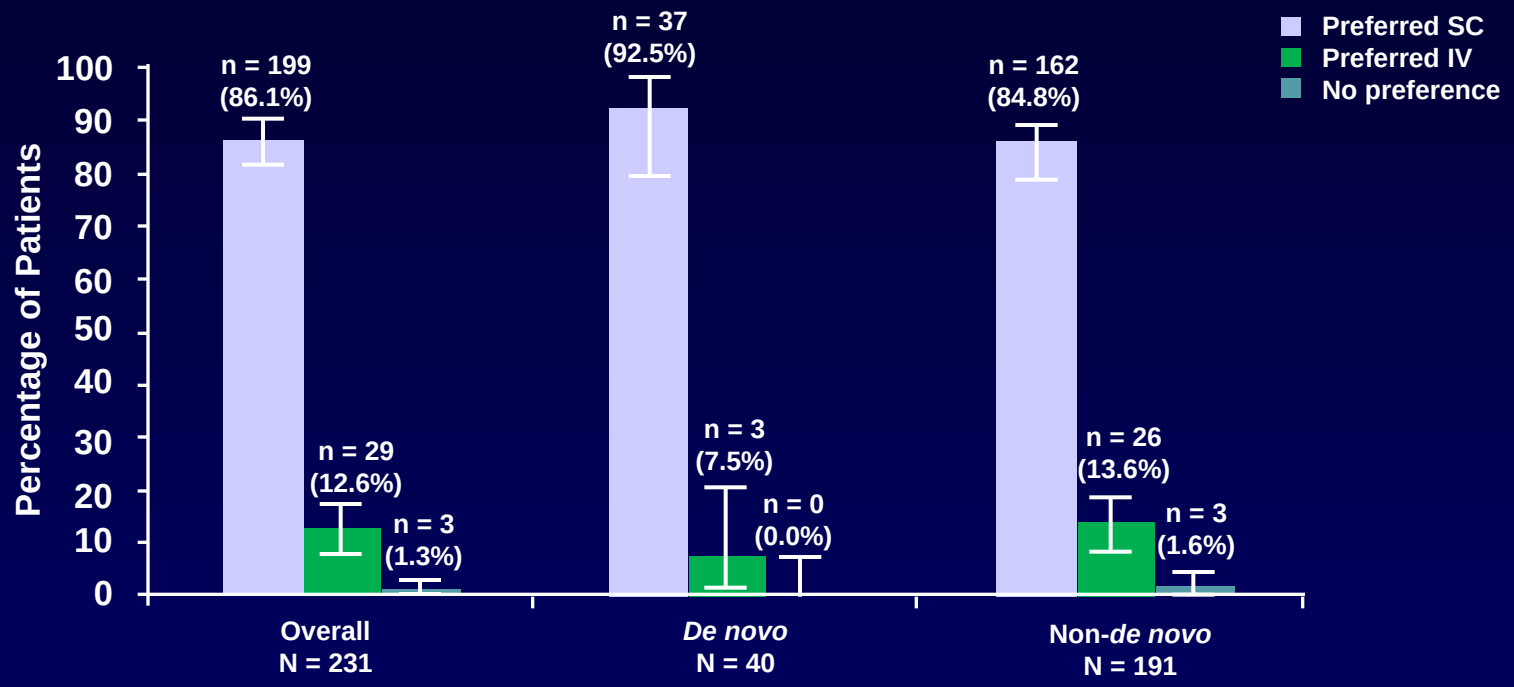
Pivot X, et al. *Lancet Oncol.* 2013;14(10):962-970.

Cohort 2



Pivot X, et al. *Cancer Res*. 2013;73(24 Suppl): Abstract P4-12-11.

Patients' Preferences



Results were similar in each study arm:

- **Handheld syringe → IV arm: 83.9% preferred SC, 13.6% preferred IV, and 2.5% had no preference**
- **IV → handheld syringe arm: 88.5% preferred SC and 11.5% preferred IV**

Pivot X, et al. *Cancer Res*. 2013;73(24 Suppl): Abstract P4-12-11.

Strength of Patients' Preferences

Strength of Preference, n (%)	Trastuzumab SC	Trastuzumab IV
"Very Strong"	144 (62.3%)	16 (6.9%)
"Fairly Strong"	36 (15.6%)	7 (3.0%)
"Not Very Strong"	19 (8.2%)	6 (2.6%)

Pivot X, et al. *Cancer Res*. 2013;73(24 Suppl): Abstract P4-12-11.

SafeHer Trial Design

Global safety study of trastuzumab subcutaneous for 1 year (administered using a syringe, needle, and manual injection or a single-use injection system) in patients with HER2-positive EBC

Patients with HER2-positive early breast cancer

N = 2500

Investigator choice of:

- Cohort
- Chemo regimen

Cohort A: Vial (n = 1800)

Cohort B: Device (n = 700) with supervised self-administration option

Follow-up period

- Primary objectives
  - Safety and tolerability
- Secondary objectives
  - Disease-free survival; overall survival
  - Self-administration: patient satisfaction (SID cohort)
- Exploratory analysis
  - Immunogenicity

National Institutes of Health. Available at: http://clinicaltrials.gov/show/NCT01566721. Accessed: December 12, 2013.

Conclusions

- Most patients in both cohorts of the PrefHer study had a strong or very strong preference for SC compared with IV trastuzumab
  - Saved time both in terms of time in center and time in chemo chair
  - Less pain / discomfort / side effects than IV administration
- There was a high level of healthcare professional satisfaction with SC trastuzumab
- The SafeHer global safety study is ongoing
- The option of SC trastuzumab should be discussed with patients

RAISING THE BAR

IN BREAST CANCER CARE:

Answering Clinically Relevant Questions