Update on Palliative Oncology Palliative Chemotherapy

13 July 2016
Napa Parinyanitikul, MD
Medical Oncologist
King Chulalongkorn Memorial Hospital and
Chulalongkorn University

Outlines

- Update incidence of cancer patients in Thai and worldwide (US)
- Palliative Chemotherapy
- Palliative Care Framework

- Update in palliative chemotherapy in several cancers

*** Focus in the common cancer patients
  - Lung cancer
  - Colon cancer
  - Breast cancer

Estimated New Cases*

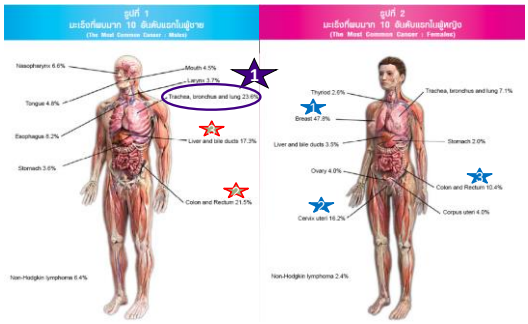
			Males	Females			
Prostate	233,000	27%			Breast	232,670	29%
Lung & bronchus	116,000	14%			Lung & bronchus	108,210	13%
Colorectum	71,830	8%			Colorectum	65,000	8%
Urinary bladder	56,390	7%			Uterine corpus	52,630	6%
Melanoma of the skin	43,890	5%			Thyroid	47,790	6%
Kidney & renal pelvis	39,140	5%			Non-Hodgkin lymphoma	32,530	4%
Non-Hodgkin lymphoma	38,270	4%			Melanoma of the skin	32,210	4%
Oral cavity & pharynx	30,220	4%			Kidney & renal pelvis	24,780	3%
Leukemia	30,100	4%			Pancreas	22,890	3%
Liver & intrahepatic bile duct	24,600	3%			Leukemia	22,280	3%
All Sites	**855,220**	**100%**			**All Sites**	**810,320**	**100%**

Estimated Deaths

			Males	Females			
Lung & bronchus	86,930	28%			Lung & bronchus	72,330	26%
Prostate	29,480	10%			Breast	40,000	15%
Colorectum	26,270	8%			Colorectum	24,040	9%
Pancreas	20,170	7%			Pancreas	19,420	7%
Liver & intrahepatic bile duct	15,870	5%			Ovary	14,270	5%
Leukemia	14,040	5%			Leukemia	10,050	4%
Esophagus	12,450	4%			Uterine corpus	8,590	3%
Urinary bladder	11,170	4%			Non-Hodgkin lymphoma	8,520	3%
Non-Hodgkin lymphoma	10,470	3%			Liver & intrahepatic bile duct	7,130	3%
Kidney & renal pelvis	8,900	3%			Brain & other nervous system	6,230	2%
All Sites	**310,010**	**100%**			**All Sites**	**275,710**	**100%**

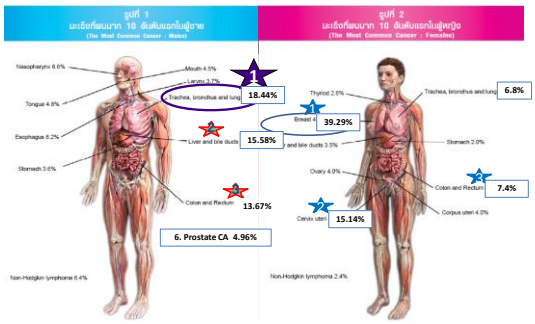
Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin*. 2014 Jan;64(1):9-29)

Leading cancer in Thailand



Hospital based cancer registry: NCI 2011 (2554)

Leading Cancer in Thailand

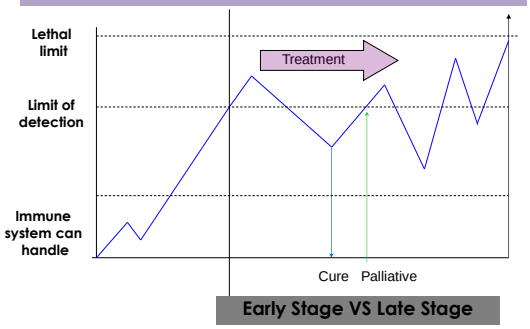


Hospital based cancer registry: NCI 2013 (2556)

Total Top Ten Cancer in Thailand 2013

1. **Breast cancer**
2. **Trachea/bronchus and lung cancer**
3. **Colorectal cancer**
4. **Cervical cancer**
5. **Liver and intrahepatic bile duct cancer**
6. **Lip and oral cavity cancer**
7. **Esophageal cancer**
8. **Non-Hodgkin lymphoma**
9. **Corpus cancer**
10. **Nasopharyngeal cancer**

Growth curve for Cancer



Cancer as a Chronic Disease

- Chronic diseases
  - Shaped by periods of acute and intensive illness followed by periods of remission
- People with cancer are living for longer with a chronic, but life threatening, illness
- Challenges the portrayal/ perception of cancer
- Challenges the concept of "palliative" in relation to cancer and its treatment
- Concept of the "survivor" having increasing relevance in cancer care

Principle of Chemotherapy Uses

- Primary modality of treatment
- Adjunct treatment
  - Adjuvant
  - Neoadjuvant
  - Concurrent
- **Palliative treatment : Palliative chemotherapy**
  - **Prolong survival: overall, DFS, PFS**
  - **Improve symptoms, QOL, toxicities**

Concept Palliative Chemotherapy

- Palliative chemotherapy is given without curative intent, but simply to decrease tumor load and increase life expectancy. For these regimens, a better toxicity profile is generally expected.

- Minimising potential toxicity is the goal
- Try not to compromise on quality of life
- Dose reduction to avoid toxicity is permissible

The goal of care for a palliative care

- The patient , who is not benefit from medical treatment aimed at cure and instead the care should be **aimed at managing symptoms and improving quality of life**
- Palliative care patients should **not be subjected to burdensome or futile treatments**

Objectives in Advanced Disease

PERSON:
- Live longer
- Quality of Life
- Dignity

STATE:
- Cost-effectiveness
- Standards of care

MEDICAL STAFF:
- Maintain quality of life
- Minimise toxicity
- Prolong survival
- Progression-free survival
- Minimise disease-related toxicity
- **Balance between all the various factors**

Considerations in Treatment

- Performance Status
- Range of agents
- Therapeutic target
- Measuring benefit
  - Symptoms
  - Radiology
  - Function
- When to break / stop

Palliative in targeted therapy era

Patients usually misled by incomplete or wrong information in the lay media. And dream to the new clinical trial. But, only about 3 % of adults with advanced cancer enroll on trials.

Because of :

1. highly selected cases. "Real-life" patients are typically older and have more comorbidities.
2. In addition, clinical trials are usually conducted only in high-volume and highly experienced centers to ensure rapid accrual of patients.
3. Many new drugs usually give shortly time of response
4. Mostly, the response is just SD or PR and not CR.

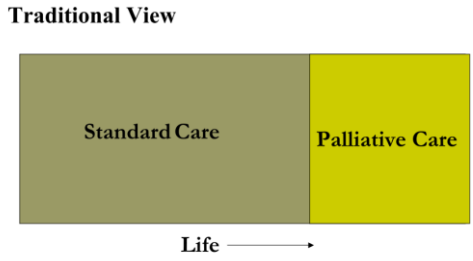
Townsley et al. 2005

Palliative in targeted therapy era

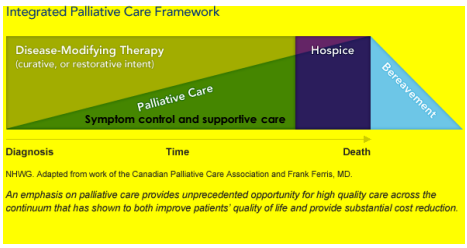
- No definite guideline of treatment with targeted therapy in patients with advanced cancer in terminal stage
- A classic "palliative" patient with known targets for drugs who never received these drugs should be informed about these treatment options
- On the other hand, if palliative care without anticancer treatment options is the way to go, it should be palliative care and not leaving the patients alone

Lester et al. 2013

What is Palliative Care??



Palliative Care Framework : New

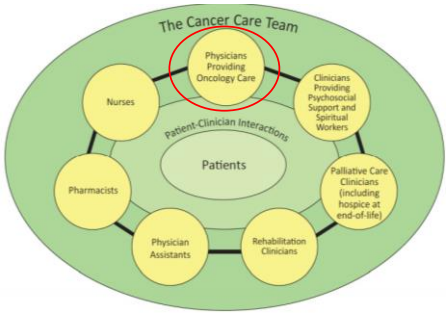


Chemotherapy in metastatic solid tumors

- Palliative chemotherapy is increasingly given near death
- More than 20% of patients receiving Medicare who had metastatic cancer started a new chemotherapy treatment regimen in the 2 weeks before death
- In 2008, a medical director of a large insurance company reported that 16% of its cancer patients receive chemotherapy within 14 days of death
- Patients are unlikely to benefit from chemotherapy when they have already been failed by the standard regimens, have poor PS, and otherwise have a poor prognosis
- Survival was significantly longer for hospice patients with lung cancer and pancreatic cancer, marginally longer for colon cancer, but no different with breast or prostate cancer

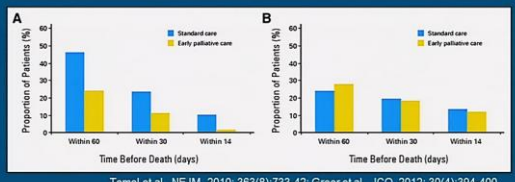
JAMA. 2008;299(22):2667-2678

Illustration of a coordinated cancer care team



Early Palliative Care for Metastatic NSCLC

- Improvements in QOL, depression, and survival
- Higher quality care at the end of life
  - Lower rates of IV chemotherapy use
  - Longer lengths of stay in hospice



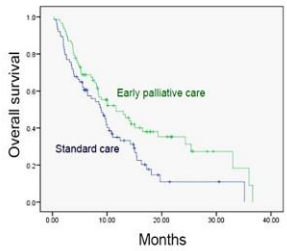
Temel et al., NEJM. 2010; 363(8):733-42; Greer et al., JCO. 2012; 30(4):394-400

"Early Palliative Care"

- Early palliative care in a broader sense has the capacity to improve the patients' well-being and survival that may rival oncologic approaches
- Metastatic lung cancer cases may live longer if they are accompanied by a dedicated team of palliative care specialists parallel to their oncologic treatment.
- **Palliative care in this study included**
  - support to better understand the disease and its treatment
  - to optimize symptom management by systematically evaluating symptoms
  - to support decision-making and to help with coping
  - to make sure that the patient adheres to the rules of treatment

  (Temel et al. 2010)
- But, this way rarely succeeds in a busy oncological practice hospital oncology ward. So, doing with multidisciplinary team may help in this situation (Okuyama et al. 2011)

Early Palliative Care for patients with Metastatic NSCLC

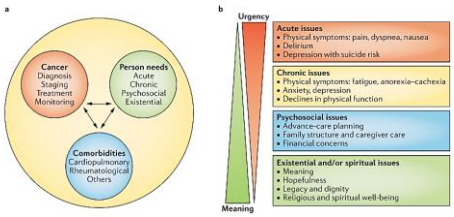


Median Survival
Early palliative care 11.6 mo
Standard care 8.9 mo
p=0.02

Median survival was longer among pts receiving early palliative care

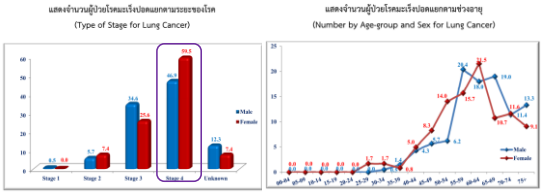
Controlling for age, gender and PS, adjusted HR=0.59 (0.40-0.88), p=0.01

Care needs of patients with advanced-stage cancer



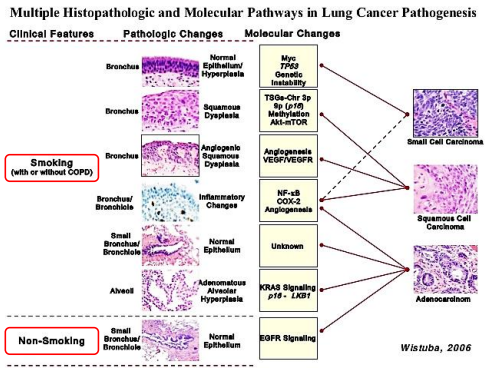
1) Cancer management
2) Symptom management and personal care needs
3) The management of comorbidities

Lung Cancer (NSCLC): Introduction

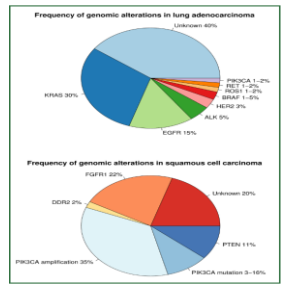


Most common stage IV disease
Peak age at diagnosis : 50-60 years
Pathology : NSCLC (AdenoCA, Squamous CA, Large cell CA) vs SCLC

Hospital based cancer registry: NCI 2010



NSCLC adenocarcinoma vs squamous cell carcinoma harboring different oncogene aberrations

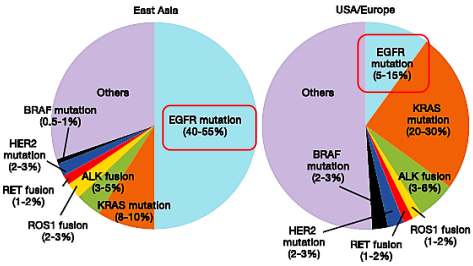


Adenocarcinoma
- EGFR
- Kras
- ALK/ROS1

Squamous cell carcinoma
- PIK3CA amplification
- PIK3CA mutation
- FGFR1

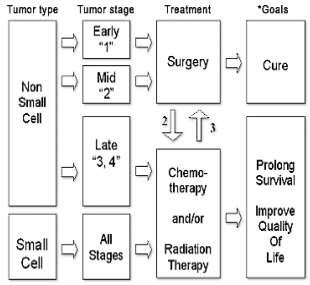
Peter Savas et al. J of Thorac Dis 2013.

NSCLC adenocarcinoma harboring oncogene aberrations



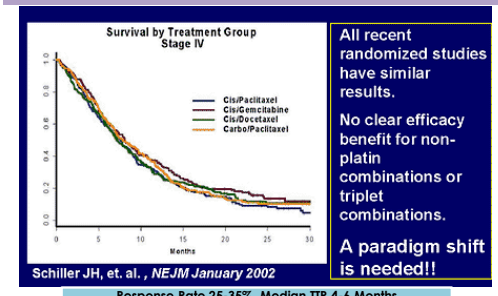
Takashi Kohno et al. Translational Lung Cancer Research, 2014.

Lung Cancer (NSCLC): Management



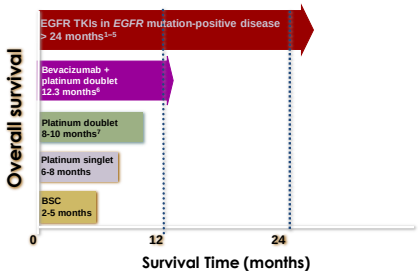
Modalities
- Surgery
- Chemotherapy
- Radiation
- Combined treatment
- Targeted therapy

Lung Cancer (NSCLC) : Palliative Chemotherapy



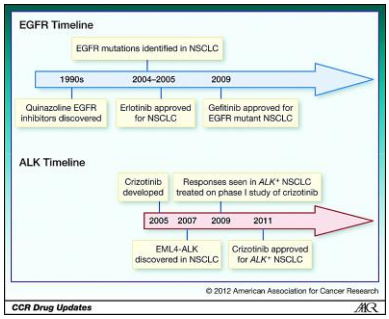
Response Rate 25-35%, Median TTP 4-6 Months
Median Survival 8-10 Months, 1-yr OS 30-40%
No Survival Different Among Histological Subtypes

Development in Treatment of Advanced NSCLC (Personalized Treatment)

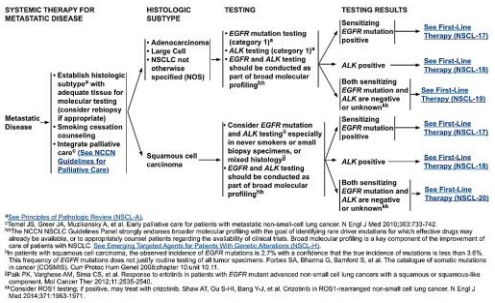


[1]Janne, et al. ASCO 2010; [2]Lee, et al. WCLC 2009
[3]Maemondo, et al. NEJM 2010; [4]Mitsudomi, et al. Lancet Oncol 2010
[5]Rosell, et al. NEJM 2009; [6]Sandler, et al. NEJM 2006; [7]Schiller, et al. NEJM 2002

Personalized Therapy for NSCLC

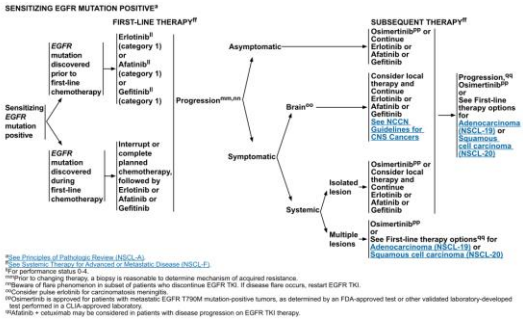


NSCLC : NCCN Guideline 4.2016



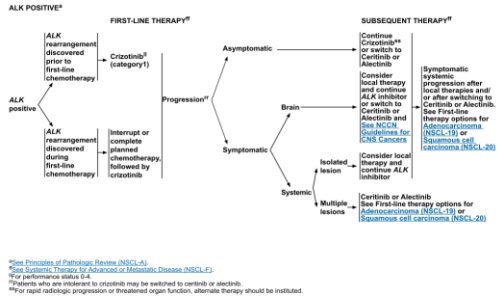
[a] See Principles of Pathologic Review (NSCL-A).
[c] Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010;363:733-742.
[f] The NCCN NSCLC Guidelines Panel strongly endorses broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC. See Emerging Targeted Agents for Patients With Genetic Alterations (NSCL-H).
[g] In patients with squamous cell carcinoma, the observed incidence of *EGFR* mutations is 2.7% with a confidence that the true incidence of mutations is less than 3.6%. This frequency of *EGFR* mutations does not justify routine testing of all tumor specimens. Forbes SA, Bhamra G, Bamford S, et al. The catalogue of somatic mutations in cancer (COSMIS). *Curr Protoc Hum Genet* 2008;Chapter 10:Unit 10.11.
[h] Paik PK, Varghese AM, Sima CS, et al. Response to erlotinib in patients with *EGFR* mutant advanced non-small cell lung cancers with a squamous or squamous-like component. *Mol Cancer Ther* 2012;11:2535-2540.
[i] Consider R(G)1 testing; if positive, may treat with crizotinib. Shaw AT, Ou S-HI, Bang Y-J, et al. Crizotinib in ROS1-rearranged non-small cell lung cancer. N Engl J Med 2014;371:1963-1971.

NSCLC : NCCN Guideline 4.2016



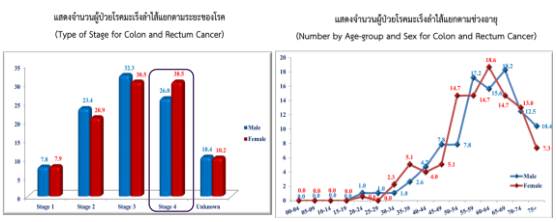
[a] See Principles of Pathologic Review (NSCL-A).
[e] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).
[ff] For performance status 0-4.
[eee] Prior to changing therapy, a biopsy is reasonable to determine mechanism of acquired resistance.
[fff] Beware of flare phenomenon in subset of patients who discontinue EGFR TKI. If disease flare occurs, restart EGFR TKI.
[ggg] Consider pulse erlotinib for carcinomatosis meningitis.
[pp] Osimertinib is approved for patients with metastatic EGFR T790M mutation-positive tumors, as determined by an FDA-approved test or other validated laboratory-developed test performed in a CLIA-approved laboratory.
[qq] Afatinib + cetuximab may be considered in patients with disease progression on EGFR TKI therapy.

NSCLC : NCCN Guideline 4.2016



[a] See Principles of Pathologic Review (NSCL-A).
[e] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).
[ff] For performance status 0-4.
[ss] Patients who are intolerant to crizotinib may be switched to ceritinib or alectinib.
[tt] For rapid radiologic progression or threatened organ function, alternate therapy should be instituted.

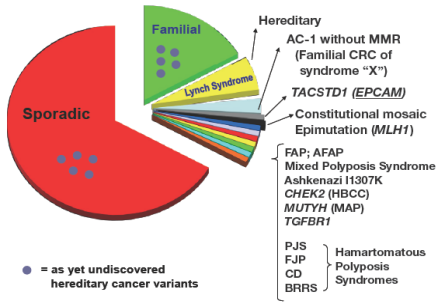
Colorectal Cancer : Introduction



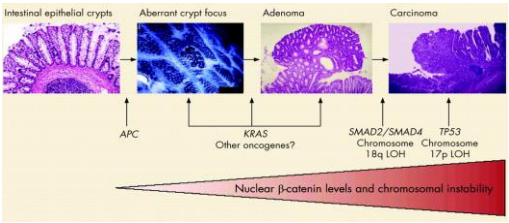
Early stage (Stage I-III) : 63%
Advanced stage : 37%
Peak age at diagnosis : 50-60 years

Hospital based cancer registry: NCI 2010

Colorectal Cancer : Introduction



Colorectal Cancer : Pathogenesis

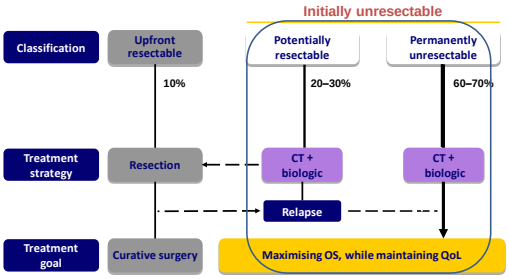


Adenoma-Carcinoma process (7-10 yrs)
Risk factor for cancer ex. High-grade dysplasia, >10 mm in size, Villous component, Number ≥3

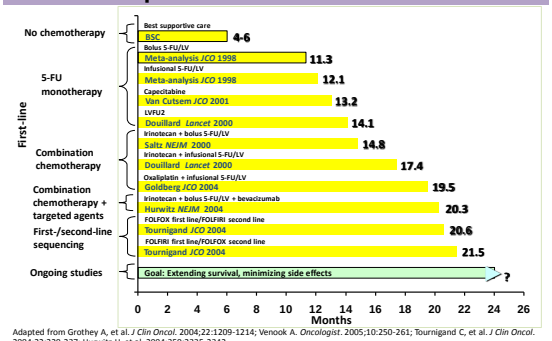
Colorectal Cancer : Clinical

- **Proximal colon (Right-sided)**
  - Polypoid or fungating exophytic mass
  - Without obstructive symptoms or alterations in bowel habits
  - Occult bleeding
- **Distal colon (Left-sided)**
  - Annular or encircling lesions: **"apple-core" or "napkin-ring"**
  - Symptoms of bowel dysfunction (constipation, diarrhea, bowel habit changes or bowel obstruction)

Initially unresectable mCRC : increasing OS -primary treatment goal



Treatment Evolution in mCRC and Impact on Median Survival

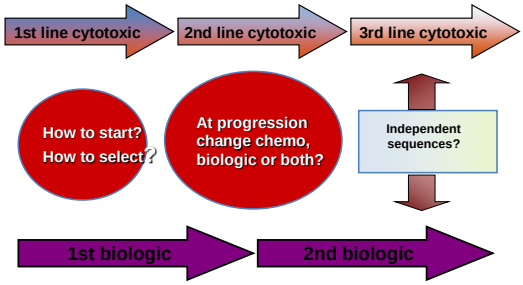


Adapted from Grothey A, et al. *J Clin Oncol*. 2004;22:1209-1214; Venook A. *Oncologist*. 2005;10:250-261; Tournigand C, et al. *J Clin Oncol*. 2004;22:229-237; Hurwitz H, et al. 2004;350:2335-2342.

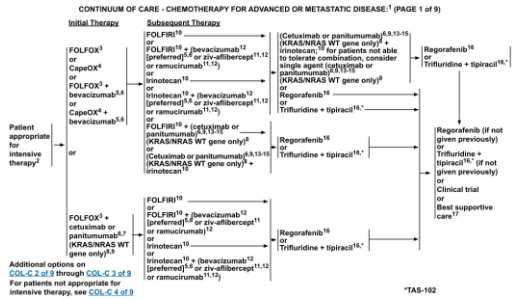
Colorectal Cancer : Systemic treatment

- Adjuvant treatment
  - 5FU/LV
  - Capecitabine
  - Oxaliplatin combination
    - FOLFOX
    - FLOX
    - XELOX
- Metastatic treatment
  - 5FU/LV
  - Capecitabine
  - Oxaliplatin combination
  - Irinotecan combination
  - Adding Targeted Rx
    - Bevacizumab
    - Cetuximab/Panitumumab
    - Aflibercept (VEGF trap)
  - Regorafenib
  - TAS-102

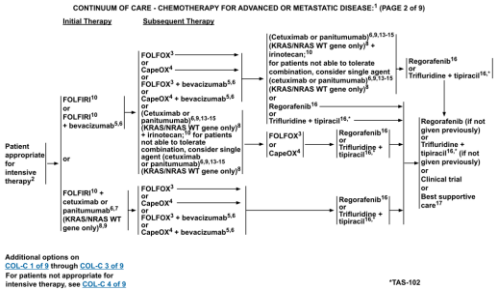
The integration of biologicals in the continuum of care of CRC



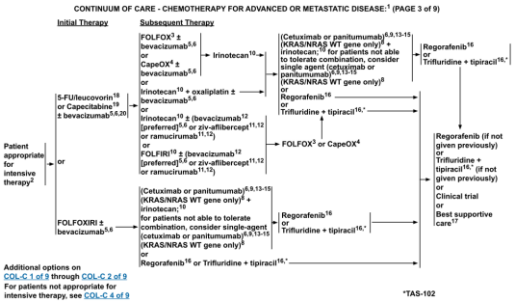
Colorectal Cancer : NCCN Guideline 2.2016



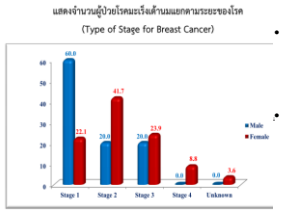
Colorectal Cancer : NCCN Guideline 2.2016



Colorectal Cancer : NCCN Guideline 2.2016



Breast Cancer : Introduction



- 20% of pts initially diagnosed with regional stage disease will develop MBC
- Approximately 6% of breast cancers are metastatic at diagnosis with a 5-year survival rate of 21%

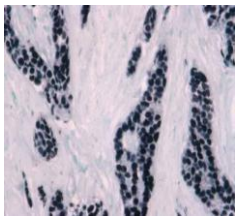
Stage and breast cancer

Early BC (stage I-II) 63.8%
Locally advanced BC (stage III) 23.9%
Advanced BC 8.8%

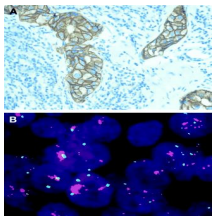
Hospital based cancer registry: NCI 2011

Annals of Oncology 20 (Supplement 4): iv15–iv18, 2009

Breast Cancer Up Until Now: Diagnosis Testing for 1 or 2 Specific Molecules



Estrogen Receptor: 75% of breast cancers are ER+

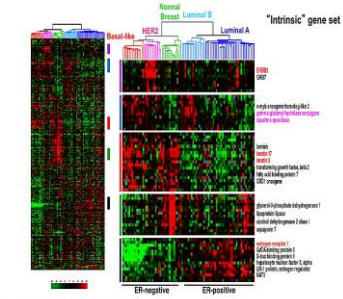


HER-2: 20-25% of breast cancers are HER-2+

TNBC :15-25% of all BC

Histopathology → IHC expression → Gene expression profiling

Molecular Classification breast cancer

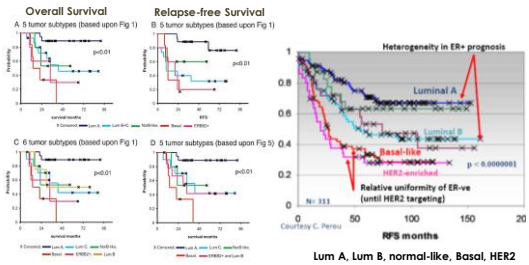


Perou et al, Nature, 2000; Sorlie et al, PNAS 2003

Breast cancer is not one disease
But a group of biologically distinct diseases

5 subtypes
: Luminal A
: Luminal B
: Basal like
: HER2 positive
: normal-like

Molecular Subtype Breast Cancer and Prognosis



Lum A, Lum B, LumC, normal-like, Basal, HER2

Lum A, Lum B, normal-like, Basal, HER2

Sorlies et al. PNAS 2001

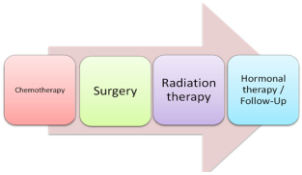
Breast Cancer : Treatment

Multidisciplinary team for breast cancer

- Radiologist
- Pathologist
- Breast cancer Surgeon
- Radiation oncologist
- Medical oncologist

Treatment

- Local treatment
  - Surgery
  - Radiation therapy
- Systemic treatment
  - Chemotherapy
  - Endocrine or hormone therapy
  - Targeted therapy



NCCN guideline Version 2.2016

CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER[1]

Preferred single agents:

Anthracyclines
- Doxorubicin
- Pegylated liposomal doxorubicin

Taxanes
- Paclitaxel

Anti-metabolites
- Capecitabine
- Gemcitabine

Other microtubule inhibitors
- Vinorelbine
- Eribulin

Other single agents:
- Cyclophosphamide
- Carboplatin
- Docetaxel
- Albumin-bound paclitaxel
- Cisplatin
- Epirubicin
- Ixabepilone

Chemotherapy combinations:
- CAF/FAC (cyclophosphamide/doxorubicin/fluorouracil)
- FEC (fluorouracil/epirubicin/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)
- Gemcitabine/carboplatin
- Paclitaxel/bevacizumab[2]

Preferred first-line agents for HER2-positive disease:
- Pertuzumab + trastuzumab + docetaxel (category 1)[3]
- Pertuzumab + trastuzumab + paclitaxel[3]

Other agents for HER2-positive disease:
- Ado-trastuzumab emtansine (T-DM1)
- Trastuzumab + paclitaxel ± carboplatin
- Trastuzumab + docetaxel
- Trastuzumab + vinorelbine
- Trastuzumab + capecitabine

Agents for trastuzumab-exposed HER2-positive disease:
- Lapatinib + capecitabine
- Trastuzumab + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)
- Trastuzumab + other agents[3,4,5]

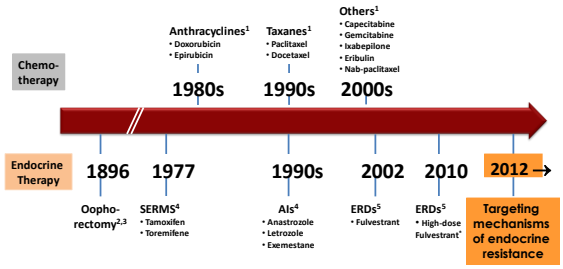
[1]There is no compelling evidence that combination regimens are superior to sequential single agents.
[2]Randomized clinical trials in metastatic breast cancer document that the addition of bevacizumab to some first- or second-line chemotherapy agents modestly improves time to progression and response rates but does not improve overall survival. The time-to-progression impact may vary among cytotoxic agents and appears greatest with bevacizumab in combination with weekly paclitaxel.
[3]Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.
[4]Trastuzumab may be safely combined with all non-anthracycline containing preferred and other single agents listed above for recurrent or metastatic breast cancer.
[5]Patients previously treated with chemotherapy plus trastuzumab in the absence of pertuzumab in the metastatic setting may be considered for one line of therapy including both trastuzumab plus pertuzumab in combination with or without cytotoxic therapy (such as vinorelbine or taxane). Further research is needed to determine the ideal sequencing strategy for anti-HER2 therapy.

NCCN guideline Version 2.2016

Premenopausal patients
- Ovarian ablation/ suppression then follow postmenopausal guidelines

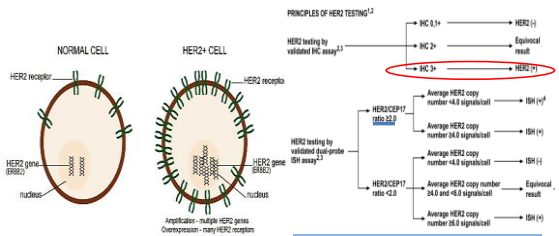
Postmenopausal patients
- Nonsteroidal AI
- Steroidal AI
- Exemestane+everolimus* Palbociclib+Letrozole**
- Fulvestrant*
- Tamoxifen or toremifene
- Megestrol acetate
- Fluoxymesterone
- Ethinyl estradiol

Breast Cancer : Historic Timeline of Therapies for HR+ subtype



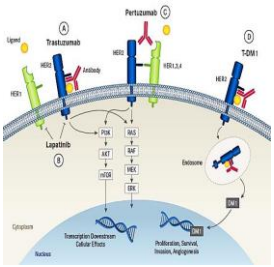
Abbreviations: AI, aromatase inhibitor; ERDs, estrogen receptor downregulator; HR+; hormone receptor positive; SERMS, selective estrogen receptor modulators.
* Marginal improvement over lower dose fulvestrant.
1. http://www.advancedbreastcancercommunity.org/treatment/drugs.htm; 2. Beatson CT. *Lancet*. 1896;2:104-107; 3. Beatson CT. *Lancet*

Breast Cancer : HER2 positive subtype



ASCO/CEP HER2 testing guideline: NCCN Breast Cancer Guideline: 1.2015

Breast Cancer : anti HER2 Therapy



Drugs that approved by FDA

- First-generation : Trastuzumab (Ab)
- Lapatinib : oral TKI
- Pertuzumab (Ab)
- T-DM1 (Antibody conjugated CMT)
- Neratinib

Breast Cancer : Rx in HER2+ subtype

Adjuvant/neoadjuvant Rx

Regimens for HER2-positive disease[6,7,8]

Preferred regimens:
- AC followed by T + trastuzumab ± pertuzumab[9] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab ± pertuzumab, various schedules)
- TCH (docetaxel/carboplatin/trastuzumab) ± pertuzumab

Other regimens:
- AC followed by docetaxel + trastuzumab ± pertuzumab[9]
- Docetaxel + cyclophosphamide + trastuzumab
- FEC followed by docetaxel + trastuzumab + pertuzumab[9]
- FEC followed by paclitaxel + trastuzumab + pertuzumab[9]
- Paclitaxel + trastuzumab[10]
- Pertuzumab + trastuzumab + docetaxel followed by FEC[9]
- Pertuzumab + trastuzumab + paclitaxel followed by FEC[9]

Duration : 1 year

Metastasis Rx

Preferred first-line agents for HER2-positive disease:
- Pertuzumab + trastuzumab + docetaxel (category 1)[4]
- Pertuzumab + trastuzumab + paclitaxel[4]

Other first-line agents for HER2-positive disease:
Trastuzumab alone or with:
- Paclitaxel ± carboplatin
- Docetaxel
- Vinorelbine
- Capecitabine

Preferred agents for trastuzumab-exposed HER2-positive disease:
- Ado-trastuzumab emtansine (T-DM1)

Other agents for trastuzumab-exposed HER2-positive disease:
- Lapatinib + capecitabine
- Trastuzumab + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)
- Trastuzumab + other agents[3,4]

Duration : Treatment until PD or toxicity (1 year)

NCCN Breast Cancer Guideline: 2.2016

Palliative Chemotherapy : Summary

- Palliative chemotherapy aims at managing symptoms, improving quality of life and minimise disease-related toxicity
- Patients are unlikely to benefit from chemotherapy when they have already been failed by the standard regimens, have poor PS, and otherwise have a poor prognosis
- Combined standard oncology care and palliative care should be considered early in the course of illness for any patient with metastatic cancer and/or high symptom burden

Q and A Session

Thank you for your attention